USE OF CHITOSAN - POLYACRYLIC ACID INTERPOLYMER COMPLEX AS A POLYMERIC OSMOTIC AGENT FOR DEVELOPMENT OF PUSH-PULL OSMOTICALLY CONTROLLED RELEASE TABLETS

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ABSTRACT

The aims of this study were to prepare chitosan-polyacrylic acid interpolymer complex and to use it as a polymeric osmotic agent for push-pull osmotically controlled release tablets of a model drug, felodipine. The interpolymer complex of chitosan (CS) and polyacrylic acid (PAA) was prepared with different ratios of CS to PAA and molecular weight (MW) of CS. The CS-PAA complex obtained was characterized and evaluated for swelling characteristics. The results showed that both polymer ratios and MW of CS affected the swelling property of the complex. To prepare the push-pull osmotically controlled release tablets (PPOT), the bilayered tablets with the drug and polymer layer were prepared as cores by double compression method. The drug layer contained felodipine, polyethylene oxide (PEO) and the polymer layer contained CS-PAA complex. The cores were coated with 3% w/v cellulose acetate in acetone. The coated tablets were drilled by CO_2 laser equipment to obtain the drug delivery orifice with a diameter of about 0.5 mm. The effects of the ratios of CS to PAA, type of plasticizers, tablet weight, and compression forces on release characteristics were investigated. The drug release from PPOT exhibited zero-order kinetics and could be prolonged up to 12 or 24 h with regard to polyethylene glycol 400 (PEG 400) or dibutyl sebacate (DBS), used as plasticizer, respectively. With DBS, the increase in tablet weight resulted in the decrease of drug release rate. The compression force had no effect on drug release of PPOT. A response surface methodology was employed to determine the optimum formulation of PPOT to achieve the desired drug release. The optimized composition of the PPOT was 50 mg of PEO, 15 mg of CS-PAA complex, 10 mg of KCl, 15% w/w of PEG 400, and 12% coating weight gain. The optimized formulation exhibited drug release conforming to the criterior of USP 28 for felodipine extended release tablets. The mathematic model related to extrusion rate and erosion rate for describing the drug release mechanism showed a good correlation between predicted and observed value.

KEY WORDS: CHITOSAN / POLYACRYLIC ACID / PUSH-PULL OSMOTIC PUMP / CHITOSAN-POLYACRYLIC ACID COMPLEX

250 pp.

การใช้สารประกอบเชิงซ้อนระหว่างโพลิเมอร์ของไคโตซานและโพลิอะคริลิกเอซิดเป็นสารก่อแรงดันออสโมติคสำหรับการพัฒนายาเม็ดออสโมติคปั๊มชนิดดึง-ดัน
(USE OF CHITOSAN - POLYACRYLIC ACID INTERPOLYMER COMPLEX AS A POLYMERIC OSMOTIC AGENT FOR DEVELOPMENT OF PUSH-PULL OSMOTICALLY CONTROLLED RELEASE TABLETS)

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อเตรียมสารประกอบเชิงซ้อนระหว่างโพลิเมอร์ของไคโตซานและโพลอะคริลิกเอซิดเป็นสารก่อแรงดันออสโมติค สำหรับยาเม็ดออสโมติคปั๊มชนิดดึง-ดันโดยใช้ฟีโลไดปีนเป็นยาต้นแบบ เตรียมสารประกอบเชิงซ้อนให้มี อัตราส่วนระหว่างไคโตซานและโพลิอะคริลิกเอซิด รวมทั้งน้ำหนักโมเลกุลของไคโตซานที่แตกต่างกัน การประเมินผลการการพองตัวของสารประกอบเชิงซ้อนที่ได้พบว่า อัตราส่วนของโพลิเมอร์ทั้งสองและน้ำหนักโมเลกุลของไคโตซานมีผลต่อการพองตัว เตรียมยาเม็ดออสโมติคปั๊มชนิดดึง-ดันโดยวิธีตอกสองครั้ง ทำให้ได้ยาเม็ดสองชั้นที่มีชั้นยาประกอบด้วย ฟีโลไดปีน โพลิเอธิลลีนออกไซด์ และชั้นโพลิเมอร์ประกอบด้วย สารประกอบเชิงซ้อนของไคโตซานและโพลิอะคริลิกเอซิด เคลือบยาเม็ดแกนด้วยเซลลูโลสอะซิเตทฟีล์มและเจาะรูขนาด 0.5 มม. ด้วยคาร์บอนไดออกไซด์เลเซอร์ ผลการทดสอบการละลายของยาเม็ดออสโมติคปั๊มพบว่า มีจลนศาสตร์ของการปลดปล่อยยาแบบอันดับศูนย์ และสามารถหน่วงเหนี่ยวการปลดปล่อยยาได้นานถึง 12 หรือ 24 ชม.เมื่อใช้โพลิเอธิลลีนไกคอลและไดบิวทิลเซบาเคตเป็นพลาสติไซเซอร์ตามลำดับ ผลของแรงตอกพบว่าแรงตอกไม่มีผลต่อการปลดปล่อยยา ในกรณีของไดบิวทิลเซบาเคต การเพิ่มน้ำหนักของยาเม็ด มีผลทำให้อัตราการปลดปล่อยยาลดลง การศึกษาหาค่าที่เหมาะสมของปัจจัยต่างๆในการตั้งสูตรตำรับเพื่อให้ได้การปลดปล่อยยาที่ต้องการ พบว่าสูตรตำรับซึ่งประกอบด้วย โพลิเอธิลลีนออกไซด์ 50 มก. สารประกอบเชิงซ้อนของไคโตซานและโพลิอะคริลิกเอซิด 15 มก. โปตัสเซียมคลอไรด์ 10 มก. โพลิเอธิลลีนไกคอล ร้อยละ15ของน้ำหนักสารเคลือบ และเคลือบยาเม็ดให้มีน้ำหนักเพิ่มขึ้นร้อยละ12 สามารถให้การปลดปล่อยยาเป็นไปตามข้อกำหนดของ USP28 สำหรับยาเม็ดออกฤทธิ์นานของฟีโลดิปีน กลไกการปลดปล่อยยาของยาเม็ดออสโมติคปั๊มชนิดดึง-ดัน สามารถอธิบายได้สอดคล้องเป็นอย่างดีกับสมการคณิตศาสตร์ที่เกี่ยวข้องกับอัตราการผลักดันยาออก และอัตราการกร่อนละลาย

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LIST OF ABBREVIATIONS

^{O} C	degree Celsius
%	percent
AA	acrylic acid
ANOVA	analysis of variance
Ca	calcium
CA	cellulose acetate
cm	centimeter
cm^2	square centimeter
cm^3	cubic centimeter
COO^-	carboxylic group
CS	chitosan
DF	degree of freedom
e.g.	*exmpli gratia*; for example
EOP	elementary osmotic pump
Eq.	equation
et al.	*et alii*; and others
etc.	*et cetera*; and other things
FTIR	fourier transform infrared
FD&C	food drug and cosmetics
g	gram(s)
GI	gastrointestinal
h	hour(s)
H-CS	high molecular weight chitosan
HPLC	high performance liquid chromatography
HPMC	hydroxypropylmethylcellulose
i.e.	id est; that is
IPC	interpolymer complex
IPN	interpenetrating polymer networks

LIST OF ABBREVIATIONS (cont.)

IVIC	in vivo-in vitro correlation
KCl	potassium chloride
L	liter
L-CS	low molecular weight chitosan
m	meter
m^3	cubic meter
mg	milligram
min	minute
mJ	millijoul
mL	milliliter
mm	millimeter
M-CS	medium molecular weight chitosan
MPa	megaPascal
MW	molecular weight
MS	mean square
N	Newton
nm	nanometer(s)
p	probability value
PAA	polyacrylic acid
PEC	polyelectrolyte complex
PEO	polyethylene oxide
PEG	polyethylene glycol
pH	the negative logarithm of the hydrogen in concentration
pKa	the negative logarithm of the dissociation constant
PPOP	push-pull osmotic pump
PPOT	push-pull osmotic pump tablet
R^2	coefficient of determination
rpm	revolutions per minute

LIST OF ABBREVIATIONS (cont.)

SD	standard deviation
SS	sum of squares
USP	the United States Pharmacopoeia
UV/VIS	ultraviolet/visible
w/w	by weight

PUBLICATION AND PRESENTATIONS

PRESENTATIONS

Ketjinda W, Sinchaipanid N, Leuenberger H, Limsuwan P, Mitrevej A. Design and evaluation of push-pull osmotically controlled release tablets using chitosan-polyacrylic acid complex as osmopolymer. RGJ-Ph.D. Congress VIII; 2007 April 20-22; Thailand. (Oral presentation)

Ketjinda W, Sinchaipanid N, Limsuwan P, Mitrevej A. Applications of chitosan complex in push-pull osmotic pump tablets. Innovative dosage form & process technology; 2007 March 15; Basel, Switzerland.(Oral presentation)

Ketjinda W, Sinchaipanid N, Limsuwan P, Mitrevej A. Use of chitosan-polyacrylic acid complex as an osmogent in the push-pull osmotically controlled release tablets. Proceeding of Asian Pharmaceutics Graduate Congress: The science of product design and pharmaceutical technology; 2006 September 25-27; Singapore. (Oral presentation)

Ketjinda W, Sinchaipanid N, Limsuwan P, Mitrevej A. Development of push-pull osmotically controlled release tablets using chitosan-polyacrylic acid interpolymer complex as polymeric osmotic agent. RGJ-Ph.D. Congress VII; 2006 April 20-22; Thailand. (Poster presentation)

Ketjinda W, Sinchaipanid N, Limsuwan P, Mitrevej A. Use of chitosan-polyacrylic acid interpolymer complex as a polymeric osmotic agent for development of push-pull osmotically controlled release tablets. Fourth Indochina Conference on Pharmaceutical Sciences, November 10-13, 2005, HoChiMinh City, Vietnam. (Poster presentation)

CHAPTER I
INTRODUCTION

Development of oral drug delivery system providing constant release of drug has been the focus of many researches, mainly with an objective to provide constant drug delivery during passage through gastrointestinal tract for prolonged period of time. The purpose is to achieve the more effective therapies while reducing frequency of dose administration, increasing in patient compliance, and reducing in side effects in comparison to the other conventional formulations. Oral administration has been the most commonly used route of drug delivery due to greater flexibility in dosage form design, high patient compliance and safety, minimal microbiological requirements and a low risk of damage at the site of administration. Number of techniques is used to achieve controlled release of drug via the oral cavity. One of the successful technologies is osmotic pump controlled release, involving the use of osmotic pressure as a driving force to deliver drug.

Osmotically controlled drug delivery is an ideal drug delivery system which provides many benefits including delivering drug at an optimal rate at an optimal time or in a specified pattern. Typically, this system offers distinct and practical advantages compared with other oral controlled delivery systems, such as matrix-type and membrane-type. The following advantages have contributed to the popularity of osmotic drug delivery system (1).

1. The delivery rate of zero-order is achievable with osmotic system.
2. The drug release is independent of gastric pH and hydrodynamic conditions.
3. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
4. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

5. A high degree from in vivo-in vitro correlation (IVIVC) is obtained in osmotic system.

These advantages are attributed to the design of osmotic system. Environment contents (e.g., GIT fluids) do not have access to the drug until the drug has been out of the device. Furthermore, osmotic systems have a high degree of IVIVC because the factors causing differences in release profile in vivo and in vitro (e.g. variable pH, agitation) affect these systems to a much lesser extent.

Osmotically controlled release drug delivery system has changed consi-derably since Rose and Nelson developed the first osmotic pump for delivering drugs to animals. From complex implantable devices to simple tablets, the extent of simplification and miniaturization has been remarkable as found in Table 1 that shows a lot of number of patents granted (2). The osmotic delivery devices of today not only deliver drug with moderate solubility, but also are capable of delivering drugs with solubility extremes. Two osmotically controlled delivery mechanisms that are widely developed in pharmaceutical industry are elementary osmotic pump (EOP) and push-pull osmotic pump (PPOP). The EOP is a simple system which consists of an osmotic core, surrounded by semipermeable membrane, with a delivery orifice. After the tablet is swallowed, the osmotic core acts by imbibing water from surrounding medium via the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice. Generally, it is suitable for the delivery of a water-soluble drug. To overcome the limit of EOP, a push-pull osmotic pump (PPOP) was developed as controlled release dosage form for an insoluble drug. It consists of two compartments, one containing drug, osmotically active hydrophilic polymer and the other containing hydrophilic expansion polymer. In operation, the delivery of drug from osmotic device is carried out by imbibition of fluid by the drug chamber composition to form a fluid composition in situ, and delivery of the suspension through the delivery orifice. Concurrently, inbibition of fluid by the second hydrogel layer causes this layer to swell and cooperates with the first composition to drive the drug via the delivery orifice. The swellable hydrophilic polymer commonly used as a polymeric osmotic agent is polyethylene oxide, hydroxypropylmethyl cellulose, polyacrylic acid or Carbopol 934P (3-7). Manufacturing uses mostly standard unit operations, which consists of granulation, tabletting, coating, and drilling.

Table 1. Classification scheme for osmotic drug delivery systems.

Category	No. of patents to December 1993
Rose-Nelson pump	11
Higuchi-Leeper-Theeuwes pump:	
Higuchi-Leeper	22
Higuchi-Theeuwes	42
Elementary Osmotic pump	
General OROS®	58
Device preparation	10
Multichamber pumps	67
Other systems	30
Total	240

Specialized equipment for PPOP includes a multilayer tablet machine and customized laser drilling facilities.

In this study, the alternative hydrogel of chitosan-polyacrylic acid interpolymer complex is introduced to be used as a polymeric osmotic agent. In general, interpolymer complexes are formed by the association of various macromolecules by some types of interaction. One interaction is polyelectrolyte complex which is form between macromolecular polyacids and polybases and stabilized by ionic bonds. Chitosan (CS) is a partially N-deacetylated product from the natural polymer chitin, which is found widely in nature. It is inexpensive, safe, nontoxic and biodegradable. When CS, a cationic polymer, interacts with an anionic polymer such as polyacrylic acid (PAA), the interpolymer complex between chitosan and polyacrylic acid can be formed due to electrostatic interaction as with ionically crosslinked network. CS-PAA interpolymer complex is a swellable polymer, producing a stiff gel which helped maintain the integrity of swellable hydrogel matrix without much erosion loss as found in case of individual polymer, chitosan or polyacrylic acid. There are few studies of CS-PAA interpolymer complex used as a matrix (8-11), mucoadhesive (12-13), nanoparticles (14-16) in oral drug delivery system. However, there is no report of using CS-PAA interpolymer complex in osmotically controlled release drug delivery system. Preferably, CS-PAA interpolymer complex does not exhibit pH-sensitive swelling in case of osmotic pump tablet due to semipermeable membrane limiting the passage of ion from the environment. Therefore, it is expected to be used as a polymeric osmogent in development of felodipine push-pull osmotic pump tablet. Various variables which control the drug release are investigated and analyzed to obtain the useful information in dosage form design.

The objectives of this study were

1. to prepare chitosan-polyacrylic acid interpolymer complex to exhibit suitable swelling property.
2. to optimize chitosan-polyacrylic acid interpolymer complex as a polymeric osmotic agent for the development of push-pull osmotically controlled release felodipine tablets.
3. to investigate the factors affecting drug release from push-pull osmotically controlled release system.

4. to reveal the mechanism of drug release from the obtained push-pull osmotically controlled release felodipine tablets.

CHAPTER II
LITERATURE REVIEW

Ideal oral drug delivery system should steadily deliver measured and reproducible amount of drug to the target site over a prolonged period and, after absorption, allow constant plasma concentration within the therapeutic range, which minimizes side effects and also reduces the frequency of administration. In practice, such a system should provide a programmable concentration-time profile that produce optimum therapeutic responses. This goal can only be achieved to a limited extent with conventional dosage forms. However, any release from oral controlled dosage form may be affected by pH, GI motility, and the present of food in GI tract.

A useful classification of controlled release drug delivery system based on the mechanism controlling the drug release is as follows (17):

1. Controlled drug release by diffusion process
    - 1.1 Membrane permeation controlled drug delivery
    - 1.2 Matrix diffusion controlled drug delivery
    - 1.3 Microreservoir dissolution controlled drug delivery
2. Controlled drug release by activation process
    - 2.1 Osmotic pressure activated drug delivery
    - 2.2 Hydrodynamic pressure activated drug delivery
    - 2.3 Vapor pressure activated drug delivery
    - 2.4 Mechanics activated drug delivery
    - 2.5 Magnetic force activated drug dlivery
    - 2.6 Ultrasound activated drug delivery
    - 2.7 Iontophoresis activated drug delivery
    - 2.8 pH activated drug delivery
    - 2.9 Ion activated drug delivery
    - 2.10 Swelling activated drug delivery
    - 2.11 Hydrolysis activated drug delivery

2.12 Enzyme activated drug delivery

Among all the controlled release drug delivery systems referred to above, the osmotic controlled release drug delivery system derives some important properties from the delivery mechanism. (18)

1. The osmotic mechanism provides the basis for systems that operate independently of agent properties, since the solvent (water) transported during delivery is the same in every application. This allows delivery of substances with broad range of molecular weights and chemical properties, such as ionic spicies, complex structure, and agents with varying solubilities.

2. Since the water molecule is small compared to molecules of active agents, osmotic delivery systems can provide high delivery rate up to 50 mg/h per cm^2 of employed membrane area.

3. The delivery characteristics are predictable; drug release can be programmed at rates that are substantially independent of environments, as described further in detail.

4. Any release from appropriately designed osmotic controlled oral drug delivery system is not influenced by pH, GI motility, and the present of food within the gut lumen.

Before describing osmotic controlled release drug delivery system, the background of osmosis is stated briefly.

Principle of osmosis

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is the osmotic pressure. The historical perspective on the study of osmosis can be described as follows:

In 1748, Abbe Nollet first reported the osmotic process.

In 1877, Pfeffer separated a sugar solution from water using a sugar-impermeable membrane and quantified the water transport.

In 1884, Hugo de Vries invoked osmotic concepts to understand the contraction of the contents of plant cells placed in solutions of high osmotic pressure, where the cell membrane acted as a semipermeable membrane. The osmotic pressure difference between inside and outside environments caused osmotic pressure loss and resulted in plasmolysis.

In 1886, Van't Hoff identified an underlying proportionality between osmotic pressure, concentration, and temperature in Pfeffer's experiment. Later, he revealed a relationship between osmotic pressure and solute concentration and temperature that was similar to the ideal gas equation as shown by the expression

$$V\pi = nRT \quad (1)$$

where π = osmotic pressure in atmospheres
V = volume of the solution in liters
n = number of moles of solute
R = gas constant, equal to 0.082 L.atm/mol.K
T = absolute temperature in K

The Van't Hoff equation also can be written as follows:

$$\pi = (n/V)RT \quad (2)$$

or

$$\pi = cRT \quad (3)$$

where c is the concentration of the solute in moles per liter. The preceding equation can be applied satisfactorily to describe the osmotic pressure of dilute solutions of nonelectrolytes such as sucrose and urea. However, the osmotic pressure of electrolyte solution is not predicted well by the general equation. Therefore, a factor i was introduced to account for the behavior of ionic solutions. The corrected equation for electrolyte solution is written as follows:

$$\pi = icRT \quad (4)$$

Osmotic pressure, a colligative property, depends on the concentration of solute (neutral molecule or ionic species) that contributes to the osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Osmotic pressures for concentrated solutions of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture. These osmotic pressures can produce high water flow across semipermeable membrane. The osmotic water flow across a membrane is given by the following equation.

$$dV/dt = A\theta\Delta\pi/l \quad (5)$$

where dV/dt = water flow across the membrane of area A, thickness l

θ = osmotic permeability

$\Delta\pi$ = osmotic pressure difference between the two solutions on either side of the membrane

In 1974, Theeuwes and Higuchi applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over existing controlled drug delivery systems. A constant osmotic pressure, and thereby a constant influx of water, can be achieved by the osmotic delivery system that results in constant release rate of drug. The first of these devices, the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles.

Evolution of Osmotic Delivery Systems

1. Rose-Nelson's pump

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. In 1955, Rose and Nelson developed the first osmotic device that represented the forerunner of the modern osmotically controlled drug delivery systems (19). Their pump, illustrated in Figure 1, consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water were separated by a rigid semipermeable. The difference

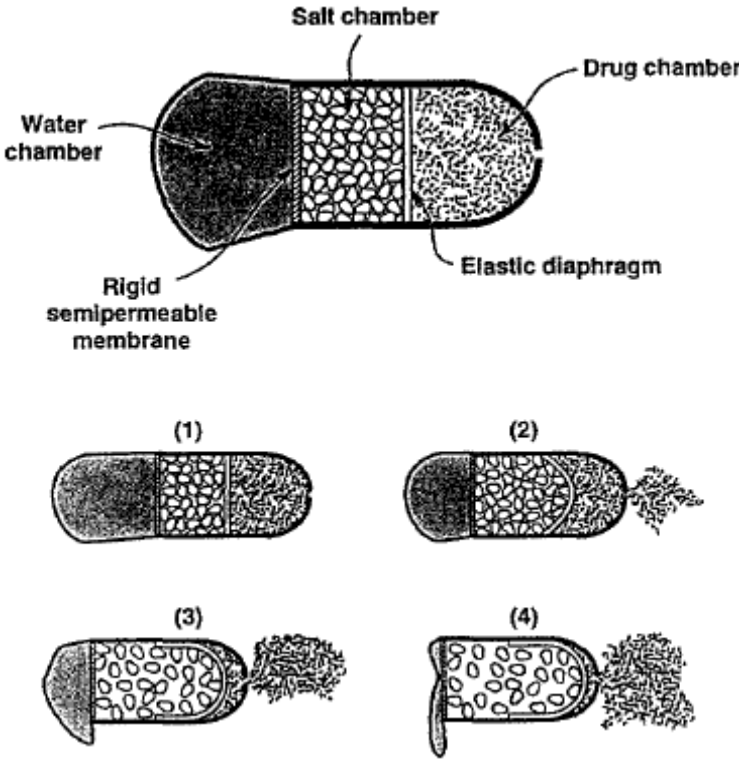

Figure 1. Principle of the three-chamber Rose-Nelson osmotic pump.

in osmotic pressure across the membrane moved water from the water chamber into the salt chamber. The volume of the salt chamber increased because of this water flowed, which distended the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device.

The pumping rate of Rose-Nelson pump is given by the Eq.6

$$dM_t/dt = (dV/dt).c \quad (6)$$

where dM/dt = drug release rate

dV/dt = volume flow of water into the salt chamber

c = concentration of drug in drug chamber

Substituting Eq.5 for the flux across the membrane gives

$$dM_t/dt = A\theta\Delta\pi c/l \quad (7)$$

These basic equations can be used to describe the behavior of most of the devices controlled release by osmotic mechanism. The osmotic pressure of the saturated salt solution is high, on the order of tens of atmospheres, and the small pressure required to pump the suspension of active agent is insignificant in comparison. Therefore, the rate of water permeation across the semipermeable membrane remains constant as long as sufficient solid salt is present in the salt chamber to maintain a saturated solution and hence a constant osmotic pressure driving force.

One of the problems with the early Rose-Nelson pumps was that the osmotic action began as soon as water came in contact with the semipermeable membrane. This mean pumps had to be stored empty and loaded with water immediately prior to use, causing an inconvenient procedure. A Pharmetrix device (20) overcame this difficulty by separating the water chamber with an impermeable seal, which was broken before administration of the pump.

2. Higuchi-Leeper pump

The Higuchi-leeper pump represented a simplified version of the Rose-Nelson three-chambered pump. The device was a two-chambered pump with no water chamber and was activated by water imbibed from surrounding environment (21).

Higuchi-Leeper pump, shown in Figure 2, contained a rigid impermeable housing, and the semipermeable membrane was supported on a perforated frame. This type of pump usually had a salt chamber containing a fluid solution with excess solid salt. In use, the device was implanted in or swallowed by an animal. Fluid from the tissues was drawn osmotically through the semipermeable membrane into the osmotic chamber and the pumping action began. The active agent was pumped at a constant rate according to Eq.7. In one of the modifications of this pump, the pulsatile drug delivery was accommodated (22). The pulsatile release was achieved by forming the orifice of elastic material that stretched in response to the osmotic pressure. Once a certain critical pressure was produced, the orifice opened, releasing the drug as a pulse. The pressure then fell, the orifice closed, and the cycle repeated. The orifice was small enough to be substantially closed when the osmotic pressure was below threshold level.

3. Higuchi-Theeuwes pump

The simplest version of the Rose-Nelson pump was developed by Higuchi and Theeuwes in 1976. As shown in Figure 3, the pump comprised a rigid, rate-controlling outer semipermeable membrane surrounding a solid layer of salted coated on the inside by an elastic diaphragm and on the outside by the membrane (23). In use, water was osmotically drawn by the salt through the semipermeable membrane. This water increased the volume of the salt chamber, forcing drug from the drug chamber. In one of the modifications of this pump, a mixture of citric acid and sodium bicarbonate was used in salt chamber of the pump. This mixture, when contacted by water from the outside environment, produced carbon dioxide gas, which then exerted a pressure on the elastic diaphragm (24).

4. Elementary osmotic pump

An important evolution in osmotic delivery occurred as the elementary osmotic pump for oral delivery of medicaments was introduced. The system represented a further simplification of the Higuchi-Theeuwes pump, and eliminates the separate salt chamber by using the drug itself as the osmotic agent (25). In its simplest form, as shown in Figure 4 , the device consisted of a compressed tablet surrounded by a semipermeable coating, and it delivered the drug solution or suspension through an

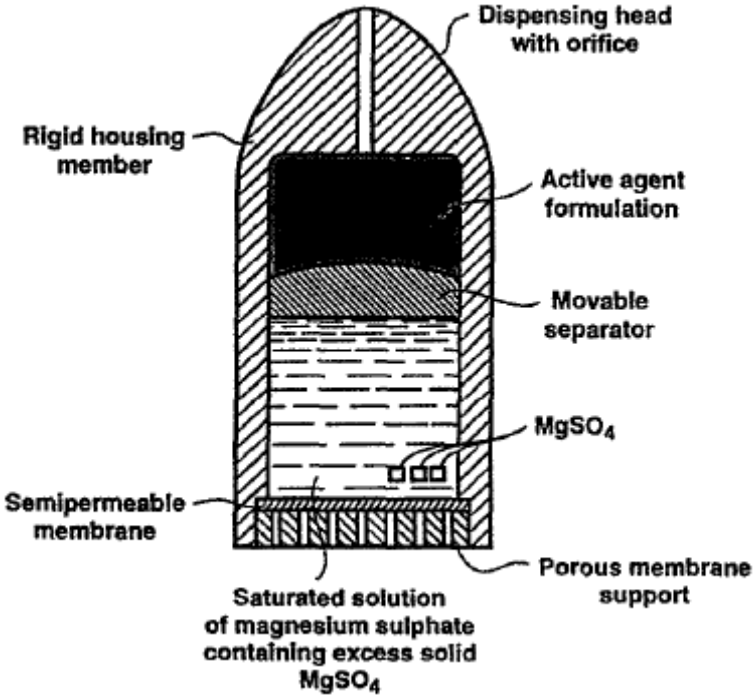

Figure 2. Higuchi-Leeper pump

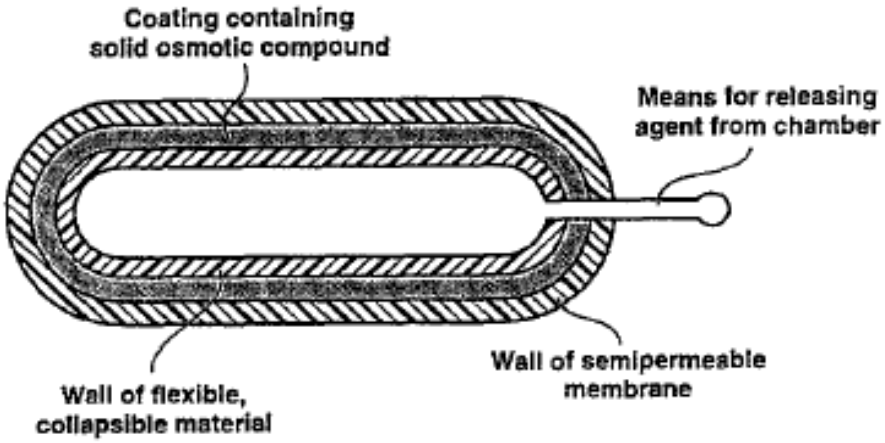

Figure 3. Higuchi – Theeuwes pump.

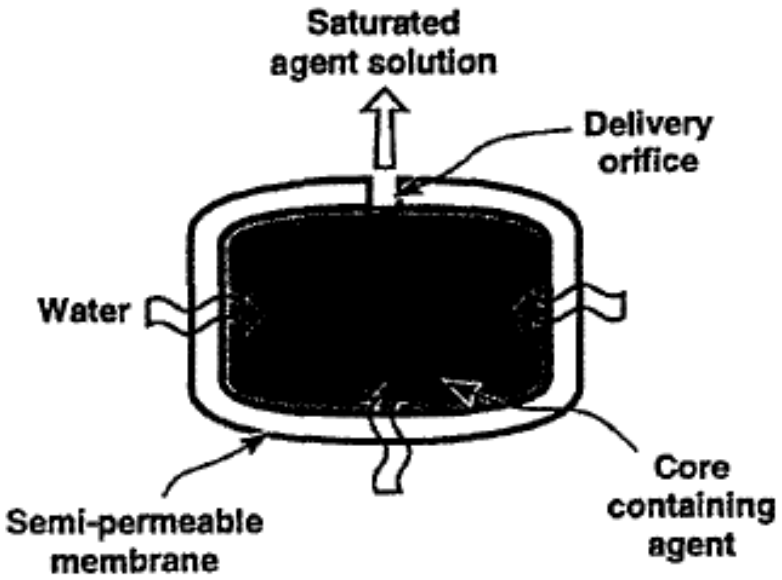

Figure 4. The basic concept of Theeuwes elementary osmotic pump

orifice in the tablet. The elementary osmotic pump was developed by ALZA under the name OROS®, and has been commercialized for a number of drugs such as nifedipine (Procardia XL® in United states, Adalat CR® in Europe), phenyl-propanolamine (Acutrim®), prazosin (Minipress XL®) and salbutamol (Volmax®). The elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles. The concept proved popular, and 135 patents have been issued for various aspects of the system.

The devices described are represented the four main types of osmotic pumps developed according to osmosis principle and are summarized in Table 2. This development of osmotic pumps from the forerunner of Rose-Nelson pump to the elementary osmotic pump is an interesting example of how true innovation is sometimes achieved by leaving thing out. The first osmotic pump produced by Rose and Nelson had six critical components, had a volume of 80 cm^3. Theeuwes F and others progressively simplified and refined this concept , leading in the end to the elementary osmotic pump. It has been described as a tablet with a hole, but is a truly elegant invention having a volume of less than 1 cm^3, containing only two components.

Classification of Osmotic Pumps

Since the early period of osmotic pump history, osmotic pump research has produced a variety of improved and specialized osmotic pump types, optimized for different performance goals. Based on their design and the state of active ingredient, osmotic delivery systems can be classified as fellows:

1. Osmotic delivery systems for solids

1.1 Single compartment

1.1.1 Elementary osmotic pump (EOP)

In this design, the drug and the osmotic agent are located in the same compartment, which is shown schematically in Figure 4. In the device, an active agent, having suitable osmotic pressure, and/or accompanying osmotic agent is compressed in the form of a tablet, which is then coated with a semipermeable membrane, and a small orifice is created in the membrane. When this tablet comes in contact with the

Table 2. Comparison of the main types of osmotic pump system

	Rose-Nelson Pump	Higuchi-Leeper Pump	Higuchi-Theeuwes Pump	Theeuwes Elementary Osmotic Pump
Approximate Volume (cm^3)	80	35	3	< 1
Components	Rigid Housing Water Chamber Salt Chamber Drug Chamber Elastic Diaphragm Membrane	Rigid Housing Salt Chamber Drug Chamber Elastic Diaphragm Membrane	Salt Chamber Drug Chamber Elastic Diaphragm Membrane	Drug Chamber Membrane
Number of Components	6	5	4	2

aqueous environment of the GI tract, the agent inside the tablet draws water through the semipermeable membrane because of the osmotic pressure gradient and forms a saturated solution inside the device. As the membrane is nonextensible, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of satuarated solution out of the device through the delivery orifice. This process continues a constant rate until the entire solid agent inside the tablet has been dissolved, and only a solution-filled coating membrane is left. This residual dissolved agent continues to be delivered at declining rate until the osmotic pressure inside and outside the tablet is equal. Normally, the EOP delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 minute as the system hydrates before zero-order delivery from the EOP is obtained (26).

Equation for EOP

In general expression for drug delivery rate dM/dt from EOP can be expressed by the following equation (27).

$$dM/dt = (dv/dt).C \quad (8)$$

where

dM/dt : drug delivery rate or amount of drug release at time t

dv/dt : water permeation rate across semipermeable membrane

C : concentration (or solubility,where excess solid is present inside the core) of drug in dispensed fluid

and

$$dv/dt = (A/h)\, L_p(\delta\Delta\pi - \Delta\rho) \quad (9)$$

L_p : hydraulic permeability

A : membrane area

h : membrane thickness

δ : reflection coefficient

$\Delta\pi$: osmotic pressure different

$\Delta\rho$: hydrostatic pressure

As the size of the delivery orifice increases, hydrostatic pressure inside the system is minimized ($\Delta\pi > \Delta\rho$). Also, when the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, π can be substituted for $\Delta\pi$. Eq. 9 then reduces to a much simpler expression in which constant K replaces the product $L_p\delta$. After simplification, the following equation is obtained.

$$dv/dt = AK\pi/h \quad (10)$$

therefore

$$dM/dt = AK\pi C/h \quad (11)$$

The release rate defined by Eq.11 remains zero order as long as the terms in the equation remain constant. The first three terms on the right-hand side of Eq.11 can be maintained constant through proper selection and optimization of semipermeable membrane. Therefore, a constant release of drug from the device is maintained as long as excess solid agent presents inside the device to maintain both π and C in Eq.11 at constant level.

There are several approaches to modulate the solubility of drugs in osmotic systems. The solubility of active ingredient within the device determines the release rate and the percentage of the drug delivered in the desired zero-order fashion.

Use of crystal habit modifier

If the drug exists in more than one crystal form, each having different aqueous solubility, it is beneficial to include a crystal modifying agents in an oral osmotic system for a slightly soluble drug. One such system consisted of a core that comprises drug (carbamazepine), crystal habit modifier (hydroxymethylcellulose and hydroxyl-ethyl cellulose), osmotic agent and other excipient. The osmotic system could provide approximately zero-order release for desired period of time (28).

Use of swellable polymers

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility such as carbamazepine, theophylline, acetylsalicylic acid and nifedipine (29). The osmotic system consists of a compartment, containing the drug, a hydrophilic polymeric swelling agents composed of a mixture of a vinylpyrrolidone-vinyl acetate copolymer and polyethylene oxide, and osmotic agent. The drug release

rate from the osmotic pump is relatively constant due to uniform rate of swelling of the polymers. Also, the pressure produced during swelling does not lead to rupture of the system.

Use of wicking agents

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs (30). A wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the fluid influx. Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. A delivery system for nifedipine used colloidal silicon dioxide, polyvinylpyrrolidone and sodium lauryl sulfate as wicking agents.

1.1.2 Controlled porosity osmotic pump (CPOP)

One interesting category of the osmotic tablets is the system , called "controlled porosity osmotic pump", that attempt to avoid the need of laser or mechanical drilling to create delivery orifice. Osmotic tablets (really the tablets as EOP) have been developed in which the delivery orifice is formed by incorporation of a leachable water-soluble component in the coating material (31-34). Once the tablet contacts with the aqueous environment, the water-soluble component dissolves, and creates voids in the coating membrane which attribute to controlling the release of drug. The resulting membrane is substantially permeable to both water and dissolved solutes. Some of the pore-forming additives that can be used are sodium chloride, urea, and potassium chloride.

Thombre AG, et al. found that microporous walls of CPOP are morphologically complex. After the water-soluble additives are leached out as contacting the aqueous environment, an intimate interconnecting complex of polymer and voids is formed (35). The mechanism of drug release from these systems was found to be primarily osmotic with simple diffusion playing a minor role.

Liu H, et al. studied a microbially triggered colon-targeted osmotic pump (MTCT-OP) (36). The effects of different formulation variables, including the level of pH-regulating excipient (citric acid) and the amount of chitosan in the core, and the level of pore former (chitosan) in the semipermeable membrane have been studied. The results showed that the amount of budesonide release was directly proportional to the initial level of pore former, but inversely related to the weight of semipermeable

membrane. The different levels of enteric-coating membrane could prevent cellulose acetate membrane from forming pore or rupture before contact with simulated colonic fluid, but had no effect on the drug release.

1.1.3 Pulsatile drug delivery

Mechanical and drug solubility-modifying techniques have been implemented to achieve the pulsed delivery of drug with an osmotic system.

Solubility modulation for pulsed release (37-39)

The pulsed delivery system of salbutamol sulfate exploited the solubility modulator to control the drug release. The elementary osmotic pump tablet was made of a mixture of salbutamol and sodium chloride. Pulsed delivery was based on drug solubility that was modulated by sodium chloride. In use, the solubility of salbutamol initially decreased due to the presence of sodium chloride. However, the solubility of salbutamol increased very quickly as the sodium chloride was exhausted. Therefore, the net result was a tablet that delivers the salbutamol at a relatively constant rate with a pulsed release at the end of the delivery period.

Multiparticulate pulsatile drug delivery system (40)

The delivery system can be a capsule or tablet composed of a large number of pellets. Each pellet has a core that contains the therapeutic drug and water-soluble osmotic agent. A water-permeable, water insoluble polymer film encloses each core. A hydrophobic water-insoluble agent that alters permeability is incorporated into the polymer film. The rate at which water passes through to the core and drug diffusion out of the core cause the film coating of each pellet population to differ from any other pellet coating in the dosage form. The osmotic agent dissolves in water, which causes the pellet to swell and thereby regulate the rate of diffusion of drug from dosage form. The effect of each pellet population releasing its drug into the environment sequentially provides a series of pulsatile administrations of the drug from a single dosage form.

Swelling layer of a rupturable pulsatile drug delivery system

Zhang Y, et al.(41) prepared a novel pulsed-release system based on bilayer coated tablets containing an osmotically active agent. The pulsed-release system containing of three laminar layers from the center to outside, the core tablet containing drug and osmotically active ingredient, swelling agent layer, and water insoluble

polymer membrane. Dissolution profile showed a typical sigmoidal pattern that was characterized by a distinctive lag-time followed by a rapid drug release. The lag-time was extended with the increase in the outer coating level. The osmotic active agent and swelling layer were proved to be essential for the fast drug release. Drug release mechanism involved both diffusion and osmotic pump effect, but the latter was more important.

1.1.4 Enteric-coated and colon-targeted osmotic dosage form (42)

The devices are designed for tablets or capsules using osmotic systems for the pH-triggered burst of the active agent. In case of tablets, the core consists of the drug, osmogent, diluents, and superdisintegrants. The tablets are coated first by semipermeable membrane of insufficient thickness and then overcoated with the pH-triggered solution contains polymers such as cellulose acetate phthalate, pH-sensitive Eudragit grades, and insoluble polymer. The tablets burst time depends on the thickness of the membrane and ratio of pH-sensitive polymer to nondissolving material in the pH-triggered membrane coating. The device offers an advantage over conventional enteric coating because it can control the tablet burst time after a change in the pH of the environment and it is more reliable in the high-pH conditions of the stomach.

1.1.5 Volume amplifier devices (43)

The elementary osmotic pump is modified to deliver the entire drug contained in the system by using the volume amplifier. The device consists of a core, and semipermeable membrane, and a delivery orifice. In addition to the drug and osmotic agent, the core contains the volume amplifier, consisting of a gas-generating couple coated with the membrane formed of an expandable material that is permeable to fluid and impermeable to the couple. In use, the active agent is delivered from the system through the passageway at a controlled rate because fluid is imbibed through the wall into the compartment to produce a solution-suspension of the drug. Simultaneously, the amplifier increases in volume (because of the generation of the gas) and fills the compartment, forcing the desired agent to be released at a rate controlled by the permeability of the wall, the osmotic pressure gradient across the wall, and the rate of imbibition and increase in the amplifier's volume. The gas-generation couple in a volume amplifier can be a mixture of an acid substance and base substance. The

volume amplifier membrane is free of passageways, and contains an expansion agent that gives membrane flexibility and expandability.

1.1.6 Effervescent activity-based systems (44)

The advantage of the devices is the delivery of the drug with limited solubility under acid condition. The osmotic device comprises a semipermeable membrane that surrounds a compartment containing a drug and a compound capable of releasing carbon dioxide in the presence of an acid. The formulation imbibes aqueous fluid across a basic solution containing drug and compound is formed, which is delivered through the passageway. The released compound reacts with the acid at the device-environment interface and evolves carbon dioxide, thereby dispenses the drug to the environment in a finely dispersed form over time. Thus the drug is delivered in a form that is rapidly absorbed and does not block the orifice of the delivery device. Drugs that can be delivered by such a system are those that exhibit a propensity for rapid precipitation in an environment that has a pH < 7, i.e., indo-methacin, aspirin, diclofenac, fenoprofen, piroxicam, and flufenamic acid.

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1.1.7 Monolithic osmotic tablet with two orifices (45)

Liu L. et al. prepared the monolithic osmotic tablet system, which was composed of a monolithic tablet coated with cellulose acetate membrane drilled with two orifices on both sides surfaces. The influences of tablet formulation variables including molecular weight and amount of polyethylene oxide (PEO), amount of KCl and amount of rice starch as well as nifedipine loading had been investigated. It was found that PEO with MW of 300,000 g/mol was suitable to be thickening agent, both amount of KCl and PEO had comparable and profoundly positive effects, while nifedipine loading had a negative influence on drug release. The optimal orifice size was in the range of 0.25-1.41 mm.

1.1.8 Swellable elementary osmotic pump (SEOP)(46)

Shokri J., et al. prepared and evaluated a new type of elementary osmotic pump tablet for efficient of poorly water-soluble/practically insoluble drugs. Drug release from the system was through a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption. The tablets composed of micronized drug, various polymers, osmotic agent and wetting agents. The results showed that the type of polymer and concentration of wetting agent in the core formulation could markedly

affect the drug release from SEOP system. Optimum aperture diameter for the formulations studied was determined to be 650 μm for zero-order release pattern.

1.2 Multiple compartment

The EOP is limited to delivery of drug with intermediate water solubility, general greater than 2-5% (26). The insoluble drugs, high release rate cannot be readily achieved by one-chamber EOP. This problem led to the development of multichamber osmotic pump. These multichannel tablets can be devided into two main categories, depending on whether one of the chambers expands into the other (push-pull osmotic pump) or whether the chambers are rigid and maintain their volume throughout the optional life of device.

1.2.1 Push-pull osmotic pump (PPOP)

The PPOP which was developed by Alza Corporation (47), is shown schematically in Figure 5. The basic push-pull system resembles tablet in shape and has two layers. The first layer or drug layer consists of the drug substance, osmotically active hydrophilic polymers and other excipients. The second layer or push layer, contains a hydrophilic expansion polymer and other osmotically active agents and tablet excipient. The drug layer accounts for 60-80% of the tablet weight, while the osmotic polymer layer accounts for 20-40% (48-49). In use, the delivery of drug from osmotic device is carried out by imbibition of fluid by the drug chamber composition to form a fluid composition in situ, and delivery of the suspension through the passageway. Concurrently, inbibition of fluid by the second hydrogel layer causes this layer to swell and cooperates with the first composition to drive the drug through the passageway. The osmotic device may be considered as a cylinder, with the second composition expanding like the movement of piston to aid in delivering the agent**.**

Equation for PPOP (48)

When the pump is in operation, both push and drug chambers imbibe water across the membrane, with a drug suspension formed in the drug chamber. The delivery rate from the push-pull system can be described by the following equation.

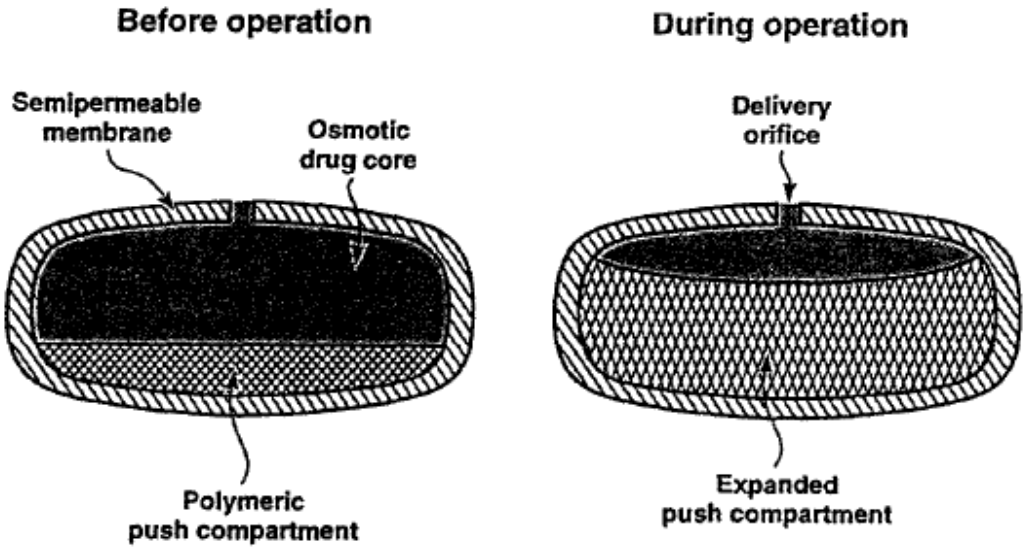


Figure 5. Drug delivery process of push-pull osmotic pump system

The volumetric flow Q in the osmotic push compartment is defined as

$$Q = (dv/dt)_o \quad (12)$$

and the volumetric flow F into drug compartment is defined as

$$F = (dv/dt)_d \quad (13)$$

The concentration of drug released from the formulation can be written as

$$C_s = F_d C_o \quad (14)$$

where C_o= concentration of solids dispensed from the system

F_d = fraction of drug formulated in drug compartment

The mass delivery rate from the dosage form, dm/dt, can be written as

$$dm/dt = (dV/dt).C_s \quad (15)$$

Therefore, the modified expression for the mass delivery rate from the push-pull system is as follows:

$$dm/dt = (Q+F).\ F_d C_o \quad (16)$$

where

$$Q = (K/h).A_p(H)\pi_p(H) \quad (17)$$

and

$$F = (K/h)(A - A_p(H)).\pi_d\ (H) \quad (18)$$

where A_p = surface area of the push compartment

A = total surface area of the dosage form

π_p = imbibition pressure of the push compartment

π_d = imbibition pressure in the drug compartment

h = thickness of the membrane

k = membrane permeability coefficient

The preceding equations apply to push-pull osmotic pumps that deliver water-soluble compounds. In that case, both drug and osmotic agent can exert constant osmotic pressure. However, in case of water-insoluble drugs, the systems are formulated with polymers that exert pressure as a function of the degree of hydration H, which is not a constant. H is expressed as follows:

$$H = W_H / W_P \qquad (19)$$

where W_H = weight of water imbibed

W_P = weight of dry polymer

Therefore, the H term in Eq.17 and 18 can expressed in terms of water uptake and initial polymer weight.

Sastry SV, et al. investigated the formulation variables of atenolol push-pull osmotically controlled tablets using response surface methodology to optimize the formulation (50). Preparation involved the fabrication of biconvex, bilayered tablets containing drug, an osmotic agent and other additives. It was found that the factors: orifice size, volume of coating and amount of Carbopol® 934P in drug layer showed significant effects on the release of atenolol from the osmotically controlled tablets. An increase of the orifice size from 0.016″to 0.02″ resulted in an increase in drug release. An increase in Carbopol® 934P in drug layer had profoundly decreased in drug release. In addition, an increase in coating level had resulted in substantial increase in drug release, since at low coating levels the polymer film was expanding to accommodate an increase in osmotic pressure and a decrease in the drug release.

Sastry SV, Khan MA prepared the bilayered osmotically controlled gastro-intestinal therapeutic system of atenolol by using aqueous-based coating system of cellulose acetate pseudolatex prepared by polymer emulsification (51). Various factors, such as orifice size, % coating weight gain, excipient quantities and amount of osmotic agent had affected the drug release. The relative importance factors for the drug release from GITS in 24 hours with constraints on percent drug release at 2,6,12

and 18 hours, was in the order: % coating weight gain > Carbopol® 934P > Polyox® N80 > Carbopol® 974P > Polyox® 303 > amount of sodium chloride > orifice size.

Prabakaran D, et al. developed a modified two-layered, push-pull osmotic tablets to deliver theophylline and salbutamol sulphate (SS) simulataneously for extended period of time (52). The basic design was a two–layered, push-pull osmotic pump tablets coated with controlled porosity membrane instead of usual semipermeable membrane. Scanning electron microscopy of cellulose acetate coating membrane after dissolution revealed that 25% (w/w) of sorbitol can be used as an optimized concentration of pore forming agent with 25% (w/w) of plasticizer. Formulation were initially developed for theophylline and the release was optimized by using two different soluble forms of theophylline with varying amount of mixture of microcrystalline cellulose and hydroxypropylcellulose in upper layer and polyethylene oxide (PEO) in lower layer. From the results, 20% (w/w) of polymer mixture and 100 mg PEO provided sufficient extended release of theophylline without rupturing of coating membrane. Further, the release of SS was optimized by keeping the drug in upper or lower layer or both layers, accommodating the formulation achieved in the release of theophylline. It was found that the formulation that kept amount of SS in both layers provided controlled release of both theophylline and salbutamol for extended period of time (16-20 hours).The release profiles of both drug statistically compared with respective marketed controlled release formulations. Also, the release rate of drugs could be effectively modified by manipulating in concentration of pore forming agent and orifice diameter.

Gondaliya D and Pundarikakshudu K studied the use of push-pull osmotic pump tablets coated with controlled porosity membrane for delayed release of highly soluble drug, diltiazem HCl (53). The bilayered tablets with the drug and polymer layer were prepared as cores by wet granulation method. The drug layer contained diltiazem HCl, sodium chloride, guar gum and the polymer layer contained Carbopol 71G, sodium carboxymethlcellulose, sodium chloride. The tablets were coated with cellulose acetate, using different plasticizers and glycerin as pore-former. The results revealed that the drug release rate decreased with the increase in both sodium chloride and guar gum concentration due to solubility-modulating effect of sodium chloride and viscolyzing property of guar gum. Higher concentration of sodium chloride and

sodium CMC in polymer layer increased the release rate from the tablets because there was more pressure on the compartment. The drug release rate increased linearly as glycerin amount increased in the coating membrane. Glycerin at a 20% (w/w) of the polymer that contained 35% (w/w) water-insoluble plasticizers showed a zero-order release kinetic. Furthermore, the drug release rate decreased with an increase in dibutylphthalate and triethylcitrate concentration; however, the release rate increased with an increase in the PEG 400 concentration. Controlled-porosity osmotic tablets released the drug at a constant rate irrespective to the pH of the medium and the agitation rate.

1.2.2 Multilayer push-pull system

In addition to the bi-layer tablet, Alza developed multilayer tablets which based on the concept of push-pull osmotic pump system to achieve a variety of drug delivery pattern (54). The desired release profile was determined by the pattern of drug concentrations in multilayer of the system's core. The push layer contained a hydrophilic polymer that expanded as water was drawn into the system by osmosis. When the push layer expanded, it pushed the subsequent layers like a piston causing drug to be released at a defined rate through an orifice in the system's membrane. The subsequent layers contained either drug or placebo. When placebo or drug suspensions or solutions from these layers were released through the orifice, different delivery profiles were generated, as illustrated in Figure 6. For example, layers containing the same concentration of a single drug could provide zero-order delivery; layers containing varying concentrations of the same drug could provide ascending or descending delivery, and layers containing drug or placebo in various combinations could provide delayed or pulsatile delivery. The example such as Concerta® extended release tablet was designed to provide sustained effect through 12 hours, a profile that was particularly advantageous in symptom control through the afternoon and early evening. As shown in Figure 7., it was a tri-layer, capsule-shaped tablet which contained two distinct drug layers, a push layer to help release drug from the system and a drug overcoat layer. The design allowed the controlled release of drug for smooth, ascending pattern, following the initially immediate release. The presence of

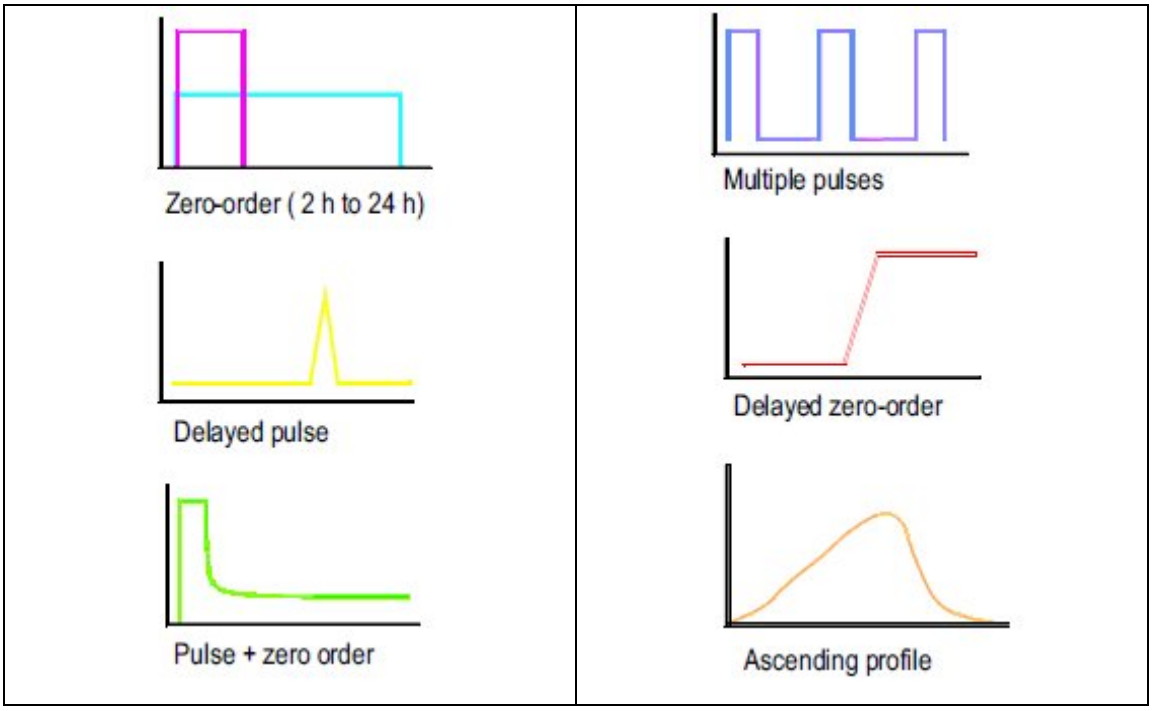


Figure 6. Effect of pattern of drug concentration in multilayer on the dissolution profiles of multilayer push-pull system.

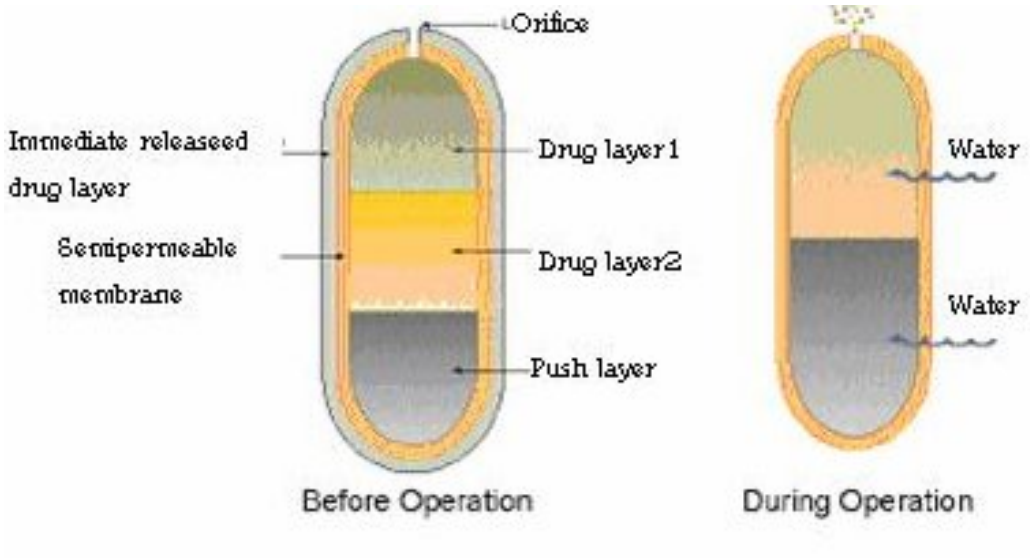


Figure 7. Multilayer push-pull system

two drug layers, as opposed to the single layer used in standard push-pull system, provides increased flexibility in controlling drug release from the system.

1.2.3 Delayed push-pull system

The delayed push-pull system was developed to delay the onset of drug delivery, and after a predetermined and controllable time period delivers a drug for its therapeutic effect (55). This type of system is available as used in Covera HS ®, extended release formulation for verapamil. It is a tablet formulation which initiates the release of verapamil hydrochloride 4 to 5 hours after ingestion and results in a maximum plasma concentration of verapamil hydrochloride in the morning hours. The Covera HS ® tablet composes of two compositions like the standard push-pull osmotic system. The first composition containing verapamil and a polyethylene oxide, where as the second composition containing a polymeric composition that imbibes fluid and expands. However, addition to the semipermeable membrane surrounding the first and second composition the device has a distinct layer between the tablet core and outer semipermeable membrane. This layer, containing a polymeric composition that hydrates slowly when contacted by fluid is introduced to delay onset of drug delivery. As water from the gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the polymer layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions.

1.2.4 Push-stick system (56)

In general, a push-pull osmotic pump system provides the benefit to delivering insoluble or extremely soluble drug at a constant rate that is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions. However, such device generally is not well suited as dosage forms for high drug loading due to size requirements necessary to accommodate large amounts of drug in a slurry, suspension

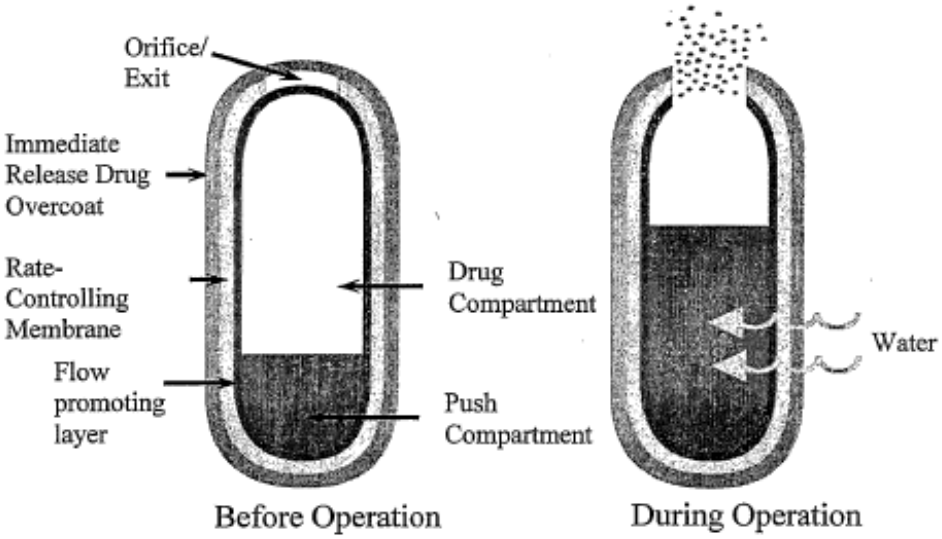


Figure 8. OROS Push – Stick system

or solution, and the need to have an oral dosage form conveniently sized so that it can be swallowed. Therefore, the push-stick system was developed to deliver high doses of poorly soluble or slowly dissolving active agents at a controlled rate.

The "push-stick" configuration is shown in Figure 8 prior to its administration to a subject, during operation and after delivery of the active agent. The dosage form comprises a semipermeable wall defining a cavity and an exit orifice. Within the cavity and remote from the exit orifice is a push displacement layer, and a drug layer is located within cavity adjacent the exit orifice. A flow-promoting layer extends at least between the drug layer and the inner surface of the wall, and can extend between the inner surface of the wall and the push displacement layer. The outer semi-permeable wall surrounds and encases the inner flow-promoting layer. The flow-promoting layer facilitates release of drug from the dosage forms by reducing the frictional forces between the semipermeable wall and the outer surface of the drug layer, thus allowing for more complete delivery of drug from the device. The commonly hydrophilic polymers used in this layer are gelatin, low MW polyethylene oxides, hydroxypropylcelluloses, etc. The dosage form is typically at high drug loading, i.e., 60% or greater, but more generally 70% or greater, active agent in the drug layer based on the overall weight of the drug layer, and is exposed to the environment of use as an erodible composition. The drug layer comprises a dry composition or substantially dry composition which is expelled from the dosage form in a plug-like state, the composition being sufficiently dry or so highly viscous that it does not readily flow as a liquid stream from the dosage form under the pressure exerted by the push layer. The drug layer itself has very little osmotic activity relative to the push layer, as the drug, binding agent and disintegrant are not well hydrated, and the drug layer does not flow out of the dosage form as a slurry or suspension. The drug layer is exposed to the environment of use as an erodible composition because it includes very little osmagent due to the high drug loading provided as well as the poor solubility of the drug to be delivered. The expandable layer pushes the drug layer from the exit orifice as the push layer imbibes fluid from the environment of use, and the exposed drug layer will be eroded to release the drug into the environment of use. Upon release from the dosage form, the drug layer imbibes water causing the

disintegrant to swell and soluble agents to dissolve, allowing the erodible solid to disperse and the analgesic agents to dissolve in the fluid at the environment of use.

1.2.5 Push-melt osmotic pump (57)

The push-melt osmotic pump system resembles push-pull system in structure but incorporates the drug in a thermoresponsive vehicle. In contrast to push-pull systems which use imbibed water to render the formulation flowable, push-melt systems use the thermal energy of the body. Other than this difference, however, the two systems function identically. In push-melt system, the drug formulation layer is at least partly lipophilic and incorporates the drug in suspension or solution. If needed , a partition between the drug and the osmotic layers can be incorporated to prevent drug entrapment after the end of the system's functional life time.

1.2.6 OROS – CT (58)

Oros-CT system is used as a once- or twice-a day formulation for targeted delivery of drugs to the colon and is based on the concept of push-pull osmotically controlled release. Oros-CT can be a single osmotic unit or can be comprised of as many as five to six push-pull osmotic units filled in a hard gelatin capsule (Figure 9). Each bilayer consists of an upper compartment (drug along with osmotic agent), surrounded by a semipermeable membrane. An orifice is created in the membrane next to the drug layer. After coming into contact with the GI fluids, the gelatin capsule dissolves and the enteric coating prevents entry of water from the stomach. As the system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core, thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate that is precisedly controlled by the rate of water transport across the semipermeable membrane.

1.2.7 Tablets with multiparticulate 2nd expandable osmotic chamber

In the modified osmotic pump for insoluble drugs as illustrated in Figure 10, particles of osmotic agent are coated with an elastic semipermeable film (59). These particles are then mixed with the insoluble drug and compressed in the form of a tablet, which is then coated with semipermeable membrane. After coming in contact with the aqueous environment, water is drawn through the two membranes into the

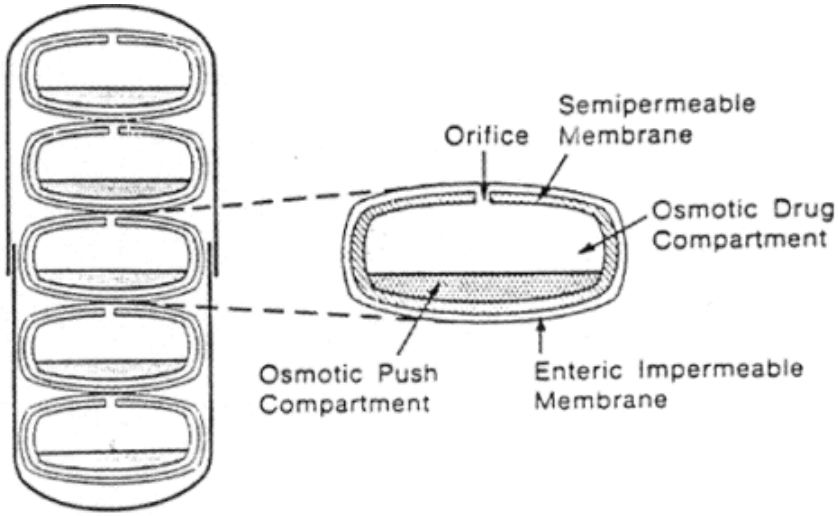


Figure 9. OROS CT ® Softcap

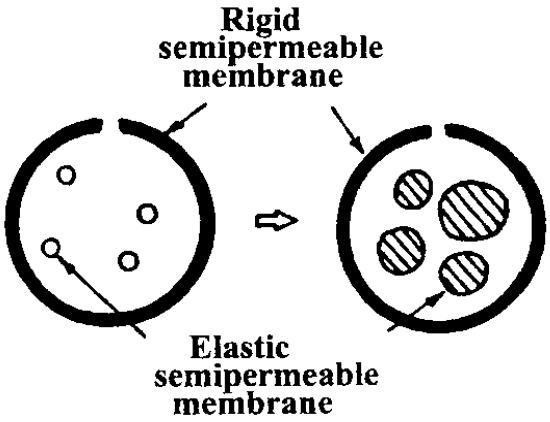


Figure 10. Modified osmotic pump for delivering insoluble drug

osmotic agent particles, which swell and hydrostatically push the insoluble drug via the delivery orifice.

1.2.8 Sandwiched osmotic tablets (SOT)

The sandwiched osmotic tablet is illustrated in Fig.11. The sandwiched tablet core consists of a middle push layer and two attached drug layers. After coating, two orifices are simply drilled on both side surfaces, which avoids side identification before drilling of that of push-pull osmotic tablet system. Also, as this system delivers drug from two opposite orifices differing from that of a single orifice of the push-pull osmotic tablet system, it may decrease the potential local irritation of drug.

Liu L, et al.(5) prepared the sandwiched osmotic tablet system of nifedipine, which was composed of a sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on both sides. Various formulations of sandwiched osmotic tablets were investigated in order to study the influence of core formulation variables on the drug release, i.e., amount of nifedipine in drug layer, amount of polyethylene oxide (PEO), potassium chloride (KCl) and microcrystalline cellulose in both drug layer and push layer. It was concluded that the mechanism of drug release was regulated by both action of push and drug layer. PEO amount of drug layer and KCl amount of push layer had profoundly positive influence on nifedipine release. Moreover, the influence of membrane variables on drug release was studied. It was reported that hydrophilic plasticizer PEG increased drug release, whereas hydrophobic plasticizer triacetin decreased the drug release rate when incorporated in the cellulose acetate membrane. The orifice with diameter ranging from 0.5 to 1.41 mm was suitable for the system. Also, it had been observed that the SOTS gave fairly comparable in vitro release features as that of commercialized push-pull osmotic tablet system.

1.2.9 Osmotic drug delivery using swellable-core technology (7)

Swellable-core technology (SCT) is developed as a drug-delivery platform that can deliver drugs with moderate to poor aqueous solubility over 8- to 24- hour period. SCT formulations consist of a core tablet that contains a drug composition and water-swellable composition. The drug composition contains the drug, an entraining polymer (e.g., polyethylene oxide), and salts as osmotic agents. The swellable composition contains a nonionic polymer (e.g., polyethylene oxide) or an ionic polymer

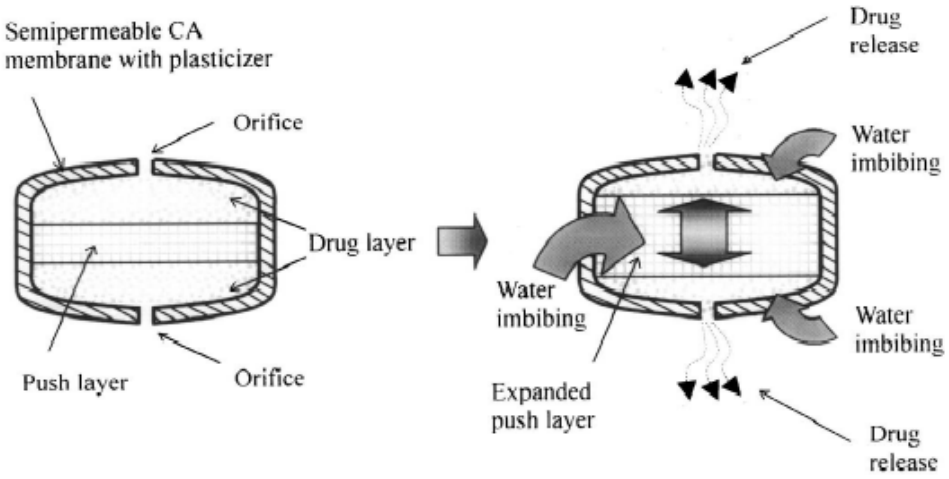


Figure 11. Sandwiched osmotic pump system

(e.g., croscarmellose sodium), which swells and expands in volume after absorption of water. The drug composition may also contain solubilizers, for example, buffering agents, which solubilize the drug by maintaining a pH microenvironment that aids in drug dissolution and absorption. Furthermore, the drug and water-swellable compositions may contain other ingredients to improve the flow and compression characteristics of the blends, aiding in the manufacture of tablets. The drug and water-swellable compositions in SCT formulations can be designed in various configurations. For example, they can be mixed together resulting in a uniform homogeneous core, or they can be physically separated from each other, resulting in a layered configuration. The tablet cores are coated with a semipermeable membrane and drilled using a laser or a mechanical drill to produce one or more exit ports.

Thombre AG, et al. studied osmotic drug delivery using swellable-core technology (SCT). The SCT formulations consisted of a core tablet containing the drug and water-swellable component, and one or more delivery ports. The in vitro and in vivo performance of two model drugs, tenidap and sildenafil, formulated in four different SCT core configurations: homogeneous core (single layer), tablet in tablet, bilayer, and trilayer core, were evaluated. In vitro dissolution profiles of both drugs from four SCT formulations under sink and non-sink conditions exhibited the evident that the drug-release rate was relatively independent of the core configuration but the extent was somewhat lower for the homogeneous-core formulation, particularly under non-sink conditions. In addition, the drug-release rate was slower with increasing coating thickness and decreasing coating permeability, and was relatively independent of drug loading and the number and size of the delivery ports. The drug-release rates were similar for the two model drugs despite significant differences in their physicochemical properties.

2. Osmotic delivery systems for liquids

Administration of liquid active agents may be preferred over the solid agents because the use of the former may expedite the onset of action. Recently, osmotic concepts were extended to address delivery of different physical states. These osmotic systems which mostly based on push-pull osmotic delivery platform were uniquely designed to deliver liquid active agents.

2.1 Liquid active agent in a capsule with a semipermeable coat

L-OROS SOFTCAP (26)

Liquid OROS controlled release systems are designed to deliver drugs as liquid formulations and combine the benefits of extended-release with high bioavailability. Figure12 shows the cross-sectional diagram for L-OROS SOFTCAP delivery system before and during operation. The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the semipermeable membrane. A delivery orifice is formed through these three layers. When the system is in contact with the aqueous environment, water permeates across the semipermeable membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. The liquid drug formulation is pumped through the delivery orifice

L-OROS HARDCAP (26)

This liquid drug delivery system consists of a liquid drug layer, a barrier layer, and an osmotic composition that acts a push layer, all encased in a hard gelatin capsule and coated with semipermeable membrane. A delivery orifice, drilled in the membrane at the end of the drug layer, provides an outlet for the liquid drug. After coming in contact with the aqueous environment, water is imbibed across the semipermeable membrane, thereby osmotic composition expands, and then pushes against the barrier, releasing drug through the delivery orifice.

2.2 Liquid active agent absorbed into the porous particles (60)

The main principle involved in release of the active agent in this design is the osmotically driven release of particles loaded with liquid active agent, followed by the release of these particles from the carrier. The construction of the delivery system is shown in Fig.13. In use, immediately after placing the dosage form in the release medium, water is taken up through the semipermeable wall owing to osmotic pressure generated by the osmotic agent, thereby the push layer expands and then the carrier containing the drug layer is expelled from the dosage from through an orifice. A flow-promoting layer forms a viscous gel by absorbing water and facilitates sliding the drug layer over the outer wall. The carrier dissolves in the medium to release containing the

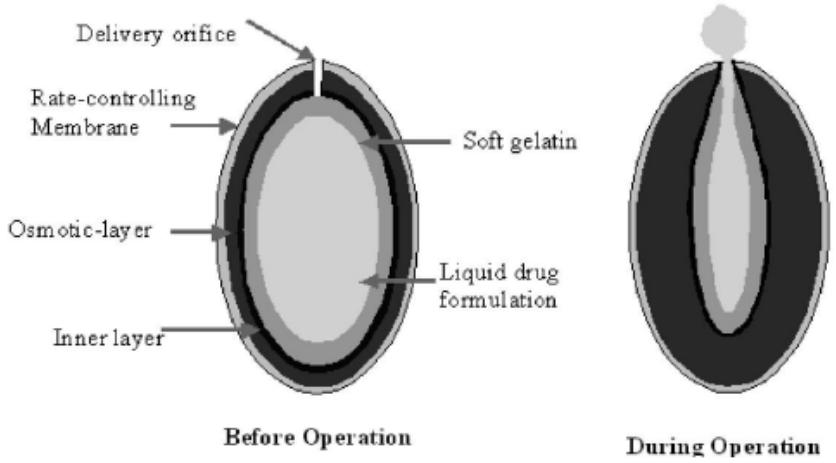


Figure 12. Cross-sectional diagram of L-OROS delivery system before and during operation.

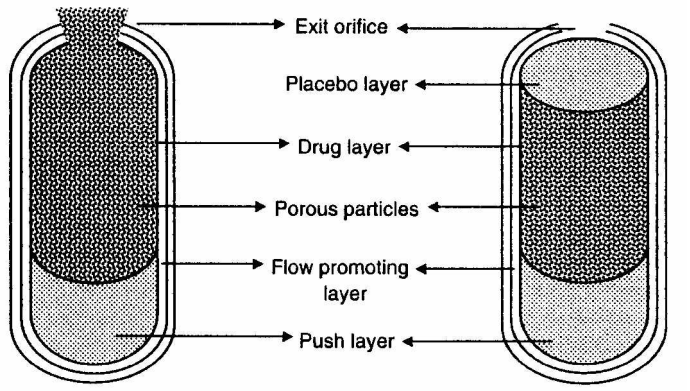


Figure 13. Liquid active agent absorbed into the porous particles

liquid active agent. The active agent is available immediately as solution, which eventually is absorbed. The porous particles erode with time, leading to release the remaining drug.

These dosage forms are prepared using wet granulation or direct compression method. Briefly, the liquid active agent is absorbed onto the porous particles, which are later blended with other components of the drug layer. The mixture is made into granules prior to compression or directly compressed. Depending on the requirement, either a tri-layer tablet containing a drug layer, a push layer, and a barrier layer or a bi-layer tablet with only a push layer, and a drug layer is compressed and coated with the flow-promoting layer followed by the semipermeable membrane. The delivery orifice can be formed during the manufacture or while delivering the drug by the erosion of erodible polymer in the membrane coating.

2.3. Liquid active agents in a reservoir with a water-impermeable (61)

These dosage forms consist of a reservoir containing the active agent in liquid form covered by a relatively water-impermeable membrane so as to decrease the contact of water with the liquid active agent during delivery. The design consists of a central reservoir, formed from a water-impermeable layer containing a liquid active agent and osmotic agent separated by a barrier layer, as shown in Figure14. The barrier layer prevents mixing of the layer contents and minimizes the residual amount of the active agent after the expandable osmotic composition has ceased its expansion. The layer also provides uniform pressure transfer from the osmotic composition to the liquid active agent, ensuring a uniform rate of release. Part of the osmotic agent is exposed from the reservoir, which is covered with a semipermeable membrane. The device is provided with an orifice at the opposite end to the osmotic layer to facilitate expulsion of the liquid during delivery.

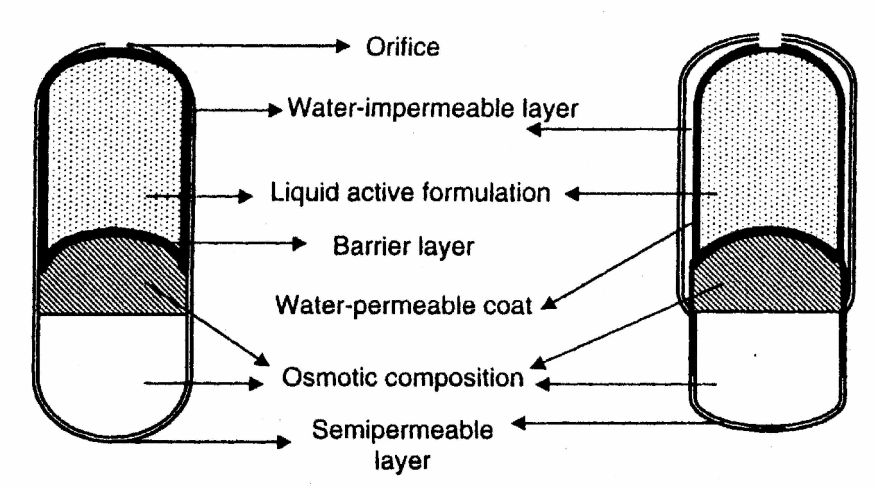


Figure 14. Design of an osmotic device for a liquid active agent with a water-impermeable coat

Factors Affect the Design of Osmotic Drug Delivery Systems

1. Delivery orifice

Osmotic controlled drug delivery systems contain at least one delivery orifice in the membrane for drug release. Some of the methods to create a delivery orifice in the osmotic tablet coating are use of a mechanical drill (45, 62, 63), laser drilling (64), use of an apparatus with slidable punch (65), and use of leachable substance in the coating. The size of delivery orifice must be optimized in order to control the drug release from osmotic systems. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. On the other hand, size of delivery orifice should not also be too large otherwise; solute diffusion from the orifice may take place. Theeuwes F reported the optimal orifice diameter in the range of 0.075-0.274 mm could be achieved in control over the delivery rate of potassium chloride (27).

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size S_{max}, to minimize hydrostatic pressure buildup in system. Therefore, the cross-sectional area of the orifice S_o should be maintained between the minimum and maximum values. The minimum cross-sectional area can be estimated from the following equation:

$$S_{min} = 5\left[(L/P_{max})\mu(dV/dt) \right]^{1/2} \qquad (20)$$

where dV/dt = volume flux through the orifice

L = length of the orifice (usually the same as thickness of membrane)

μ = viscosity of the drug solution flowing through the orifice

P_{max} = maximum tolerated hydrostatic pressure difference across the membrane before the occurrence of deformation of housing

The maximum cross-sectional area of the orifice is obtained by specifying that the diffusional contribution to the release rate must be smaller than a fraction f of the zero-order pumping rate and is defined by the following equation:

$$S_{max} = (M_{tz}\, f\, L)/(D_s\, C_s) \qquad (21)$$

where M_{tz} = amount of the drug delivered in zero-order fashion

D_s = drug diffusion coefficient in the permeating solvent

C_s = drug solubility

In practice, a fraction smaller than 0.025 generally is necessary to minimize diffusional contributions (66).

2. Solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation (67, 68):

$$F(z) = 1 - S/\rho \qquad (22)$$

where $F(z)$ = fraction released by zero-order kinetics

S = drug solubility (g/cm^3)

ρ = density of core tablet (g/cm^3)

Highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load, whereas drug with low solubility would be released with high percentage of zero-order kinetics but the zero-order release rate would be slow according to Eq.11 in section 1.1 (EOP) as follows:

$$dM/dt = AK\pi C/h \qquad (23)$$

Therefore, drug should have sufficient solubility to be delivered by osmotic delivery. In case of low solubility compounds, several alternate strategies may be employed and divided into two categories. First, swellable polymers can be added that

result in the delivery of poorly soluble drugs in form of a suspension, such an example as push-pull osmotic controlled release system. Second, the drug solubility can be modified employing different methods such as co-compression of the drug with other excipients, with improve the solubility. For example, cyclodextrin can be included in the formulation to enhance drug solubility (69). Additionally alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxyprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained (70).

3. Osmotic pressure

The osmotic pressure π expressed in Eq.23 directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Occasionally, the osmotic pressure generated by the saturated solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added in order to enhance the osmotic pressure. Some of the compounds that can be used as osmagent are described further. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevent clogging of the orifice by precipitated drug by producing an effervescent action in acid media (2). Additionally, polymeric osmagents are mainly used in the fabrication of PPOP and other modified devices for controlled release of drugs with poor water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state. These polymers have a capacity to retain a significant portion of the imbibed water within the polymer structure.

4. Semipermeable membrane

Since, the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. However, the release rate depends on some of the membrane variables that are important in the design of oral osmotic systems.

4.1 Type and nature of membrane

Film of the system has semipermeable characteristics which permits only the passage of water into the system but is substantially impermeable to the passage of a drug which wall surrounds and forms. Cellulose acetate (CA) has been widely used to

form rate-controlling membranes for osmotic systems. CA film is insoluble, yet semipermeable to allow water to pass through the tablet coating. The water permeability of CA membrane is relatively high and can be easily adjusted by varying the degree of acetylation. As the acetyl content in the CA increases, the CA film permeability decreases, and solvent resistance increases. Additionally, the use of Eudragit acrylic latexes as membrane formers for osmotic systems has been reported (71). Potassium chloride tablets were coated with mixtures of Eudragit RS30D and RL30D containing triethyl citrate or acetyl tributyl citrate as plasticizers and urea as a pore-forming agent. The release rate was most affected by the ratio of Eudragit RS30D to RL30D and the level of urea was found to have effect on lag time and burst strength. In another study by Linstedt B, et al. (72), it was reported that tablet cores of potassium chloride coated with mixture of ethyl cellulose and up to 24% of HPMC, were shown to release the contents mainly through osmotic mechanism.

4.2 Membrane thickness

Thickness of the membrane has a profound effect on the drug release from osmotic systems. It can be seen from Eq.23 that release rate from osmotic systems is inversely proportional to membrane thickness. Liu L et al. studied a monolithic osmotic tablet system for nifedipine delivery (45). On studying the release as a function of coating thickness, release rates were found to decrease with increase in membrane thickness from 85 to 340 μm. An increased resistance of the membrane to water diffusion resulted in this effect.

4.3 Type and amount of plasticizer

In pharmaceutical coatings, plasticizers are added to modify the physical properties and improve film-forming characteristic of polymers. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films. Liu L et al. studied the influences of plasticizers of CA membrane on drug release rate of nifedipine from sandwiched osmotic tablets (45). Hydrophilic plasticizer (PEG 400) was found to increase the drug release, whereas hydrophobic plasticizer (triacetin) was found to decrease the drug release from osmotic pumps of nifedipine. Films plasticized with PEG developed completely porous structure after 24 h leaching, whereas film plasticized with triacetin retained their dense structure and

porosity was observed only on the surface. These changes in physical morphology of CA membrane affect the permeability of polymer films.

Components of Osmotic Systems

The important component in osmotic pump formulation, excluding the drug or active agent, is the two additive materials which influence the drug delivery by an osmotic process at a controlled rate, i.e., semipermeable membrane and osmotic agent. Control resides in the: (a) water permeation characteristics of a semipermeable membrane surrounding the formulated agent, and (b) osmotic properties of the formulation. Therefore these ingredients play much role in mechanism of drug release.

1. Osmotic components

Osmotic agent is the osmotically effective compounds that are inorganic or organic compounds which exhibit an osmotic pressure gradient against an external fluid across wall and film. The osmotic agents are present in the compartment for: (i) imbibing fluid to concentrate solution and (ii) to fill and expand in volume with a corresponding collapse of compartment. Osmotic agents can be inorganic salts such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, sodium carbonate, etc. Some osmotic agents are carbohydrate, such as raffinose, sucrose, glucose, sodium alginate, gum, etc.

Hydrophilic polymers encompass osmopolymers, osmogels, or hydrogels. These materials maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Swellable polymers such as polyalkylene oxide, polyethylene oxide, and polyalkalicarboxymethylcellulose are included in the push layer of push-pull osmotic controlled release systems. Further, hydrogels such as Carbopol (polyacrylic acid), Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used (60).The polymers may be formulated along with poly(cellulose), osmotic solutes (73).

2. Semipermeable membrane

An important part of the osmotic drug delivery system is the semi-permeable membrane (SPM) which possesses certain characteristics, such as impermeability to

the passage of drug and other ingredients present in the compartments. Additionally, the membrane should be intact and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Numerous polymers are currently available to form SPM. One class includes cellulosic polymers such as cellulose ethers, cellulose esters, and cellulose ester-ethers. The cellulosic polymers have a degree of substitution (DS) of 0 to 3 on the anhydroglucose unit. The DS is the number of hydroxyl groups present on the anhydrogluclose unit being replaced by a substituting group. Examples of this group include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and mono-, di-, and tricellulose alkanylates. Cellulose acetate is available in different grades, such as cellulose acetate having a DS of 1 to 2 and acetyl content of 21 to 35 percent or cellulose acetate having an acetyl content of 32 to 39.8 percent. Other forms of cellulose polymers with a more specific substitution are cellulose propionate with a DS of 1.8, a propyl content of 39.2 to 45 percent, and a hydroxyl content of 2.8 to 5.4 percent or cellulose acetate butyrate with DS of 1.8, an acetyl content of 13 to 15 percent, and a butyrate content of 34 to 39 percent. Moreover, the semipermeable membrane may consist of a mixture of cellulose acetates, alkanylates, or acrylates with different degree of substitution.

Additional semipermeable membrane-forming polymers are selected from the group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethylamino acetate, semipermeable polyamides, semiper-meable polyurethanes or semipermeable sulfonated polystyrenes.

3. Emulsifying agents

Some patented technologies invoke self-emulsifying agents to deliver liquids from osmotic delivery systems. In one example, an emulsion consisting of up to 65 percent drug, usually hydrophobic, and a surfactant from 0.5 to 99 percent is cited. The surfactant selected for this purpose is polyoxyethylenated castor oil, polyoxyethylenated sorbitan tristearate, or polyoxyethylenated sorbitan monopalmitate containing different proportions of ethylene oxide. The emulsion initially consists of an oil phase, obtained from vegetable, mineral, or animal origin, in which the hydrophobic drug is dissolved.

4. Flux-regulating agents

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances such as polyethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g. diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose (60).

5. Plasticizers

To give the semipermeable membrane flexibility, plasticizers such as phthalates (dibenzyl, dihexyl, or butyl octyl), triacetin, epoxidized tallate, or tri-isocetyl trimellitate are added (60). In the design of osmotic controlled release systems, these plasticizers help to modulate and achieve the required release rate.

6. Barrier layer formers

To restrict water entry into certain parts of the delivery system and to separate the drug layer from the osmotic layer, different materials are used as barrier layers. In multilayered reservoir, the water-permeable coat consists of hydrophilic polymers. In contrast, water-impermeable layers are formed from latex material such polymethacrylates (Table 3). Further, a barrier layer can be provided between the osmotic composition and the drug layer that consists of substantially fluid-impermeable materials such as high-density polyethylene, a wax, a rubber, and the like (61).

Interpolymer complex

Interaction between macromolecules may lead to the formation of polymer complexes. Polymer complexes are insoluble, macromolecular structures formed by the noncovalent association of polymers with the affinity for one another. The complexes form due to association of repeating units on different polymer chain or on separate regions of the same polymer chain, defined to interpolymer and intrapolymer complexes, respectively (73).

Table 3. Material used in different layer formulations

Component	Example
Hydrophilic layer (water soluble)	Polysaccharides, hydroxypropylmethylcellulose, hydroxyethylcellulose, poly(vinylalcohol-co-ethyleneglycol)
Water-impermeable layer	Kollicoat, SR latex, Eudragit SR
Barrier layer	Styrene butadiene, calcium phosphate, polysilicone, Nylon, Teflon, polytetrafluoroethylene, halogenated polymers

Interpolymer complexes are formed by the association of various macro-molecules and can be grouped into four major categories depending on the dominant type of interaction (75).

1) Stereocomplexes formed by interaction through van der Waaals forces.
2) Polyelectrolytes (or polymeric) complexes which are formed by interactions between macromolecular polyacids and polybases or their salts and stabilized by ionic bonds.
3) Complexes formed by hydrogen bonding.
4) Coordination complexes.

Interpolymer complexes formed by polyelectrolyte are more common polymers of this type and known as polyelectrolyte complexes. They are the products of interaction between oppositely charged polyelectrolytes. A variety of polyelectrolyte complexes can be obtained by changing the chemical structure of component polymers, such as molecular weight, flexibility, functional group structure, charge density, hydrophilicity and hydrophobicity balance, stereoregularity and compatibility, as well as reaction conditions: pH, ionic strength, concentration, mixing ratio, and temperature (76).

1. Chitosan based polyelectrolyte complexes

Among the natural polymers, chitosan, a cationic polymer, is of interest to simulate the intermolecular interactions with various anionic polymers. The most commonly used polyanions are polysaccharides bearing carboxylic groups such as alginate , pectin or xanthan. Protiens, such as collagen, synthetic polymer, such as PAA , or even DNA have also been investigated.

1.1 Preparation of polyelectrolyte complex

The preparation of polyelectrolyte complex requires, besides chitosan, only a polyanionic polymer. No auxiliary molecules such as catalysts or initiators are needed and the reaction is generally performed in aqueous solution, which represents the main advantage over covalently cross-linked networks and thus favours biocompatibility and avoids purification before administration.

In order to form polyelectrolyte, both polymers have to be ionized and bear opposite charges. This means that the reaction can only occur at pH values in the vicinity of the pK_a of chitosan is about 6.5 (77). During complexation, polyelectrolyte

can either coacervate, or form a more or less compact hydrogel. However, if ionic interactions are too strong, precipitation can occur, which is quite common and hinders the formation of hydrogels. Precipitations can be avoided if electrostatic attraction is weakened by the addition of salts, such as NaCl. Their presence reduces the attraction between the oppositely charged polyelectrolytes by contributing to counter-ion environment. Hence, no phase separation occurs, and a viscous and macroscopically homogeneous blend is obtained, which may gel as temperature is lowered (78). Polyelectrolyte complex (PEC) can be reinforced by additional covalent cross-linking of chitosan. This is possible with collagen (79), PAA (80, 81) and leads to formation of semi-interpenetrating polymer networks (82). However, the addition of covalent cross-linkers may decrease the biocompatibility. PEC can also be reinforced by addition of ions inducing the formation of ionically crosslinked systems. Ca^{2+} can be added with pectin (83).

Since the properties of PEC depend on the degree of interaction between the polymers, the main factors determined for the interaction are their global charge densities and their relative proportion in the PEC. In general, the lower the charge density of the polymer, the higher is the polymer in PEC, since more polymeric chains are required to react with the other polymer. As this proportion and the chemical environment are the main factors influencing swelling, it is possible to modulate the properties of PEC by controlling the complexation reaction. The most important factor that has to be controlled is the pH of the solution, but temperature, ionic strength (84, 85) and order of mixing (86) are also important. In addition, there are secondary factors, related to the components that have to be considered, such as flexibility of polymers (81), molecular weight and degree of deacetylation of chitosan (87), the substitution degree of the other polyelectrolyte and the nature of the solvent. PEC formation is influenced by more parameters than the formation of covalently cross-linked hydrogel which is one of their main drawbacks encountered with large scale process during PEC preparation. Consequently, it is important to prepare PEC under reproducible conditions, for example, by mixing the polymer solutions at a pH value where complexation does not occur in order to obtain homogeneous mixture. Subsequently, the pH of the solution is adjusted to the desired value, where the interactions are formed.

According to the types of polyelectrolyte used in the complexation reaction, the complexes obtained are classified as follows: a. polyelectrolyte complex between natural polymers, b. polyelectrolyte complex between synthetic polymers, c. poly-electrolyte complex between a polyion and d. a surfactant, e. polyelectrolyte complex between a natural polymer and a synthetic polymer (82).

1.2 Chitosan-based polyelectrolyte complexes in medical uses

The widespread application of polyelectrolyte complexes is linked to their unique property of exhibiting pH, and to a minor extent, ion-sensitive swelling. In addition, they have a high water content and electrical charge density and allow the diffusion of water and/or drug molecules(88). Moreover, chitosan is known for its biocompatibility and for its ability to promote wound healing and both properties are maintained after PEC formation. In addition, depending on polyanionic polymer used, these systems are generally biodegradable and biocompatible. Therefore, chitosan hydrogels formed by PEC are well tolerated system and can be used in various applications.

pH-sensitive swelling and drug release

PEC can be used to prepare drug delivery systems, the swelling and release profiles of which can be modulated by appropriate selection of preparation conditions. As with ionically cross-linked hydrogels (82), PEC exhibits pH-sensitive swelling not only in acidic but also in basic conditions. As pH changes after administration, the charge balance inside the gel and therefore the degree of interaction between the two polymers is modified and swelling occurs because of the dissociation of the complex. In acidic medium, the polyacid is neutralized and due to free ammonium groups of chitosan, free positive charges appear inside the gel. Their mutual repulsion and the entry of water together with counter ions to neutralize these charges cause swelling. However, for prolonged immersion times in water, shrinkage can be observed as a result of the segmental mobility of the polyelectrolyte chains in the swollen state, which allows the completion of the interpolyelectrolyte reaction. In basic medium, the mechanism is the same but swelling is induced by the free negative charges of the polyacid. This mechanism reveals that swelling is also ionic-sensitive and that the swelling rate, when the pH changes, is controlled by the diffusion of mobile ions and changes in the degree of ionization. Moreover, osmotic pressure and electrostatic repulsion responsible for swelling are balanced by the contractile force of the network,

which depends on elasticity (89). This latter determines the maximum degree of swelling, which can vary considerably. As swelling of PEC is influenced by many factors, fine modulation of drug release is possible. Dissolution of the complex can occur at certain pH values if the global charge density of one of the polymers is no longer sufficiently high to ensure complexation. This happens with PEC containing PAA, xanthan or xylan.

Cell culture and enzyme immobilization (78)

Chitosan hydrogels formed by PEC exhibit interesting properties as scaffolds in cell culture and enzyme immobilization. They can form networks to stabilize cells or enzymes, allowing diffusion of substrates, products and additives for cell culture such as dexamethasone . It is possible to further improve the scaffolds by enhancing the swelling capacity, the permeability and the mechanical strength of the PEC via ionic cross-linking. Examples of applications are given in Table 4. As no potentially toxic auxiliary molecules or covalent cross-linkers are added to these hydrogels, they represent a better medium for cell culture than covalent cross-linked hydrogels. However, their secondary interactions could not completely prevent dissolution and release of incorporated cells in extreme pH conditions.

Tissue reconstruction and wound healing (78)

The glycosaminoglycan (GAG) analogous structure of chitosan is interesting for the preparation of chitosan hydrogels formed by PEC with GAG polyions found in the cartilage or skin matrix, such as chondroitin sulfate or hyaluronic acid. These hydrogels can be specifically used in cartilage reconstruction and wound-healing. They mimic the GAG-rich extracellular matrix of articulatory chondrocytes ; the cells producing the cartilage matrix allow their culture and can be used as a cell-carrier. In addition, the GAG incorporated in PEC are protected from their specific hydrolytic enzymes, increasing their lifespan until incorporation in the cartilage matrix after their release, which is ensured by PEC dissolution. During dissolution, chitosan is also released and incorporated into the cartilage matrix, where it may have bioactivities related to its analogous structure, such as specific interactions with growth factors, receptors and adhesion proteins. Therefore, the use of chitosan, in association with cartilage components such a chondroitin sulfate or hyaluronic acid is a logical

Table 4. Examples of polyelectrolyte complexes containing chitosan and their medical uses.

Polyelectrolyte	Enzyme and cell support	Tissue reconstruction
Alginate	Gel microparticles for cell culture or microencapsulation of biochemicals	Sponges impregnated with silver sulfadiazine and dehydroepiandrosterone
Chondroitin sulfate	Hydrogel for engineering of cartilage-like tissue	Matrix for reconstruction of skin from co-cultured human keratinocytes and fibroblasts on a dermal substrate
Chitin carboxymethylated	Matrix for the culture of human periodontal ligament fibroblasts	
Dextran sulfate		Hydrogel for dermal wound healing
Heparin		Membrane for dermal wound healing
Hyaluronic acid		Film or sponges for wound healing
Xanthan	Scaffold for immobilization of enzymes, such as xylanase, lipase, hemicellulase	Bandage formed by impregnation of woven cotton
Collagen	Skin analogue in vitro toxicological tests	Wound covering for patients suffering extensive burn.

approach for improving cellular assistance for cartilage recovery. Examples of applications are also given in Table 4.

2. Interpolymer complex of chitosan and polyacrylic acid

2.1 Chitosan

Chitosan (CS) is a polysaccharide, similar in structure to cellulose. Both are made by linear *B*-(1-4)-linked monosaccharides as shown in Figure15. However, an important difference to cellulose is that CS is composed of 2-amino-2-deoxy-*B*-D-glucan combined with glycosidic linkages. The primary amine groups render special properties that make CS very useful in pharmaceutical applications. Chitosan is obtained by deacetylation of chitin, i.e., N-acetylamino-1,4-*B*-glucan. Chitin belongs, besides cellulose and starch, to the most abundant natural polymers and can be isolated from shells of crustacean and insects as well as from fungal mycelia. However, applications of chitin are limited compared to CS because chitin is structurally similar to cellulose, but chemically inert. Acetamide group of chitin can be converted into amino group to give CS, which is carried out by treating chitin with concentrated alkali solution. For the industrial of chitin, crab-shells and recently yeast products of fermentation processes are used, combining a mechanical processing with a chemical treatment with dilute aqueous NaOH. For the subsequent deacetylation to chitosan strong aqueous alkali (40-50% NaOH by weight) at elevated temperature ($\geq 100\ ^{o}C$) is employed; the degree of deacetylation as well as the viscosity of the product vary widely depending on conditions of the reaction (90).

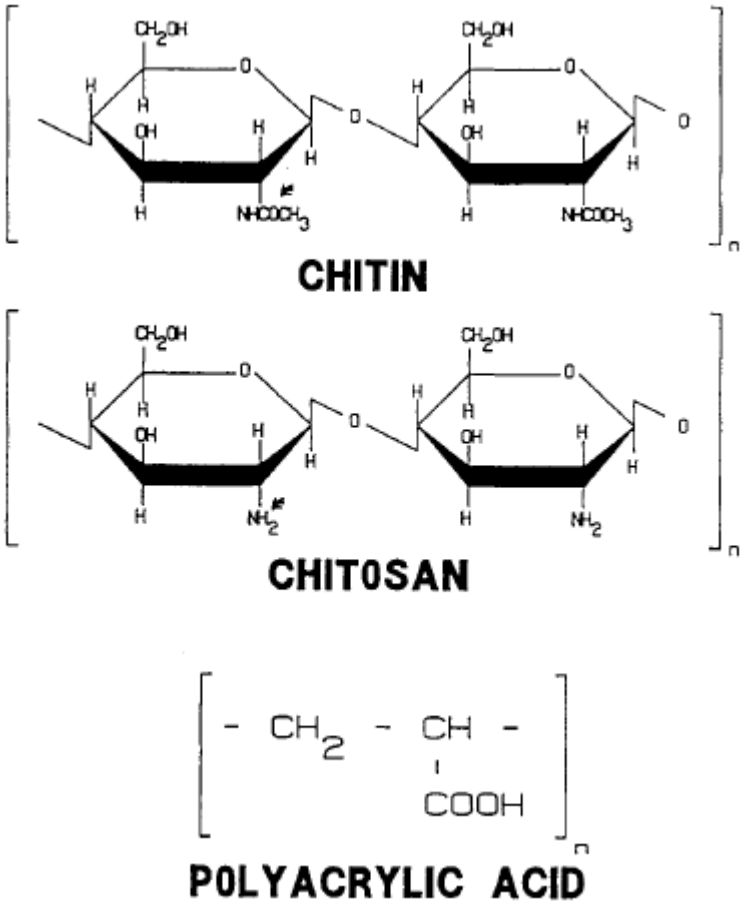


Figure 15. Molecular structure of chitin , chitosan and polyacrylic acid

The word chitosan refers to a family of aminopolysaccharides, which differ in the degree of N-deacetylation (40-98%) and molecular weights (50 kDa-200 kDa). These two characteristic features are important because they have an impact on the physicochemical properties (e.g. solubility, viscosity). Chitosan is insoluble at neutral and alkaline pH values. However, the degree of deacetylation is of pronounced influence on chitosan solubility. Chitosan with low degree of deacetylation (40%) has been found to be soluble up to pH 9, while chitosan with a high degree of deacetylation (85%) is soluble only up to pH 6.5. The solubility of chitosan is also greatly influenced by the addition of salt to the solution. The higher the ionic strength the lower the solubility. The viscosity of chitosan solution increases in viscosity with increase in chitosan concentration and decrease in temperature. The viscosity also increases with increasing degree of deacetylation. This is due to the different conformations of the molecule for high and low deacetylated chitosan. At high degree of deacetylation, where the molecule is highly changed, chitosan has an extended conformation with a more flexible chain, whereas at a lower degree of deacetylation the chitosan molecule adopts a more rod-lke shape or coiled shape due to a lower charged (91).

Chitosan, being a cationic polysaccharide in neutral or basic pH conditions, contains free amino groups and hence, is insoluble in water. In acidic pH, amino groups can undergo protonation thus, making it soluble in water. Solubility of CS depends upon the distribution of free amino and N-acetyl groups. Usually 1-3% aqueous acetic acid solutions are used to solubilize CS. Some dilute inorganic acids, such as nitric acid, hydrochloric acid, perchloric acid and phosphoric acid can also be used to prepare a chitosan solution, but after prolonged stirring and warming. In addition to dissolving chitosan in acid solution, such mixtures as dimethylformamide with dinitrogen tetroxide at a ratio of 3:1 also appear to be good solvents for chitosan .

The pharmaceutical requirements of chitosan are: particle size < 30 μm, density between 1.35 and 1.40 g/cm^3, pH 6.5-7.5, insoluble in water, and partially soluble in acids (92).

Chitosan has biodegradability and biocompatibility. Moreover, chitosan is non-toxic due to low oral toxicity with an LD_{50} in rats of 16g/kg (93) and easily bioabsorbable with gel-forming at low pH. Also, chitosan matrix formulations appear

to float and swell gradually in acid medium (90). All this interesting properties of chitosan make this natural polymer attractive in controlled drug release formulations.

Because chitosan has biological properties such as hypocholesterolemic effect, bacteriostatic effect and wound healing, it has attracted a lot of attention to use in various medical applications.

2.2 Polyacrylic acid

Polyacrylic acid (PAA) is an anionic polymer or polyanion with the simple structure of linear polymer chains as shown in Figure 15. These linear polymer chains are soluble in polar solvent, such as water or alcohol. Polyacrylic acid is commercially available under the trade name of Carbopol®. Carbopol resins are very high molecular weight polymer of acrylic acid, cross-linked with polyalkenyl ethers. Cross-linked polymers do not dissolve in water, but form colloidal gel dispersions. The polymers swell up to 1000 times their original volume (and ten times their original diameter) in water to form a gel when exposed to a pH environment above 4-6. Above their pK_a of 6 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the anions and further increasing the swelling of the polymer. At low pH (5.0 or less), less than 10% of the Carbopol acid groups will be ionized, resulting in relatively little stiffening by electrostatic charge repulsion, and relatively little swelling compared to full neutralized Carbopol polymer systems. The swelling rate of the polymers depend on cross-linking degree. Carbopol 971P NF, which is a lightly cross-linked polymer, swells at a faster rate and achieves greater overall swelling than either Carbopol 974P NF or Carbopol 934P NF polymers, which are more highly cross-linked.

Polyacrylic acid (Carbopol) have been used wildly to thicken, modify flow characteristics, emulsify, and suspend insoluble ingredients. Recently, because Carbopol has a good gel-forming ability and mucoadhesive property, it is interested to use for extended-release dosage forms.

3. Applications of chitosan - polyacrylic acid interpolymer complex in controlled release drug delivery system

3.1 Formation of IPC by simple mixing in aqueous solution

The formation of an interpolymer complex between polyacrylic acid and chitosan has been previously reported (84). The complexation is due to an electrostatic interaction between the carboxylate group of polyacrylic acid as the polyanionic polymer and the protonated amine group of chitosan as the polycationic polymer. No insoluble complex formation at pH = 2 was detected. In the 3 to 6 pH range, the maximum complex formation occurred at different mole ratios. Takahashi T et al. investigated polyion complexes composed of chitosan with sodium polyacrylate(AC). The results suggested that the ionic bonding was a primary binding force for the complex formation between CS and AC and was found that the binding ratios of AC with CS changed with increasing pH values (81).

The interpolymer complexes of polyacrylic acid and chitosan were prepared in a wide range of copolymer compositions by dissolving both polymers in acidic conditions with incorporation of amoxicillin trihydrate (A) to all formulations (10, 11). The addition of PAA to the hydrogel slowed down the rate of erosion, thus the formulation PAA:CS:A (1:2.5:2)-1.75 M presented the maximum swelling ratio and suitable controlled release, about 70.98% of amoxicillin was released after 2 h. These release results will ensure maximum availability of drug in the stomach. Moreover, Paloma M, et al. used the polyacrylic-chitosan interpolymer complex to develop a stomach-specific drug delivery system in the further study. The polyionic complex (PAA:CS:A 2.5:5:2) with the high network density showed less pH-dependent swelling-eroding behavior and a sustained drug release profile in simulated gastric fluid and pH 4.0. The proposed hydrogel showed a prolonged gastric emptying time of up to 3 h (9).

Sung-Hyun P, et al. prepared an extended-release matrix using chitosan-Carbopol interpolymer complex (8). The interpolymer complex was formed using a precipitation method in an acidic solution and was used as a matrix material to prepare a theophylline tablet. The drug release profile showed a pH-independent release profile. The mechanism for drug release from IPC tablet were diffusion through the

swollen matrix at pH 6.8 and relaxation due to synchronization between swelling and erosion of polymer.

Rossi S, et al. prepared films based on chitosan and polyacrylic acid as buccal delivery of acyclovir(13). The stoichiometry of the ionic interaction occurring between chitoan hydrochloride (HCS) and polyacrylic acid in distilled water is in the range of HCS/PAA weight ratio equal to 1:0.4-1:0.8. Films containing acyclovir and based on HCS and PAA in different ratios were prepared by casting technique. An increase in PAA amount produced a decrease in film hydration and drug release. Films based on HCS/PAA weight ratio close to interaction product stoichiometry exhibited higher rigidity and better "wash away" properties with respect to the other films. However, the worst mucoadhesive properties were shown by films on based on this weight ratio. All the films examined promoted the permeation of acyclovir when compared with acyclovir suspension and the commercial cream, whereas HCS/PAA weight ratio of 1:1.3 showed the highest amount of drug permeated.

3.2 Formation of IPC by template polymerization of acrylic acid in the presence of chitosan.

The template polymerization is a process of forming a polymer chain in the presence of a macromolecule (template) that was introduced into the reaction system beforehand. The complex formation between the formed polymer chain and the template may arise from electrostatic forces, hydrogen bonding, van der Waal forces etc.

Ahn JS, et al. studied use of chitosan-polyacrylic acid interpolymer complex as a mucoadhesive polymer loading triamcinolone acetonide (TAA) for transmucosal drug delivery system and prepared the mucoadhesive polymer complex by template polymerization of acrylic acid in the presence of chitosan (12). The aqueous acrylic/chitosan solutions were added with photoinitiator before casting to films which were irradiated for 10 min using UV. The FTIR result revealed that polymer complex was formed between polyacrylic acid and chitosan through hydrogen bonding. The adhesive force of PAA/chitosan polymer complex increased as the content of acrylic in complex increased. Release of TAA from the mucoadhesive polymer film was dependent on pH, content of drug and chitosan/PAA ratio. The drug release might be controlled by non-Fickian diffusion mechanism, a combination of diffusion of drug from matrix and dissolution of matrix.

Hu Y, et al. prepared chitosan-polyacrylic acid complex nanoparticles by template polymerization of acrylic acid (AA) in chitosan solution (15). Chitosan was dissolved in acrylic acid solution, and then the polymerization of AA was initiated by $K_2S_2O_8$ at 70 ^{o} C under a nitrogen steam with continued stirring. When the polymerization of AA reached a certain level, the inter- and intra-molecular linkages occurred between carboxyl groups from PAA and positively charged amino groups of CS. Consequently, the system changed initially from clear solution to an opalescent emulsion, indicating the formation of CS-PAA nanoparticles. It was found that the prepared nanoparticles carried a positive charge and showed the size in the range from 50 to 400 nm. These nanoparticles were stable under acidic and neutral conditions ranging from 4 to 8. The in vitro silk peptide release showed that these nanoparticles provided a continuous release of the entrapped peptide for 10 days, and the release behavior was influenced by the pH value of the medium. Sajeesh S and Chandra PS reported the preparation of polymethacrylic acid (PMAA) - chitosan microparticles for oral insulin delivery using seemly similar method, polymerizing methacrylic acid by $K_2S_2O_8$ under mild aqueous condition in the presence of chitosan. PMAA-CS microparticles were found to be aggregated and irregular with size ~20 μm. The insulin-loaded microparticles displayed a pH depended release profile and exhibited sustained release of insulin for 3-4 h at neutral pH (94).

Shim JW and Nho YC introduced radiation polymerization as alternative technique for polymerization of polyacrylic acid in an aqueous chitosan solution to prepare polyacrylic acid - chitosan interpolymer complex (95). These interpolymeric hydrogels were synthesized by a γ-irradiation polymerization technique. The results showed that the PAA-CS hydrogels exhibited different degrees of gelation and cross-linking, depending on the composition of chitosan or AA and radiation dose. The equilibrium swelling measurements showed the mucoadhesive and pH-responsive nature of these hydrogels. The drug release of 5-fluouracil from PAA-CS hydrogel was related to swelling degree of the hydrogel according to the result which showed that the drug release increased as the AA and radiation dose decreased.

3.3 Formation of IPC by formation of interpenetrating polymer network

Interpolymer complexation between polymer pairs through secondary binding forces such as electrostatic interaction, hydrogen bonding was disintegrated upon

dissociation of interpolymer interaction, which was due to environmental change. However, introduction of cross-links into the polymer: polymer complex may result in the formation of an interpenetrating polymer network which can prevent the complex-forming blend from collapsing. Interpenetrating polymer network (IPN) hydrogels composed of chitosan and polyacrylic acid were prepared by many researchers. Wang H, et al. blended CS and PAA, and used glutaraldehyde to crosslink chitosan(96). Lu JW and colleagues studied formation of template interpenetrating polymeric networks, prepared by photopolymerization of acrylic monomer in aqueous chitosan solution in which photoinitiator and photocrosslinker were added. The CS-PAA IPN had good mechanical property even at the swollen state (77).

The combination of interpolymer complexes and interpenetrating network structure leads to novel polymer materials with special properties, potentially useful in controlled drug delivery. Hollow polymeric nanospheres have great potential ability to encapsulate large quantities of drug in their hollow inner cavities and release them later. Hu Y, et al. prepared chitosan-PAA hollow nanospheres by dissolving chitosan into acrylic acid (AA) aqueous solution, followed by polymerization of AA initiated by $K_2S_2O_8$, and then selective cross-linking of chitosan using glutaraldehyde. The hollow structure of polymeric nanospheres is spontaneously formed by polymerization of acrylic acid monomers inside the chitosan-acrylic acid assemblies formed before the polymerization. The hollow structure of nanospheres is stabilized by both physical cross-linking in the inner shell and chemical cross-linking in the outmost shell as it was found that the cross-linked nanosphere can maintain stable in aqueous solution for more than 6 months at room temperature. The size of the hollow nanospheres can be manipulated by changing the pH value, salt concentration and temperature (14).

Ding Y and colleague studied chitosan-acrylic acid polymer-monomer pair as a reaction system for the synthesis of magnetic Fe_3O_4-polymer hybrid hollow spheres (97). The chitosan and AA polymer-monomer pair and Fe_3O_4 nanoparticles stabilized by poly(vinyl alcohol) were mixed and formed micelles loaded with Fe_3O_4 nanoparticles; the cores consisted of the polyionic chitosan chains and AA and the shells consisted of protonated chitosan chains. Initiation of the polymerization of AA with $K_2S_2O_8$ followed by cross-linking of the shells with glutaraldehyde at the end of polymerization led to the formation of magnetic hollow Fe_3O_4-polymer hybrid

spheres. However the Fe_3O_4 content of the obtained CS-PAA spheres was low (8%) due to formation of hydrogen bonding between polyvinyl alcohol and polyacrylic acid, leading to minor incorporation of polyvinyl alcohol-stabilized Fe_3O_4 nanoparticles into CS-PAA hollow spheres. Wu Y, et al. modified the recent method to prepare CS-PAA polymer magnetic microspheres by polymerization of AA onto CS–coated Fe_3O_4 cores, which were prepared by interaction between cationic chitosan and Fe_3O_4 nanoparticles with citrate groups (16). The polymer magnetic microspheres obtained had a high Fe_3O_4 loading content, and showed unique pH-dependent behaviors on the size and zeta potential. The CS-PAA magnetic microspheres exhibited a small burst drug release of ammonium glycyrrhizinate initially, followed by a very slow drug release.

3.4 Composite of IPC with the third polymer

Combination of chitosan-polyacrylic acid interpolymer complex to the third polymer resulted in novel material with special properties, exploited for design of potentially controlled drug delivery.

Sailaja GS et al. prepared hydroxyapatite (HAP) filled chitosan-polyacrylic acid polyelectrolyte complexes intended for bone substitute applications to improve the interfacial bonding between the HAP and the polymer matrix (98). The composites were prepared by adding 1 %w/v PAA solution in 1% w/v CS solution in aqueous acetic acid dispersed with HAP. The pH values were below 6 during the preparation. It was found that the complexation reaction between CS and PAA and filler incorporation could favour uniform distribution of HAP in the PEC matrix. HAP loading in the optimum range is preferred since the higher percentage could dilute the chemical interaction and the mechanical interlocking.

Sajeesh S and Chandra PS prepared novel polymethacrylic acid - chitosan polyethylene glycol (PCP) nanoparticles by polymerizing methacrylic acid in presence of chitosan and polyethylene glycol(PEG), using a water-soluble initiator (99). The PCP particles in dried stage had an aggregated and irregular morphology, however, TEM revealed that aggregated particles disintegrated to smaller fragments with size less than 1 μ at pH = 7. The release of both insulin and bovine serum albumin from the nanoparticles was less than 15% at pH 1.2 and more than 90% at pH 7.4. Release kinetics seems to be appropriate for oral peptide delivery system due to their good

drug retention capacity at gastric region. Incorporation of PEG as a third polymer in the system forms strong interpolymer complex with polycarboxylic acid polymers, which holds the network together and protects peptide from diffusing out.

Laser Equipment (100-101)

A laser is a mechanical device that produces coherent radiation. The term “laser” is an acronym: Light Amplification by Stimulated Emission of Radiation. A typical laser emits light in a narrow beam of monochromatic, coherent light in the visible, infrared or ultraviolet parts of spectrum. The underlying principle of the laser goes back to a discovery of Albert Einstein in the year 1917. Einstein discovered at that time the so-called stimulated emission basis for the structure of an outstanding source of light and with it also a source of energy. Technically, this discovery was for the first time converted to working laser made by Theodore H. Maiman in 1960. Maiman used a solid-state flashlamp-pumped synthetic ruby crystal to produce red laser at 694 nanometers wavelength, as illustrated in Figure 16.

The operation principles and basic components of a laser are explained in the following. A laser usually comprises an optical resonator (cavity) in which light can circulate (e.g. between two mirrors), and within this cavity a laser medium or gain medium, which serves to amplify the light. The gain medium requires some external supply of energy (so-called optical pumping or electrical pumping). The principle of laser amplification is stimulated emission. The pump energy is absorbed by the laser medium, placing some of its particles into high-energy quantum states. Particles can interact with light both by absorbing photons and by emitting photons. Emission can be spontaneous or stimulated. In the latter case, the photon is emitted in the same direction as the light that is passing by. When the amount of stimulated emission due to light that passes through is larger than the amount of absorption, hence the light is amplified. As light circulates through the cavity, passing through the gain medium, if the gain (amplification) in the medium is stronger than the resonator losses, the power of the circulating light can rise exponentially. Some fraction of the light power circulating in the resonator is usually transmitted by a partially transparent mirror, the so-called output coupler mirror. The resulting beam constitutes the useful output of the

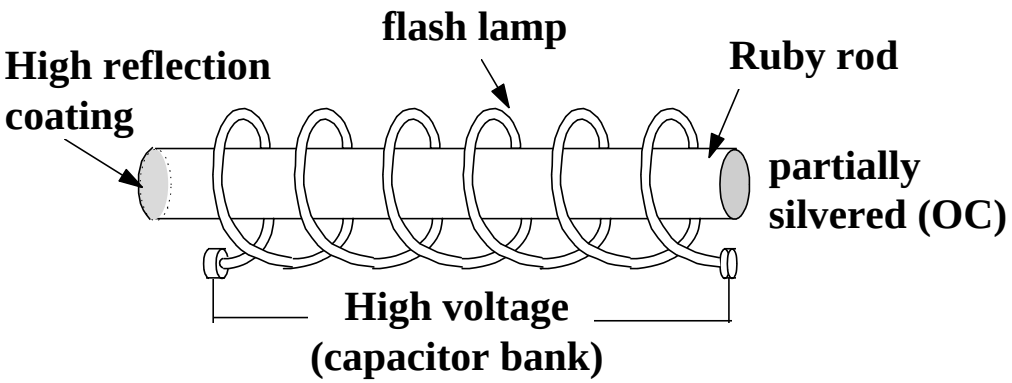


Figure 16. Schematic of a ruby laser. Capacitor bank is a cabinet containing many capacitors in parallel. The resultant capacitance could be as large as a Farad.

laser. If the chosen pump power is too small, gain is not sufficient to overcome the resonator losses, and the laser will emit only very small light powers. The minimum pump power needed to begin laser action is called the laser threshold. Lasers can be classified to the following different types.

By active media

- Gas laser, e.g. He-Ne laser, Ar^+ laser, CO_2 laser, N_2 laser, HCN laser.
- Dye laser - active medium: dye molecules in liquid solvent (sometimes in solids also).
- Solid state laser - crystal, or glass, doped with impurities, e.g. ruby laser, Ti: sapphire laser, semiconductor laser.

By mode of operation

- Continuous wave
- pulsed pumping

A carbon dioxide laser is one of the most popular and useful sources of coherent electromagnetic waves in the infrared spectrum. This is due to the several ways in which the laser operates (high voltage power supply in continuous wave (CW) or pulsed operation; emission of laser lines in regular, hot or sequential bands of CO_2 laser molecules) and the several orders of magnitude range of possible laser powers (from milliwatts to Gigawatts) that permit laser application in science, medicine and technology. Carbon dioxide lasers present over a hundred different emission laser lines with wavelengths ranging from 9 to 11 μm. The most powerful laser line are centered at 9.3, 9.6, 10.3 and 10.6 μm, respectively. The 10.6 μm laser line is the strongest one, and most of the commercially available medical CO_2 lasers operate only at this wavelength. The laser medium in CO_2 laser is mixture of CO_2 , N_2 and He, with CO_2 being the active laser medium and other components serving as light-emitting enhancer. High voltage electric current is used to achieve excitation of the laser medium. The CO_2 molecules are first excited so they vibrate in an asymmetrical stretching mode. The molecules then lose energy by dropping to one of two other lower-energy vibrational states, resulting in emitting photons and the large families of laser lines ranging from 9 to 11 μm are obtained after photons are amplified. The nitrogen molecules help to excite CO_2 to the upper laser level. Collisional energy transfer between the nitrogen and the CO_2 molecules causes vibrational excitation of

the carbon dioxide. Helium serves as a buffer gas to aid in the heat transfer and helps the CO_2 molecules drop from the lower laser levels to the ground state. Therefore, both N_2 and He play the advantage role in maintaining the population inversion needed for laser operation.

Because of the high power levels available and reasonable cost for the laser, CO_2 lasers have many applications in both medical an industry. They are very useful in surgical procedures because water which makes up most biological tissue absorbs this frequency of light very well. Some examples of medical uses are laser surgery, skin resurfacing ("laser facelift") which essentially consist of burning the skin to promote collagen formation, and dermabrasion. CO_2 lasers are frequently used in industrial applications for cutting and welding, while lower power level lasers are used for engraving. Additionally, because the atmosphere is quite transparent to infrared light, CO_2 lasers are also used for military rangefinding using LIDAR techniques.

Laser had been used prior to 1978 to bore, for example in baby-bottle nipple. In pharmaceutical field, laser was known to have enough energy to drill the hole required in osmotic tablet. Laser hole-drilling system described in US patent 4,088,864 (102) comprises of laser equipment, optical tracking and focusing system and apparatus to align and move tablet as in Figure17. Tablets are positioned under a laser beam by a modified high–speed tablet labeling machine. The optical tracking and focusing equipment moves the laser beam as the tablet moves. However, to obtain the required processing speeds, the lasers must be able to drill the hole in a tablet moving tablets. But as the speed is increased, the hole becomes elliptical because of movement of the tablet during the laser firing time. The solution to this problem is an optical tracking system which causes the laser beam to oscillate at the same speed as the tablet, firing at each tablet in succession. High speed machines incorporating this system have been built. Other approaches continue to be developed such as the method of forming tablet indentation prior to coating as in US Patent 4,271,113 (103). The indentation produces a recess that is only partially covered during subsequent coating of the tablet, thus forming the hole.

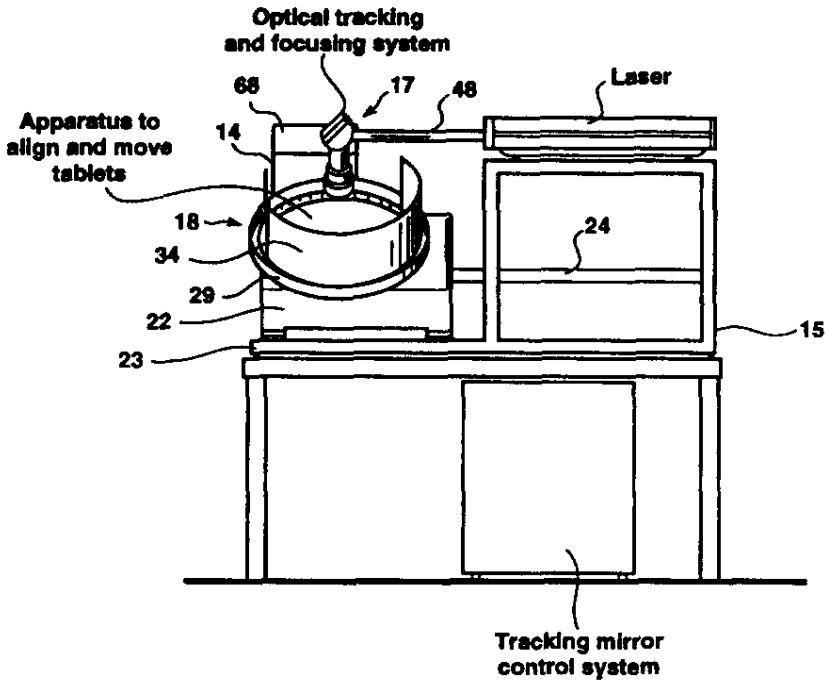


Figure 17. Laser hole drilling system described in US patent 4,088,864

Felodipine (ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate; $C_{18}H_{19}Cl_2NO_4$)

Felodipine is a dihydropyridine calcium antagonist (calcium channel blocker) which is indicated for the management of hypertension. It is a slightly yellowish, crystalline powder and is insoluble in water but is freely soluble in dichloromethane and ethanol. Following oral administration, felodipine is well absorbed from gastro-intestinal tract and undergoes extensive first-pass metabolism, resulting in an absolute bioavailability of 13 to 16% in fasted individuals. Felodipine is 99% protein binding bound with a blood /plasma ratio of 0.7. Oral administration of 10 mg dose in tablet form produced mean maximum plasma concentrations of 22 to 25 nmol/L within 45-120 minutes and plasma level of felodipine also declined polyexponentially with mean terminal half-life of 11 to 16 hours (104-105).

To overcome the changing concentration that occur when a drug is administrated frequently, the extended-release felodipine tablet was developed. The goal was to provide constant concentration throughout a 24-hour period to lower blood pressure by a uniform amount throughout the entire day. Blychert E, et al. (106) investigated the rate and extent of felodipine absorption from an oral solution, conventional and extended-release tablets. It was found that the extended-release tablet taken once daily gave more sustained plasma concentrations than the conventional tablet taken twice daily and both had similarity in blood pressure control.

Since the early 1980, there have been increasing numbers of pharmaceutical products using novel drug delivery system prescribed for the treatment of systemic hypertension as shown in Table 5 (107). Plendil® is the commercial extended-release tablet containing 5 to 20 mg felodipine. The drug is embedded in a matrix which forms a gel on contact with gastrointestinal fluid and is then gradually eroded, releasing felodipine at a controlled rate. However the drug is released in first order kinetics manner which is not a constant rate but slows down in late period. To design the drug release in zero order pattern, felodipine will be fabricated in the drug delivery system of push-pull osmotic pump tablet in this study. In addition, this delivery system can deliver the drug with the independence of pH or gastrointestinal motility.

Table 5. Antihypertensive drugs with extended release systems

Drug	Tradename	Year	Novel drug delivery system
Clonidine	Catapres® TTS	1984	Transdermal therapeutic system
Diltiazem	Cardizem® SR	1988	Polymeric coated varying thickness beads
Diltiazem	Cardizem®CD	1991	Two phase multiparticulate system
Diltiazem	Cardizem®XL	2003	Encapsulated beaded delivery system
Diltiazem	Dilacor® XR	1992	Geomatrix multilayer tablet
Diltiazem	Tiazac®	1995	Multiparticulate polymer coated beads
Doxazosin	Cardura®CR	2001	GTIS (osmotic pump)
Felodipine	Plendil®	1991	Hydrophilic gel matix (coat-core)
Isradipine	Dynacirc® CR	1997	GTIS (osmotic pump)
Metoprolol	Toprol ®XL	1991	Multiple-unit pellet tablet system
Nicardipine	Cardene® SR	1992	Beads and immediate-release
Nifedipine	Adalat® CC	1993	Hydrophilic gel matix (coat-core)
Nifedipine	Procardia® XL	1989	GITS (osmotic pump)
Nisoldipine	Sular®	1995	Hydrophilic gel matrix (coat-core)
Propranolol	Inderal® LA	1983	Multiparticulate spheroid diffusion
Propranolol (+hydrochlorothiazide)	Inderide® LA	1987	Multiparticulate spheroid diffusion
Propranolol	InnoPran® XL	2003	Multiparticulate polymer coated beads
Verapamil	Calan®SR/ Isoptin®SR	1986	Sodium alginate matrix
Verapamil	Covera®HS	1986	GITS (osmotic pump), delayed coat
Verapamil	Verelan®	1990	Multiparticulate polymer coated beads
Verapamil	Verelan®PM	1998	Multiparticulate polymer coated beads

GITS = gastrointestinal therapeutic system

CHAPTER III
MATERIALS AND METHODS

Materials

1. Felodipine (Batch No. 20030110, Zhejjiang Yiyuan Pharmaceutical Chemical Co. Ltd., China)
2. Polyacrylic acid (Carbopol® 934 P, BFGoodrich, U.S.A.)
3. Chitosan (Low molecular weight, lot. No. 1078112, Fluka, Switzerland)
4. Chitosan (Medium molecular weight, lot. No. 364955/1, Fluka, Switzerland)
5. Chitosan (High molecular weight, lot. No. 414555/1, Fluka, Switzerland)
6. Polyethylene oxide (Polyox® 303, Aldrich, U.S.A.)
7. Polyethylene glycol 400
8. Cellulose acetate (Batch No.14926MO, Aldrich, U.S.A.)
9. Dibutyl sebacate (Batch No. 07729JB, Aldrich, U.S.A.)
10. Acetone, AR grade (Lab-Scan, Thailand)
11. Glacial acetic acid , AR grade (Lab-Scan, Thailand)
12. Sodium hydroxide, AR grade (Carlo Erba,U.S.A.)
13. Hydrochloric acid, AR grade (JT. Baker, Japan)
14. Potassium chloride (Univar, Ajax chemicals, Australia)
15. Microcrystalline cellulose (Avicel® PH101, Asahi chemical industrial,Japan)
16. Pregelatinized starch (Starch 1500®, Colorcon Co., Ltd., Japan)
17. Magnesium stearate BP

Equipments

1. Tumbling mixer (Rotomixer® Model BS 170, Foster equipment Co., Ltd., UK.)
2. Instrument Rotary tablet machine (Colton model 216, Vector Corporation, U.S.A.)
3. Strain amplifier (Dpm-612A, Kyowa Electronic instruments Co. Ltd., Japan)
4. Strip chart oscillographic recorder (Model SC 274, Gould Instrument Inc., U.S.A.)
5. Diametral crushing strength , diameter and thickness tester (Pharma Test® PTB 311, D6452, Hamberg, Germany)
6. Friabilator (Pharma Test® PTFR-A, D-63512, Germany)
7. Peristaltic pump (Watson-Marlow 505S, England)
8. Perforated pan coater (Thai coater® , Model 15¨ (L), Pharmaceutical and Medical Supply LP.,Thailand)
9. CO_2-Laser equipment (Laser Technology Laboratory, KMITT, Thailand)
10. Fourier transform infrared (FTIR) spectrophotometer (Model Magna-IR 550, Nicolet, U.S.A.)
11. Scanning electron microscope (Model JSM-5410 LV, JOEL®, Japan)
12. High performance liquid chromatography
    - High pressure pump (Model LC-10AT VP, Shimadzu, Japan)
    - UV detector (Model SPD-10 VP, Shimadzu, Japan)
    - System controller (Model SCL-10A VP, Shimadzu, Japan)
13. Porosimeter (PoreSizer 9320, Micromeritics, Norcross, Germany)
14. Texture analyzer (TA-XT plus, Stable Micro Systems, UK)
15. Tensitometer (Kruss ® processor tensitometer K100, Germany)
16. pH meter (Model MP 220, Mettler Toledo, Switzerland)
17. Magnetic stirrer (Pyro-Mac Stir, Model L 344, Netherlands)
18. Hot air oven (Kang Seng Lee Engineering Co. Ltd., Thailand)

Methods

1. Preparation of polymeric osmotic agent

1.1 With different molecular weights of CS and different ratios of CS:PAA

To determine the appropriate molecular weight of CS and optimum ratio of CS:PAA for CS-PAA interpolymer complexes, the study investigated CS with three levels of molecular weight. i.e., low (150,000), medium (400,000) and high (600,000), and three ratios of polymer blends, i.e., CS:PAA; 1:2,1:1,2:1.

The polymer blends were prepared by dissolving CS and PAA (Carbopol®934P) in 1M acetic acid (3.3% w/v) and neutralizing with 3 M sodium hydroxide to reach a pH of 5.0. The mixtures were kept at room temperature overnight and then washed with distilled water. Thereafter, the wet mass was dried at 50 ^{o}C for 24 h and pulverized to fine powder.

1.2 Evaluation of physicochemical characteristics of powdered hydrogel

1.2.1 Fourier transform infrared (FTIR) spectrophotometry

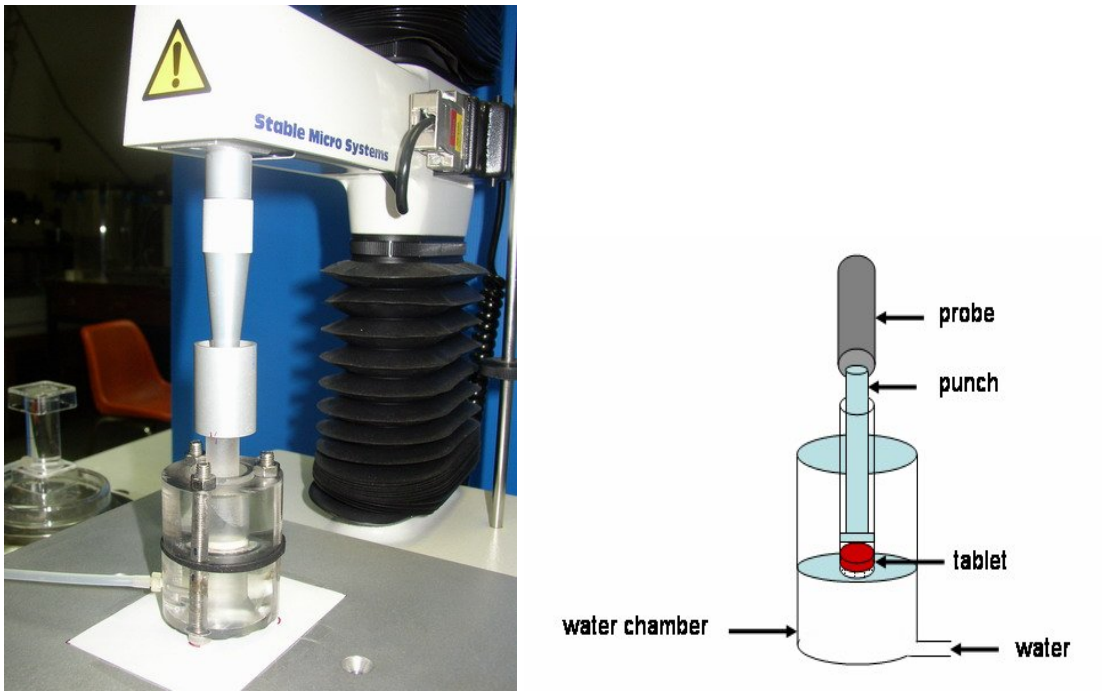
The IR spectrum could be used to identify the new functional group which was introduced into the polymer. They were determined by FTIR spectrophotometer. The KBr method was used. A 1 mg of powdered CS-PAA complex were mixed with 1 g of KBr powder. The mixture was filled in the die and compressed at 390 Mpa for 2 minutes. The compressed disk was placed in the sample holder. The sample was scanned from 4000 to 400 cm^{-1}.

1.3 Evaluation of swelling characteristics

The powdered CS-PAA hydrogel were directly compressed to flat-faced tablets of 13-mm diameter x 3-mm thickness by hydraulic press at the 296 Mpa of the pressure loaded for 1 minute. Then the hydrogel tablets were further evaluated on swelling characteristics.

1.3.1 Swelling force

A comparison of swelling performance of CS with different molecular weights in the polymer mixture with different blend ratios was carried out using texture analyzer TA-XT plus (Figure 18). The pre-test speed, the test speed and post-test speed



(a) (b)

Figure 18. Texture analyzer used in swelling force measurement (a), and graphic illustration of water chamber (b) in which the complex tablet was mounted on the sieve at the water level. The probe of the analyzer was exerted by the swelling force created by the tablet after water uptake.

were set up at 0.5, 0.5 and 10 mm/s, respectively, with an acquisition rate of 0.1 point. The trigger force and distance are 5 g and 0.1 mm, respectively. The swelling forces were investigated for 6 h. At least three repetitions were obtained for each formulation.

1.3.2 Swelling ratio

The swelling study was examined using dissolution testing apparatus 2. The pre-weighted tablets were immersed in 500 mL of deionized water at a temperature of 37 ^{o}C. The paddle's rotation speed was set at 25 rpm. At 15-minute time intervals, the samples were removed from swelling medium and blotted on piece of filter paper prior to weighing to remove excess surface water. The swelling ratio (S_w) was determined according to the following expression:

$$S_w = W_S / W_D \quad (24)$$

where W_S is the weight of swollen tablet and W_D is the initial weight of tablet. The data represented mean ± SD from three determinations of each formulation. The studies were carried out for 6 h.

2. Preparation of osmotic pump tablets: Preliminary study

2.1 Preparation of core tablets

A batch of 150 mg-bilayered tablets was prepared by double compression method. The upper layer was comprised of 10 mg felodipine as an active ingredient, 20-60 mg polyethylene oxide (MW: 300,000) as suspending agent, 10 mg potassium chloride as an osmogent, mixture of microcrystalline cellulose and starch 1500® as a filler and 0.5 mg magnesium stearate as a lubricant. The lower layer was comprised of 10-40 mg polymeric hydrogel and 5-20 mg potassium chloride as osmogents, mixture of microcrystalline cellulose and starch 1500® as a filler, 0.25 mg magnesium stearate as a lubricant and 0.05 mg FD&C red No.2 as a coloring agent. Both layers were mixed separately. The bilayered tablet was compressed on an instrument tablet machine with 7-mm standard concave punch. The compression forces were applied at three different pressures,i.e., 156, 234 and 312 MPa.

The influence of tablet core variables on drug release, i.e., amount of polyethylene oxide in drug layer, polymeric osmotic agent, and potassium chloride in push layer were studied by using the central composite design as described in section 3.

2.2 Preparation of semipermeable membrane coated tablets

Core tablets were coated with 3% w/v cellulose acetate in acetone, with various amount of dibutyl sebacate and polyethylene glycol 400 as plasticizer and various additional weights using perforated pan coater. The operative coating conditions were shown in Table 6. The central composite design was also used to study the influence of these membrane variables on drug release as described in section 3.

2.3 Drilling the orifice by laser beam

The coated tablets were drilled by CO_2-Laser equipment with the computer based control to automatically perform in batch production, as shown in Figure 19. The energy of 100 mJ was selected since it can form the suitable orifice size and does not cause burning effect at the surface of tablets. The batch size of 50 tablets were drilled by laser beam from the moveable laser head which go around to the precise position above the targeting core tablets, laying in the plastic plate. By focusing the laser at the center of coated tablets, the holes can be drilled. The speed and power of the Laser equipment was set up by computer program to achieve the desired orifice size.

3. Preparation of osmotic pump tablets: Central composite design for optimization

To study the influence of tablet core and membrane variables on drug release, the central composite design was selected for fitting response surfaces in this study. Generally, the central composite design consists of a 2^{5-1} factorial or fractional factorial of resolution V, axial runs and center runs. In this study three tablet core variables, i.e., amount of polyethylene oxide in drug layer, amount of polymeric osmotic agent, potassium chloride in push layer, including two membrane variables, i.e., amount of plasticizer and coating level are studied using a 2^{5-1} fractional factorial design. Variables and experimental domain, and experimental design are shown in Tables 9 and 10, respectively.

Table 6. The operative coating conditions for PPOT at various % coating weights gained.

Conditions	6%	8%	10%	12%	14%
Batch size	2 kg	2 kg	2 kg	2 kg	2 kg
Volume of spray liquid	3024 mL	4032 mL	5040	6048 mL	7056 mL
Preheating time	15 min	15 min	15 min	15 min	15 min
Air inlet temperature	40-45 ^{o}C	40-45 ^{o}C	40-45 ^{o}C	40-45 ^{o}C	40-45 ^{o}C
Air inlet temperature	30-35 ^{o}C	30-35 ^{o}C	30-35 ^{o}C	30-35 ^{o}C	30-35 ^{o}C
Pumping rate	25 ml/min	25 ml/min	25 ml/min	25 ml/min	25 ml/min
Atomizing pressure	0.8 kg/cm^2	0.8 kg/cm^2	0.8 kg/cm^2	0.8 kg/cm^2	0.8 kg/cm^2
Pan speed	6-9 rpm	6-9 rpm	6-9 rpm	6-9 rpm	6-9 rpm
Coating time	120 min	160 min	200 min	240 min	280 min
Drying air temperature	35 ^{o}C	35 ^{o}C	35 ^{o}C	35 ^{o}C	35 ^{o}C
Drying time	10 min	10 min	10 min	10 min	10 min

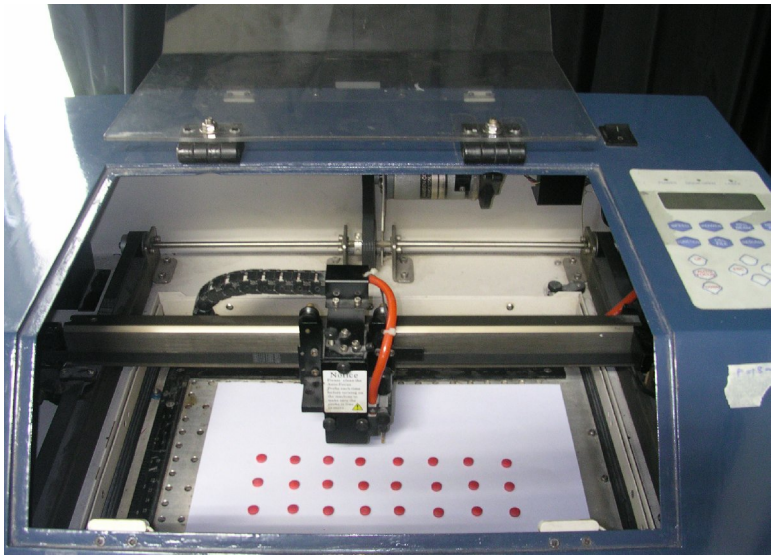


Figure 19. The CO_2-Laser equipment with the computer based control of drilling the delivery orifice in the production of PPOP tablets.

Table 7 Variables and experimental domain

Variables	Experimental domain				
	(-2) level	(-1) level	(0) level	(+1) level	(+2) level
x_1 = amount of polyethylene oxide (mg)	20	30	40	50	60
x_2 = amount of polymeric hydrogel (mg)	0	10	20	30	40
x_3 = amount of potassium chloride in push layer (mg)	0	5	10	15	20
x_4 = amount of plasticizer (%)	0	5	10	15	20
x_5 = coating level (%)	6	8	10	12	14

Table 8 Experimental designs for PPOP tablets

Run	Variables				
	x_1	x_2	x_3	x_4	x_5
1	-	-	-	-	+
2	+	-	-	-	-
3	-	+	-	-	-
4	+	+	-	-	+
5	-	-	+	-	-
6	+	-	+	-	+
7	-	+	+	-	+
8	+	+	+	-	-
9	-	-	-	+	-
10	+	-	-	+	+
11	-	+	-	+	+
12	+	+	-	+	-
13	-	-	+	+	+
14	+	-	+	+	-
15	-	+	+	+	-
16	+	+	+	+	+
17	-2	0	0	0	0
18	+2	0	0	0	0
19	0	-2	0	0	0
20	0	+2	0	0	0
21	0	0	-2	0	0
22	0	0	+2	0	0
23	0	0	0	-2	0

Table 8 Experimental designs for PPOP tablets (cont.)

Run	Variables				
	x_1	x_2	x_3	x_4	x_5
24	0	0	0	+2	0
25	0	0	0	0	-2
26	0	0	0	0	+2
27	0	0	0	0	0
28	0	0	0	0	0
29	0	0	0	0	0
30	0	0	0	0	0
31	0	0	0	0	0
32	0	0	0	0	0

Run 1-16 = 2^{5-1} fractional factorial design

Run 17-26 = axial point of central composite design

Run 27-32 = central point of central composite design

4. Tablet evaluation

4.1 Evaluation of core tablets

4.1.1 Weight variation

Weight variation of core tablets was determined by weighing twenty tablets individually. The average weight and their standard deviation were calculated.

4.1.2 Thickness, diameter and hardness

Tablet thickness, diameter and hardness of core tablets were monitored using a multipurpose measuring device (Pharma Test®PTB311, PharmaTest, Germany). Twenty tablets were measured individually. Their means and standard deviations were reported.

4.1.3 Content uniformity

Content uniformity of core tablets was determined by the assay of ten tablets individually. Each tablet was powdered and transferred into a 100-mL volumetric flask. The assay method was followed under the content uniformity in felodipine extended release tablets as directed in Assay of USP 28 by HPLC method.

High performance liquid chromatography (HPLC)

A high performance liquid chromatograph equipped with an UV-detector and computerize recorder was used. A C8 column (25 cm x 4.6 mm internal diameter) packed with porous silica (5 μm particles) was staionaty phase. The flow rate was 1.0 mL/min and the detector was set at the wavelength of 362 nm.

Mobile phase: The mobile phase was composed of 40% v/v acetonitrile, 20% v/v methanol and 40% v/v of buffer (0.05 M NaH_2PO_4, adjusted to pH 3 with H_3PO_4).

Standard preparation: An accurate weight about 50 mg of standard felodipine was dissolved and adjusted to 100 mL of buffer solution in volumetric flask. Appropriate dilutions were made to obtain felodipine standard solutions of 5, 10, 20, 30, 40 mg/mL. The solutions were filtered through a 0.45 μm polyamide membrane filter. A portion of each standard solution was injected into HPLC column. The peak areas of drugs were plotted against the concentrations of drug.

Sample preparation: To prepare an sample solution, felodipine powder, equivalent to about 10 mg of drug, was transferred to a 100-mL volumetric flask and mixed with 40 mL of acetonitrile and 20 mL of methanol, and sonicated for 5 minutes. An 30 mL of buffer solution was then added to mixture in volumetric flask, followed

by shaking for 30 minutes. After diluting with buffer solution to volume and mix, a portion of solution was centrifuged at 7200 rpm for 15 minutes. The 10 mL of supernatant was transferred to dilute with mobile phase to volume in 50 mL volumetric flask. The solution was filtered through a 0.45 μm polyamide membrane filter. A portion of sample solution was injected into HPLC column.

4.1.4 Porosity

The porosity of core tablets was analyzed by mercury porosimeter. Measurements were performed with the pressure ranging from 0.5 psia to 30,000 psia, which corresponded to pore diameters in the range of 400 μm to 6 nm. The amount of sample was 1.7 g, corresponding to the acceptable stem volume of the penetrometer after measurement. The surface tension (γ) and contact angle (θ) of mercury were 485 dynes/cm and 130 degrees, respectively. Total pore volume (V_{tot}), mean pore diameter, % porosity, bulk and apparent density were calculated with PoreSizer 9320 software, Version 2.05. The plot between the incremental intrusion volume and pore diameter demonstrated the pore size distribution. The total pore surface area is calculated on the basis of the work required to intrude mercury into the pores under increasing pressure.

4.2 Evaluation of osmotic pump tablets

4.2.1 Drug release from osmotic pump tablets

The drug release from osmotic pump tablets was determined using USP 28 dissolution test for felodipine extended release tablets which required the stationary tablet basket to operate with dissolution apparatus II (paddle method) .A 500 mL of 0.1 M phosphate buffer (pH 6.5) with 1% sodium lauryl sulfate was used as a dissolution medium. The temperature of medium was maintained at 37±0.5 ^{o}C. The rotation speed of paddle was 50 rpm. The samples were collected every 30 min or 1h over the range of 12 or 24 h to determine the amount of felodipine release by UV spectrophotometry. The absorbances of samples were detected at the wavelength of 362 nm. The drug concentration in the dissolution media was calculated from the calibration curve.

4.2.3 Water uptake of osmotic pump tablets

Kruss ® processor tensiometer K100 (Figure 20) was used to measure the water uptake of the PPOP tablets in deionized water at room temperature. Each tablet was placed in the small glass tube (5 cm x 9mm diameter) over the sintered glass inside (closing at the end of the tube). The other end of the tube was suspended to the lever over the tested medium. In use, the glass tube automatically lowered to position that the tablet immersed in the medium for 5 mm in depth. Then the program was started to record the amount of water penetrate from the medium to the tablet every 2 min throughout the duration of the study (12h).

5. Evaluation of drug release from felodipine push-pull osmotic pump tablet

5.1 Determination of drug release kinetics

The dissolution data of various formulations were fitted with the different mathematical models, as shown below, to determine the drug release kinetics, i.e., zero -order, first order and Higuchi's model.

$$Q_t = K_0 t + Q_0 \quad (25)$$

$$\log (Q_\alpha - Q_t) = K_1 t + C \quad (26)$$

$$Q_t = K_H t^{1/2} \quad (27)$$

K_0 is the zero-order release constant (%.min^{-1}), K_1 is the first order release constant (min^{-1}), and K_H is the Higuchi dissolution constant (%.min^{-2})

5.2 Factors affecting the drug release

The correlation between drug release and formulation variables will be determined by statistical analysis of ANOVA. Surface response plots of variables influencing drug release are also determined using the Minitab® 15 software.

5.3 Osmotic suspension delivery mechanism

The extended study of drug release mechanism was investigated based on the assumption that the drug release was controlled by two consecutive mechanisms of osmotic pump and erosion. Therefore, the extrusion rate constant (K_{ext}) and erosion rate constant (K_{ero}) due to both mechanisms were determined as follows:

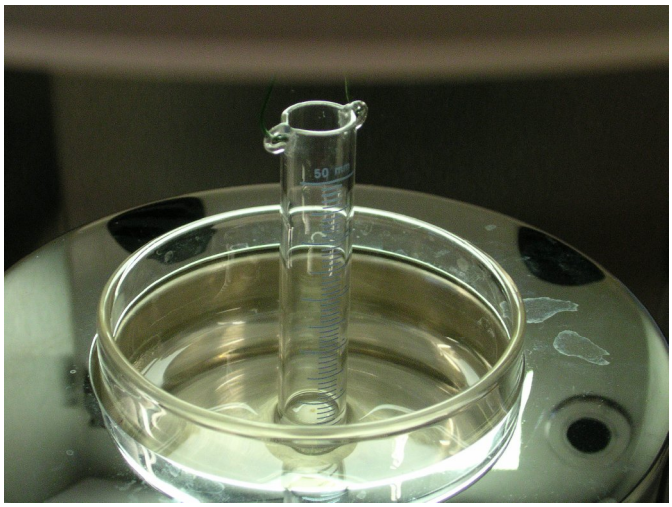


Figure 20. The determination of water uptake into PPOP tablets by Kruss ® processor tensiometer.

5.3.1 Extrusion rate constant (K_{ext})

The osmotic pump mechanism was to extrude the drug layer to the environment as an erodible composition and, then subsequent mechanism was the erosion and dissolution of the extruded drug layer in the environment. The amount of drug extruded at definite time could be determined by dissolution test as described in section 4.2.1. At pre-determined sampling times, the tablets were physically removed from the dissolution vessel, any extruded material at or near the exit port was carefully wiped off, and the residual undelivered drug from the tablet was extracted for analytical quantification. The amount of drug extruded was then calculated by subtracting the amount recovered from the known initial drug loading. The sample-collection times were 2, 3, 4, 5, 6, and 7 h. The extrusion rate constant (K_{ext}) was obtained from the slope of linear regression plot between amount of drug recovery and time.

5.3.2 Erosion rate constant (K_{ero})

The wet mass of drug layer composition of PPOP tablets was prepared by wet granulation method. Thereafter, the wet mass was transferred to glass syringe with exit port of 0.5 mm diameter at the end, and was then extruded via that exit port. The extrudate was cut off to small pieces and dried in hot air oven. The dissolution test of the drug based extrudate was performed in accordance with the method of PPOP tablets. Erosion rate constant (K_{ero}) was calculated from the slope of linear regression plot between amount of drug eroded and time.

CHAPTER IV
RESULTS AND DISCUSSION

Preparation of CS-PAA Interpolymer Complexes

CS-PAA interpolymer complexes were prepared at various ratios of polymer blend. The precipitates were observed after mixing of the polymer solutions and increased suddenly as pH value was adjusted to 5. It could be reasoned that this pH was optimal for complexation between CS and PAA. The more the pH increased , the more the ionization of PAA increased. The electronic bonding was formed at this pH between the COO^- group of ionized PAA and amino group of CS which could be protonated . The precipitates of the interpolymer complexes obtained by this way are shown in Figure 21. Chavasit V et al. proposed a mechanism for complex formation between chitosan and polyacrylic acid (84). In the 3 to 5 pH range, most of CS amine groups are in the NH_3^+ form while most of the PAA carboxyl groups are in the COOH form. This suggests the following complex formation mechanism.

$$\underset{\text{(chitosan)}}{NH_3^+} + \underset{\text{(polyacrylic acid)}}{HOOC} \longrightarrow \underset{\text{(complex)}}{NH_3^+ {}^-OOC} + H^+ \qquad (28)$$

At pH = 6, the degree of ionization of CS decreases, while that of PAA increases. Most of amine groups are in the NH_2 form while most of PAA carboxyl groups are in the COO^- form. This suggests the following complex formation mechanism:

$$\underset{\text{(chitosan)}}{NH_2} + \underset{\text{(polyacrylic acid)}}{COO^-} \xrightleftharpoons{+H^+} \underset{\text{(complex)}}{NH_3^+ {}^-OOC} \qquad (29)$$

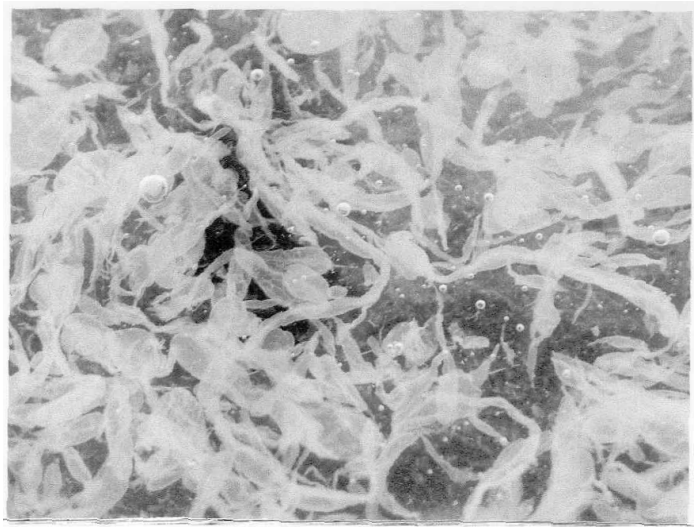


Figure 21 The precipitates of the interpolymer complexes of chitosan and polyacrylic acid after adjusting pH of the medium to 5

Evaluation of Physicochemical Characteristics of CS-PAA Complex

1. FTIR studies Figures 22a-c show FTIR spectrum of CS, CS-PAA complex and PAA. Characteristic peak of CS was located at 1595 and 1654 cm^{-1} for the amine group of 2-aminoglucose unit and the carbonyl group of the 2-acetaminoglucose unit of chitosan, respectively (108). At 1714 cm^{-1} in the spectrum of PAA (Figure 22c), has been assigned to C=O stretching vibration of carboxylic groups.

In comparison with Figure 22a and 22b, it is shown important changes in spectrum of CS-PAA complex. In Figure 21a, two peaks at 1654 and 1596 cm^{-1} decrease dramatically, and two new peaks at 1550 and 1640 cm^{-1} are observed. The peak of 1595 cm^{-1}assigned to the amine group of chitosan is shifted to 1640 cm^{-1}, indicating that the amine group was protonated to a NH_3^+ group in the interpolymer complex. Moreover, the 1550 cm^{-1} can be assigned to the NH_3^+ absorption peaks which overlapped to peak of COO^- group (8). The peak of 1408 cm^{-1} is assigned to the asymmetric stretching of the COO^- group, whereas the symmetric stretching of the COO^- group was known to appear at 1550 cm^{-1} (11, 109). These results suggest that the carboxylic groups of PAA are dissociated into COO^- groups which complex with protonated amino groups of CS through electrostatic interaction to form the polyelectrolyte complex.

2. Evaluation of Swelling Characteristics The swelling forces and swelling ratios of CS-PAA complexes were plotted in Figures 23 and 24, respectively. The plots of swelling ratios have different characteristics from swelling forces. In case of swelling force, the force was increased with time until it reached the equilibrium within 180 min for all complexes and then the force remained constant. In case of swelling ratio, it was similarly increased with time and reached equilibrium within 60, 120, 300 min for the complex of 1:2,1:1,2:1 respectively, however it was decreased after equilibrium. This is due to the fact that the complex could swell and remain intact during measurement, thus the swelling force was not changed after equilibrium. In the contrary, complex could swell and erode in swelling medium during measurement of swelling ratio. Initially the swelling rate was faster than the erosion rate, thus the swelling ratio was increased with time. After equilibrium the erosion rate was faster than the swelling rate, consequently the swelling ratio was decreased with time.

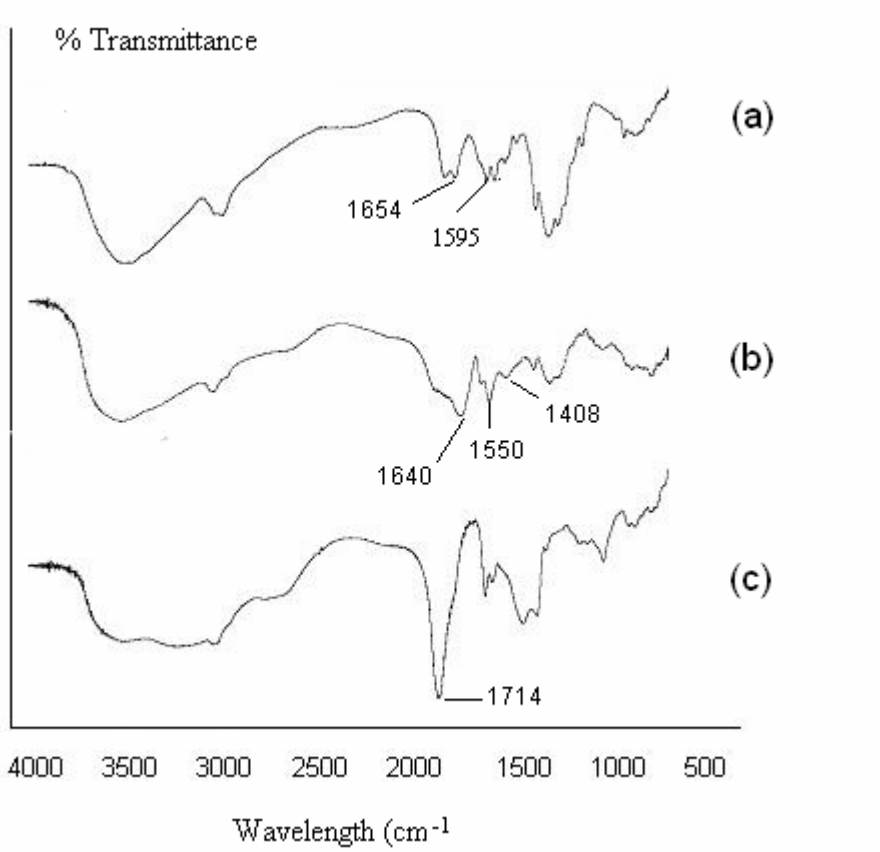


Figure 22. FTIR spectrum of CS (a), CS-PAA complex (b), and PAA (c)

The swelling forces and ratios were increased with the CS proportion. The complex at the ratio of 2:1 exhibited the high maximum swelling ratio (S_w = 19) and force (S_f = 27 N) in 300 min. While the swelling ratio and force was 9 and 17 N for complex at the ratio 1:1 and was 5 and 12 N for complex at the ratio 1:2. This result suggests that complex at the ratios of 1:2 and 1:1 rapidly hydrated, swelled and reached the equilibrium within 10-60 min and the complex at the ratio of 2:1 gave slower swelling and reached the equilibrium in the longer time. This could be attributed that the swelling behavior of these complexes is retarded by ionic interaction, which exist between both polymer chains. Increase PAA proportion in a ratio of CS:PAA 1:2 results in increase interaction between carboxylic group of PAA and amine of CS. However, this electrostatic interaction is less effective when the CS:PAA ratio is higher (as seen in complex at ratio of 2:1) due to the increase in electrostatic repulsion of ionized amine of CS. This result is according to the swelling properties of freeze-dried interpolymer complexes based on PAA and CS reported by Torre PM et al. which was found that the lower PAA proportion in polyionic complexes exhibited the maximum swelling ratio. Park SH, et al.(8) also prepared chitosan/Carbopol interpolymer complex and revealed the complexation ratio between CS/PAA to be 1/4 in mole ratio which is approximately equivalent to 1/1.3 of weight ratio. This information is also in good agreement with the swelling behavior of CS-PAA complex at ratio of 1:1 and 1:2 in this study.

The effect of the molecular weight (MW) of chitosan in CS-PAA complex on the swelling forces and swelling ratios are shown in Figures 25 and 26. It was found that the molecular weight of chitosan influenced the swelling degree of complexes. The swelling forces and ratios were increased with the molecular weight of CS. This might be due to the fact that the chitosan with low molecular weight can react well with the anion polymer because its diffusion was greater. The diffusion of the macromolecular chains of chitosan relate to the interaction between carboxylic group of PAA and amine of CS. The chitosan with high molecular weight diffused more slowly than the chitosan with low molecular weight, resulting in the less intermixing between chitosan and polyacrylic acid which created a less compact structure of complex that swelled more. Therefore, the swelling degree of the complex made with low molecular weight chitosan was smaller than that made with high molecular weight chitosan (76).

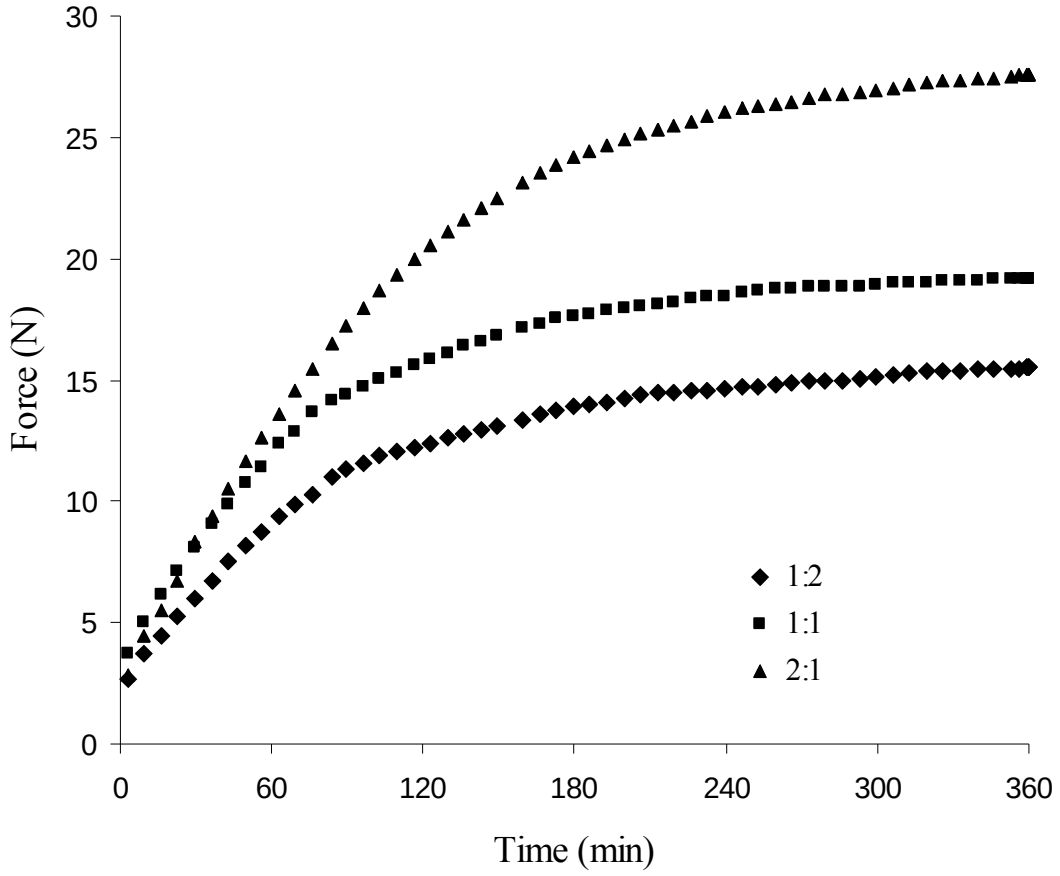


Figure 23. Effect of various ratios of CS:PAA on swelling force of complex

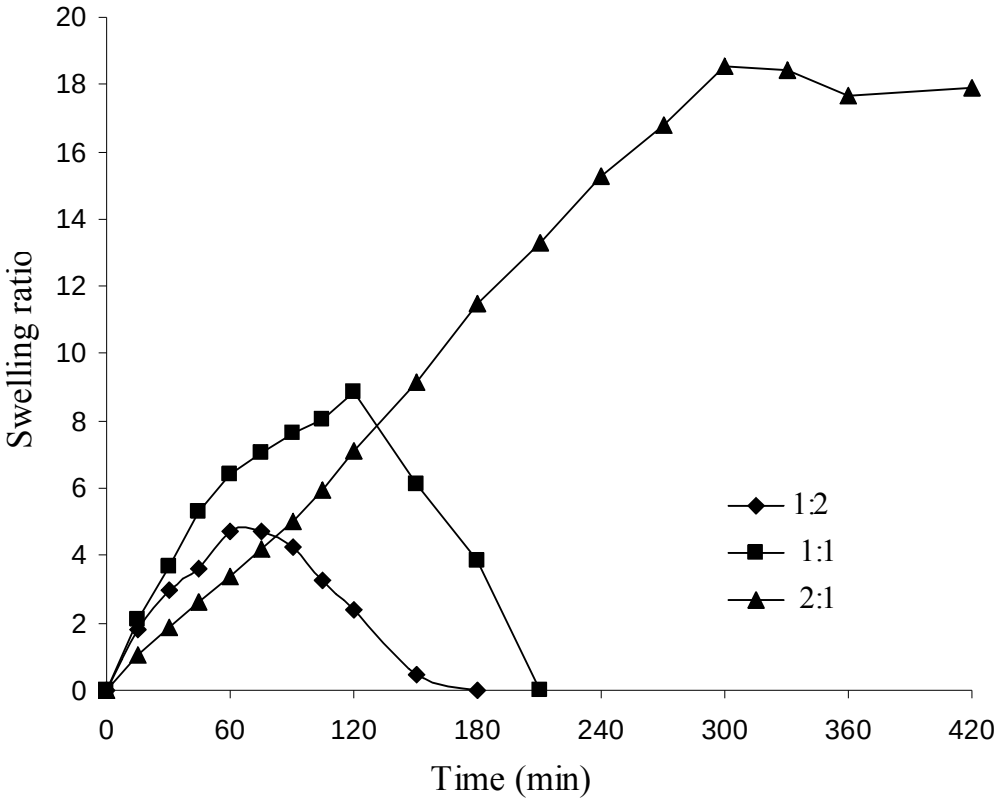


Figure 24. Effect of various ratios of CS:PAA on swelling ratio of complex.

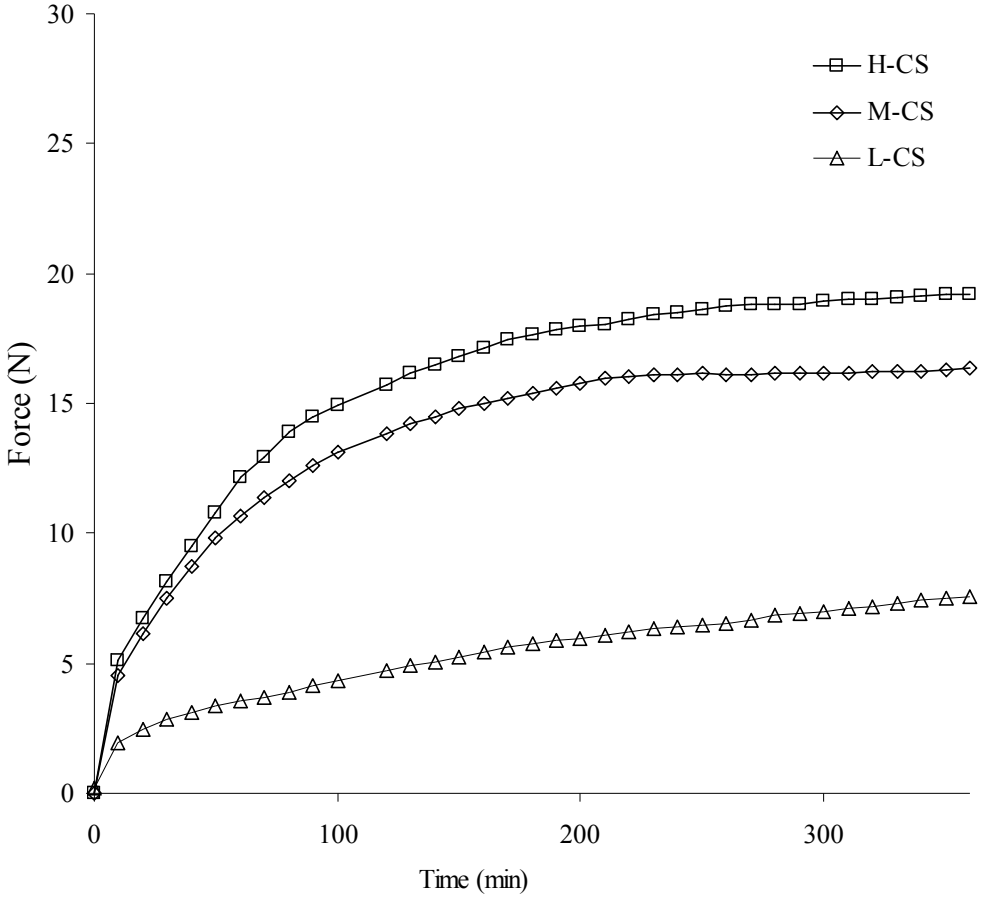


Figure 25. Effect of molecular weight of chitosan on swelling force of complex : H-CS (high MW), M-CS (medium MW), L-CS (low MW)

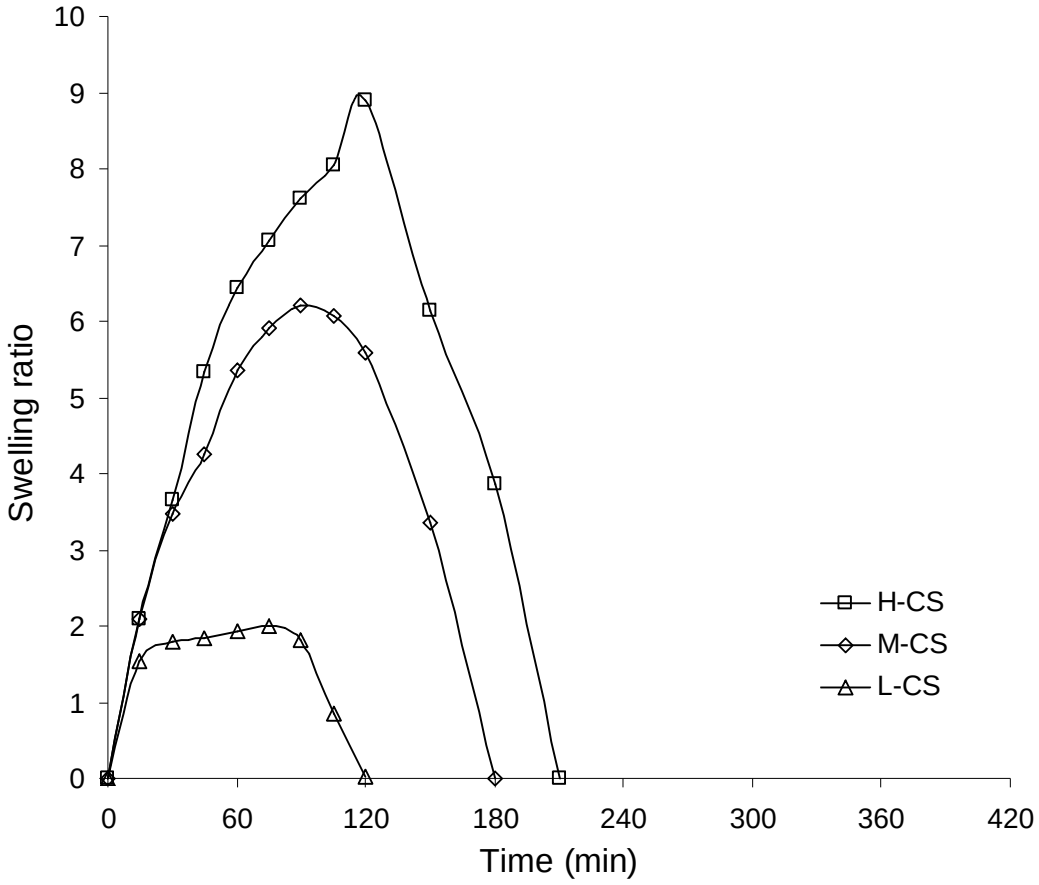


Figure 26. Effect of molecular weight of chitosan on swelling ratio of complex : H-CS (high MW), M-CS (medium MW), L-CS (low MW)

Development of Push-Pull Osmotically Controlled Release Tablets

1. Preliminary Study

1.1 Preparation of felodipine push-pull osmotic pump Tablets (PPOT) The different formulations of core tablets were prepared to investigate the influences of the proportion of the CS-PAA composition, weight of tablet, compression force and type of plasticizer on physical property and drug release of osmotic pump tablet. The bilayered tablet was prepared by double compression method. The upper layer was comprised of 10 mg felodipine as an active ingredient, 40 mg polyethylene oxide (MW: 300,000) as suspending agent, 10 mg potassium chloride as an osmotic agent, 20-40 mg (according to tablet weight of 130-150 mg) mixture of microcrystalline cellulose and starch 1500® as a filler and 0.5 mg magnesium stearate as a lubricant. The lower layer is comprised of 20 mg CS-PAA complex with different ratios i.e., 1:2, 1:1 and 2:1 as polymeric osmogent and 10 mg potassium chloride as osmotic agent, 20 mg mixture of microcrystalline cellulose and starch 1500® as a filler, 0.25 mg magnesium stearate as a lubricant and 0.05 mg FD&C red No.2 as a coloring agent. The core tablets could be made by direct compression due to the fact that most ingredients in both layers possessed ability to flow. Each formulation was compressed on an instrumented Colton® rotary punch tablet machine using 7 mm standard concave punch. The compression forces were applied at 156 MPa for all formulations. Exceptionally in the study of compression force effect, the 150 mg core tablets with CS:PAA complex at ratio of 1:1 were prepared using three different lower punch forces i.e., 156, 234 and 312 MPa.

Core tablets batches of 2 kg were coated with 3% w/v cellulose acetate in acetone with 5% dibutyl sebacate (DBS) or polyethylene glycol 400 (PEG) as plasticizer to achieve 10% additional weight using perforated pan coater (Thai coater, Model 15”(L) Pharmaceuticals and Medical Supply LP., Thailand). The operating coating conditions were adjusted to obtain good appearance and smooth film. In the initial step, the pan speed and spray rate of coating solution were adjusted to low level in order to prevent the core tablets from chipping at the edge and sticking during coating. After the thin film surrounded the core tablets, these coating conditions could be adjusted to higher level to reduce the total coating time.

Coated felodipine tablets were drilled by CO_2 - laser equipment as shown in Figure 19. Two main parts of CO_2 - laser equipment are the CO_2- laser tube and movable laser head, controlled by the computer. The diagram of the CO_2 - laser tube is shown in Figure 27. The active medium in a CO_2-laser is a mixture of carbon dioxide, nitrogen and helium which plays a distinct role as mentioned earlier. The laser beam produced by CO_2 - laser tube is conducted to the laser head which prompts to fire the coated tablet. Each coated tablet was placed in each hole of plastic plate designed for drilling the tablet. The plastic plate was located in the laser equipment underneath the laser head which could move directly to each tablet. By focusing the laser at the center of coated tablets, the holes could be drilled. The speed of drilling and power of laser beam were programmed by computer and must be optimized to produce the holes of the precise size without damage of the tablets.

1.2 Evaluation of Felodipine Core Tablets Felodipine core tablets were evaluated for their physical properties, weight variation, thickness, diameter and hardness, to ascertain that they had properties appropriate for further study.

1.2.1 Weight variations The core tablets were produced in different polymer ratio, weight of tablet and compression force. Their average and standard deviation were shown in Table 9. All formulations met the USP XX requirements on weight variation test.

1.2.2 Hardness, thickness and diameter Hardness, thickness and diameter and of 20 tablets were monitored by using a multipurpose measuring device (Pharma Test® PTB311, Pharmatest, Germany). Their means and standard deviation are also shown in Table 9. As expected, the thickness increased with the increase in tablet weight and decreased with the increase in compression force. The hardness increased with increase in both tablet weight and compression force. It can be explained based on the more amount of filler which has the compressibility inherently hence the particulate bonding was enhanced. However, the different ratio of polymer do not affect the hardness because the polymer layer in bilayered tablet is very thin, compared with drug layer. Therefore, the hardness of the tablet is wholly dominated by the drug layer.

1.2.3 Friability The friability increased with decreased in tablet weight and compression force. This result was in agreement with the hardness of tablet.

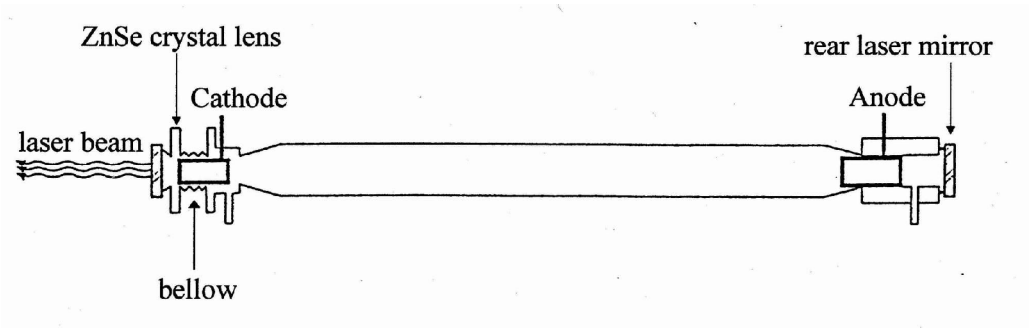


Figure 27 The diagram of the CO_2 - laser tube

Table 9. Weight variation, thickness, hardness, % friability of core tablets prepared in preliminary study.

Formulation	Weight variation mg (SD)	Thickness mm (SD)	Hardness kg (SD)	Friability %
W130C2-1	135.75 (1.33)	3.59 (0.03)	2.8 (0.24)	4.20
W130C1-1	135.25 (1.45)	3.62 (0.04)	3.1 (0.20)	0.85
W130C1-2	134.65 (0.99)	3.58 (0.03)	3.05 (0.35)	1.08
W150C2-1	155.45 (2.01)	4.07 (0.03)	3.85 (0.55)	1.70
W150C1-1	152.65 (2.25)	3.97 (0.03)	4.28 (0.52)	0.22
W150C1-2	154.55 (1.28)	4.01 (0.05)	3.81 (0.4)	0.65
W150F156	152.65 (2.25)	3.97 (0.03)	4.28 (0.52)	0.22
W150F234	151.70 (1.45)	3.87 (0.05)	4.50 (0.45)	0.18
W150F312	152.00 (1.56)	3.83 (0.03)	4.55 (0.42)	0.14

However, the different polymer ratio had affected the friability. At ratio of 2:1 of both tablet weights gave the highest friability and at ratio of 1:1 of both tablet weights gave the lowest friability. It may suggest that the complex at the ratio of 2:1 has lower binding property than the complex at ratio of 1:1 and 1:2, therefore the lower particulate bonding in the polymer layer caused the higher fine powder during the friability test.

1.2.4 Tablet Porosity Table 10 gives the porosity and pore diameter of the felodipine core tablets prepared using different compression forces. The results indicated that these properties were slightly influenced by the compression force. As the compression force was distinctly changed from 156 to 312 MPa, the porosity was slightly changed from 14.55 to 18.40 %. It can be explained based on calculation of tablet porosity as follows:

$$\varepsilon = (v - v_{\alpha})/v \quad (30)$$

where v and v_{α} were the volume of tablet at any applied load and the volume at the theoretical zero porosity, respectively.

$$v = 2\pi r(3R^2 + r^2)/6 + \pi R^2 h \quad (31)$$

where R is the radius of tablet; r is the curvature of the standard concave punch and h is the thickness of tablet.

As shown in the Eq.31, v at any applied load is related to the tablet thickness, which depends on the compression force. The more compression force was applied, the less thickness and less porosity of the tablets were resulted. Nevertheless, Table 9 shows that the thickness of tablets at different applied forces was not quite different, hence the tablet porosity was slightly changed.

According to these results, it is possible to prepare felodipine core tablet by the method of direct compression with selected polymer ratio of complex, tablet weight and compression force to have high hardness and low friability that can withstand the movement of tablets beds in pan coater.

Table 10. Porosity and pore diameter of felodipine PPOP core tablet at different compression forces.

Formulation	Porosity (%)	Mean pore diameter (μm)
W150F156	18.40	0.1364
	(0.84)	(0.062)
W150F234	17.57	0.1159
	(0.47)	(0.012)
W150F312	14.55	0.080
	(0.67)	(0.029)

(n = 3, standard deviation in parenthesis)

Table 11. Drug content of felodipine PPOP tablets.

Formulation	Drug content, % (SD)
W130C2-1	98.95 (1.53)
W130C1-1	100.52 (2.45)
W130C1-2	101.54(0.54)
W150C2-1	101.15(1.45)
W150C1-1	99.57(2.28)
W150C1-2	100.45(1.32)
W150F156	99.31 (1.95)
W150F234	98.47 (1.38)
W150F312	100.15 (0.98)

(n = 3, standard deviation in parenthesis)

1.3 Drug content The results of drug content determinations are shown in Table 11. All formulations were acceptable to USP28 within the range of 90.0% - 110% of label claim. The lowest and the highest values were found to be 98% and 101%, respectively. The standard deviation was small, the highest value was 2.45.

1.4 Drug release Figure 28 illustrates cross-section of push-pull osmotic pump tablet (PPOT) using dibutyl sebacate as plasticizer after dissolution test. It shows that the core progressively hydrated and that the volume occupied by the polymer layer increased with time. The maximum increased after 20 h according to decreasing release rate in dissolution profile. It was implied that the drug release of push-pull osmotic pump tablet related with the swelling of CS-PAA complex used as polymeric osmotic agent.

Figure 29 and 30 depict the dissolution profiles of felodipine from PPOT using different kinds of plasticizers and polymer ratios at tablet weight of 150 and 130 mg respectively. It is well known that plasticizers modify the physical properties and improve film-forming characteristics by changing viscoelastic behavior. Plasticizers turn a hard and brittle polymer into a softer, more-pliable material and possibly make it more resistant to mechanical stress. These changes may affect the aqueous permeability of polymer films. As it was seen in the Figure 29-30, the drug release could be prolonged up to 12 or 24 h depending on plasticizer. At the same polymer ratio, the drug release of PPOT using DBS gave longer lag time and slower drug release. It can be attributed to the difference of hydrophobicity of PEG and DBS. As DBS was a hydrophobic plasticizer, it was difficult to leach and the residual DBS acted as a barrier preventing water to penetrate the membrane. As a consequence, the permeability of membrane and drug release were depressed. On the other hand, hydrophilic PEG easily leached from the membrane and left behind a porous structure and thereby increased permeability of membrane and the drug release from PPOT.

To explain the drug release kinetics of felodipine from PPOT, the mean dissolution curves included the fraction between 10-80% of drug release was calculated by linear regression analyses of conventional mathematical models. It was found that the drug release mechanism of felodipine from PPOT is zero-order kinetics, due to the coefficients of the regression (R^2) closed to 1 as shown in Table 12-13.

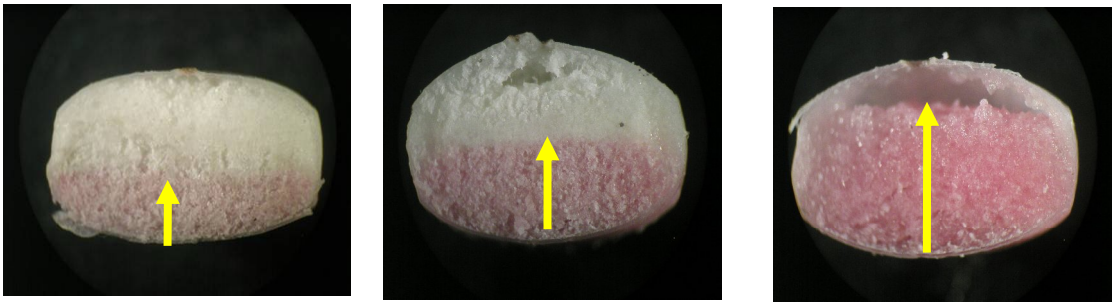


Figure 28. Cross-section of felodipine PPOP tablets after dissolution in time sequence.

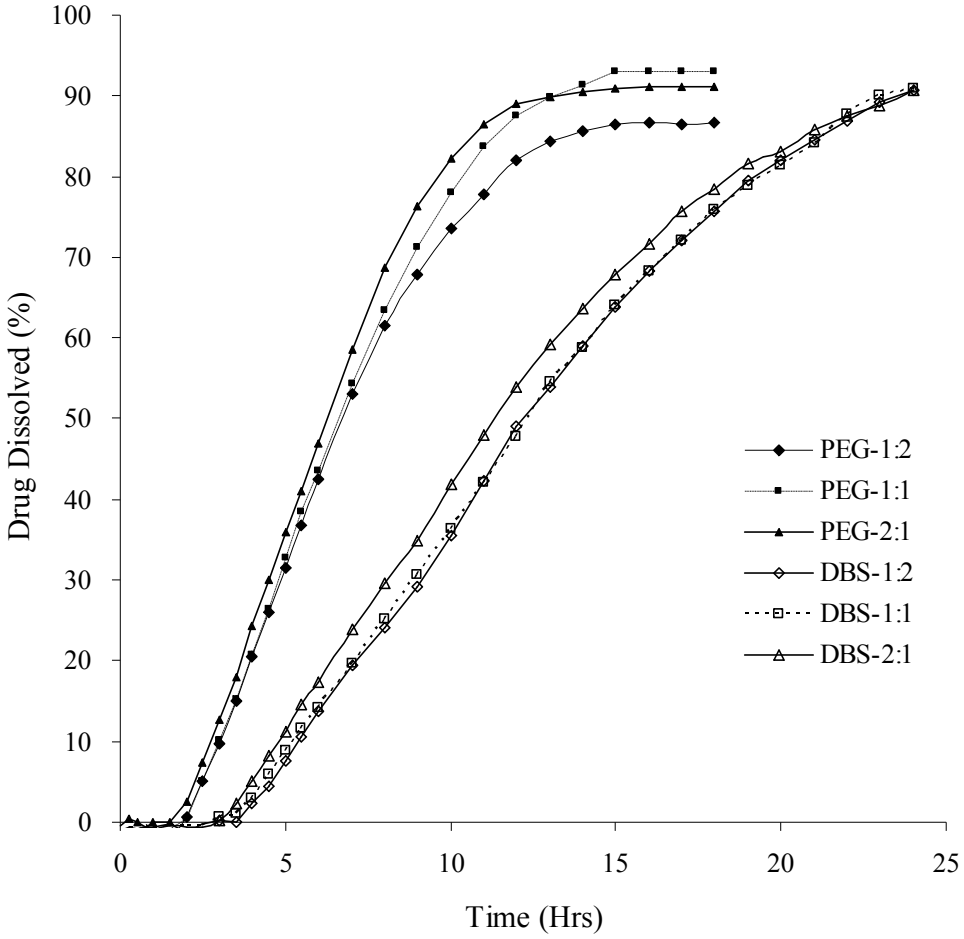


Figure 29. Effect of various ratios of CS:PAA and plasticizers on drug release of felodipine PPOP tablets with 150 mg weight.

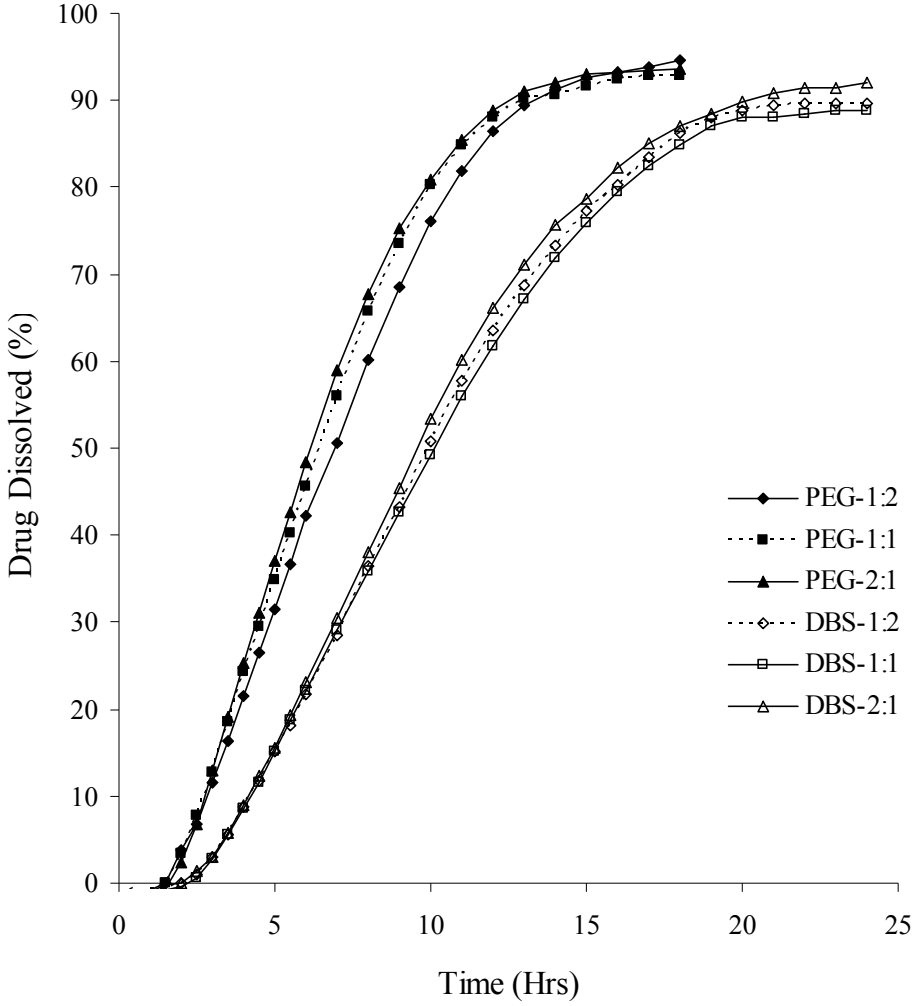


Figure 30. Effect of various ratios of CS:PAA and plasticizers on drug release of felodipine PPOP tablets with 130 mg weight.

It may suggest that this system could deliver the drug at an approximately constant rate whereby the osmotic mechanism predominated.

The influence of polymer ratio on drug release was also observed in Figure 29-30, which show that the drug release increased as the chitosan proportion increased for both studies of PPOT with DBS and PEG. The percent release at 8 h of PPOT using complex at ratio of 1:2, 1:1 and 2:1 were 61.43%, 63.44% and 68.66%, respectively for PEG and were 24.13%, 25.06% and 29.65% respectively for DBS. It might be explained that the drug release was co-controlled by the push layer and the drug layer. The function of drug layer was to liquefy its contents and suspend the drug stably, while the function of the push layer was to expand its volume gradually to force the drug suspension release. From the result of swelling study, the complex at ratio of 2:1 exhibited markedly higher swelling than those at ratio of 1:1 and 1:2. Consequently, higher release rate could be obtained in the case of complex at ratio of 2:1.

Figure 31 and 32 illustrate the dissolution profiles of PPOT at different tablet weights. The PPOT of high tablet weight gave longer lag time and slower drug release than that of low tablet weight, in case of both DBS and PEG. It might be explained that the increase of tablet weight increased the amount of drug layer, resulting in increase of the workload of push layer to force the drug suspension out. The influence of tablet weight was more pronounced in the case of DBS. It might be due to the less water permeation of membrane with DBS resulting in longer lag time at the higher tablet weight. In case of PEG, the water permeation is high enough to liquefy the drug layer prompt to be released, leading to no difference of lag time at both tablet weights.

Figure 33 shows the drug release of various compression forces. In this study, the 150 mg core tablets with CS:PAA complex at ratio of 1:1 were prepared. These revealed that compression force scarcely affected drug release. It was ascribed by the evidence that the % porosity of the three compression force were not quite different, i.e, 18.40, 17.57, 14.55 % for compression forces of 156, 234 and 312 MPa respectively. Moreover, it was observed that the high viscous gel was formed in the drug layer and expelled via the delivery orifice as seen in Figure 34. It was possible that this viscous gel acted as a barrier limiting amount of water penetration into the glassy drug layer and subsequently controlled the drug release with regardless to the influence of tablet porosity.

Table 12. Linear regression analyses of drug-release kinetics of felodipine PPOP tablets, using polyethylene glycol 400 as plasticizer

Formulation	Intercept	Slope	R^2
W130C2-1	- 15.938	10.232	0.9917
W130C1-1	- 15.582	9.934	0.9965
W130C1-2	- 14.265	9.070	0.9969
W150C2-1	- 15.023	9.900	0.9894
W150C1-1	- 16.505	9.593	0.9919
W150C1-2	- 14.911	9.030	0.9874

Table 13. Linear regression analyses of drug-release kinetics of felodipine PPOP tablets, using dibutyl sebacate as plasticizer

Formulation	Intercept	Slope	R^2
W130C2-1	- 14.995	6.464	0.9919
W130C1-1	- 14.533	6.159	0.9952
W130C1-2	- 14.983	6.288	0.9938
W150C2-1	- 14.405	5.370	0.9914
W150C1-1	- 16.703	5.251	0.9919
W150C1-2	- 18.340	5.362	0.9959

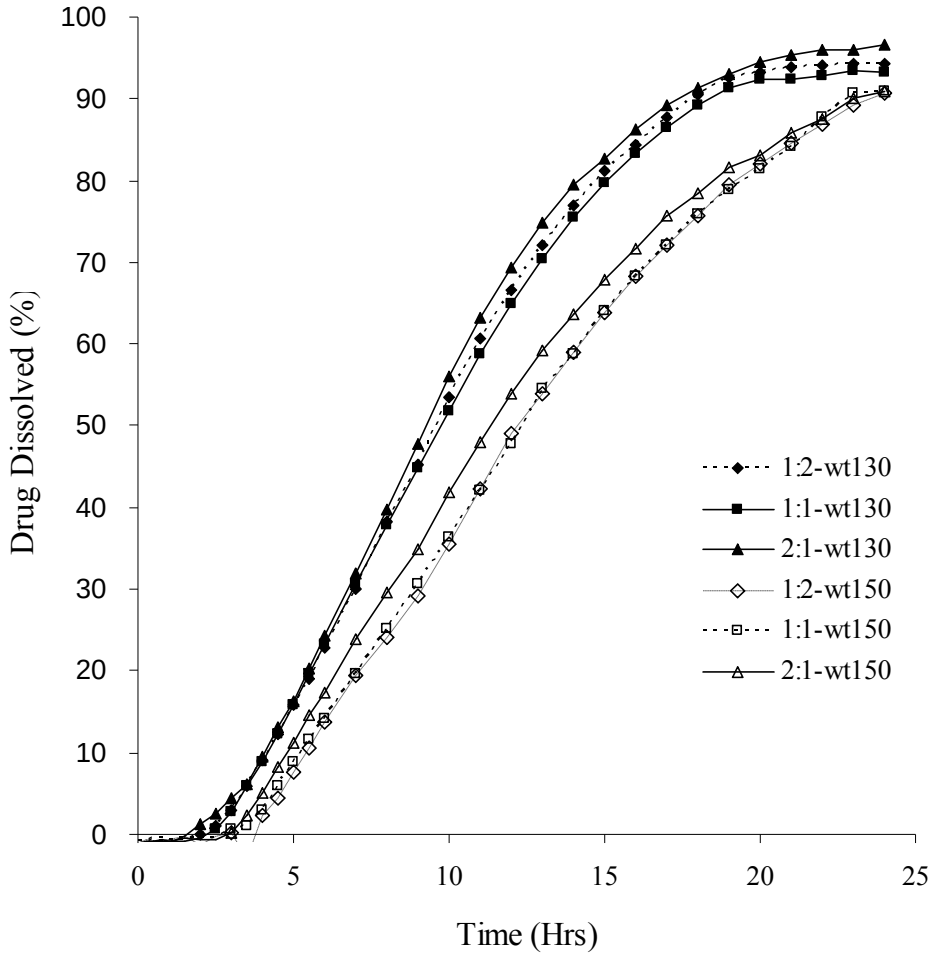


Figure 31. Effect of tablet weight on drug release of felodipine PPOP tablets using dibutyl sebacate as plasticizer.

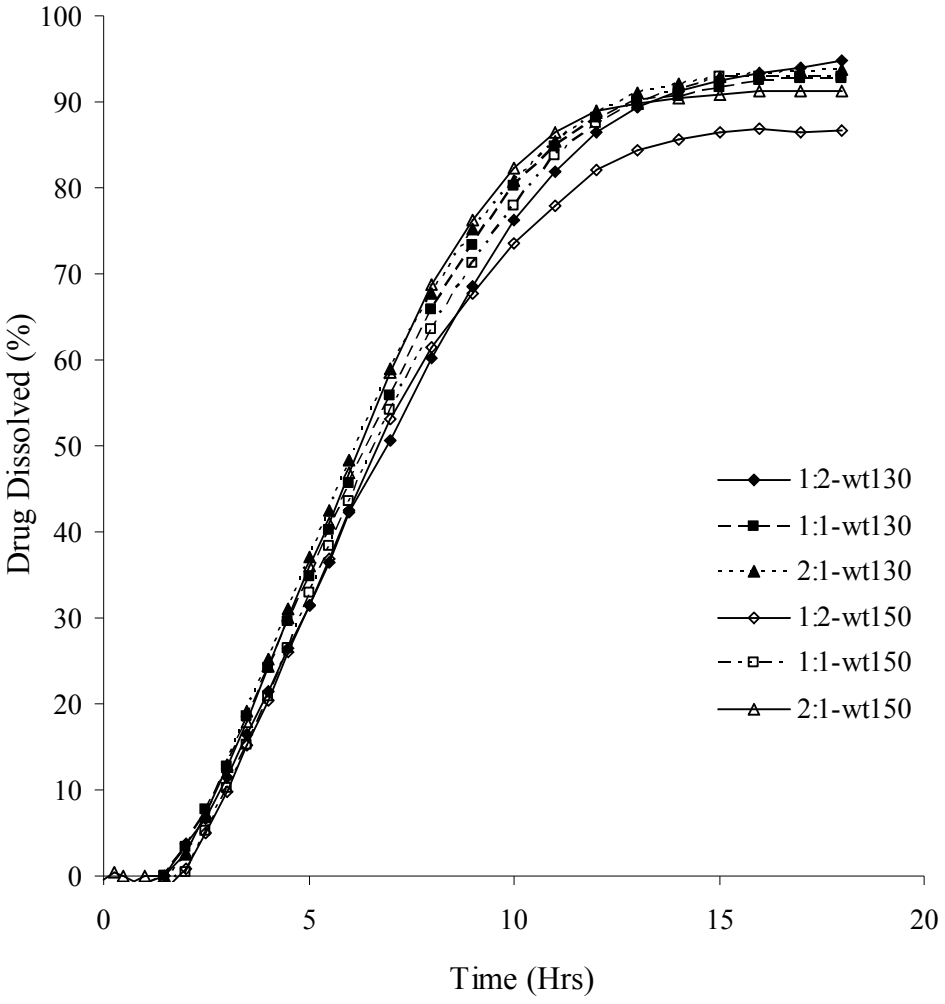


Figure 32. Effect of tablet weight on drug release of felodipine PPOP tablets using polyethylene glycol 400 as plasticizer

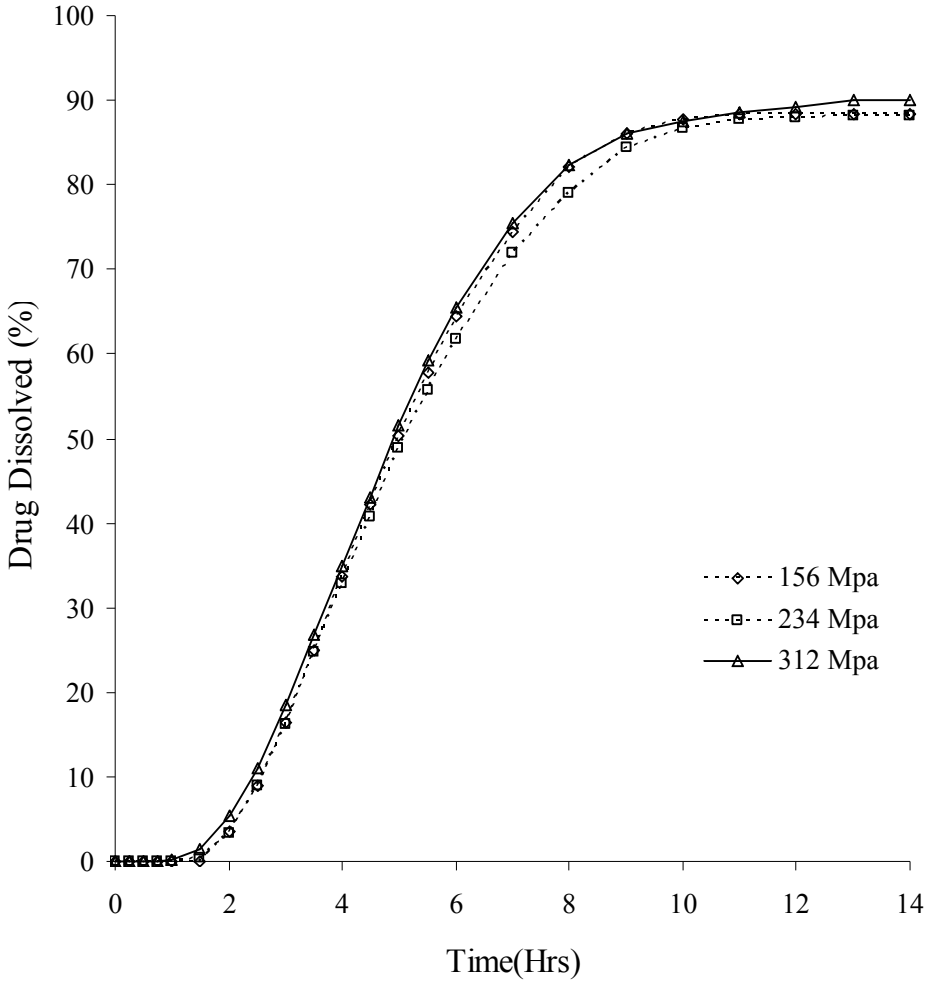


Figure 33. Effect of compression force on drug release of felodipine PPOP tablets

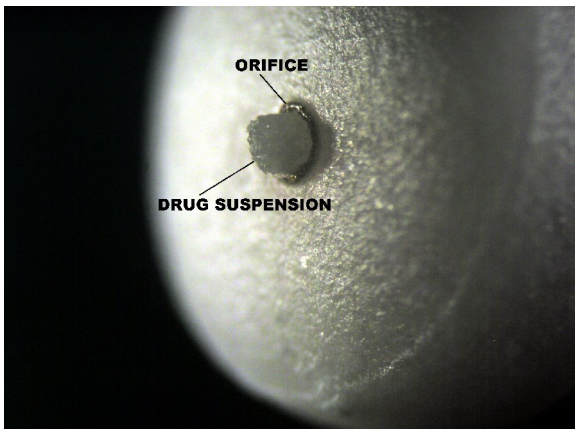


Figure 34. Photograph of PPOP tablet with the delivery orifice, through which the high viscous gel of drug layer inside was extruded

In summary, this part of the study revealed that preparation of PPOT using CS-PAA complex as polymeric osmogent was feasible with regard to influences of various factors on the physical property and drug release. With these selected factors, i.e., polymer ratio of 1:1, tablet weight of 150 mg, compression force of 234 MPa and PEG 400 as plasticizer, the optimal basic PPOT was obtained for the further study of optimization of the formulation variables to achieve desired drug release.

2. Optimization of Felodipine Push-Pull Osmotically Controlled Tablet

2.1 Preparation of felodipine push-pull osmotic pump Tablets The different formulations of core tablets were prepared to optimize the formulation and membrane variables by using response surface methodology**.** The central composite design was selected for fitting response surfaces in this study. As a part of optimization process, the quadratic relationships, main effects, interaction effects on the release characteristics of the drug were investigated. Although several factors principally influence the rate of drug release from osmotically controlled drug delivery systems, five factors, i.e., amount of polyethylene oxide in drug layer, amount of CS-PAA complex and KCl in push layer, amount of PEG 400 and coating level were selected to study using central composite design, which consists of a 2^{5-1} fractional factorial design of resolution V, axial runs and center runs. Therefore a total of 32 formulations shown in Table 14 were prepared in similar manner as discussion in preliminary study.

2.2 Evaluation of felodipine core tablets Felodipine core tablets were evaluated for their physical properties, weight variation, thickness, diameter and hardness, to ascertain that they had properties appropriate for further study.

2.2.1 Weight variations Twenty tablets were randomly sampled and individually weighed. There average and standard deviation were shown in Table 15. All formulations met the USP XX requirements on weight variation test.

2.2.2 Thickness, diameter and hardness Hardness, thickness and diameter of 20 tablets were monitored by using a multipurpose measuring device (PharmaTest® PTB311, Pharmatest, Germany). Their means and standard deviation are also shown in Table 15.

Table 14. Experimental design for PPOT

	Variables					Response			
Formular	x_1	x_2	x_3	x_4	x_5	y_1	y_2	y_3	y_4
F-1	30	10	5	5	12	0	31.85	63.14	73.38
F-2	40	10	5	5	8	11.95	67.36	87.74	88.62
F-3	30	30	5	5	8	7.97	64.36	88.12	88.12
F-4	50	30	5	5	12	2.89	40.48	70.87	82.28
F-5	30	10	15	5	8	7.40	66.70	81.20	82.80
F-6	50	10	15	5	12	1.77	37.69	70.65	80.06
F-7	30	30	15	5	12	1.07	40.93	80.52	89.75
F-8	50	30	15	5	8	11.82	75.41	90.04	90.04
F-9	30	10	5	15	8	12.38	75.08	84.62	84.62
F-10	50	10	5	15	12	9.36	60.91	83.73	87.91
F-11	30	30	5	15	12	7.86	69.27	91.68	91.68
F-12	50	30	5	15	8	19.22	83.85	92.86	92.86
F-13	30	10	15	15	12	8.38	62.16	81.40	81.40
F-14	50	10	15	15	8	17.87	81.69	85.94	85.94

x_1 = amount of polyethylene oxide (mg), x_2 = amount of CS-PAA complex (mg)

x_3 = amount of potassium chloride (mg), x_4 = amount of PEG 400 (mg)

x_5 = coating level (%)

y_1 = cumulative percent of drug release in 2 h

y_2 = cumulative percent of drug release in 6 h

y_3 = cumulative percent of drug release in 10 h

y_4 = cumulative percent of drug release in 12 h

Table 14. Experimental design for PPOP (cont.)

	Variables					Response			
Formular	x_1	x_2	x_3	x_4	x_5	y_1	y_2	y_3	y_4
F-15	30	30	10	15	8	17.04	80.46	89.27	89.27
F-16	50	30	10	15	12	12.93	73.90	92.14	92.14
F-17	20	20	10	10	10	6.98	55.12	85.02	89.03
F-18	60	20	10	10	10	1.35	45.34	78.34	79.89
F-19	40	0	10	10	10	4.82	55.74	79.16	81.78
F-20	40	40	10	10	10	9.30	63.71	92.21	92.21
F-21	40	20	0	10	10	6.78	64.27	84.58	84.58
F-22	40	20	20	10	10	6.14	46.91	73.12	80.10
F-23	40	20	10	0	10	2.93	36.87	67.30	77.81
F-24	40	20	10	20	10	17.40	77.31	89.69	90.86
F-25	40	20	10	10	6	15.91	83.29	91.77	91.77
F-26	40	20	10	10	14	2.72	44.54	76.83	85.57
F-27	40	20	10	10	10	7.44	62.76	90.16	91.01

x_1 = amount of polyethylene oxide (mg), x_2 = amount of CS-PAA complex (mg)

x_3 = amount of potassium chloride (mg), x_4 = amount of PEG 400 (mg)

x_5 = coating level (%)

y_1 = cumulative percent of drug release in 2 h

y_2 = cumulative percent of drug release in 6 h

y_3 = cumulative percent of drug release in 10 h

y_4 = cumulative percent of drug release in 12 h

Table 14 Experimental designs for PPOT (cont.)

	Variables					Response			
Formular	x_1	x_2	x_3	x_4	x_5	y_1	y_2	y_3	y_4
F-28	40	20	10	10	10	7.71	61.95	87.31	97.20
F-29	40	20	10	10	10	7.06	63.49	90.20	90.20
F-30	40	20	10	10	10	8.01	63.70	90.20	90.20
F-31	40	20	10	10	10	7.13	64.07	89.95	90.20
F-32	40	20	10	10	10	7.58	62.62	90.20	90.20

x_1 = amount of polyethylene oxide (mg),

x_2 = amount of CS-PAA complex (mg)

x_3 = amount of potassium chloride (mg),

x_4 = amount of PEG 400 (mg)

x_5 = coating level (%)

y_1 = cumulative percent of drug release in 2 h

y_2 = cumulative percent of drug release in 6 h

y_3 = cumulative percent of drug release in 10 h

y_4 = cumulative percent of drug release in 12 h

The hardness of all formulations were moderately high enough to carry through the coating process. It may be explained that chemical mainly used in formulation, i.e., polyethylene oxide, Avicel PH102, Starch 1500 were inherently compressible. Yang L, et al. reported that polyethylene oxide had good compressibility and consolidated predominately by plastic deformation and, however, produced relatively soft tablet (110). The hardness were somewhat affected with different amount of chemicals. Therefore, increase of PEO level in tablet composition decreased the hardness of tablet. It was suggested that polyethylene oxide need to be blend with highly compactible excipients in order to produce tablets on the high-speed production press. However, the hardness of the PPOP tablet was more complicate due to the influence of the second layer or polymer layer, which may impair the hardness of tablet wholly.

2.2.4 Friability The friability of all formulations were in the range of 0.06 to 0.38 % and were lower than the requirement in USP 28 that is 0.8% (Table 15). The results were accordant with the hardness of tablet. However, the PEO amount of drug layer had less negative influence on friability than the CS-PAA complex amount of push layer. This might be due to low compressibility of CS-PAA complex, compared to PEO. Therefore, the higher amount of CS-PAA complex resulted in the higher fine powder during the friability test owing to the lower particulate bonding in the polymer layer.

2.2.5 Drug content The results of drug content determinations are shown in Table 16. All formulations were acceptable to USP28 within the range of 90.0%-110% of label claim. The lowest and the highest values were found to be 94% and 101%, respectively. The standard deviation was small. It could be seen that the content could vary somewhat from formulation to formulation. Nevertheless, the result could be very well due to most values of drug content closing to 100%.

2.3 Drug release Based on central composite design, the 32 experimental runs were performed. This number is equal to 16 runs of 2^{5-1} fractional factorial design, 10 runs of axial points and the six replicated center points. Generally, factorial design demonstrates how the process parameters affect the response variable at the experimental border. To investigate the influences of these parameters inside the experimental domain, the axial design and center point has to be additionally employed. The results would illustrate the effect of the process parameters as a

Table 15. Weight variation, thickness, hardness, % friability of core tablets prepared in optimization study

Formulation	Weight variation mg (SD)	Thickness mm (SD)	Hardness kg (SD)	Friability %
F-1	150.30 (0.66)	3.92 (0.03)	4.13 (0.19)	0.12
F-2	152.85 (1.50)	3.95 (0.04)	3.10 (0.20)	0.12
F-3	155.05 (1.70)	3.99 (0.04)	4.17 (0.22)	0.18
F-4	151.95 (1.39)	3.91 (0.03)	4.49 (0.34)	0.27
F-5	152.50 (1.85)	3.89 (0.02)	3.24 (0.35)	0.27
F-6	151.80 (1.06)	3.90 (0.02)	3.25 (0.26)	0.21
F-7	154.85 (1.31)	3.93 (0.02)	3.98 (0.09)	0.27
F-8	152.00 (1.45)	3.89 (0.01)	4.06 (0.15)	0.29
F-9	154.50 (1.00)	3.95 (0.07)	4.20 (0.93)	0.06
F-10	152.70 (1.17)	3.89 (0.02)	4.14 (0.15)	0.06
F-11	153.55 (1.60)	3.94 (0.02)	3.87 (0.31)	0.24
F-12	153.10 (1.37)	3.92 (0.020	4.08 (0.18)	0.24
F-13	152.75 (1.16)	3.92 (0.02)	3.12 (0.20)	0.12
F-14	153.15 (1.310	3.90 (0.02)	3.83 (0.29)	0.15
F-15	153.40 (1.50)	3.94 (0.020	3.20 (0.28)	0.32

Table 15. Weight variation, thickness, hardness, % friability of core tablets prepared in optimization study. (cont.)

Formulation	Weight variation mg (SD)	Thickness mm (SD)	Hardness kg (SD)	Friability %
F-16	153.30 (1.62)	3.89 (0.03)	3.90 (0.23)	0.38
F-17	151.90 (1.37)	3.92 (0.03)	4.92 (0.19)	0.15
F-18	154.05 (1.39)	3.93 (0.03)	3.16 (0.21)	0.23
F-19	154.15 (1.32)	4.02 (0.02)	4.92 (0.19)	0.06
F-20	153.80 (1.50)	3.94 (0.02)	4.12 (0.19)	0.35
F-21	152.25 (1.48)	3.85 (0.03)	4.22 (0.15)	0.13
F-22	152.85 (1.46)	3.94 (0.03)	4.61 (0.32)	0.09
F-23	153.80 (0.89)	3.92 (0.02)	4.35 (0.31)	0.18
F-24	153.45 (1.79)	3.91 (0.02)	4.27 (0.30)	0.18
F-25	154.10 (1.48)	3.96 (0.02)	4.00 (0.09)	0.29
F-26	154.95 (1.20)	4.02 (0.02)	4.08 (0.15)	0.23
F-27	154.05 (1.33)	3.98 (0.02)	4.14 (0.28)	0.22
F-28	153.85 (1.45)	3.94 (0.03)	4.11 (0.20)	0.23
F-29	154.15 (1.31)	3.96 (0.02)	4.05 (0.18)	0.20
F-30	154.22 (0.42)	3.99 (0.04)	4.08 (0.31)	0.20
F-31	154.26 (0.48)	3.99 (0.03)	4.01 (0.18)	0.22
F-32	154.36 (1.06)	4.01 (0.02)	4.00 (0.11)	0.23

Table 16 Drug content of felodipine PPOP tablets in optimization study

Formulation	Drug content, % (SD)
F-1	98.28 (1.33)
F-2	100.72 (1.45)
F-3	97.85 (0.99)
F-4	100.73 (0.24)
F-5	98.29 (0.23)
F-6	100.73 (0.23)
F-7	97.55 (0.23)
F-8	100.73 (0.90)
F-9	97.18 (0.99)
F-10	101.12 (0.66)
F-11	97.18 (0.23)
F-12	101.12 (0.88)
F-13	97.18 (0.13)
F-14	101.12 (0.43)
F-15	97.12 (0.22)

Table 16 Drug content of felodipine PPOP tablets in optimization study (cont.)

Formulation	Drug content, % (SD)
F-16	101.12 (1.45)
F-17	99.74 (0.99)
F-18	95.82 (0.73)
F-19	100.55 (0.55)
F-20	99.63 (0.88)
F-21	99.63 (0.88)
F-22	99.63 (0.88)
F-23	97.60 (0.77)
F-24	97.66 (0.99)
F-25	97.66 (0.99)
F-26	97.66 (0.99)
F-27	99.61 (0.99)
F-28	99.61 (0.99)
F-29	99.61 (0.99)
F-30	99.61 (0.99)
F-31	99.61 (0.99)
F-32	99.61 (0.99)

curvature of the response surface profile. In this study, the independent and the dependent variables used in the design are shown in Table 14. The dissolution profiles obtained are shown in Figures 35-39. From these figures the response values from Y_1 to Y_4 were obtained. These values are shown in Table 14 and were analyzed by ANOVA using Minitab 15 program and determined the statistical significance of the main effects as well as the interaction effects ($p < 0.05$). Second order polynomial regression was selected for estimating the response variables based on the variance analysis. The form of polynomial equation is indicated below:

$$\begin{aligned} Y = {} & b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_6X_1^2 + b_7X_2^2 + b_8X_3^2 \\ & + b_9X_4^2 + b_{10}X_5^2 + b_{11}X_1X_2 + b_{12}X_1X_3 + b_{13}X_1X_4 + b_{14}X_1X_5 + b_{15}X_2X_3 \\ & + b_{16}X_2X_4 + b_{17}X_2X_5 + b_{18}X_3X_4 + b_{19}X_3X_5 + b_{20}X_4X_5 \end{aligned} \quad (32)$$

Where Y, response; b_0, intercept; b_i, regression coefficients; X_1, PEO; X_2, CS-PAA complex; X_3, KCl; X_4, PEG400; X_5, coating level; X_iX_j, interaction effect; X_i^2, curvature effect.

The polynomial equations for all response variables, i.e., Y_1, Y_2, Y_3, Y_4 are shown in Table 17. In these equations, the term with more than one factor combination and those with higher order represent interaction and quadratic relationships respectively. The values of X_1, X_2, X_3, X_4 and X_5 were substituted in the polynomial equation to calculate the theoretical values of response Y_1, Y_2, Y_3 and Y_4 . The theoretical (predicted) values and observed values were in close agreement as seen from Table 18-21. The significance of the ratio of mean square variation due to regression and residual error was tested using ANOVA. The ANOVA indicated a significant ($p < 0.05$) effect of factors on response (Fcal (5.91, 5.76, 5.97, 3.48) > Fcrit (2.65)).

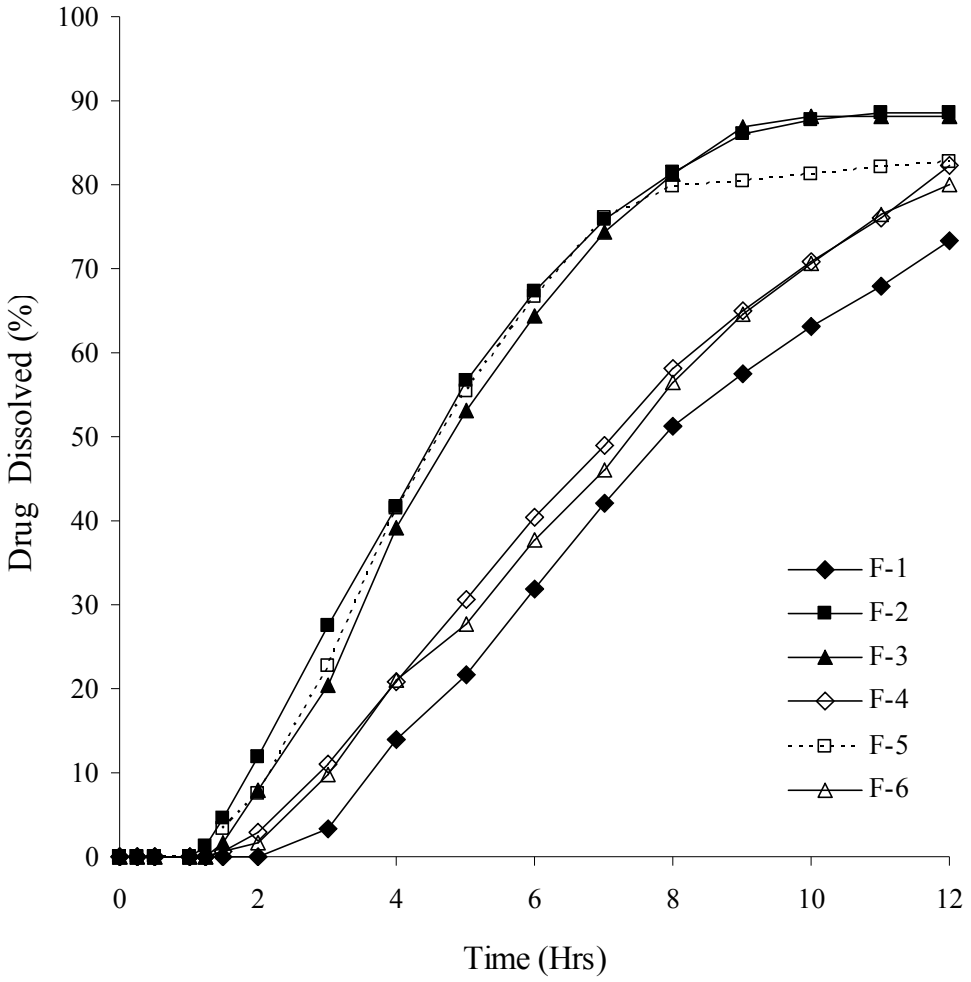


Figure 35. Dissolution profiles of felodipine PPOP tablets for formulations of F-1 – F-6

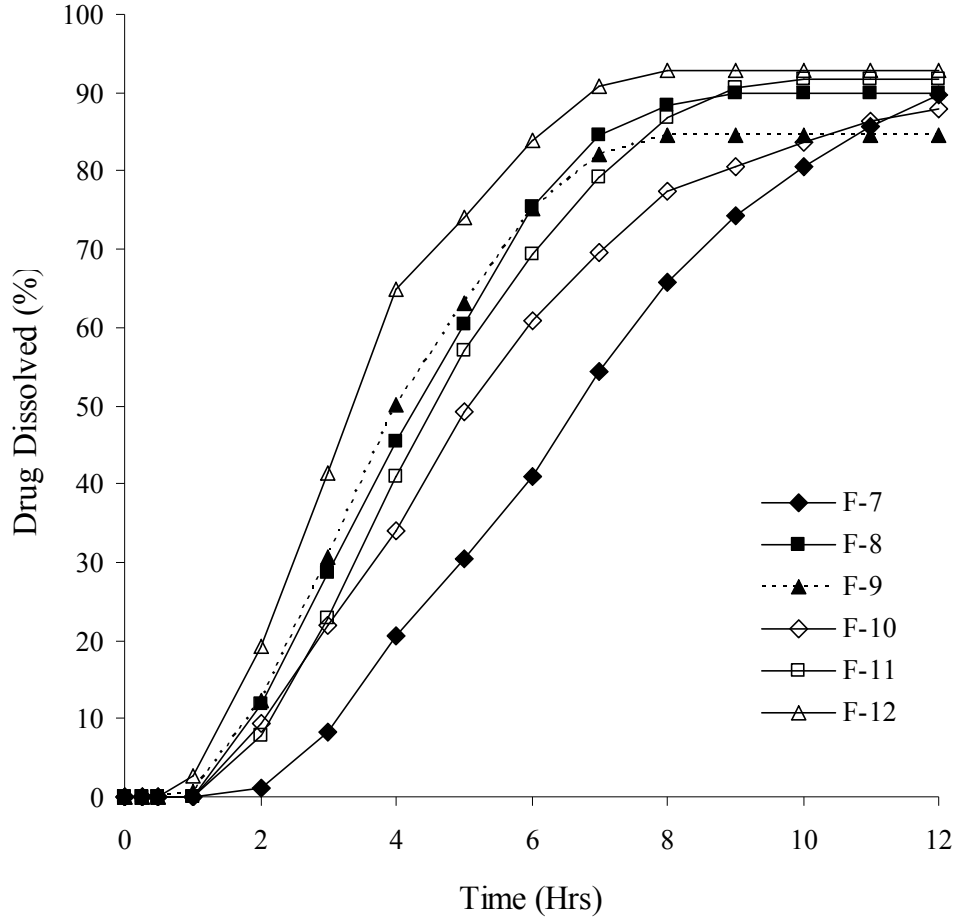


Figure 36. Dissolution profiles of felodipine PPOP tablets for formulations of F-7 – F-12

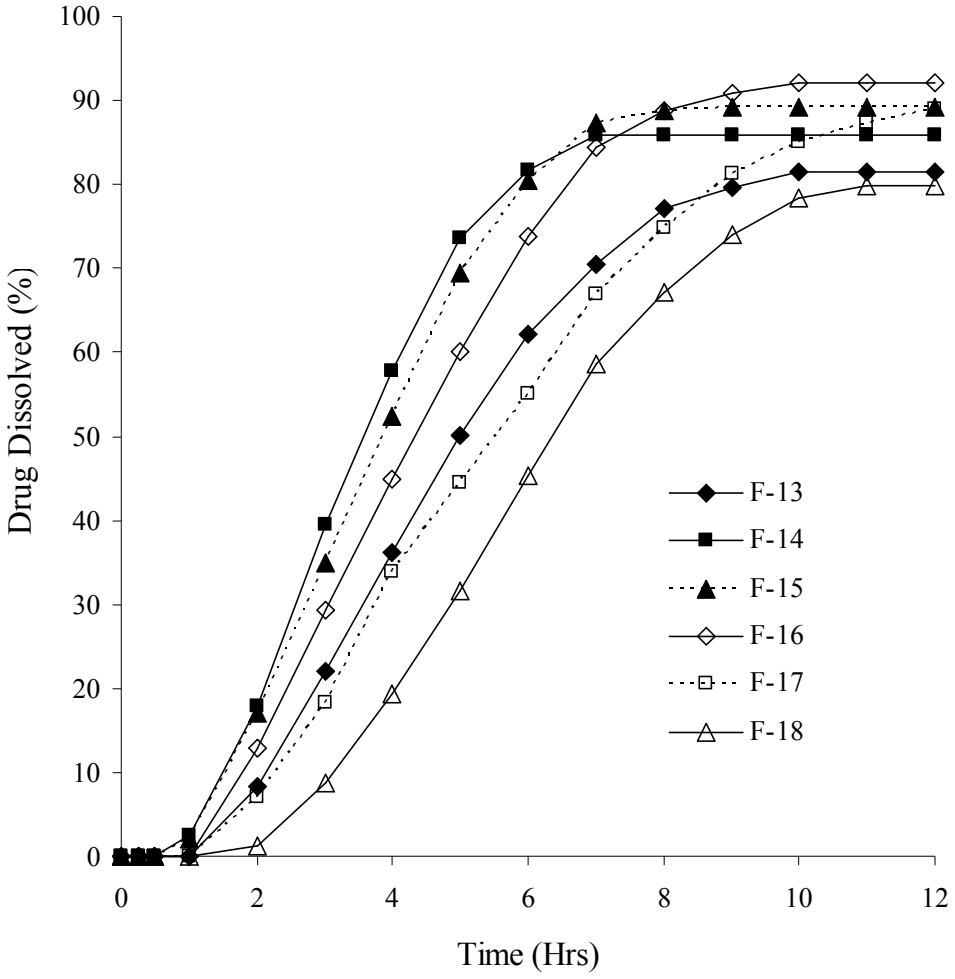


Figure 37. Dissolution profiles of felodipine PPOP tablets for formulations of F-13 – F-18

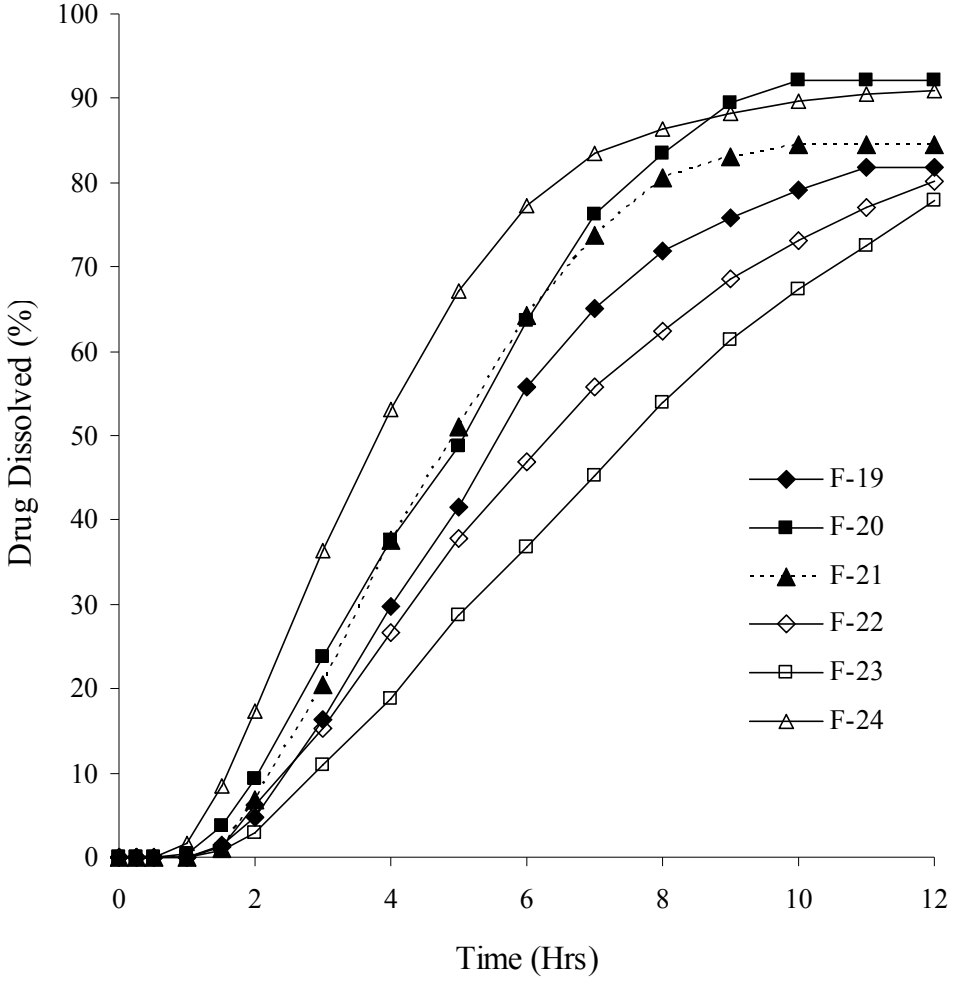


Figure 38. Dissolution profiles of felodipine PPOP tablets for formulations of F-19 – F-24

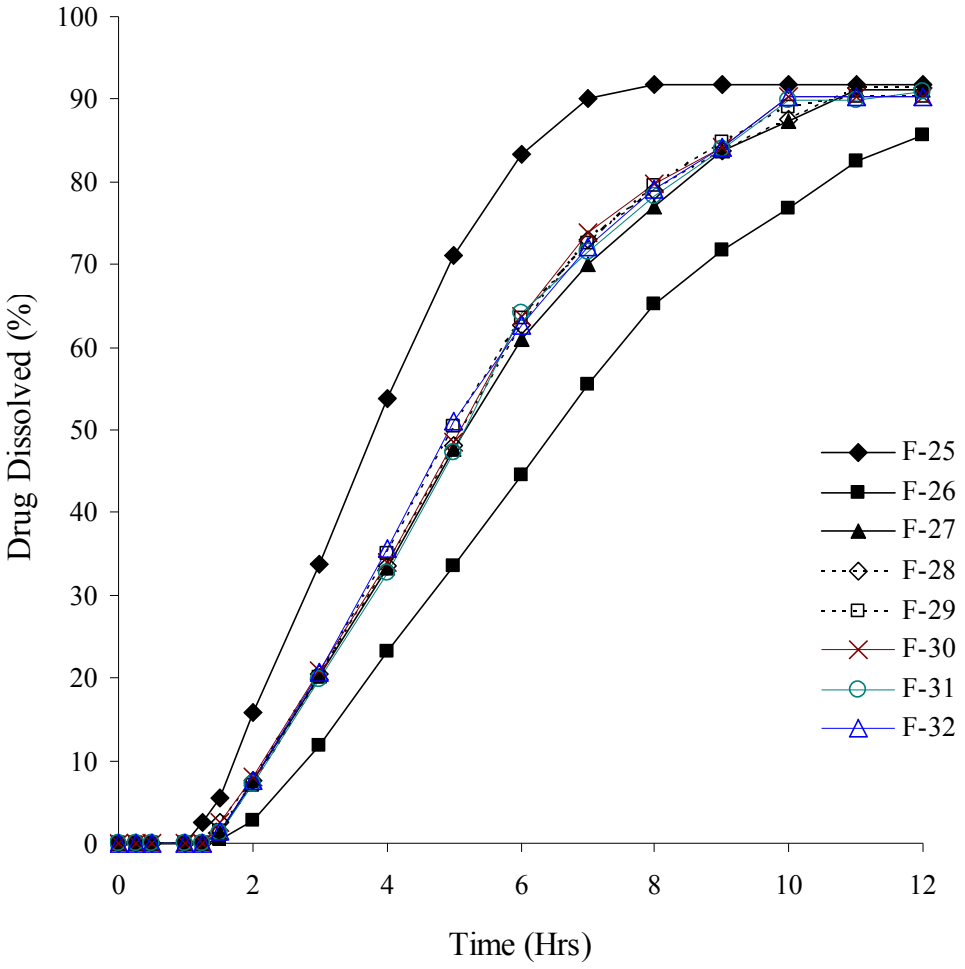


Figure 39. Dissolution profiles of felodipine PPOP tablets for formulations of F-25 – F-32

Table 17. Regression equations for the applied time constraints.

$$Y_1 = 30.064 + 0.677 X_1 - 0.0.099 X_2 - 0.171 X_3 - 0.867 X_4 - 5.434 X_5 - 0.005 X_1^2 + 0.002 X_2^2 + 0.004 X_3^2 + 0.041 X_4^2 + 0.203 X_5^2 - 0.006 X_1X_3 + 0.002 X_1X_4 - 0.02 X_1X_5 + 0.004 X_2X_3 + 0.008 X_2X_4 - 0.004 X_2X_5 + 0.020 X_3X_4 + 0.009 X_3X_5 + 0.034 X_4X_5$$

$$Y_2 = 139.480 + 1.817 X_1 - 0.828 X_2 + 0.366 X_3 - 1.990 X_4 - 16.855 X_5 - 0.019 X_1^2 + 0.005 X_2^2 - 0.024 X_3^2 + 0.006 X_4^2 + 0.391 X_5^2 + 0.004 X_1X_2 + 0.008 X_1X_3 - 0.005 X_1X_4 - 0.040 X_1X_5 + 0.013 X_2X_4 + 0.059 X_2X_5 - 0.019 X_3X_4 - 0.009 X_3X_5 + 0.425 X_4X_5$$

$$Y_3 = 68.672 + 1.745 X_1 + 0.384 X_2 + 0.401 X_3 - 0.712 X_4 - 2.915 X_5 - 0.014 X_1^2 - 0.004 X_2^2 - 0.082 X_3^2 - 0.009 X_4^2 - 0.175 X_5^2 - 0.013 X_1X_2 - 0.002 X_1X_3 + 0.002 X_1X_4 - 0.040 X_1X_5 + 0.011 X_2X_3 + 0.004 X_2X_4 + 0.048 X_2X_5 - 0.042 X_3X_4 + 0.139 X_3X_5 + 0.364 X_4X_5$$

$$Y_4 = 65.081 + 1.429 X_1 + 0.437 X_2 + 1.015 X_3 + 0.060 X_4 - 2.915 X_5 - 0.011 X_1^2 - 0.004 X_2^2 - 0.066 X_3^2 - 0.047 X_4^2 + 0.002 X_5^2 - 0.014 X_1X_2 - 0.011 X_1X_3 + 0.006 X_1X_4 - 0.020 X_1X_5 + 0.013 X_2X_3 + 0.046 X_2X_5 - 0.046 X_3X_4 + 0.090 X_3X_5 + 0.154 X_4X_5$$

The ANOVA results revealed that the process parameters significantly affected the response variables, i.e.,Y_1, Y_2, Y_3 and Y_4. These significant influences were notified in term of the estimated effect as summarized in Table 22. The magnituded and sign of estimated effect value can imply to the strength and the direction of that process parameter on the corresponding response variable. A positive sign indicates a positive effect whereas a negative sign refers to a negative effect.

From the estimated effects of response Y_4 and p-value shown in Table 22, it was found that the factor X_2, X_4 with positive estimated effect had significantly synergistic effect on response Y_4 ($p < 0.05$) while factor X_5 with negative estimated effect had significantly antagonistic effect on response Y_4 ($p < 0.05$). However, the influences of tablet formulation and membrane variables on felodipine release rate can be further explained by using response surface plots based on the model.

Figure 40 shows the effect of factors X_1, X_2 at mid-point of factor X_3, X_4, X_5. An increase in amount of polyethylene oxide (X_1) from 20 to 60 mg did not show profound effect on Y_4. At low amount of CS-PAA complex (X_2) when X_1 increased from 20 to 60 mg Y_4 increased from 72 to 85%. Conversely, at high amount of CS-PAA complex when X_2 increased from 20 to 60 mg Y_4 decreased from 95 to 85%. However, Figures 41-43 show effect of factor X_1 with X_3, X_4, and X_5 at mid-point of the rest of factors respectively. All results were agreed with the fact that the optimal amount of PEO had a positive effect on response Y_4 while increase amount of PEO higher than optimal value resulted in negative effect.

The observed results of dissolution profiles at the axial design (20, 40, 60 mg of PEO) as shown in Figure 44 were also agreed with those results of the response surface plot. It might be explained that the positive effect of PEO might be due to the presence of PEO in the upper layer, leading to generating the more hydrodynamic and osmotic pressure. On the other hand, the negative effect could be explained based on its physico-chemical character of Polyox®303 used as PEO in the study. This type of PEO was medium molecular weight and could swell after uptake water, forming a viscous gel in case high amount of this polymer used. This property of Polyox®303 may be responsible for the decrease in response Y_4.

Table 18. Observed and predicted values of response Y_1

Run	Observed	Predicted	Residuals
1	0.00	0.763	-0.763
2	11.95	10.34	1.61
3	7.97	8.63	-0.66
4	2.89	1.90	0.99
5	7.4	7.42	-0.02
6	1.77	0.14	1.63
7	1.07	1.71	-0.64
8	11.82	10.09	1.73
9	12.38	12.69	-0.31
10	9.36	8.02	1.34
11	7.86	8.79	0.93
12	19.22	17.78	1.44
13	8.38	8.66	-0.28
14	17.87	15.78	2.09
15	17.04	17.22	-0.18
16	12.93	11.46	1.47
17	6.98	4.02	2.96
18	1.35	6.43	5.08
19	4.82	6.40	-1.58
20	9.30	9.85	-0.55
21	6.78	7.08	-0.30
22	6.14	7.97	-1.83
23	2.93	3.80	-0.87
24	17.4	18.66	-1.26

Table 18. Observed and predicted values of response Y_1 (cont.)

Run	Observed	Predicted	Residuals
25	15.91	17.69	-1.78
26	2.72	3.07	0.35
27	7.44	7.13	0.31
28	7.71	7.13	0.58
29	7.06	7.13	-0.07
30	8.01	7.13	0.88
31	7.13	7.13	0.00
32	7.58	7.13	0.45

ANOVA for Y_1

Source	DF	SS	MS	F	P
Regression	20	751.417	37.571		
Residual	11	69.938	6.358	5.91	0.002
Total	31	821.355			

$R^2 = 0.9149$ R^2 (adj) $= 0.7600$

Table 19. Observed and predicted values of response Y_2

Run	Observed	Predicted	Residuals
1	31.85	34.07	-2.22
2	67.36	65.73	1.63
3	64.36	65.08	-0.72
4	40.48	39.24	-1.24
5	66.7	63.88	2.81
6	37.69	32.92	4.77
7	40.93	38.51	2.42
8	75.41	69.14	6.27
9	75.08	76.32	-1.24
10	60.91	60.20	0.71
11	69.27	70.90	-1.63
12	83.85	81.64	2.21
13	62.16	60.26	1.90
14	81.69	75.94	5.75
15	80.46	77.06	3.40
16	73.9	68.55	5.34
17	55.12	53.40	1.72
18	45.34	55.22	9.88
19	55.74	58.71	-2.97
20	63.71	68.90	-5.19
21	64.27	60.18	4.09
22	46.19	58.45	-12.26
23	36.87	40.89	-4.02
24	77.31	81.46	-4.15

Table 19. Observed and predicted values of response Y_2 (cont.)

Run	Observed	Predicted	Residuals
25	83.29	89.26	-5.97
26	44.54	46.73	-2.19
27	62.76	61.74	1.02
28	61.95	61.74	0.21
29	63.49	61.74	1.75
30	63.7	61.74	1.96
31	64.07	61.74	2.33
32	62.62	61.74	0.88

ANOVA for Y_1

Source	DF	SS	MS	F	P
Regression	20	5895.36	294.77	5.76	0.002
Residual	11	563.37	51.22		
Total	31	6458.73			

R^2 = 0.9128 R^2 (adj) = 0.7542

Table 20. Observed and predicted values of response Y_3

Run	Observed	Predicted	Residuals
1	63.14	63.96	-0.82
2	87.74	86.62	1.12
3	88.12	88.49	-0.37
4	85.94	83.40	2.54
5	81.20	79.52	1.68
6	70.65	67.51	3.14
7	80.52	78.87	1.65
8	90.04	86.45	3.59
9	84.62	86.04	-1.42
10	83.73	83.69	0.04
11	91.68	93.13	-1.45
12	92.86	92.37	0.49
13	81.40	80.80	0.60
14	85.94	83.40	2.54
15	89.27	88.22	1.05
16	92.20	89.69	2.51
17	85.02	83.55	1.47
18	78.34	83.67	5.33
19	79.16	80.68	-1.52
20	92.20	94.55	-2.35
21	84.58	81.99	2.59
22	73.12	79.58	-6.46
23	67.30	70.91	-3.61
24	89.69	89.94	-2.53

Table 20. Observed and predicted values of response Y_3 (cont.)

Run	Observed	Predicted	Residuals
25	91.77	94.19	-2.42
26	76.83	78.27	-1.44
27	90.16	89.03	1.03
28	87.31	89.03	-1.72
29	90.20	89.03	1.17
30	90.20	89.03	1.17
31	89.95	89.03	0.92
32	90.20	89.03	1.17

ANOVA for Y_3

Source	DF	SS	MS	F	P
Regression	20	1814.43	90.72	5.97	0.002
Residual	11	167.20	15.20		
Total	31	1981.63			

$R^2 = 0.9156$ R^2 (adj) $= 0.7622$

Table 21. Observed and predicted values of response Y_4

Run	Observed	Predicted	Residuals
1	73.38	74.06	-0.68
2	88.62	87.04	1.58
3	88.12	88.45	-0.33
4	82.28	80.25	2.03
5	82.8	82.70	0.10
6	80.06	77.61	2.46
7	89.75	89.20	0.55
8	90.04	87.23	2.81
9	84.62	86.24	-1.62
10	87.91	87.18	0.73
11	91.68	92.85	-1.17
12	92.86	91.77	1.09
13	81.40	82.15	-0.75
14	85.94	84.42	1.51
15	89.27	89.66	-0.39
16	92.20	90.23	1.97
17	89.03	85.65	3.38
18	79.89	85.75	-5.86
19	81.78	82.20	-0.42
20	92.20	94.25	-2.05
21	84.58	84.16	0.42
22	80.10	83.00	-2.90
23	77.81	80.83	-3.02
24	90.86	90.32	0.54

Table 21. Observed and predicted values of response Y_4 (cont.)

Run	Observed	Predicted	Residuals
25	91.77	92.91	-1.14
26	85.57	86.91	-1.34
27	91.01	90.22	0.79
28	91,20	90.22	0.98
29	90.20	90.22	-0.02
30	90.20	90.22	-0.02
31	91.01	90.22	0.79
32	90.20	90.22	-0.02

ANOVA for Y_4

Source	DF	SS	MS	F	P
Regression	20	680.301	34.015	3.48	0.019
Residual	11	408.976	81.795		
Total	31	787.781			

$R^2 = 0.8636$ R^2 (adj) $= 0.6155$

Table 22. Estimated effects and p-values

	Estimated effects (p-value)			
	Y_1	Y_2	Y_3	Y_4
Intercept	7.134(0.000)	61.738(0.000)	89.026(0.000)	90.224(0.000)
Main effect				
PEO (X_1)	1.204(0.267)	0.910(0.761)	0.060(0.971)	0.050(0.969)
CS-PAA (X_2)	1.721(0.123)	5.097(0.109)	6.935(0.001)	6.026(0.001)
KCl ((X_3)	0.448(0.672)	-0.865(0.773)	-1.205(0.465)	-0.580(0.658)
PEG 400 (X_4)	7.425(0.000)	20.285(0.000)	9.517(0.000)	4.744(0.003)
Coating (X_5)	-7.314(0.000)	-21.268(0.000)	-7.956(0.000)	-3.000(0.038)
Interaction effect				
PEO - CS-PAA (X_1X_2)	0.032(0.990)	1.690(0.818)	-5.330(0.199)	-5.442(0.110)
PEO - KCl (X_1X_3)	-1.178(0.650)	1.600(0.827)	-0.330(0.940)	-2.212(0.494)
PEO - PEG (X_1X_4)	0.432(0.867)	-0.930(0.899)	0.360(0.928)	1.248(0.697)
PEO - Coating (X_1X_5)	-1.608(0.537)	-3.235(0.660)	-3.165(0.434)	-1.602(0.618)
CS-PAA - KCl (X_2X_3)	0.798(0.758)	-0.075(0.992)	2.135(0.595)	2.662(0.413)
CS-PAA - PEG (X_2X_4)	1.608(0.537)	2.515(0.732)	0.875(0.827)	0.202(0.950)
CS-PAA - Coating (X_2X_5)	-0.302(0.907)	4.680(0.527)	3.890(0.340)	3.712(0.260)
KCl - PEG (X_3X_4)	2.038(0.436)	-1.895(0.796)	-4.155(0.309)	-4.628(0.167)
KCl - Coating (X_3X_5)	0.358(0.890)	-0.360(0.961)	5.560(0.182)	3.582(0.276)
PEG - Coating (X_4X_5)	1.358(0.601)	17.010(0.037)	14.560(0.003)	6.152(0.075)
Curvature effect				
PEO^2 (X_1^2)	-1.905(0.328)	-7.426(0.188)	-5.416(0.087)	-4.527(0.076)
CS-PAA ^{2} (X^2)	0.990(0.606)	2.069(0.703)	-1.415(0.633)	-2.000(0.406)
KCl^2 ((X_3^2)	0.390(0.838)	-2.426(0.655)	-8.246(0.015)	-6.647(0.015)
$PEG\ 400^2$ (X_4^2)	4.095(0.050)	-0.566(0.917)	-8.600(0.012)	-4.652(0.069)
Coating $level^2$ (X_5^2)	3.245(0.109)	6.259(0.261)	-2.796(0.352)	-0.317(0.893)

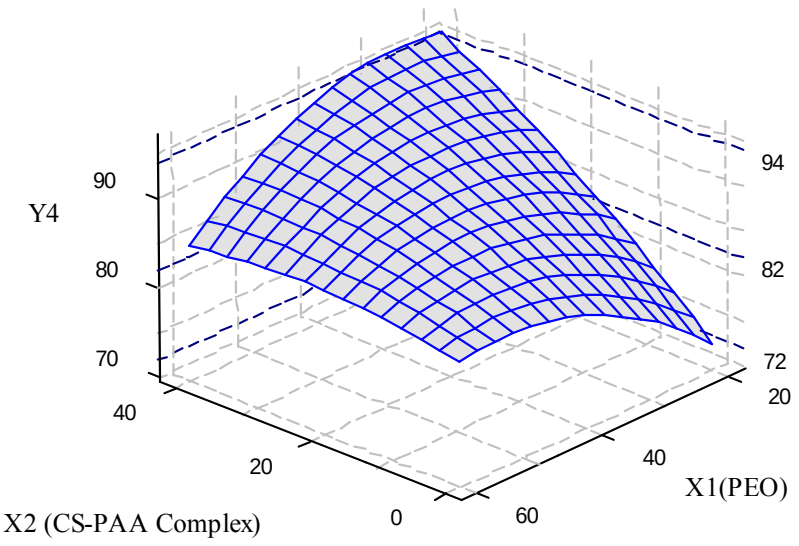


Figure 40. Response surface plot showing the effect of polyethylene oxide amount (X_1) and CS-PAA complex amount (X_2) on the cumulative percent felodipine dissolved in 12 h (Y_4).

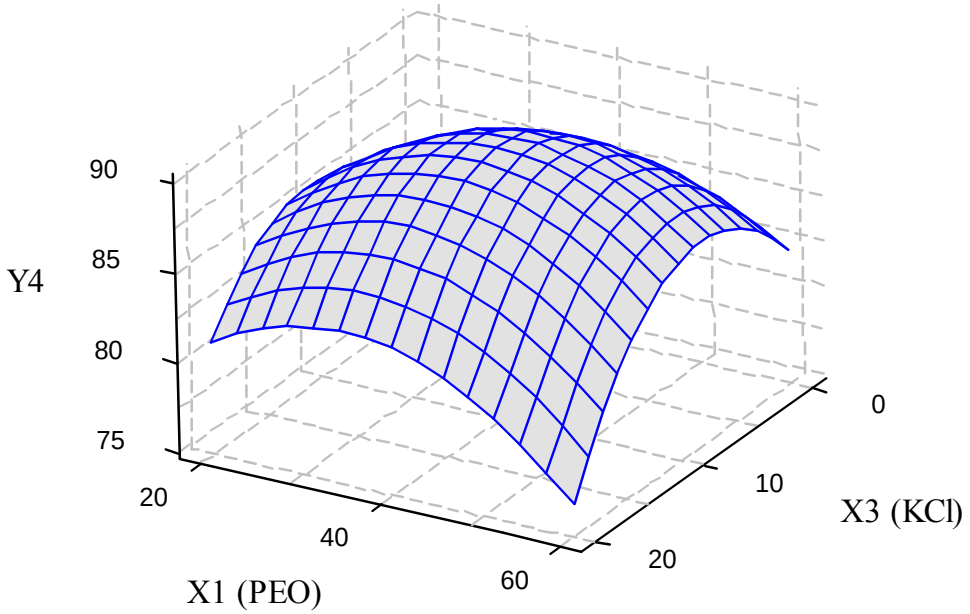


Figure 41. Response surface plot showing the effect of polyethylene oxide amount (X_1) and KCl amount (X_3) on the cumulative percent felodipine dissolved in 12 h (Y_4).

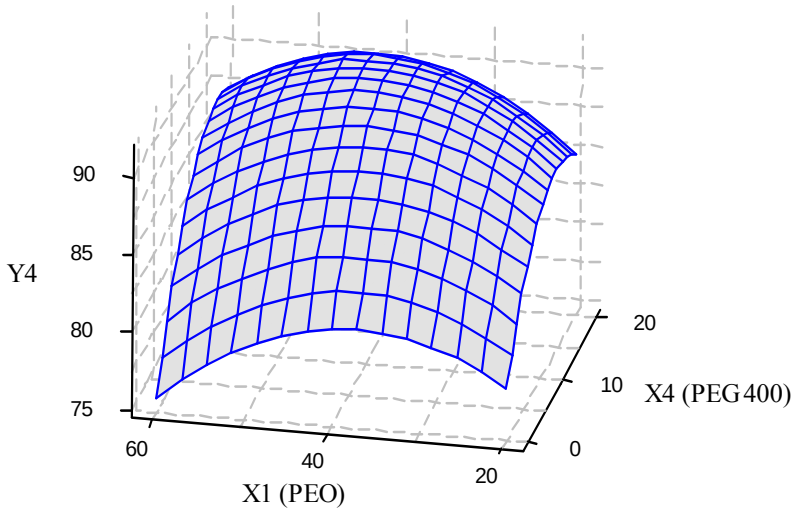


Figure 42. Response surface plot showing the effect of polyethylene oxide amount (X_1) and PEG 400 amount (X_4) on the cumulative percent felodipine dissolved in 12 h (Y_4).

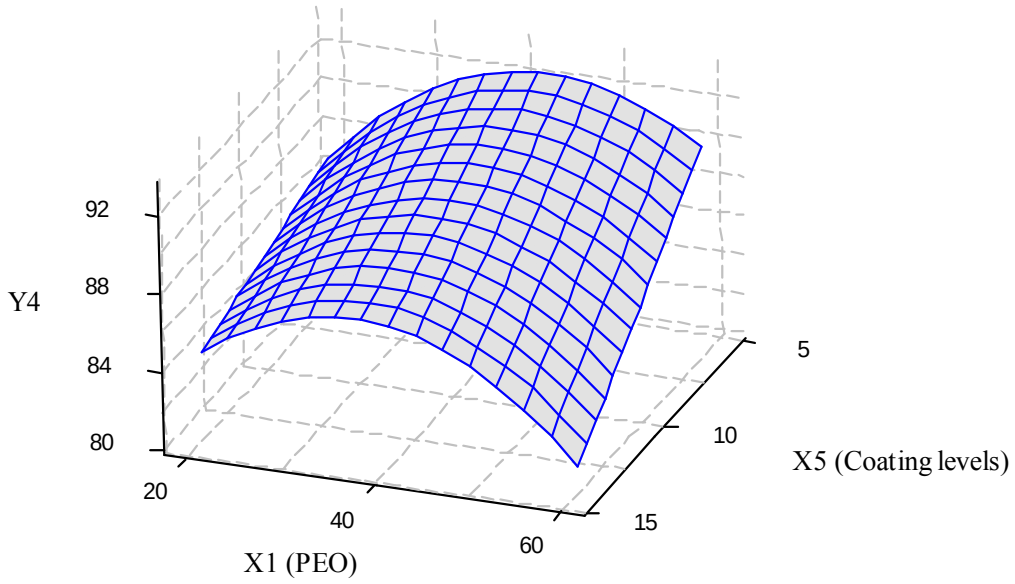


Figure 43. Response surface plot showing the effect of polyethylene oxide amount(X_1) and coating levels (X_5) on the cumulative percent felodipine dissolved in 12 h (Y_4)

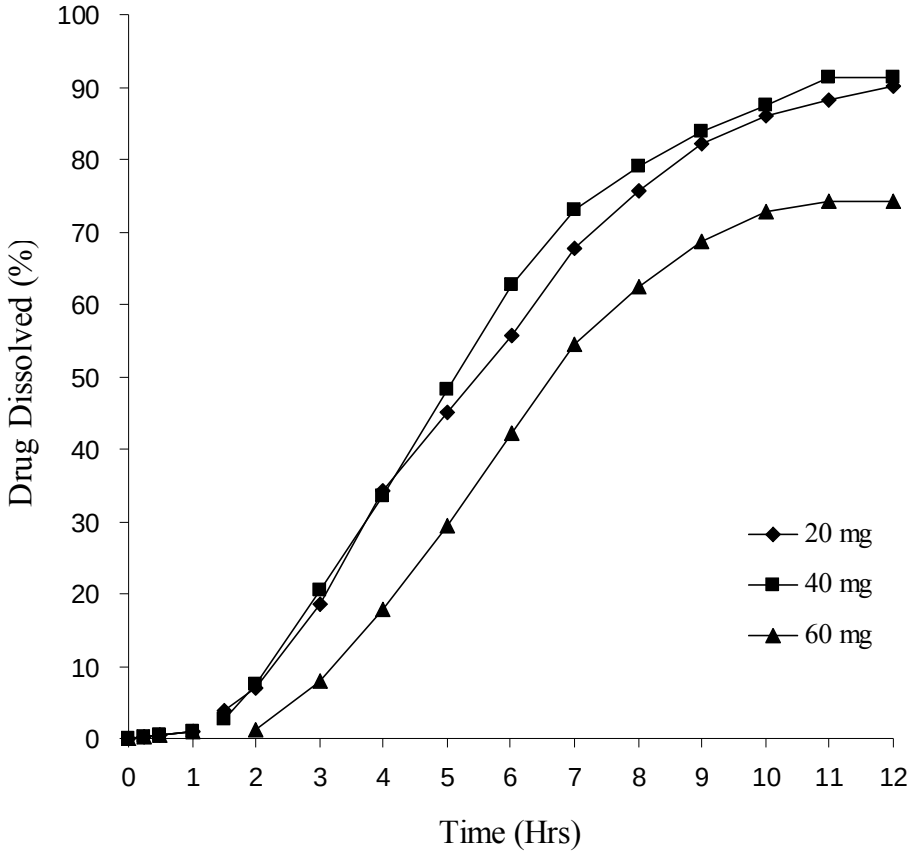


Figure 44. Effect of amount of polyethylene oxide on drug release of felodipine PPOT at midpoint of CS-PAA complex (20 mg), KCl (10 mg), PEG 400 (10%), coating level (10%)

Effect of factor X_2 and X_3 at mid-point of factor X_1, X_4, X_5 are shown in Figure 45. It can be observed from this figure that an increase in X_2 level has resulted in substantial increase in response Y_4. It could be ascribed to the fact that the increase of CS-PAA complex of push layer increased the expansion of push layer to force the drug suspension release. This behavior is true at both low and high level of X_3. The observed results of dissolution profiles at the axial design (0, 20, 40 mg of CS-PAA complex) as shown in Figure 46 were also agreed with those results of the response surface plot. As seen in Figure 45 at high level of X_3, Y_4 increased from 72 to 88%, when X_2 increased from 0 to 40 mg. The increase in Y_4 was 16%. At low levels of X_3, Y_4 increased from 78 to 83%, when X_2 increased from 0 to 40 mg. The increase in Y_4 was 5%. It can be notified that at high amount of KCl the release of felodipine was higher increase as compared with the drug release at low amount of KCl when the amount of CS-PAA complex increased from 0 to 40 mg. It might be due to the collapse in the network structure of CS-PAA complex with the presence of high amount of KCl (10), leading to the smaller expansion of the complex and the drug release decreased, especially at low amount of CS-PAA complex. The increase in amount of CS-PAA complex could compensate the effect of KCl by increasing the expandable hydrogel, resulting in the rising of drug release dramatically. Comparing to the drug release at low amount of KCl, the initial drug release was higher due to no negative effect of KCl. Therefore the release of felodipine was lower increase when the amount of CS-PAA complex increased from 0 to 40 mg.

Figure 40, 47, 48 also show effect of factor X_2 with X_1,X_4, X_5 at mid-point of the rest of factors respectively. All results were agreed with the fact that the increase in amount of CS-PAA complex results in a positive effect on response Y_4. There was no significant interaction effect between X_2 with X_1, X_3, X_4, X_5.

The influence of X_3 amount of push layer at mid-point of factor X_1, X_2, X_5 on response Y_4 was also shown with X_4 in Figure 49. It was observed that, at high amount of plasticizer (X_4), Y_4 gradually increased from 88 to 90% as factor X_3 increased from 0 to 10 mg ,then Y_4 decreased from 90 to 75% with the increase in factor X_3 from 10 mg to 20 mg. Additionally, at low amount of plasticizer (X_4) Y_4 increased from 72 to 80% as factor X_3 increased from 0 to 15 mg, then Y_4 decreased a little from 80 to 77% with the increase in factor X_3 from 15 to 20 mg. It might be explained that

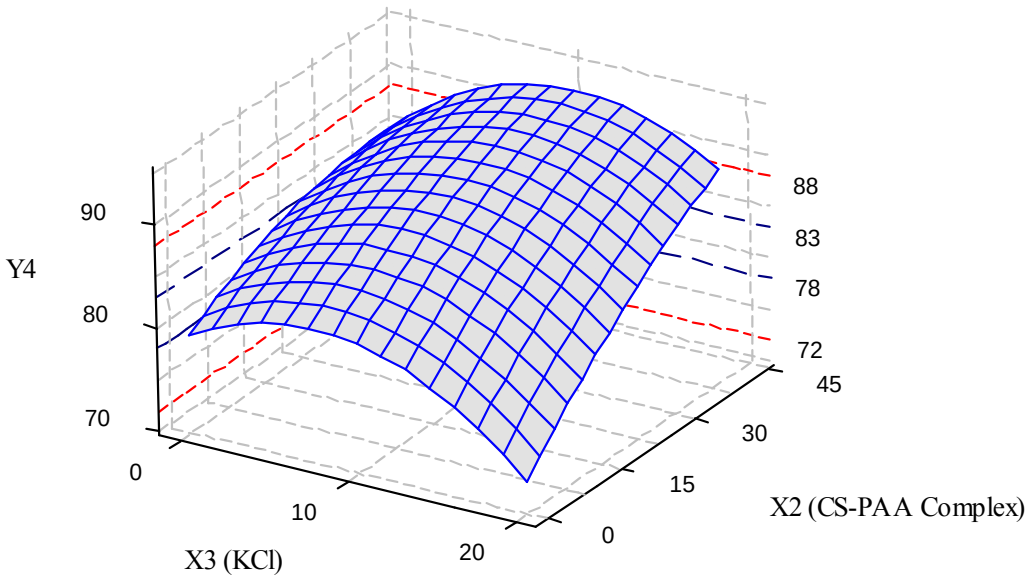


Figure 45. Response surface plot showing the effect of CS-PAA complex amount (X_2) and of KCl amount (X_3) on the cumulative percent felodipine dissolved in 12 h (Y_4).

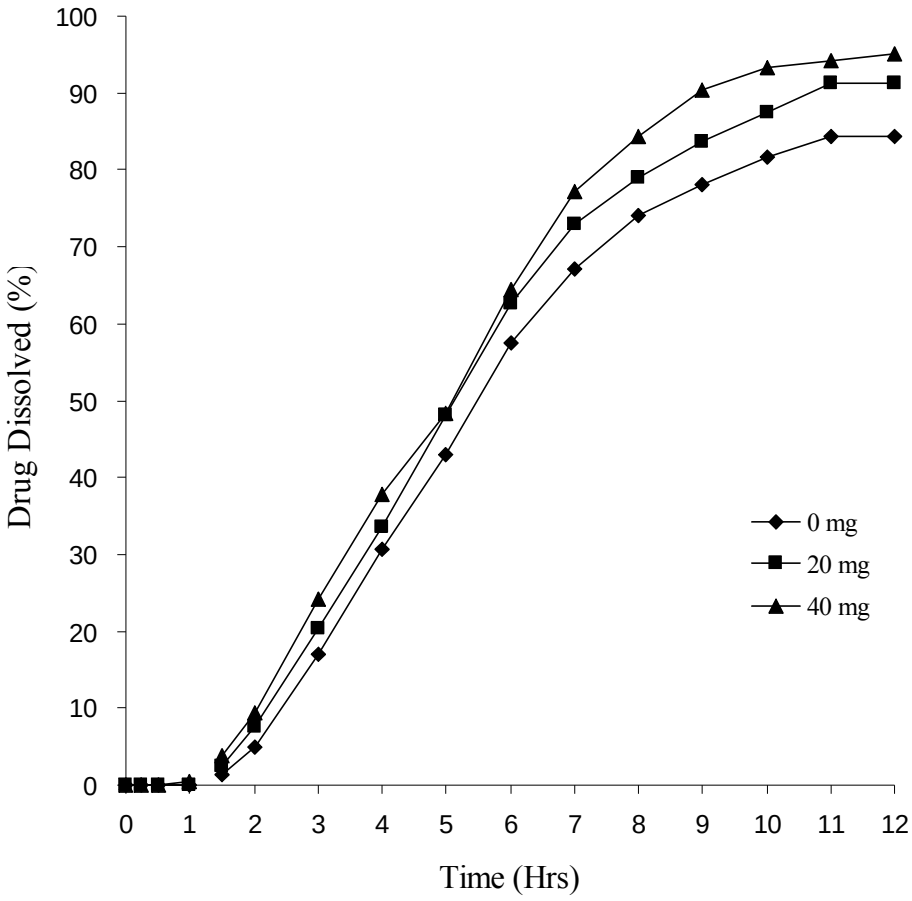


Figure 46. Effect of amount of CS-PAA complex on drug release of felodipine PPOT at midpoint of PEO(40 mg), KCl (10mg), PEG 400(10%), coating level (10%)

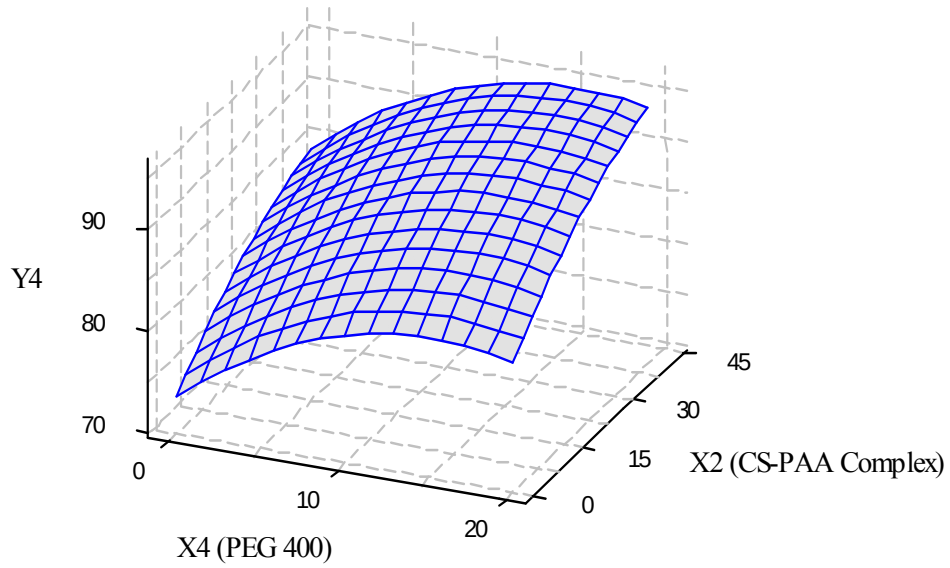


Figure 47. Response surface plot showing the effect of CS-PAA complex amount (X_2) and PEG 400 amount (X_4) on the cumulative percent felodipine dissolved in 12 h (Y_4).

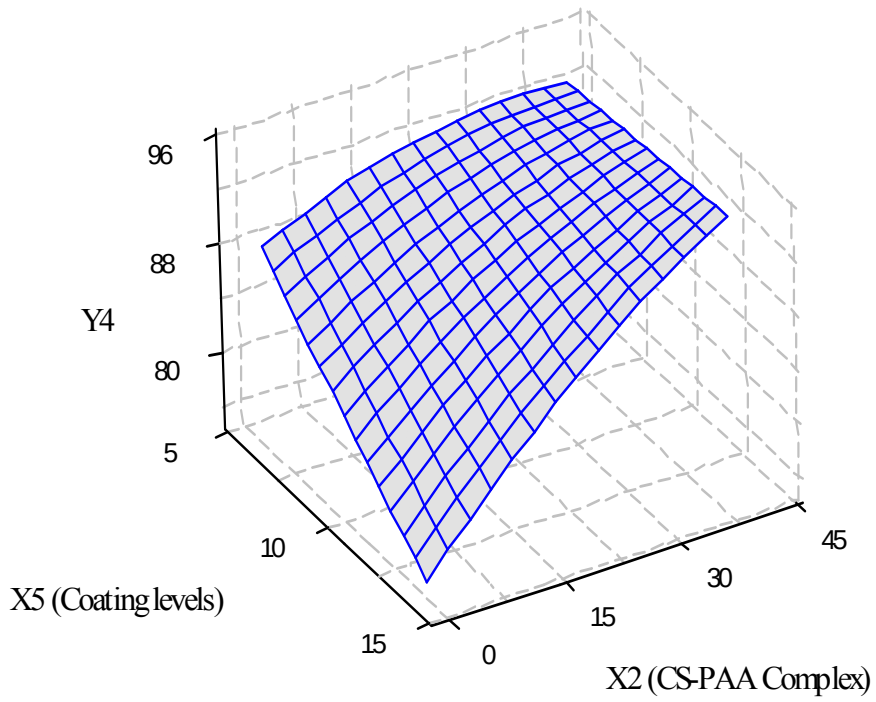


Figure 48. Response surface plot showing the effect of CS-PAA complex amount (X_2) and coating level (X_5) on the cumulative percent felodipine dissolved in 12 h (Y_4).

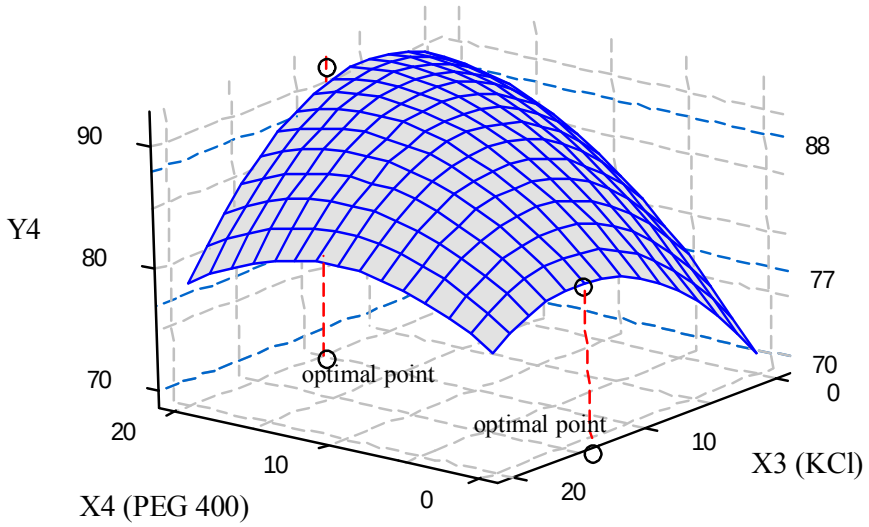


Figure 49. Response surface plot showing the effect of KCl amount (X_3) and PEG 400 amount (X_4) on the cumulative percent felodipine dissolved in 12 h(Y_4).

the optimal amount of KCl had a positive effect on response Y_4 while increase amount of KCl higher than optimal value resulted in negative effect. The positive effect of KCl might be due to the function of KCl as osmotic agent, which could induce the osmotic gradient across the membrane after dissolved by penetrated water. Then, the osmotic pressure differences played the role of engine to imbibe water from environment continuously. Consequently, higher release could be obtained in the case of higher amount of KCl. Surprisingly, the results was not agreed as anticipation when X_3 increased from 10 mg to 20 mg. It could be explained based on the lower expansion of CS-PAA complex with the presence of high amount of KCl. PM de la Torre, et al. reported that increasing ionic strength would cause a greater collapse in the structure of the network, therefore erosion was quick and extensive, resulting in the decrease of swelling. In the case of this study, the increase in amount of KCl resulted in the increase in ionic strength of in situ solution within push layer formed by penetrated water.

Figure 41, 45, 50 also shows effect of factor X_3 with X_1,X_2 ,X_5 at mid-point of the rest of factors respectively. All results were agreed with the fact that the optimal amount of KCl had a positive effect on response Y_4 while increase amount of KCl higher than optimal value resulted in negative effect. There was no significant interaction effect between X_3 with X_1, X_2, X_4 ,X_5. Additionally, the observed results of dissolution profiles at the axial design (0, 10, 20 mg of KCl) as shown in Figure 51 were also agreed with those results of the response surface plot.

The effect of amount of plasticizer (X_4) at mid-point of factor X_1, X_3, X_5 on response Y_4 was shown with X_5 in Figure 52. It was found that an increase in X_4 level has resulted in substantial increase in response Y_4 at high amount of X_5. However, at low amount of X_5, Y_4 gradually increased from 89 to 92% as factor X_5 increased from 0 to 7 %, then Y_4 gradually decreased from 92 to 86% with the increase in factor X_4 from 7 to 20 %. In general, coating with high PEG 400, soluble plasticizer, released drug more rapidly compared to coating with low PEG 400 consistent with increasing water permeability of membrane as hydrophilic PEG 400 easily leached from the membrane and left behind a porous structure and thereby increased permeability of the membrane. This could be attributed to effect of plasticizer (X_4) at high amount of X_5,

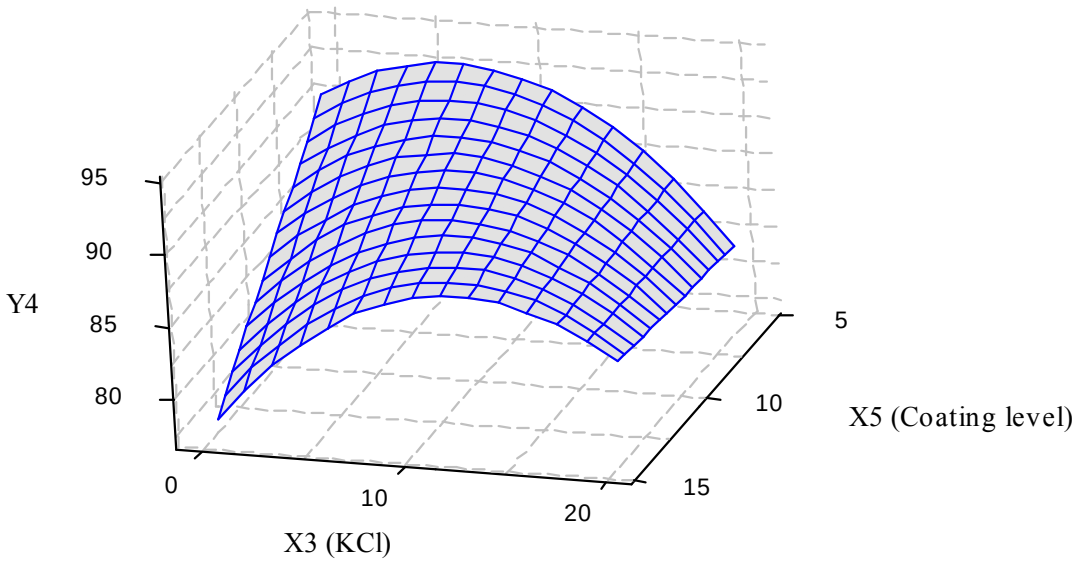


Figure 50. Response surface plot showing the effect of KCl amount (X_3) and coating levels (X_5) on the cumulative percent felodipine dissolved in 12 h (Y_4).

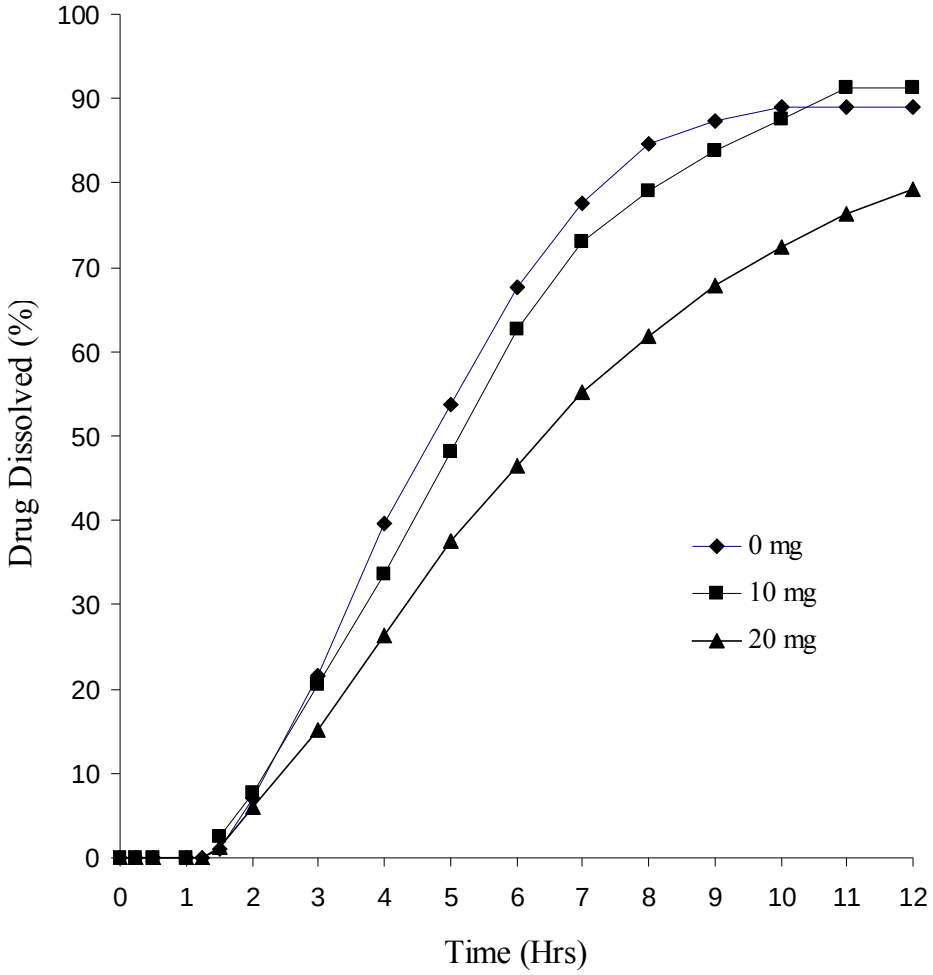


Figure 51. Effect of amount of KCl on drug release of felodipine PPOT at midpoint of PEO(40 mg), CS-PAA complex (20 mg), PEG 400(10%), coating level(10%)

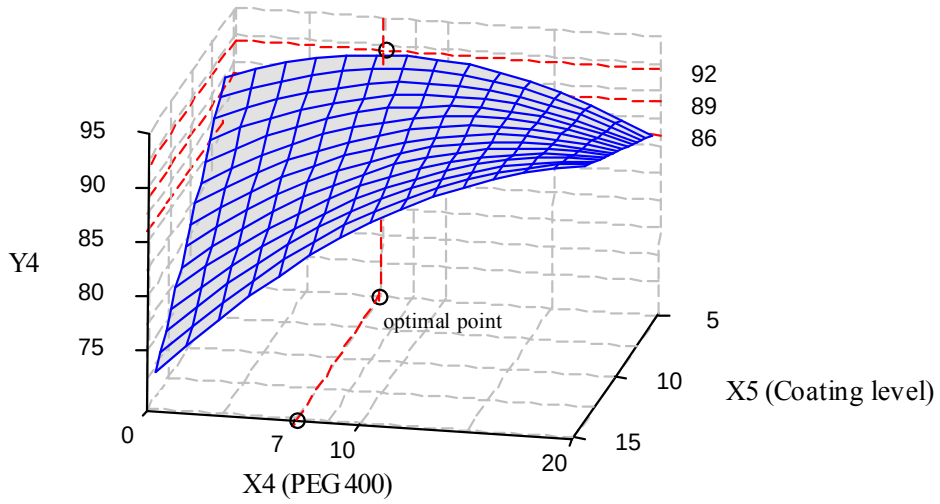


Figure 52. Response surface plot showing the effect of PEG 400 amount (X_4) and coating level (X_5) on the cumulative percent felodipine dissolved in 12 h (Y_4).

however the result at low amount of X_5 seemed to be different as Y_4 gradually decreased with the increase in factor X_4 from 7 to 20 %. It could be explained that at low coating level the thickness of the membrane is minimal, and with high amount of plasticizer the flexibility of the membrane was maximal. Therefore, the coating membrane expanded because of high osmotic pressure, resulting in a net decrease in driving force. This resulted in less amount of drug delivery from the orifice. On the contrary, at high coating level the increased membrane thickness withstood the osmotic pressure buildup, resulting in an increased output of the drug. However, comparison of the effect of factors X_4, X_5 on response Y_1 and response Y_4 gave a different result as seen in Figure 53. It indicated that an increase in X_4 level has resulted in an increase in response Y_1 at both low and high level of X_5. This might be due to the good physical integrity of membrane after the dissolution test at 2 hours, resulting in no change in mechanical strength at low coating level and high amount of plasticizer as profoundly affected the response Y_4. Similarly, the observed results of dissolution profiles at the axial design (0, 10, 20% w/w of PEG 400) as shown in Figure 54 were also agreed with that of the response Y_1 in the response surface plot.

The effect of amount of coating (X_5) and plasticizer (X_4) at mid-point of factor X_1, X_2, X_3 on response Y_4 was also shown in Figure 52. The factor X_5 adversely affected the drug release compared to the factor X_4. It could be explained that the drug release was directly to the rate of water enter, which was dependent on the permeability of the coating. Changing the coating thickness could alter the permeability of coating in the contrary manner as compared to amount of plasticizer. In general, the thicker coating had lower permeability but the higher amount of plasticizer had higher permeability. This effect is consistent to the observed results of dissolution profiles at the axial design (6, 10, 14% w/w of coating level) as shown in Figure 55. It was found that an increase in X_5 level has resulted in substantial decrease in drug release of PPOP tablets at midpoint; i.e., PEO of 40 mg, CS-PAA complex of 20 mg, KCl of 10 mg, PEG 400 of 10%.

2.4 Optimization of PPOT formulation The optimum formulation was selected based on the criteria of attaining the maximum value of Y_4 which could be obtained at constrained conditions of Y_1 to Y_3. The computerized optimization was used to obtain the level of X_1, X_2, X_3, X_4, X_5 from the mathematical models.

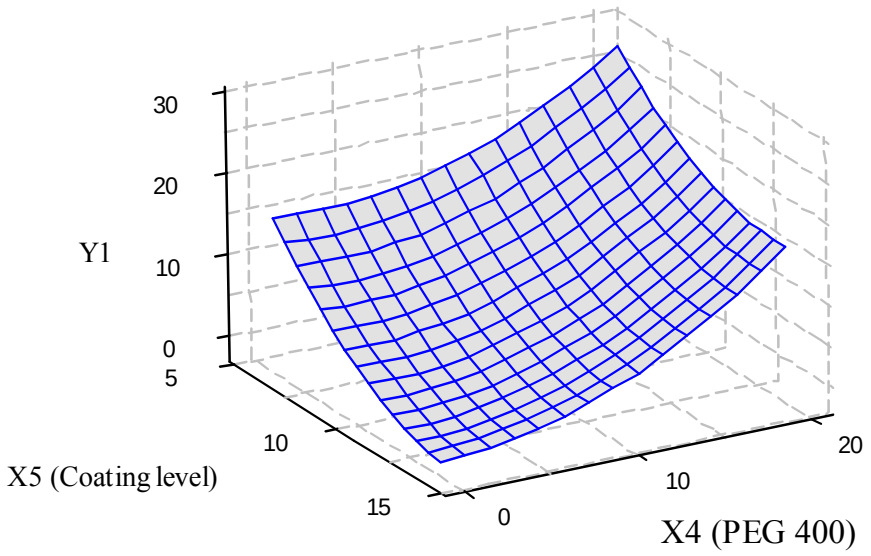


Figure 53. Response surface plot showing the effect of PEG 400 amount (X_4) and coating level (X_5) on the cumulative percent felodipine dissolved in 2 h (Y_1).

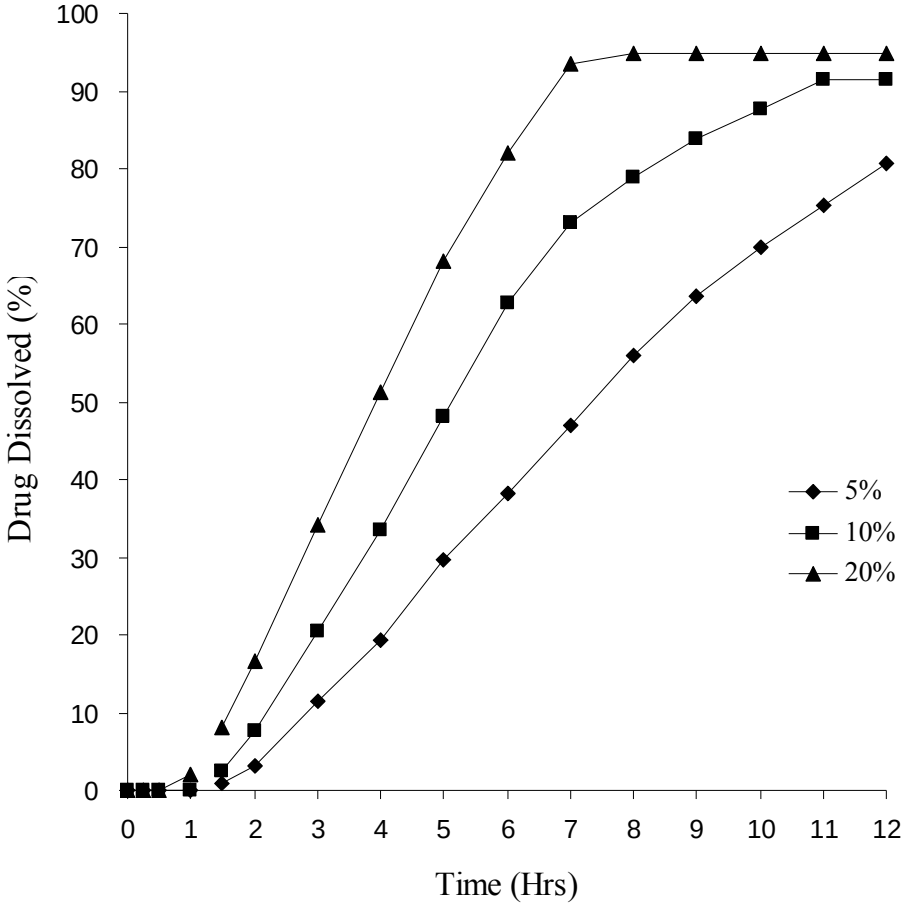


Figure 54. Effect of amount of PEG 400 on drug release of felodipine PPOT at midpoint of PEO(40 mg), CS-PAA complex (20 mg), KCl (10 mg), coating level (10%)

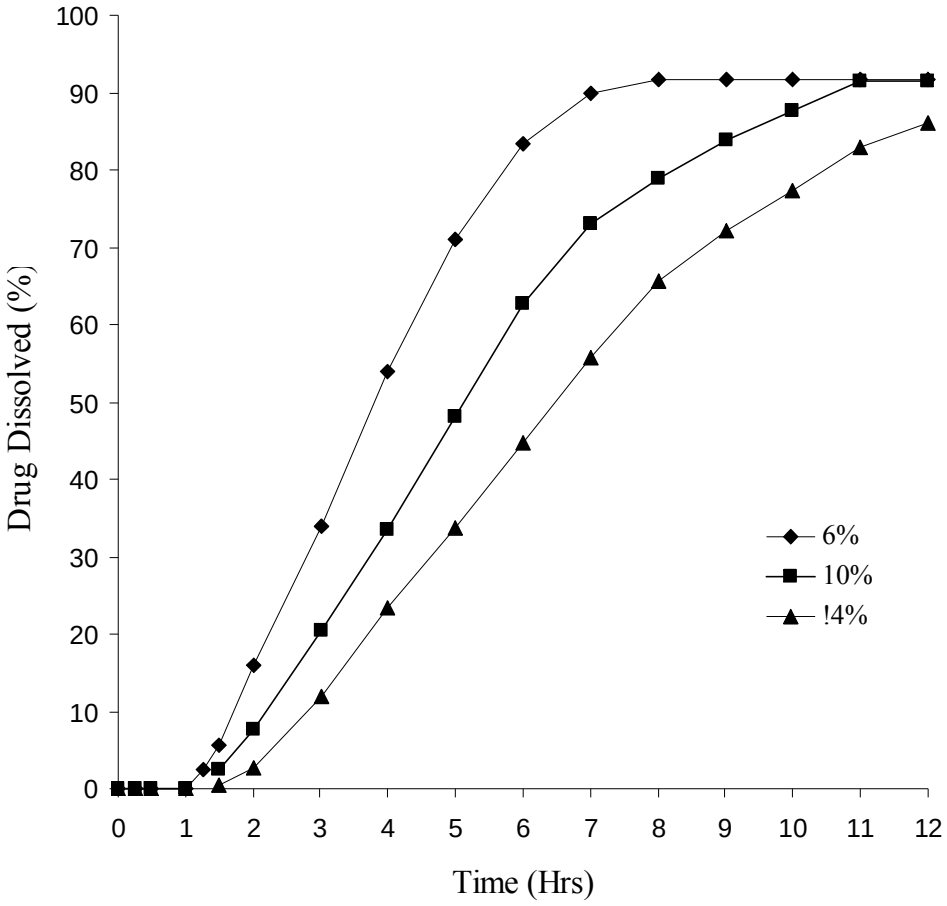


Figure 55. Effect of coating level on drug release of felodipine PPOT at midpoint of PEO(40 mg), CS-PAA complex (20 mg), KCl (10 mg), PEG 400 (10%)

The optimized formulation composition was achieved as follows: amount of PEO 50 mg, CS-PAA complex 15 mg, KCl 10 mg, PEG 400 15% (w/w) and coating weight gained 12% (w/w). An optimized formulation was prepared and yielded Y_1 to Y_4 which was in close agreement with predicted value as shown in Table 23. This proves the validity of model and ascertains the effect of amount of PEO, CS-PAA complex, KCl, PEG 400 and coating level on drug release of felodipine from osmotically controlled drug delivery systems. Additionally, the dissolution profile of the optimized formulation compared to the blank formulation using the same factor levels without CS-PAA complex is shown in Figure 56. The blank formulation lacks the potential to achieve drug release at constrained condition of Y_1.

2.5 Kinetics of drug release from PPOT Several mathematical models were used to explain release kinetics of felodipine from the various formulations of PPOT. By linear regression analyses, the coefficients of determinations were determined. As shown in Table 24, zero-order model could provide good coefficients of determination for most of the formulations in this study. However, there are some formulations of which the dissolution data were fitted well to Higuchi or first order model. It might be explained that the main mechanism of drug release was governed by osmotic mechanism in delivering drug to the outside of the PPOT. However, the drug existed as insoluble composition and the drug release may be concerned with the second mechanism such as erosion or diffusion, depending on the nature of the drug composition.

2.6 Water uptake of PPOT formulation According to mechanism of drug release from push-pull osmotically controlled release tablet, the important factor affecting rate of drug release is rate of water enter the tablet core. The water diffuses through the film coating, hydrating the core. The hydration of core causes the viscosity of drug-entraining polymer to decrease, and drug is extruded through the exit ports via hydrostatic pressure generated by expansion of the water-swellable composition. In this section the study of the hydration rate of PPOT was carried out.

The water uptake profiles for 27 PPOT formulations were shown in Fig. 57-63. These profiles show different change in amount of water enter the PPOT with time due to the effect of formulation variables, X_1, X_2, X_3, X_4, X_5. From the changes observed from water uptake profiles, it displayed the typical characteristics of these profiles

Table 23. Optimized values obtained by maximizing Y_4

Variable	Optimized level	Response	Expected values	Observed values
X_1	50 mg	Y_1	10.00	10.70
X_2	15 mg	Y_2	62.22	65.66
X_3	10 mg	Y_3	86.82	88.50
X_4	15% w/w	Y_4	88.76	90.43
X_5	12% w/w			

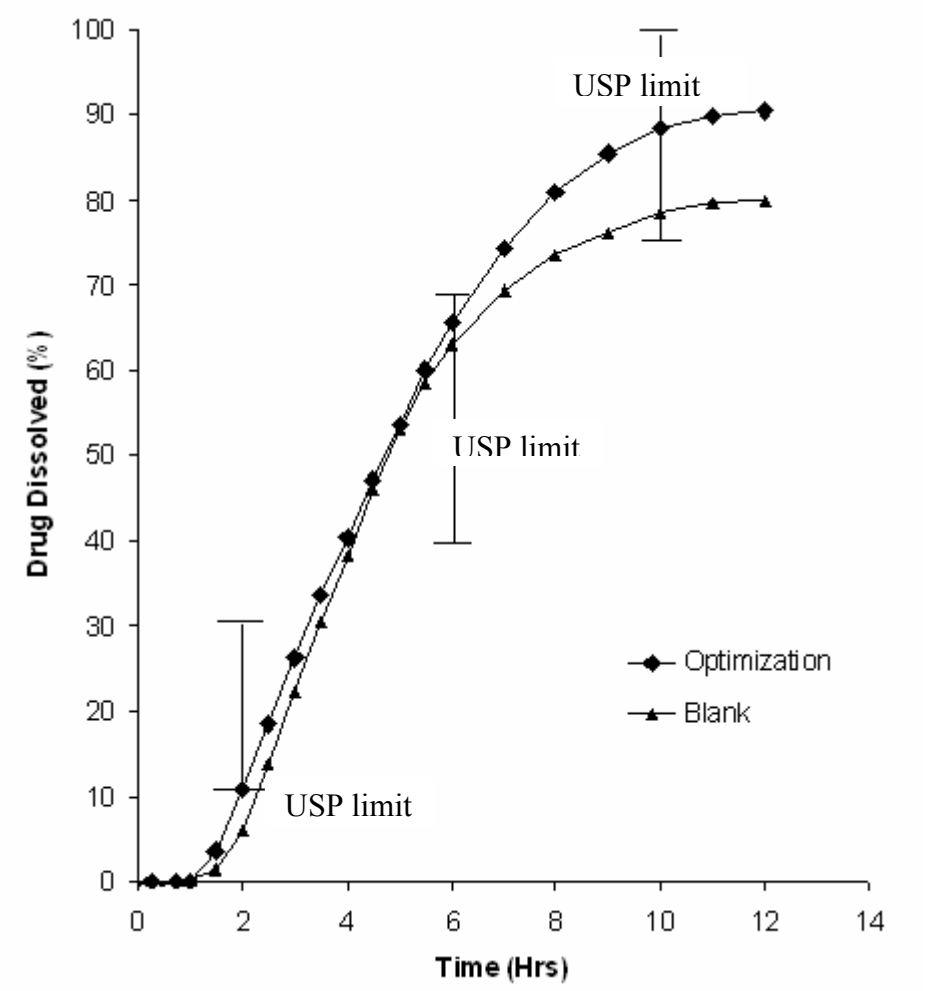


Figure 56. Dissolution profiles of optimized formulation of felodipine PPOT and blank formulation using the same factor level without CS- PAA complex

Table 24. Linear regression analyses of dissolution data corresponding to 10-80% of drug release using different mathematical models

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Formulation	Zero order $Q_t = K_0t + Q_0$		First order $\log (Q_\alpha - Q_t) = K_1t + C$		Higuchi $Q_t = K_Ht^{1/2}$	
	K_0	R^2	K_1	R^2	K_H	R^2
F-1	7.92	0.9885	-0.059	0.9895	38.88	0.9894
F-2	12.56	0.9860	-0.106	0.9898	48.011	0.9933
F-3	12.83	0.9888	-0.108	0.9840	50.47	0.9911
F-4	8.13	0.9928	-0.068	0.9763	37.19	0.9864
F-5	12.81	0.9796	-0.108	0.9895	50.58	0.9897
F-6	8.14	0.9929	-0.066	0.9760	37.21	0.9814
F-7	10.98	0.9864	-0.086	0.9522	42.30	0.9684
F-8	14.85	0.9963	-0.130	0.9641	52.72	0.9896
F-9	13.93	0.9854	-0.119	0.9691	46.79	0.9618
F-10	10.98	0.9864	-0.096	0.9879	44.42	0.9879
F-11	13.32	0.9894	-0.124	0.9643	50.70	0.9809
F-12	16.57	0.9841	-0.147	0.9720	52.46	0.9698
F-13	11.85	0.9907	-0.096	0.9888	45.63	0.9857
F-14	16.62	0.9858	-0.140	0.9800	50.01	0.9736
F-15	14.84	0.9875	-0.141	0.9665	50.43	0.9698
F-16	14.50	0.9972	-0.141	0.9720	53.30	0.9865
F-17	10.82	0.9931	-0.092	0.9780	44.93	0.9909
F-18	10.22	0.9861	-0.083	0.9726	44.91	0.9739
F-19	9.88	0.9758	-0.083	0.9893	41.70	0.9800
F-20	12.55	0.9961	-0.103	0.9451	48.10	0.9815

Q_0 , Q_t , and Q_α are the amount of drug release at initial and t = t , t = α respectively
K_0 is the zero order release constant (%.min^{-1}), K_1 is the first order release constant (min^{-1}),and K_H is the Higuchi dissolution constant (%.min^{-2})

Table 24. Linear regression analyses of dissolution data corresponding to 10-80% of drug release using different mathematical models (cont.)

Formulation	Zero order $Q_t = K_0t + Q_0$		First order $\log (Q_\alpha - Q_t) = K_1t + C$		Higuchi $Q_t = K_Ht^{1/2}$	
	K_0	R^2	K_1	R^2	K_H	R^2
F-21	12.13	0.9846	-0.103	0.9776	47.91	0.9825
F-22	8.42	0.9820	-0.067	0.9951	36.93	0.9934
F-23	7.62	0.9943	-0.060	0.9795	41.70	0.9800
F-24	14.23	0.9832	-0.126	0.9816	47.24	0.9767
F-25	16.23	0.9871	-0.165	0.9751	59.05	0.9917
F-26	9.41	0.9918	-0.074	0.9755	39.52	0.9758
F-27	11.36	0.9885	-0.101	0.9817	45.82	0.9848
F-28	11.52	0.9852	-0.104	0.9822	46.49	0.9822
F-29	12.41	0.9906	-0.103	0.9812	47.20	0.9832

Q_0 , Q_t , and Q_α are the amount of drug release at initial and t = t , t = α respectively.
K_0 is the zero order release constant (%.min^{-1}), K_1 is the first order release constant (min^{-1}),and K_H is the Higuchi dissolution constant (%.min^{-2})

Generally, there was initially high sorption rate along time up to 10,000 -15,000 sec. and the following lower sorption rate was kept almost constant along time. The sorption rate was slow, as can see in Figure 64 and 65. The amount of water uptake in 12 h was ranged from 0.253 to 0.450 g. It was notified in the previous study that CS-PAA complex with the polymer ratio of 1:1 gave the lower degree of swelling in comparison with that of 2:1, however the difference in swelling property had no much different effect on drug release when using both complexes in PPOT. This might be ascribed to low amount of water uptake during dissolution test. Since the water penetrated slowly into the tablet core, the complex was also slowly hydrated, leading to low degree of swelling in both cases of the polymer ratios. As a consequence, the drug release was not different so much as expected under this condition.

From the changes observed from the water uptake profiles and the extent of water imbibed to the tablet formulations in 12 h, it could be suggested that the process variables such as PEO, CS-PAA complex and KCl amount in the core tablet formulation, including the amount of plasticizer, membrane thickness influenced the characteristics of water uptake.

As an example, the obtained water uptake profiles for PPOT at three axial points, i.e., F-19, F-27, F-20, containing different amount of CS-PAA complex were shown in Figure 66. As it could be observed in the Figure 66, when amount of CS-PAA complex increased, the hydration rate increased. It is due to the fact that the complex acts as hydrogel which exhibits the ability to swell in water and retain a significant portion of the imbibed water within polymer structure. This similar results are observed with PPOT of F-2, F-10 containing 10 mg of CS-PAA complex, compared to F-3, F-11 containing 15 mg of CS-PAA complex as shown in Figure 67. These results are in agreement with the effect of CS-PAA complex on drug release. It may imply that the drug release was dependent on the swelling degree of the CS-PAA complex of push layer.

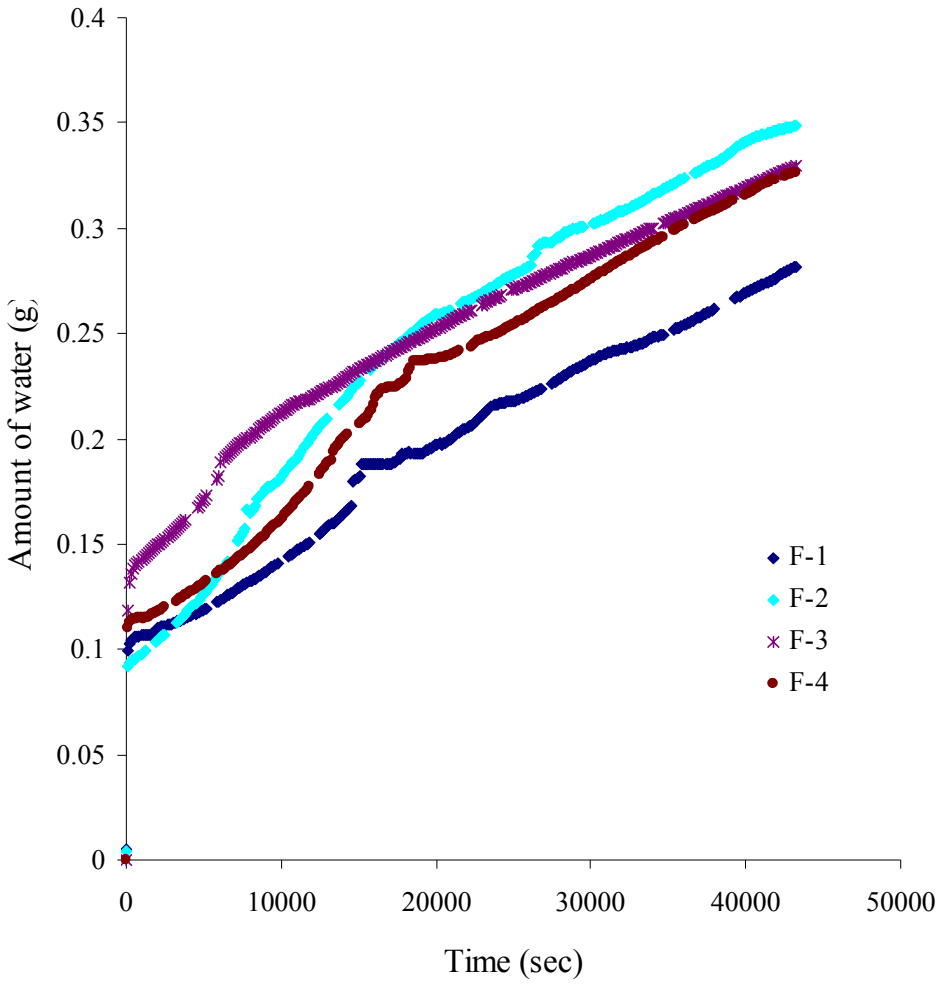

Figure 57. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

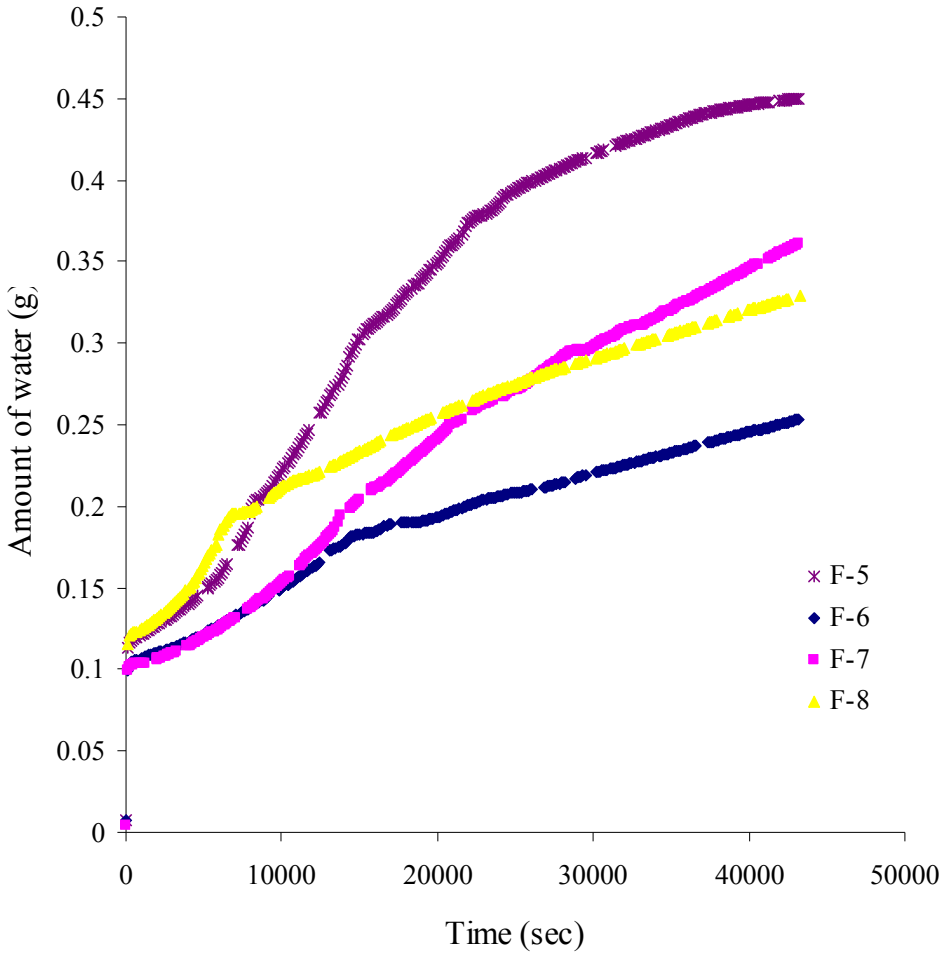

Figure 58. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

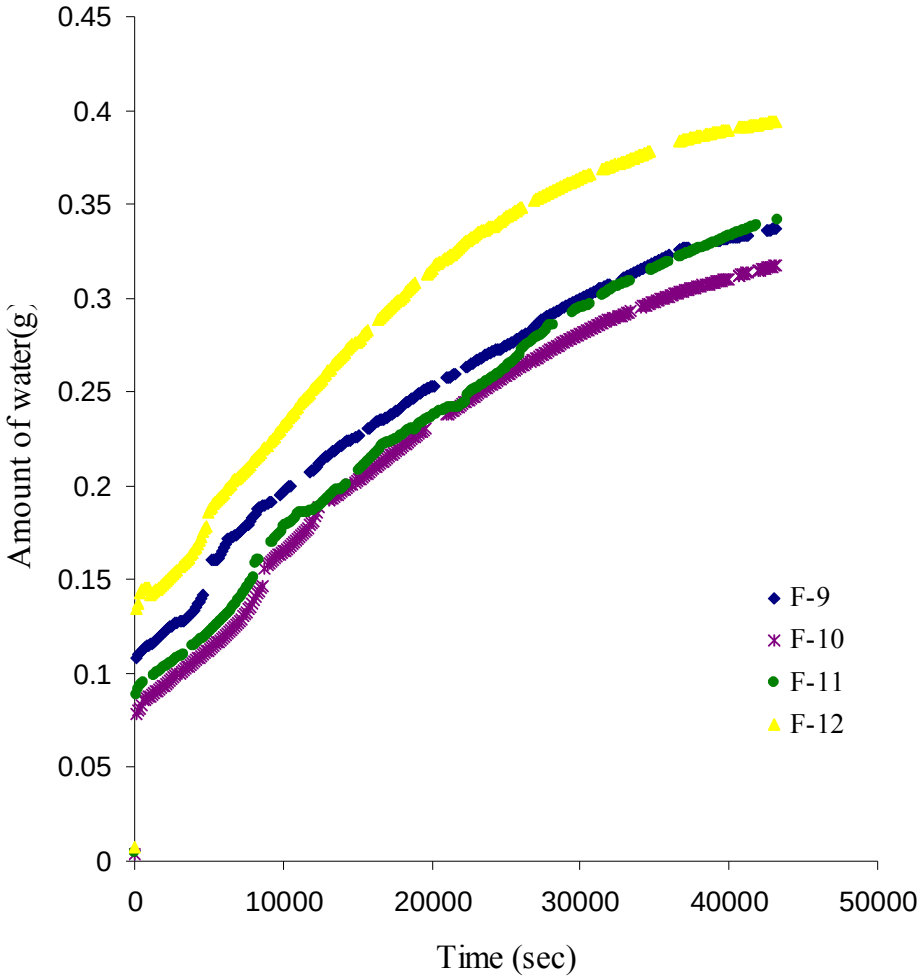

Figure 59. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

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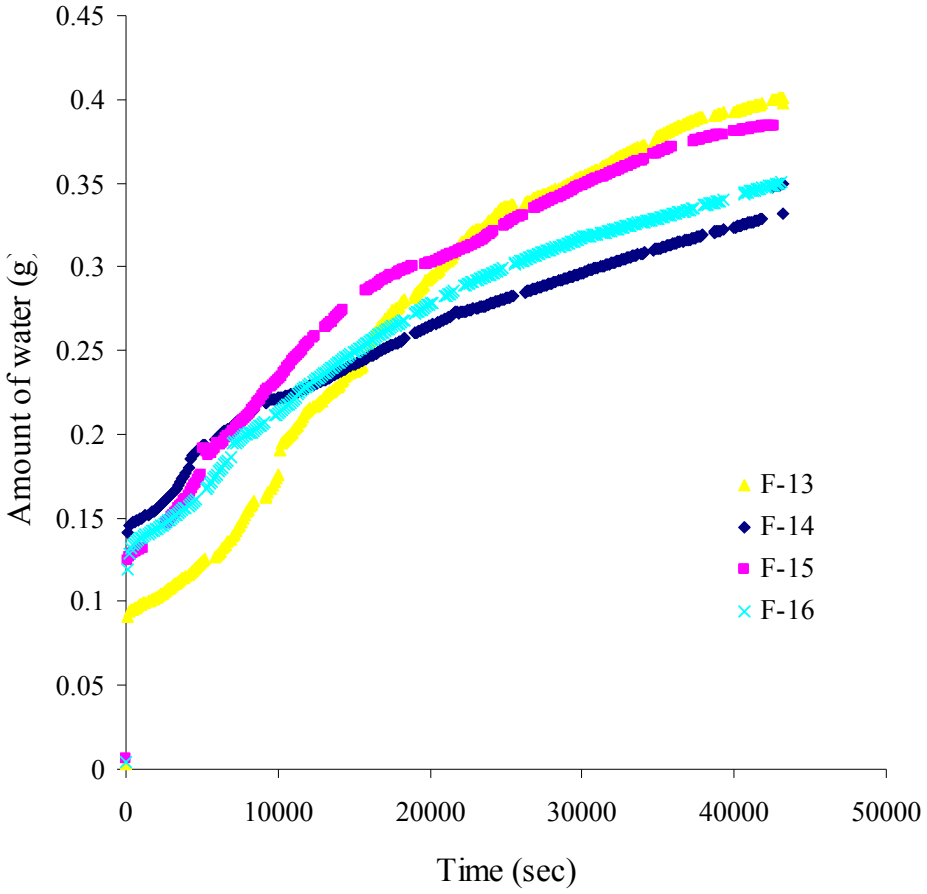

Figure 60. Water uptake of various PPOP tablets with different formulation and membrane variables in optimization study.

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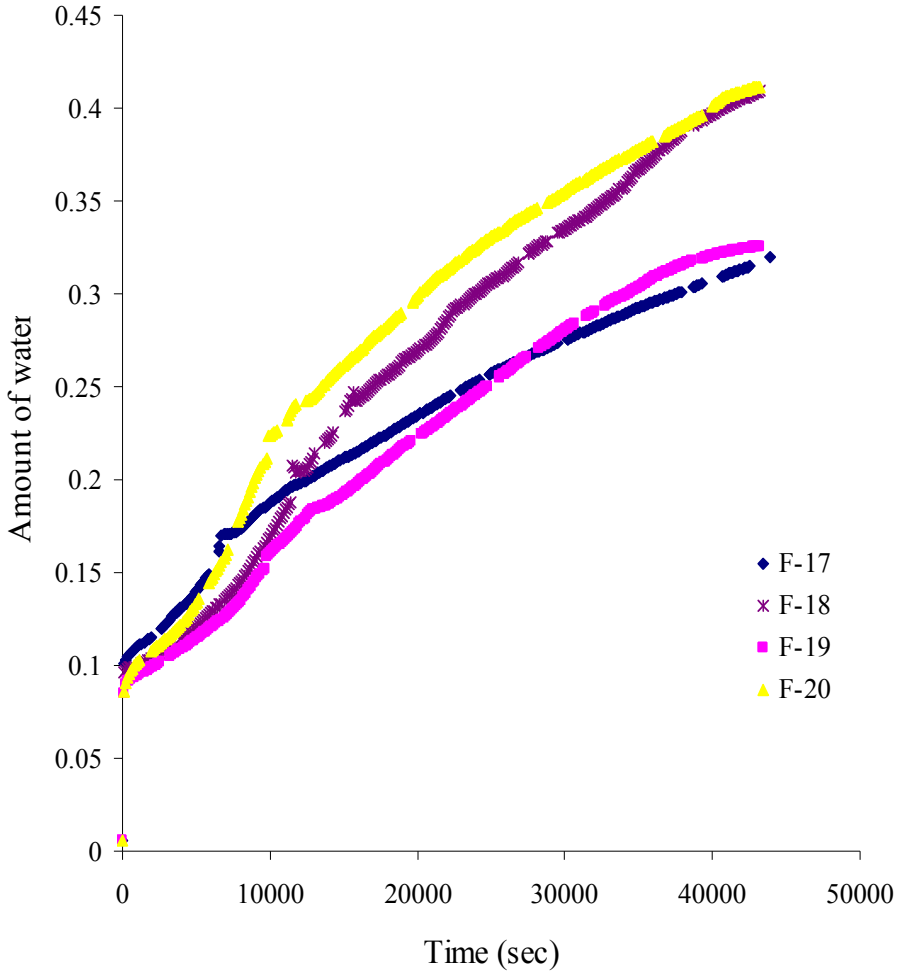

Figure 61. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

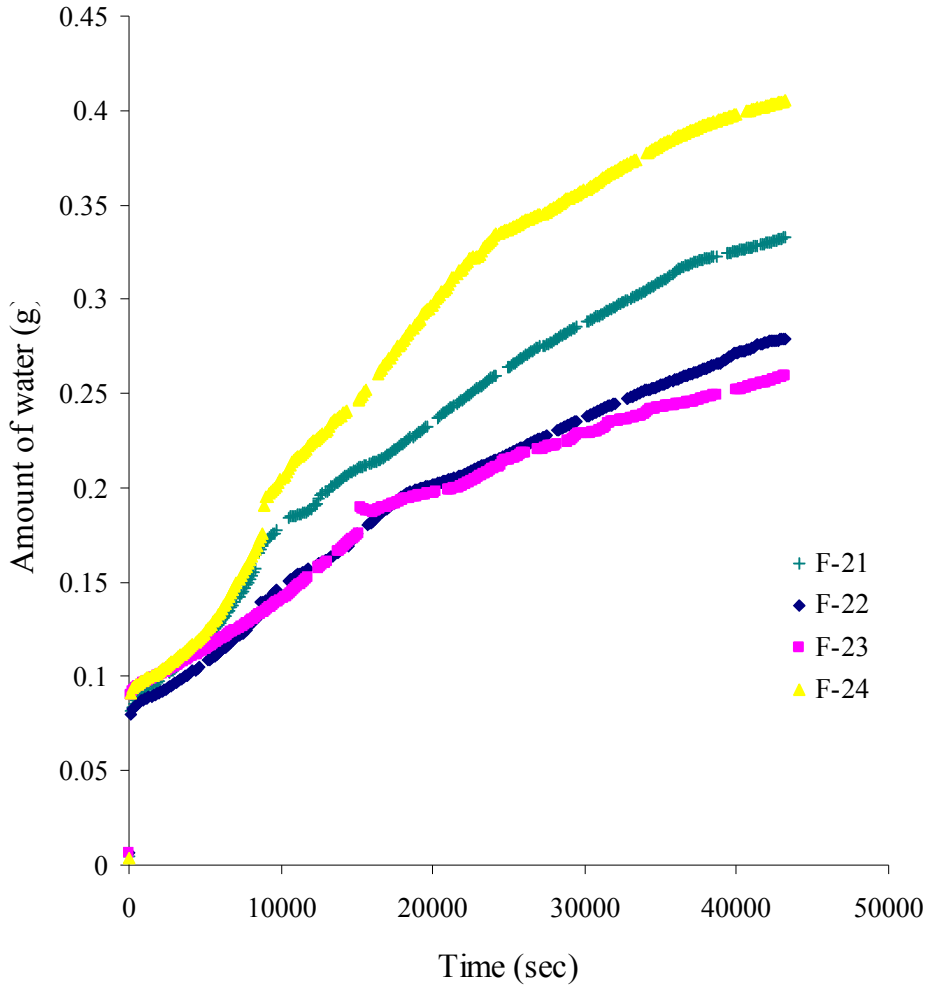

Figure 62. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

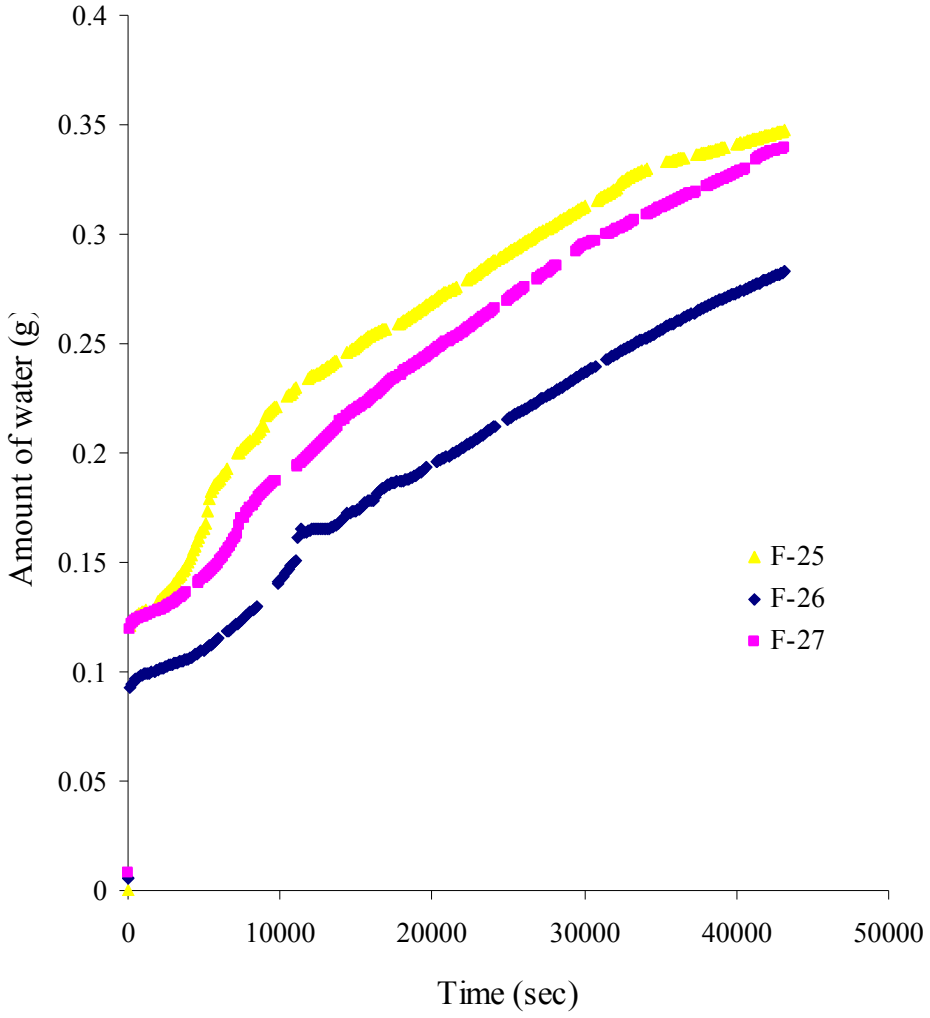

Figure 63. Water uptake of various PPOT with different formulation and membrane variables in optimization study.

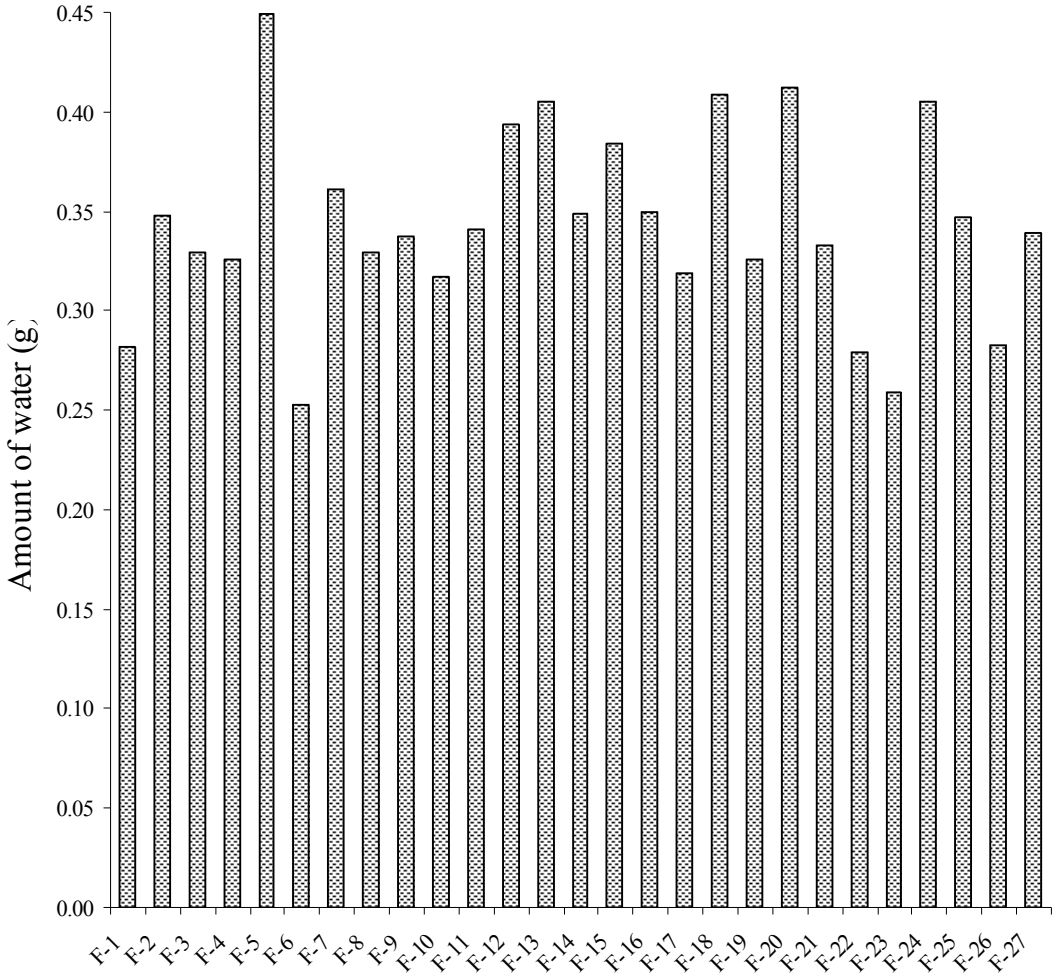

Figure 64 Effect of formulation and membrane variables on water uptake of PPOT in 12 h.

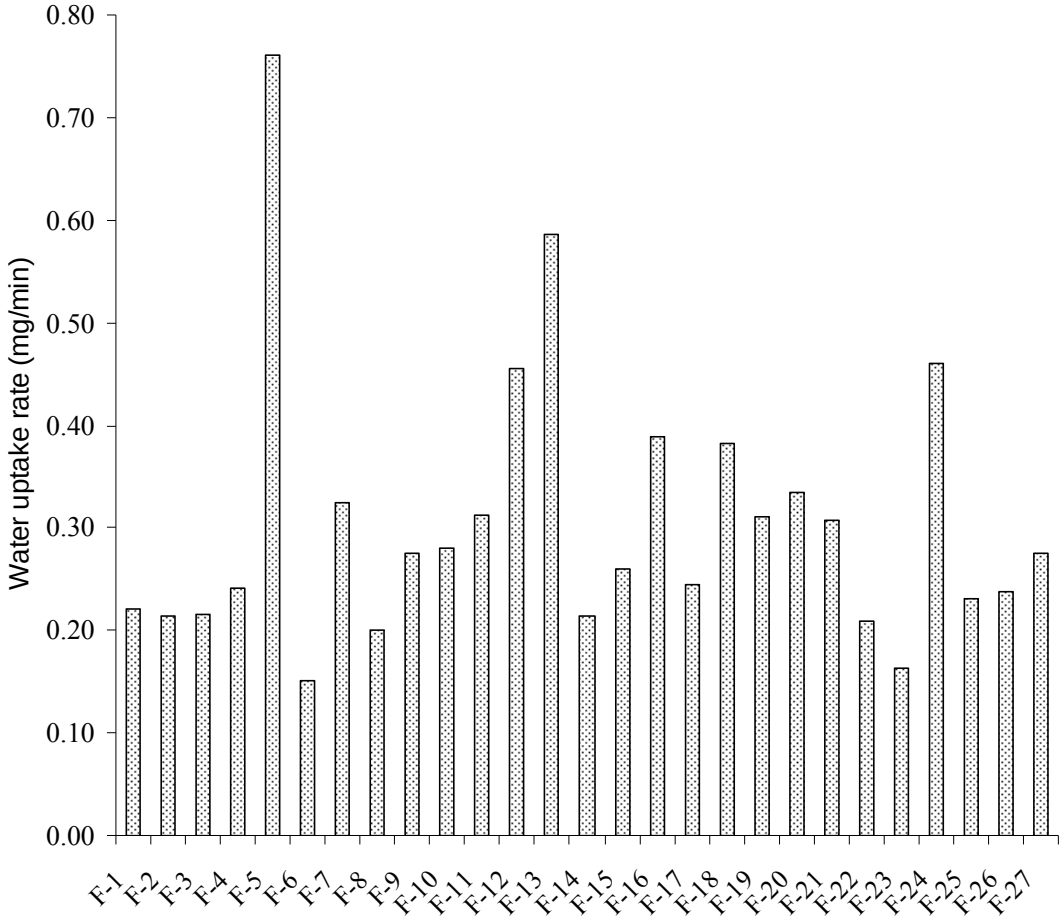

Figure 65. Effect of formulation and membrane variables on water uptake rate of PPOT.

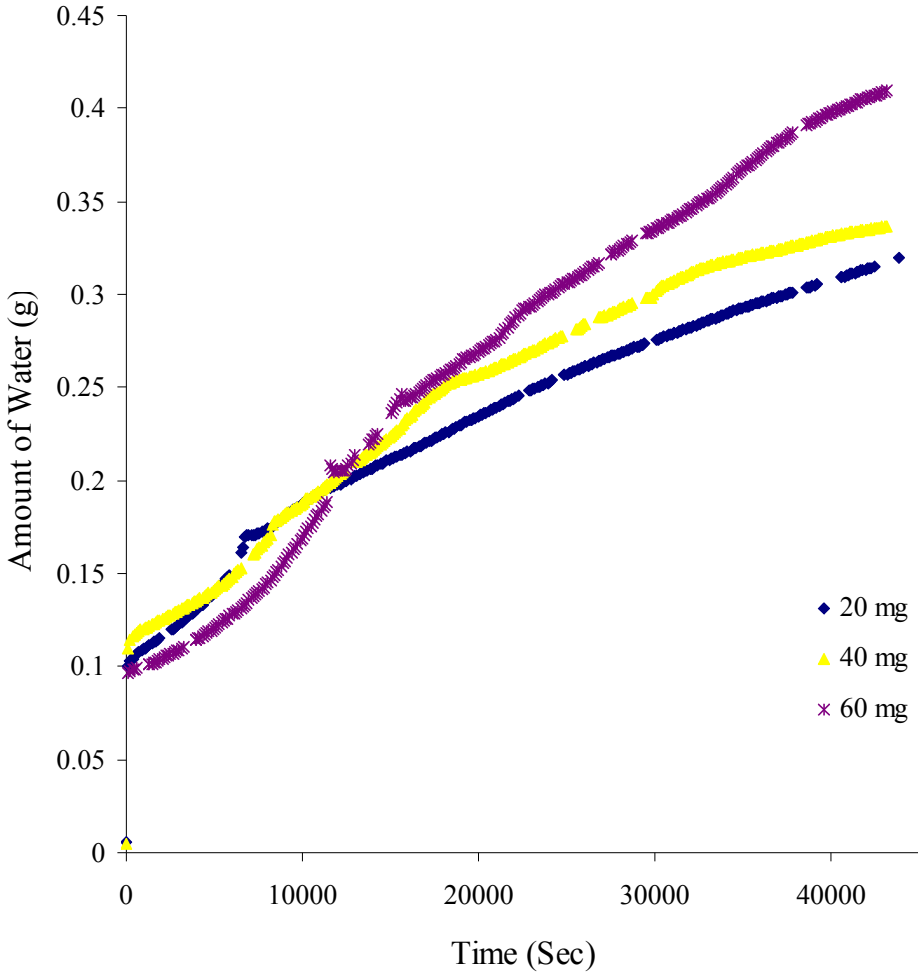

Figure 66. Effect of amount of CS-PAA complex on water uptake of felodipine PPOT at midpoint of PEO(40 mg), KCl (10mg), PEG 400(10%), coating level (10%)

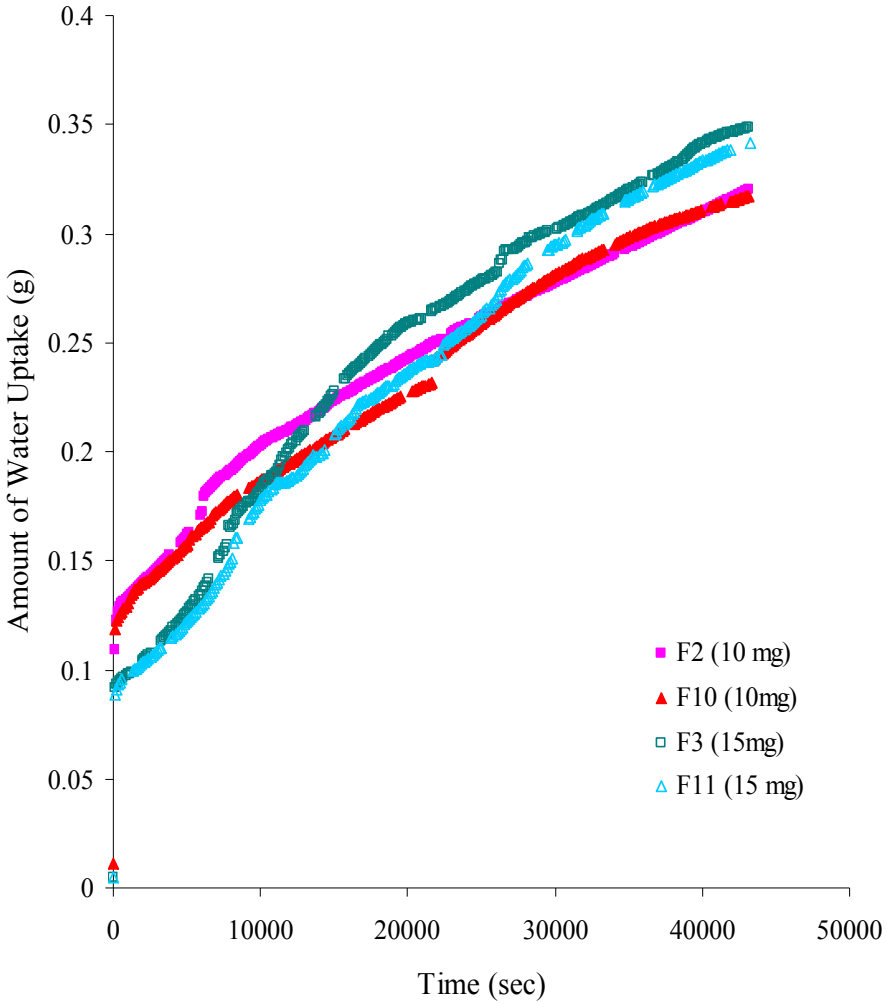

Figure 67. Effect of amount of CS-PAA complex on water uptake of felodipine PPOT.

Figure 68 illustrates the selected water uptake profiles for PPOT at three axial points, i.e., F-21, F-27, F-22 containing different amount of KCl in push layer. The results show that the more water uptake can be observed in the cases of KCl amount of 10 mg, compared to that of 0 mg. This effect seemed to be pronounced in the beginning state and was found to be comparable in the latter state. This is because an increase in amount of KCl created more osmotic pressure difference and pulled more water into the dosage form in the initial time. As the water imbibition underwent not only by osmotic pressure difference but also by swelling of CS-PAA complex, polymeric osmogent, consequently, the water uptake in case of no amount of KCl could increase comparatively in the latter time. However, water uptake decreases significantly as the increase of KCl amount from 10 to 20 mg. This finding can be explained by the same reason as described in effect of KCl on drug release. Since KCl had an interaction to the polyelectrolyte complex of CS and PAA, resulting in an decrease in polymer swelling. Thus, the imbibed water decreased as the increase of KCl amount from 10 to 20 mg. This supported the results of drug release in the corresponding manner.

Figure 69 exhibits the selected water uptake profiles for PPOT at three axial points, i.e., F-17, F-27, F-18 containing different amount of PEO in push layer. As it could be observed in this Figure 69, when amount of PEO increased, the hydration rate increased. This may be because of the physico-chemical characteristics of PEO hydrogel which can swell and retain water within its structure. Therefore, high amount of PEO could pull more water into the dosage form. Nevertheless, this effect is believed to be conformed when there is enough amount of CS-PAA complex in the core formulation. As seen in Figure 70, the water uptake profiles of F-9, F-14 containing PEO amount of 30 and 50 mg respectively at low amount of CS-PAA complex, the result shows that no significant difference can be observed as amount of PEO increased. This observation is possibly because PEO formed viscous gel around the core tablet, resulting in preventing the water penetration. It seems, therefore, likely that in the presence of low amount of complex the push layer expanded in small volume, consequently, the viscous gel of drug layer could not be diminished, resulting in low water penetration into the core.

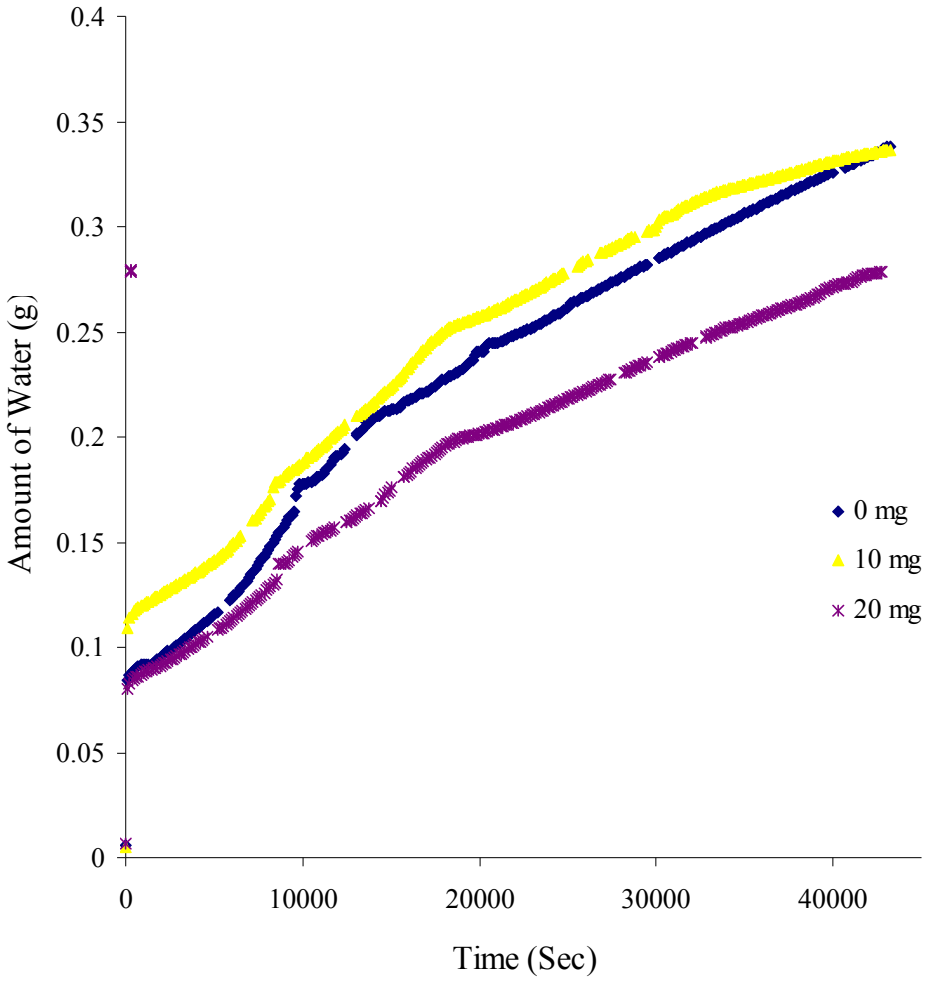

Figure 68. Effect of amount of KCl on water uptake of felodipine PPOT at midpoint of PEO(40 mg), CS-PAA complex (20mg), PEG400 (10%), coating level (10%).

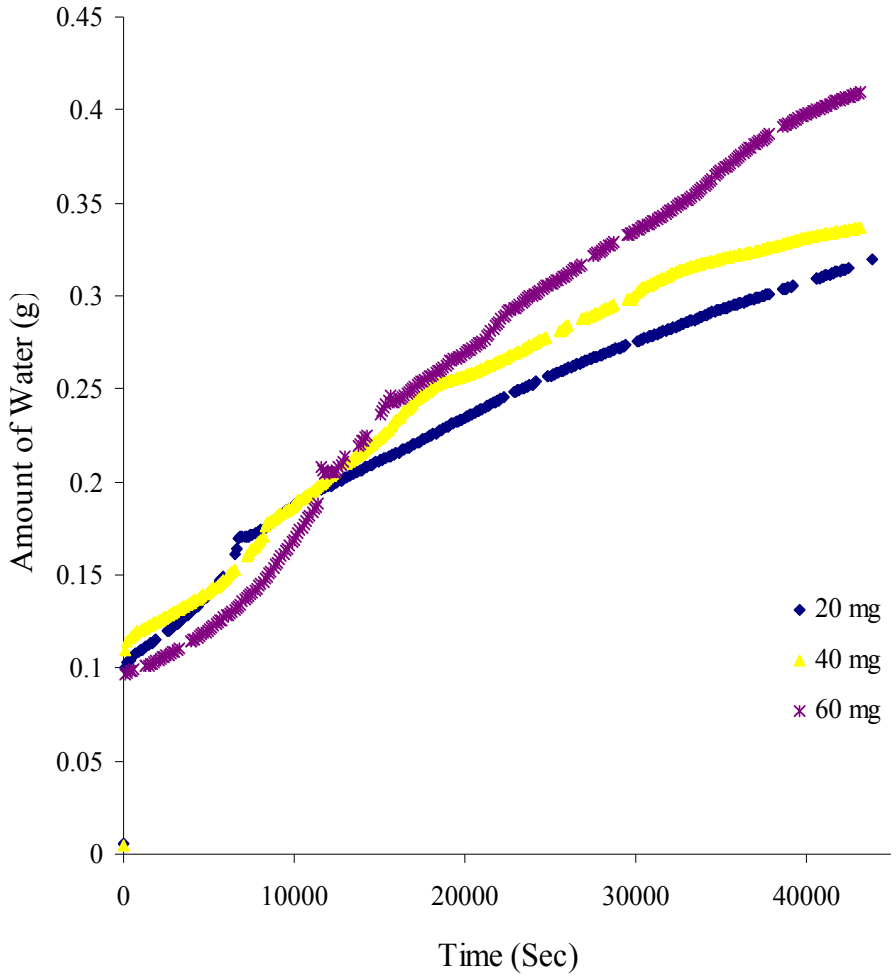

Figure 69. Effect of amount of PEO on water uptake of felodipine PPOT at midpoint of CS-PAA complex (20mg), KCl (10 mg), PEG400 (10%), coating level (10%).

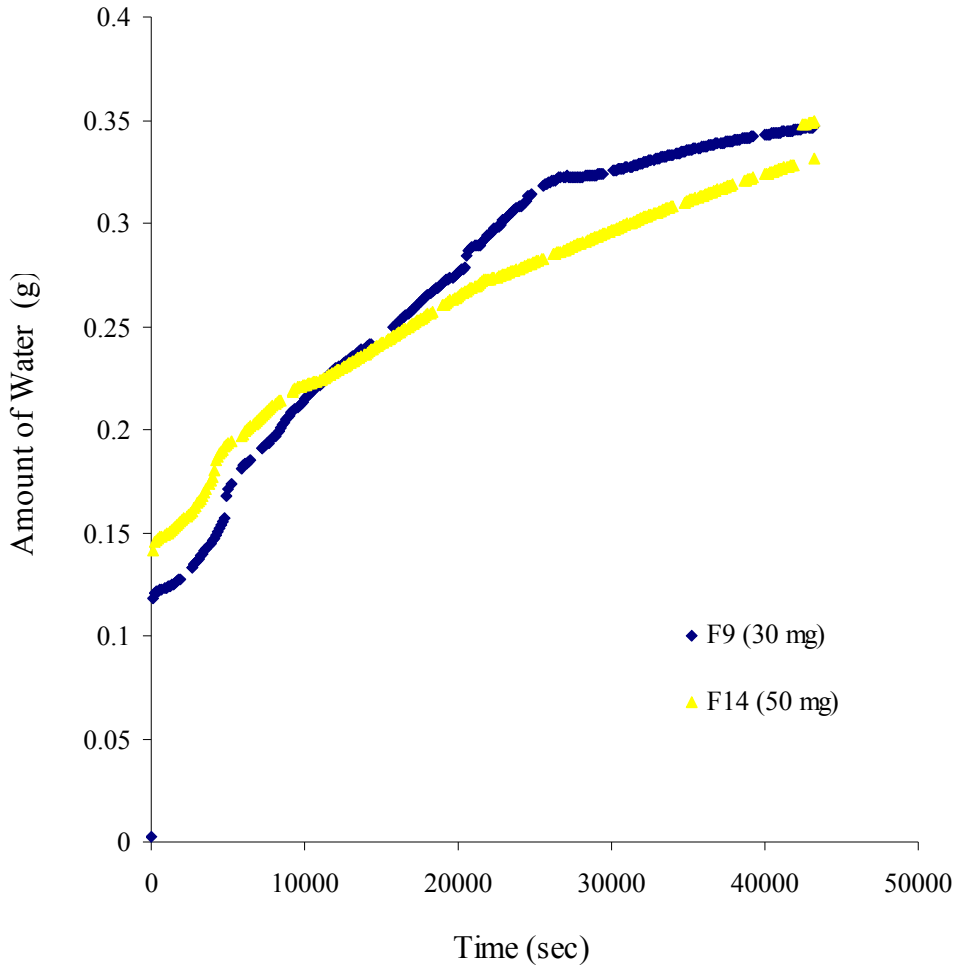

Figure 70. Effect of amount of PEO on water uptake of felodipine PPOT at midpoint of CS-PAA complex (20mg), KCl (10 mg), PEG 400 (10%), coating level (10%)

On the other hand, when the amount of CS-PAA complex in core formulation was high, the viscous gel of drug layer could be diminished by high expansion of push layer. As a result, more water could penetrate into the core. The other evidence could support this assumption shown by the water uptake characteristic of F-18 containing high amount of PEO (60 mg). As for the F-18, the water uptake gradually increased in small amount, from 0.1 to 0.15 after 10000 sec. This was due to low swelling degree of the complex in the initial period and left the high viscous gel remaining. However, the water uptake increased continuously in high amount, from 0.15 to 0.4 after 10000 sec. This was because the complex exhibited high degree of swelling, causing the viscous gel diminished, consequently, more water could enter. In case of F-17 containing low amount of PEO (20 mg), the characteristic profile showed more water uptake increased from 0.1 to 0.2 within 10000 sec, after that the water uptake increased continuously in lower amount from 0.2 to 0.3 within 40,000 sec. It can be explained based on low viscous gel forming which was smaller hindrance for the water penetration. In addition, the lower amount of water uptake in the following time was due to the lower amount of PEO as described previously.

The effect of amount of plasticizer on water uptake, examining at three axial points, i.e., F-23, F-27, F-24 was shown in Figure 71. As expected, it was found that an increase in PEG 400, plasticizer, had resulted in substantial increase in water uptake. This was because PEG 400 was a soluble plasticizer which easily leached from the membrane and left behind a porous structure, providing the opening for water ingress. Therefore, the increase of PEG 400 amount resulted in an increase of the opening for water flux. As a consequence, the water uptake increased. The result was accordant with the effect of amount of plasticizer on drug release, as stated earlier. Furthermore, the effect of plasticizer was more pronounced at higher amount of KCl as in the case of water uptake profile of F-13 containing 15 mg KCl , 15% PEG 400. The amount of water increased substantially due to the synergist effect between plasticizer and KCl. The high water ingress was dependent both on an increase of the opening for water flux and osmotic pressure difference.

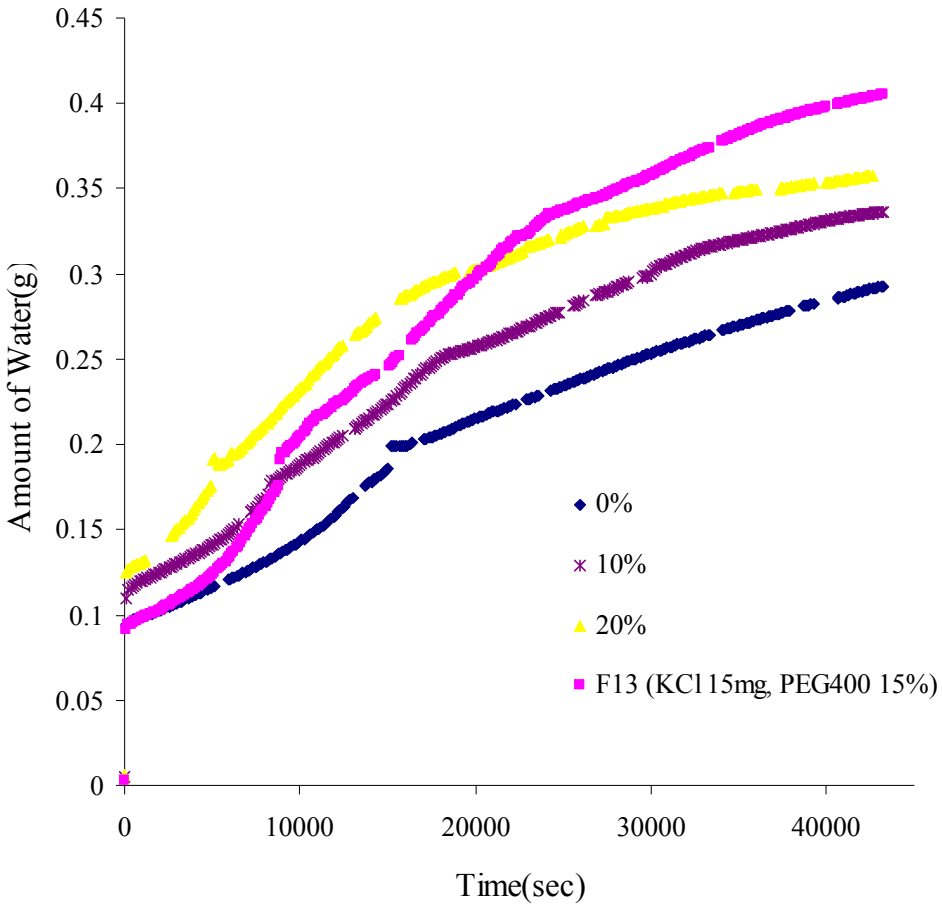

Figure 71. Effect of amount of PEG 400 on water uptake of felodipine PPOT at midpoint of PEO (40mg), CS-PAA complex (20mg), KCl (10 mg), coating level (10%) and the synergist effect between plasticizer and KCl on water uptake of F-13.

Figure 72 shows the water uptake profiles of F-25, F-27, F-26 to study the influence of amount of coating. It could be seen that the increase in amount of coating resulted in the decrease in water uptake. This finding was simply due to the changing in permeability of the coating as the thickness changed: the thicker coating had higher resistance to water diffusion, resulting in lower permeability. The amount of coating adversely affected the water uptake compared to the amount of plasticizer. The dependence of water uptake on the coating thickness and amount of plasticizer were found to consistent with dependence of drug release on both membrane variables. Furthermore, the effect of coating amount was more pronounced at higher amount of KCl as in the case of water uptake profile of F-5 containing 15 mg KCl , 6% coating amount. The amount of water increased substantially due to the synergist effect between coating amount and KCl. The high water ingress was dependent both on an increase of the water permeability and osmotic pressure difference.

3. Osmotic suspension delivery mechanism

3.1 Drug release mechanism The PPOT was composed of a bilayered osmotic tablet core surrounded by CA membrane with one orifice drilled on the drug layer side. The bilayered core tablet of this study consisted of an upper drug layer containing felodipine, osmotic agent KCl and thickening agent, polymeric osmotic agent PEO with MW of 300,000 g/mol, and a lower push layer containing osmotic agent KCl and expandable CS-PAA complex.

Based on the previous results of drug release and water uptake, the release mechanism of PPOT may be proposed as following described. In a starting-up step, water penetrated through the CA membrane and entered into the PPOT by diffusion. Subsequently, the system was covered in an osmotic mechanism with KCl as an osmotic agent and PEO as an osmotic and thickening agent. The function of KCl in the drug layer and push layer was to dissolve in the penetrated water, resulting in the osmotic pressure difference, which was the energy source to imbibe water, between the internal system and external environment. In addition, PEO could exhibit the action of osmotic agent. It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmogent for the release of water-insoluble drug (111). PEO could form viscous gelling solution by the penetrated water and hence, to enhance the osmotic pressure of core tablet. Then, the osmotic pressure

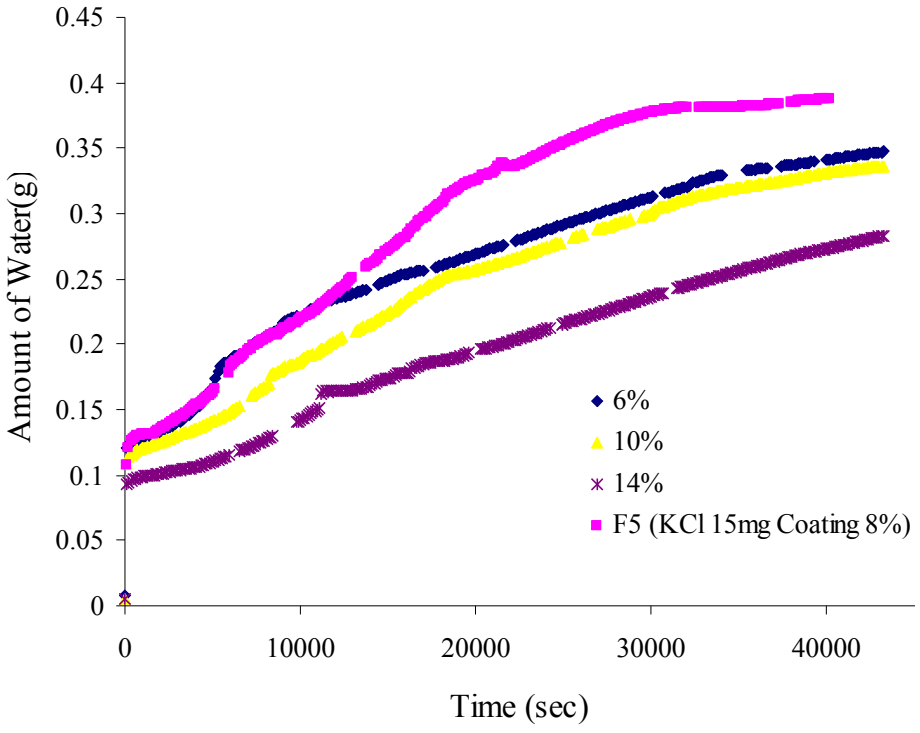

Figure 72. Effect of amount of coating on water uptake of felodipine PPOT at midpoint of PEO (40mg), CS-PAA complex (20mg), KCl (10 mg), PEG400(10%) and the synergist effect between coating level and KCl on water uptake of F-5.

differences played the role of engine to imbibe water from the environment continuously. The action of the imbibe water was to liquefy the contents of the drug layer and produce a stable viscous suspension of drug in the presence of PEO. Meanwhile, the push layer also imbibed water steadily. However, the action of imbibed water in the push layer was quite different from that of drug layer. The water was retained within the CS-PAA complex, hydrogel like, therefore expanding the volume of the push layer. This expansion supplied a driving force which was applied against the drug layer, consequently, diminishing the volume of the drug layer. As a result, the drug suspension was delivered through the orifice of PPOT. Nevertheless, the drug release mechanism due to the expansion of push layer was not initially predominated. It might be attributed to insufficient amount of water imbibed for liquefaction of drug layer in the beginning. Since hydration at the interface between drug layer and push layer was less than the outermost of the core formulation, the expansion of the push layer could not occupy the volume of drug layer. Therefore, the drug release from PPOT was not controlled by the push layer but the presence of PEO and KCl in drug layer played a role in releasing drug instead. The mechanism of drug release was accordant with those of elementary osmotic pump (EOP) by using PEO and KCl as osmotic agent. As the sufficient amount of water imbibed could liquefy the drug layer, the drug release was co-controlled by the drug layer and push layer, which expanded its volume gradually to force the drug suspension release. In brief, the two mechanisms of drug release were summarized. The first mechanism occurred when low amount of water imbibed into the tablet core at initial state of hydration, the drug release was predominated by osmotic pressure difference, created by the presence of osmogent in drug layer. The second mechanism was expanding the volume of push layer to deliver the drug suspension. This function occurred later when high amount of water imbibed into the tablet core.

In general, the portion of drug expelled from the delivery orifice of push-pull osmotic pump system is exposed to an environment as suspension or slurry. In the present study, visual observation was made during dissolution test of PPOT. It was found that the composition forming the drug layer of PPOT was expelled from the tablet in a plug-like state, the composition being so highly viscous that it could not be fluidized, as shown previously in Figure 34. The drug layer was exposed to the

environment as an erodible composition, in contrast to usual osmotic dosage forms in which the drug layer was exposed to the environment as suspension or slurry. It could be explained that the drug layer contained substantially high amount of filler, Avicel PH102 and Starch 1500®, which were not well hydrated and promoted binding property. The exposed drug layer would be eroded to release the drug to the environment. The drug release mechanism is considered to proceed as following in Figure 73.

3.2 Mathematic model of drug release Based on the drug release mechanism shown in Figure 73, it was hypothesized that there were two mechanisms contributed to drug release: the osmotic pump and erosion or dissolution. The function of the first was to extrude the drug layer to the environment as an erodible composition and, then subsequent mechanism was the erosion and dissolution of the extruded drug layer in the environment. According to these mechanisms, the following equations can describe drug release from PPOT.

I. Osmotic pump mechanism:

$$dM/dt = [(K/h).A_p\pi_p + (K/h).A_d\pi_d]. F_dC_o \quad (33)$$

where
A_p : the area of the push chamber
A_d : the area of the drug chamber
π_p : the osmotic pressure of the push chamber
π_d : the osmotic pressure of the drug chamber
h : membrane thickness
C_o : the solid concentration of the suspension dispensed from the systems
F_d : the initial drug fraction in the drug chamber

II. Erosion mechanism:

$$dM/dt = DAC_s/h \quad (34)$$

where
D : diffusion coefficient
A : surface area of erosion
C_s : solubility of drug layer composition
h : thickness of boundary layer

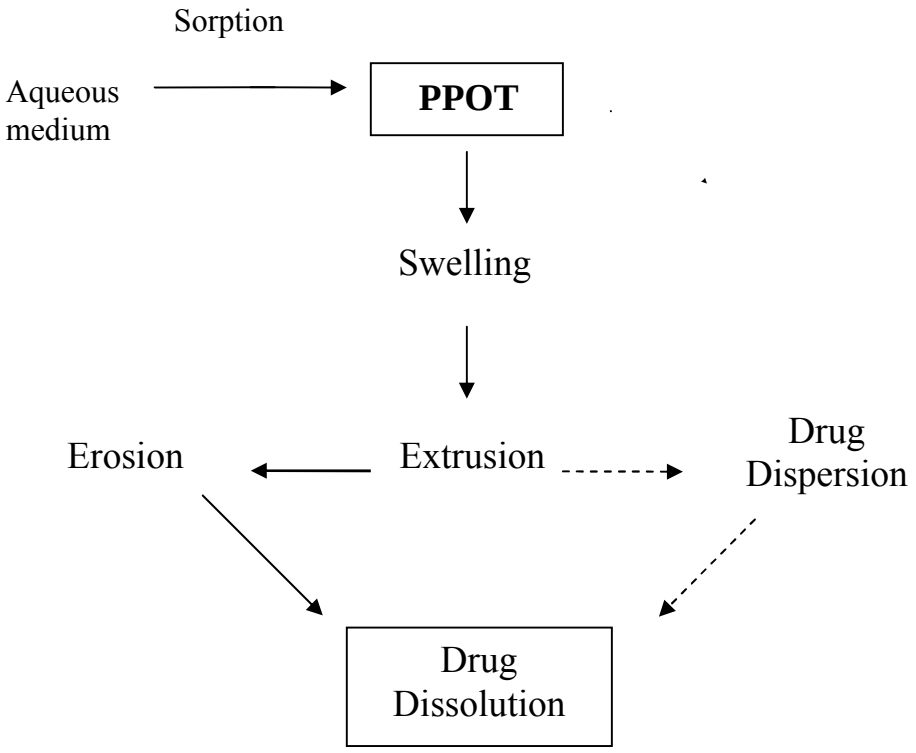

Figure 73 Schematic diagram of drug release from felodipine push-pull osmotically controlled release tablet (PPOT)

By controlling the various parameters defining the total mass delivery rate in Eq.33, the push-pull osmotic system can be programmed for various delivery rate profiles. If the osmotic pressure of the push chamber is very high, $\pi_p >> \pi_d$, the expansion of push layer governs on drug release. Therefore, Eq.33 can be rewritten as:

$$dM/dt = [(K/h).A_p\pi_p]. F_dC_o \quad (35)$$

The zero-order delivery profile has been programmed based on the constant product of area times the osmotic pressure in the push compartment. In the present study, the mass delivery rate in Eq.35 can define for the extrusion rate of the drug layer and can be written as Eq.36.

$$dM/dt = K. F_dC_o \quad (36)$$

$$= K.C_s \quad (37)$$

$$= K_{ext} \quad (38)$$

where K_{ext} is extrusion rate constant and C_s is solubility of felodipine .

In Eq.34, erosion mechanism governs on drug release from extruded drug layer. The zero-order delivery or constant rate of drug release will be achieved due to the invariable parameters in the right-hand side of the equation and can be written as;

$$dM/dt = K_{ero} \quad (39)$$

where K_{ero} is erosion rate constant, derived from D, A ,C_s, h in Eq.34
(A can keep constant due to constant extrusion rate, resulting in consistency of the extrudate left in dissolution medium)

The amount of drug release obtained from Eq.39 should be consistent to the amount of drug dissolved in the investigation of dissolution test. This is because the drug release by erosion is rate limiting step prior to subsequent drug dissolving in the dissolution medium. To verify this assumption, the amount of drug release by erosion is calculated to compare with the dissolution data as follows:

E_t = amount of drug release by erosion at time = t

$$E_t = \sum_{n=2}^{t} W_n = W_2 + W_3 + W_4 + ...+W_t \quad (40)$$

W_t = amount of drug erosion in each hour (t = 2,3,4,…)

$$= (X_{t-1} - X_{t-2}).E \quad (41)$$

where X_t = amount of drug extrusion at time = t

E = amount of drug erosion/hour/mg of extruded drug

therefore $E_2 = X_1.E$

$E_3 = X_1.E + (X_2 - X_1).E$

$E_4 = X_1.E + (X_2 - X_1).E + (X_3 - X_2).E$

$E_t = X_1.E + (X_2 - X_1).E + (X_3 - X_2).E + ...(X_{t-1} - X_{t-2}).E$

$$= X_1.E + (t - 2)(X_{t-1} - X_{t-2}).E \quad (42)$$

whereas $X_t = K_{ext}.t + C_{ext}$ and $X_{t-1} - X_{t-2} = K_{ex}$

therefore $E_t = (K_{ext} + C_{ext}).E + (t - 2). K_{ext}.E \quad (43)$

$$= [K_{ext} + (t - 2). K_{ext} + C_{ext}].E \quad (44)$$

$$= [(t -1). K_{ext} + C_{ext}].E \quad (45)$$

whereas $E = K_{ero} + C_{ero} \quad (46)$

$E_t = (K_{ero} + C_{ero}).[(t -1). K_{ext} + C_{ext}] \quad (47)$

K_{ero}, C_{ero} are slope and y-intercept of linear regression plot between amount of drug eroded and time, where K_{ero} represents the erosion rate constant as described in Eq.39. K_{ext}, C_{ext} are slope and y-intercept of linear regression plot between amount of drug extruded and time, where K_{ext} represents extrusion rate constant as described in Eq.38.

As previously described, the drug release was controlled by two consecutive mechanisms of osmotic pump and erosion. The amount of drug layer composition extruded by osmotic pump could be experimentally determined by recovery of the remaining drug in PPOT at specified time. The extrusion rate constant (K_{ext}) was obtained from the slope of linear regression plot between amount of drug recovery and

time. K_{ext} played important role in the overall drug release process and was further used to determine amount of drug release by erosion as according to Eq.45. Whereas E could be calculated by Eq.46 in which K_{ero} and C_{ero} could be experimentally determined by dissolution study of the drug layer solely without the push layer. By this way, both parameters were obtained from the slope and intercept of linear regression plot of the dissolution profile. Finally, E_t could be calculated according to Eq.47 and was compared to the dissolution data of PPOT. As an example for the formulation of F-20, the slopes of the linear regression obtained from Figure 74 and 75 represent the $K_{ext}$and K_{ero} respectively. By substituting the Eq.45 for K_{ext}, K_{ero}, including the corresponding intercepts, E_t could be calculated as follows:

$$E_t = (K_{ero} + C_{ero}).[(t-1). K_{ext} + C_{ext}]$$
$$= (6.9787/5.8 -0.7876/5.8)[(t-1).1.3372 +0.4314)] \quad (48)$$

Therefore, E_t could be calculated in comparison with amount of drug dissolved at 2,3,4,5,6,7 h as shown in Table 25. It can be seen that the experimental results were in close agreement of theoretical results as shown in Table 25. However, the Eq.47 was well fitted to the result of dissolution experiment, regarding to sequence first time point of 2 h. This is because the lag time required for sufficient water being presented to liquefy the core so that it can be extruded was approximate to 1 h. Therefore, the negligible amount of drug release in first hour was quit to add in the Eq.47.

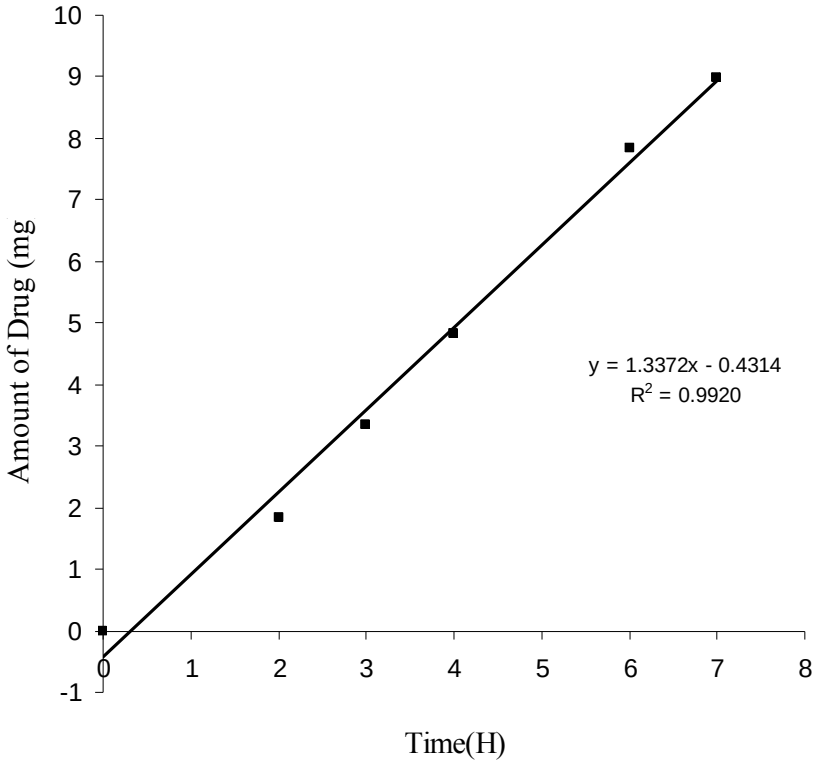

Figure 74. Regression plot showing extrusion rate (K_{ext}) of drug layer from PPOT of F-20

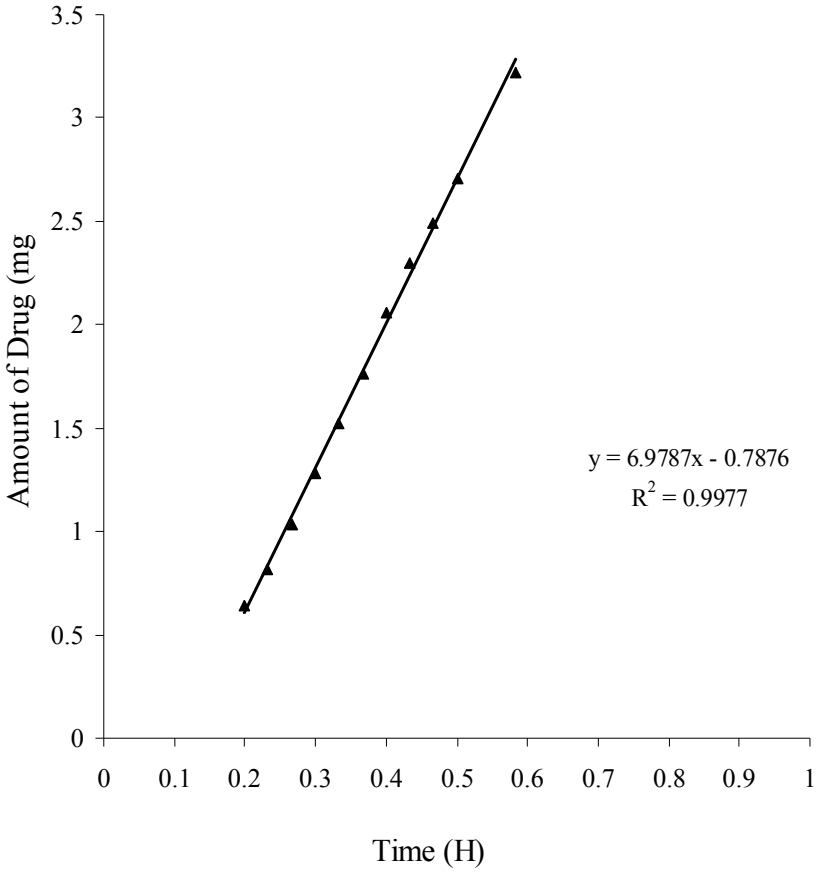

Figure 75. Regression plot showing erosion rate (K_{ero}) of drug layer after extrusion from the PPOT (F-20).

Table 25. Comparison of amount of drug release by erosion (predicted) to amount of drug dissolved during dissolution (observed) from PPOT(F-20)

Time (h)	Amount of drug release by erosion (predicted)(mg)	Amount of drug dissolved (observed)(mg)
2	0.967	0.920
3	2.394	2.395
4	3.822	3.87
5	5.249	5.345
6	6.676	6.820
7	8.104	8.295

CHAPTER V
CONCLUSIONS

On the basis of the present findings, the following can be concluded:

1. The interpolymer complexes of chitosan and polyacrylic acid can be prepared by simple mixing chitosan and polyacrylic acid in 1 M acetic acid solution at pH = 5. The FTIR analysis revealed complex formation between chitosan and polyacrylic acid.

2. The interpolymer complexes of chitosan and polyacrylic acid at different ratios and molecular weight of CS provided the different swelling properties. The swelling forces and ratios increased with the CS proportion and molecular weight of CS. The CS-PAA complex at the ratios of 1:2 and 1:1 rapidly hydrated, swelled and reached the equilibrium within 10-60 min. The complex at the ratio of 2:1 gave slower swelling.

3. The push-pull osmotic pump tablets can be prepared by double compression of drug and polymer layer to obtain a bilayerd tablet. The drug layer contained felodipine as active ingredient, polyethylene oxide as suspending agent and osmotic agent, KCl as osmotic agent, mixture of Avicel PH102 and starch 1500 (1:1) as filler and the push layer contained CS-PAA interpolymer complex as polymeric osmotic agent, KCl as osmotic agent and mixture of Avicel PH102 and starch 1500 (1:1) as filler. The core tablets could be achieved by direct compression method.

4. The tablet evaluations revealed that the proportion of PAA in complex influenced the friability. The friability decreased as the increasing in PAA ratio.

5. CO_2 - Laser equipment was used for drilling the coated tablet. The energy of 100mJ was suitable to form an orifice size of 500-600 micron without burning. In addition, the computer program was developed to control the operation for batch production. The drilling time and intensity of Laser indicate the desired diameter of the orifice.

6. Using CS-PAA interpolymer complexes as polymeric osmogent in PPOT ,the drug release exhibited the zero order manner and could be prolonged up to 12 or 24 h depend on plasticizer type. The PPOT with CA containing dibutyl sebacate showed longer lag time and slower drug release than those with CA containing polyethylene glycol 400.

7. At the same polymer ratio, the PPOT having high tablet weight gave longer lag time and slower drug release than that having low tablet weight. This effect was more pronounced in case of DBS used as plasticizer.

8. The compression force scarcely affected drug release of PPOT with the accordance to the slightly changing in tablet porosity from 14.55 to 18.40 %.

9. The optimized composition of the PPOT by response optimizing process was 50 mg of polyethylene oxide, 15 mg of CS-PAA interpolymer complex, 10 mg of KCl, 15% of polyethylene glycol 400, and 12% coating weight gain and gave 90.43% of cumulative percent dissolved in 12 h. In accordance with maximal value predicted by this optimized condition (88.76%), it showed a good correlation between predicted and observed value.

10. The ANOVA results revealed that amount of CS-PAA interpolymer complex , amount of polyethylene glycol 400 had significantly synergist effect on drug release of PPOT while percent coating weight gain had significantly antagonist effect on drug release.

11. Response surface plots showed that amount of polyethylene oxide (PEO) and KCl had either synergist or antagonist effect on drug release due to the optimal amount in PPOT formulation. Drug release increased with increase amount of PEO and KCl to optimal amount while increase amount of both ones higher than optimal value resulted in decreasing drug release.

12. Degree of swelling of CS-PAA complex can be affected by the ionic strength, leading to the decrease in drug release at high amount of KCl.

13. The water uptake profiles of PPOT revealed that the sorption rate was slow according to the amount of water uptake in 12 h ranged from 0.253 to 0.450 g. and the PEO, CS-PAA complex and KCl amount in the core tablet formulation, including the amount of plasticizer, membrane thickness influenced the characteristics of water uptake.

14. The main mechanism of drug release was governed by osmotic mechanism in delivering drug to the outside of the PPOT. However, the drug existed as insoluble composition and the drug release was concerned with the second mechanism such as erosion.

15. The mathematic model related to extrusion rate (K_{ext}) and erosion rate (K_{ero}) for describing the mechanism of drug release showed a good correlation between predicted and observed value.

REFERENCES

1. Kaushal A, Garg S. An update on osmotic drug delivery patents. Pharmaceutical Technology 2003;8:38-97
2. Santus G, Baker RW. Osmotic drug delivery: a review of the patent literature. J Controlled Release 1995;35:1-21.
3. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system : optimization of formulation variables using response surface methodology. J Conrolled Release 1997;45:121-30.
4. Sastry SV, Khan MA. Aqueous based polymeric dispersion: Plackett-Burman design for screening of formulation variables of atenolol GITS. Pharm Acta Helv 1998;73:105-12.
5. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine delivery by sandwiched osmotic tablet system. J Controlled Release 2000;68: 145-56.
6. Lu E-X, Jiang Z-Q, Zhang Q-Z, Jiang X-G. A water-insoluble drug monolithic osmotic tablet system utilizing gum arabic as an osmotic, suspending and expanding agent. J Controlled release 2003;92:375-382.
7. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LAF, Sutton SC. Osmotic drug delivery using swellable-core technology. J Controlled Release 2004;94:75-89.
8. Park SH, Chun MK, Choi HK. Preparation of extended-release matrix tablet using chitosan/ Carbopol interpolymer complex. Int J Pharm 2007 (in press).
9. Torrado S, Prada P, de la Torre PM, Torrado S. Chitosan-poly(acrylic) acid polyionic complex : in vivo study to demonstrate prolonged gastric retention. Biomaterials 2004;25:917-23.
10. de la Torre PM, Torrado S, Torrado S. Interpolymer complexes of poly(acrylic acid) and chitosan : influence of the ionic hydrogel - forming medium. Biomaterials 2003;24:1459-68.

11. de la Torre PM, Enobakhare Y, Torrado G, Torrado S. Release of amoxicillin from polyionic complexes of chitosan and poly(acrylic acid); Study of polymer/polymer and polymer/drug interactions within the network structure. Biomaterials 2003;24:1499-506.
12. Ahn J-S, Choi H-K, Chum M-K, Ryu J-M, Jung J-H, Kim Y-U, Cho C-S. Release of triamcinolone acetonide from mucoadhesive polymer composed of chitosan and poly(acrylic acid) in vitro. Biomaterials 2002; 23:1411-1416.
13. Rossi S, Sandri G, Ferrari F, Bonferoni MC, Carmella C. Buccal delivery of Acyclovir from films based on chitosan and polyacrylic acid. Pharm Dev Technol 2003;8(2) :199-208.
14. Hu Y, Chen Y, Chen Qi, Zhang L, Jiang X, Yang C. Synthesis and stimuli-responsive properties of chitosan / poly(acrylic acid) hollow nanospheres. Polymer 2005;46:12703-12710.
15. Hu Y, Jiang X, Ding Y, Ge H, Yuan Y, Yang C. Synthesis and characterization of chitosan-poly(acrylic acid) nano-particles. Biomaterials 2002;23:3193-3200.
16. Wu Y, Guo J, Yang W, Wang C, Fu S. Preparation and characterization of chitosan-poly(acrylic acid) polymer magnetic microspheres. Polymer 2006;47:5287-5294.
17. Chien YW. Novel drug delivery systems:Fundamental concepts and biomedical assessments New York:Marcel Dekker, 1982.
18. Theeuwes F. Drug delivery systems. Pharmc. Ther.1981;13:149-191.
19. Rose S and Nelson JF. A continuous long-term injector. Aust J Exp Biol. 33:415.
20. Baker RW and Castro AJ. Current US Patents. J Controlled Release 1989 ;9(3) :289-292
21. Higuchi T and Leeper HM. Osmotic dispensers. US Patent 3732865. May 15, 1973.
22. Linkwitz A et al., inventors. Alza Corporation, assignee. Osmotically driven delivery device with expandable orifice for pulsatile delivery effect. US Patent 5,221,278. June 22, 1993.

23. Higuchi T and Theeuwes F, inventors. Alza Corporation, assignee. Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient. US Patent 3,995,631. May 5, 1976.
24. Theeuwes F, inventors. Alza Corporation, assignee. Osmotically triggered device with gas generating means. US Patent 4,203,441. May 20, 1980.
25. Theeuwes F, inventors. Alza Corporation, assignee. Osmotic dispensing device for releasing benefit agent. US Patent 3,845,770. Dec 11, 1974.
26. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Controlled Release 2002;79(1-3):7-27.
27. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975;64(12):1987-91.
28. Koparkar AD and Shah SB, inventors. Alza Corporation, assignee. Oral osmotic system for slightly soluble active agents. US Patent 5,284,662. Feb 8, 1994.
29. Khanna SC, inventors. Alza Corporation, assignee. Therapeutic system for sparingly soluble active ingredient. US Patent 4,992,278. Feb 12, 1991.
30. Rudnic EM, et al. inventors. Alza Corporation, assignee. Osmotic drug delivery system. US Patent 6,110,498. Aug 29, 2000.
31. Okimoto K, Rajewski RA, Stella VJ. Release of testosterone from an osmotic pump tablet utilizing (SBE)7m-beta-cyclodextrin as both a solubilizing and an osmotic pump agent. J controlled Release 1999;58 (8):29-38.
32. Okimoto K, Miyake M, Ohnishi N, Rajewski R, Stella VJ. Design and evaluation of an osmotic pump tablet (OPT) for prednisolone, a poorly water soluble drug, using (SBE)7m-beta-CD. Pharm Res 1998;15(10):1562-8.
33. Okimoto K, Ohike A, Ibuki R, Aoki O, Rajeweski RA, et al. Design and evaluation of an osmotic pump tablet (OPT) for chlorpromazine using (SBE)7m. Pharm Res 1999;16(Apr):549-54.
34. Okimoto K, Ohike A, Ibuki R, Aoki O, Ohnishi N, Rajewski RA, et al. Factors affecting membrane-controlled drug release for osmotic pump tablet(OPT) utilizing (SBE)7m-[beta]–CD as both a solubilizer and osmotic agent. J Controlled Release 1999;60(2-3):311-9.

35. Thombre AG, Zentner GM, Himmelstein KJ. Mechanism of water transport in controlled porosity osmotic devices. J Membr Sci 1989;40:279-310.

36. Lui H, Yang X-G, Nie S-F, Zhou L-L, Liu H, Tang R, Pan W-S. Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in vitro investigation. Int J Pharm 2006 (In Press).

37. Magruder PR, et al.,inventors. Alza Corporation,assignee. Composition comprising salbutamol. US Patent 4,751,071. June 14, 1988.

38. Magruder PR, et al.,inventors. Alza Corporation,assignee. Constant release system with pulsed release. US Patent 4,777,049. Oct. 11,1988.

39. Magruder PR, et al.,inventors. Alza Corporation,assignee. Composition comprising a therapeutic agent and a modulating agent. US Patent 4,851,229 July 25, 1989.

40. Chen CM, inventor. AnDrx Pharmaceuticals, Inc, assignee. Multiparticulate pulsatile drug delivery system. US Patent 508040. April 16, 1996.

41. Zhang Y, Zhirong Z, Fang W. A novel pulsed-release system based on swelling and osmotic pumping mechanism. J Controlled Release 2003;89:47-55.

42. Abramowitz et al., assignee. Bristol-Myers Squibb company, assignee. Colonic drug delivery system. US Patent 5,536,507 July 16, 1996.

43. Theeuwes F, inventor. Alza Corporation, assignee. Laminate made of a cellulose acetate layer and an elastomeric material layer. US Patent 4,331,728. May 25, 1982.

44. Theeuwes F, inventor. Alza Corporation, assignee. Osmotic dispenser with gas generating means. US Patent 4,036,228. July19,1977.

45. Liu L, Khang g, Rhee JM, Lee HB. Monolithic osmotic tablet system for nifedipine delivery. J Controlled Release 2000;67:309-322.

46. Shokri J, Ahmadi P, Rashidi P, Shahsavari M, Nokhodchi A. Swellable elementary osmotic pump (SEOP): an effective device for delivery of poorly water-soluble drugs. Eur J Pharm Biopharm 2007 (In Press).

47. Cortese R, Theeuwes F, inventor. Alza Corporation, assignee. Osmotic device with hydrogel driving member. US Patent 4,327,725. May 4, 1982.

48. Swanson DR, Barclay BL, Wong PS, Theeuwes F. Nifedipine gastrointestinal

therapeutic system. Am J Med 1978;83(Suppl 6B):3-9.

49. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: controlled release formulation of nifedipine. Am J Med 1987;83(Suppl 6B):10-4.
50. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system :optimization of formulation variables using response surface methodology. J Conrolled Release 1997;45:121-30.
51. Sastry SV, Khan MA. Aqueous based polymeric dispersion: Plackett-Burman design for screening of formulation variables of atenolol GITS. Pharm Acta Helv 1998;73:105-12.
52. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP. Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and in vitro characterization. Int J Pharm 2004;264:95-108.
53. Gondaliya D, Pundarikakshudu K. The fabrication and evaluation of the formulation variables of a controlled-porosity osmotic drug delivery system with Diltiazem hydrochloride. Pharmaceutical technology 2003;27(9):2003.
54. Alza Corporation. Concerta®- A success story. Delivery times 2001;1(1):1-11.
55. Jao F, et al., inventor. Alza Corporation, assignee. Verapamil therapy. US Patent 5,160,744. Nov 3, 1992.
56. Evangelline C, et al., inventor. Alza Corporation, assignee. OROS push-stick for controlled delivery of active agents. European Patent 1663145. May 7, 2005.
57. Eckenhoff B, Theeuwes F, Urguhart J. Osmotically actuated dosage forms for rate controlled drug deliver. Pharm Technol 1987;Jun:96-105.
58. Verma RK, Gargs S. Current status of drug delivery technologies and future direction. Pharm Technol 2001;25(2):1-14.
59. Theeuwes F, inventor. Alza Coperation, assignee. Second expandable chamber osmotic system for delivering selected beneficial agents having varying degrees of solubility. US Patent 4,111,201 Sep 5, 1978.
60. Wong PS, inventor. Alza Corporation, assignee. Controlled release liquid active agent formulation dosage forms. US Patent 6,596,314 July 22, 2003.

61. Dong LC, inventor. Alza Corporation, assignee. Controlled release capsule for delivery of liquid formulation. US Patent application publication 2004/ 005800, 2004.

62. Theeuwes F, Swanson DR,Wong PSL, Bonsen P, Place V, Heimlich K, Kwan KC. Elementary osmotic pump for indomethacin. J Pharm Sci 1983;72:253-258.

63. Ozdemir N and Sahin J. Design of a controlled release osmotic pump system of ibuprofen. Int J Pharm 1997;158(1):91-7.

64. Theeuwes F, inventor. Alza Corporation, assignee. Process for forming outlet passageways in pills using a laser. US Patent 4,088,864. May 5,1978.

65 Ayer AD and Balkie HH, inventor. Method and apparatus for forming a hole in a drug dispensing device. US patent 5,071,607. Dec 10, 1991.

66. Theeuwes F and Higuchi T, inventor. Alza Corporation, assignee. Osmotic dispensing device with maximum and minimum sizes for the passageway. US Patent 3,916,899 Nov 4, 1975.

67. McClelland GA, Sutton SC, Engle K, Zentner GM. Solubility - modulated osmotic pump:in vitro/in vivo release of diltiazem hydrochloride. Pharm Res 1991;8(Jan):88-92.

68. Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility and resin-modulated osmotic drug delivery systems for release of diltiazem hydrochloride. J Controlled Release 1991;16(Jun-Jul):237-44.

69. Okimoto K, Ohike A, Ibuki R, Aoki O, Ohnishi N, Irie T, Uekama K, Rajewski RA, Stella VJ. Factors affecting membrane-controlled drug release for osmotic pump tablet (OPT) utilizing (SBE)7m-[beta]–CD as both a solubilizer and osmotic agent. J Controlled Release 1999;60(2-3):311-9.

70. Theeuwes F,et al. Osmotic delivery systems for the beta-adrenoceptor antagonists metroprolol and oxyprenolol: Design and evaluation of systems for once-daily administration. Br J Clin Pharmacol 1985;19(2): 69S-76S.

71. Seminoff LA, Zentner GM, inventor. Alza Coperation, assignee. Cellulosic coating US Patent 5,126,146. Jun 30,1992.

72. Lindstedt B, Ragnarssn G, Hjartstam J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Int J Pharm 1989;56:261-68.

73. Dong LC, inventer. Alza Corporation, assignee. Dosage form comprising liquid formulation. US Patent 6,174,547. Jan 16, 2001.

74. Lowman AM, Peppas NA. Hydrogel. In: Mathiowitz E, editor. Encyclopedia of controlled drug delivery. New York: John Wiley&Sons;1999 p 397-418.

75. Peniche C, Elvira C, Roman JS Interpolymer complexes of chitosan and polymethacrylic derivatives of salicylic acid: preparation, characterization and modification by thermal treatment. Polymer 1998;39 (25):6549 - 6554.

76. Dumitriu S, Chornet E. Inclusion and release of proteins from polysaccharide-based polyion complexes. Advance drug delivery reviews 1998;31:223-46

77. Lee JW, Kim SY, Kim SS, Lee YM, Lee HK, Kim SJ. Synthesis and characteristics of interpenetrating polymer network hydrogel composed of chitosan and poly(acrylic acid). J Appl Polm Sci 1999;73:113-120.

78. Berger J, Reist M, Mayer JM, Felt O, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eu J of Pharm and Biopharm 2004;57:35-52.

79. Zhang QQ, et al. Preparation and characterization of collagen-chitosan composites. J Appl Polym Sci. 1997;64:2127-2130.

80. Regardh CG, Baarnhielm C, Edgar B, Hoffmann KJ. Pharmacokinetics and biotransformation of 1, 4 - dihydropyridine calcium antagonist. In:Gibson, editor. Progress in drug metabolism, Vol. 12, London: Taylor and Francis; 1990: 42-86.

81. Takahashi T, et al. Characteristics of polyion complexes of chitosan with sodium alginate and sodium polyacrylate. Int J Pharm 1990;61:35-41.

82. Berger J, Reist M, Mayer JM, Felt O, Peppas NA, Gurny R. Structure and interactions in covalently and ionically crosslinked chitosan hydrogels formed for biomedical applications. Eu J of Pharm and Biopharm 2004;57:35-52.

83. Munjeri O, Collett JH, Fell JJ. Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug releases. J Controlled Release 1977;46:278-373.

84. Chavasit V, Kienzle-Sterzer CA, Torres JA. Formation and characterization of an insoluble polyelectrolyte complex: chitosan-polyacrylic acid. Polym Bull 1988;19:223-230.

85. Lee KY, Park WH, Ha Ws. Polyelectrolyte complexes of sodium alginate with chitosan or its derivatives for microcapsules. J Appl Polym Sci 1997;63: 425-432.

86. Fukuda H, Kikuchi Y. In vitro clot formation on the polyelectrolyte complexes of sodium dextran surface with chitosan. J Biomed Mater Res 1978;12 :531-539.

87. Arguelles-Monal W, Garciga M, Peniche-Covas. Study of the stoichiometric polyelectrolyte complex between chitosan and carboxymethylcellulose. Polymer Bull. 1990;23:307-313.

88. Denuzien A, et al. Chitosan-chondroitin sulfate and chitosan-hyaluronate poly-electrolyte complexs: Biological properties. Biomaterials 1998;19:1275-1285.

89. Sakiyama T, et al. Polyelectrolyte complex gel with high pH-sensitivity prepared from dextran sulfate and chitosan. J Appl Polym Sci 1999;73:2227-33.

90 Majeti NV, Kumar R. A review of chitin and chitosan applications. Reactive & Functional Polymers 2000;46:1-27.

91. Illum L. Chitosan and its use as a pharmaceutical delivery systems. Pharm Res 1998;15:1326-1331.

92. Hejazi R, Amiji M. Chitosan - based gastrointestinal delivery system. J Controlled Release 2003;89: 151-165.

93. Agnihotri S, Mallikarjuna N, Aminabhavi T. Recent advances on chitosan-based micro-nanoparticles in drug delivery. J Controlled Release 2004;100:5-28.

94. Sajeesh S, Chandra PS. Interpolymer complex microparticles based on poly-methacrylic acid-chitosan for oral insulin delivery. J Appl Polym Sci 2006;99:506-512.

95. Shim JW, Nho YC. Γ-Irradiation preparation of poly(acrylic acid)-chitosan hydrogels for in vitro drug release. J Appl Polym Sci 2003;90:3270-77.

96. Wang H, Li W, Lu Y, Wang Z, Zhong W. Studies on chitosan and poly(acrylic

acid) interpolymer complex II. Solution behaviors of the mixture of water-soluble chitosan and poly(acrylic acid). J Appl Polym Sci 1996; 61:2221-4.

97. Ding Y, Hu Y, Zhang L, Chen Y, Jiang X. Synthesis and magnetics properties of biocompatible hybrid hollow spheres. Biomacromolecules 2006;7:1766-1772.

98. Sailaja GS, Velayudhan S, Sunny MC, Sreenivasan K, Varma HK, Ramesh P. Hydroxyapatite filled chitosan-polyacrylic acid polyelectrolyte complexes. Journal of Materials Science. 2003;38:3653-3662.

99. Sajeesh S, Chandra PS. Novel pH responsive polymethacrylic acid-chitosan-polyethylene glycol nanoparticles for oral peptides delivery. Biomaterials. 2006;76B(2):298-305.

100. Hecht J. The laser guidebook. Singapore:McGraw-Hill Book 1986.

101. Verdegen JT. Laser electronics, 3rd ed. New Jersy: Prentice-Hall 1995.

102. Theeuwes F, inventor. Alza Corporation, assignee. Process for forming outlet passageways in pills using a laser. US Patent 4,088,864 May 5,1978.

103. Luschen JG, inventor. Alza corporation, assignee. Process for forming a passageway in an osmotic device. US Patent 4,277,113. Jun 2,1981.

104. Saltiel E, Ellrodt AG, Monk JP, Langley MS. Felodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs 1988;36:387-428.

105. Todd PA, Faulds D. Felodipine. A review of the pharmacology and therapeutic use of the extended release formulation in cardiovascular disorders. Drugs 1992;44(2):251-77.

106. Blychert E, Wingstrand K, Edgar B, Lidman K. Plasma concentration profiles and antihypertensive effect of conventional and extended-release felodipine tablets. Br J Clin Pharmacol.1990;29(1):39-45.

107. Prisant LM, Elliot WJ. Drug delivery systems for treatment of systemic hypertention. Clin Pharmacokinet. 2003;42(1):931-40.

108. Tien CL, Lacrix M, Ispas-szabo P, Mateescu MA. N-acetylated chitosan: hydrophobic matrices for controlled drug release. J Controlled Release 2003;93:1-13.

109. Nunthanid J, Laungtna-anan M, Sriamornsak P, Limmatvaprirat S, Puttipipatkhachorn S, Lim S, Khor LY. Characterization of chitosan acetate as a binder for sustained release tablet. J Controlled Release 2004;99:15-26.

110. Yang L, Venkatesh G, Fassihi R. Characterization of compressibility and compacttibility of poly(ethylene oxide) polymers for modified release application by compaction simulator. J Pharm Sci.1996;85(10):1085-90.

111. Janicki S, et al. Gastrointesting therapeutic system delivering of a water insoluble drug : isosorbide dinitrate (ISDN). Pharmazie 1987;42:95-96.

APPENDIX

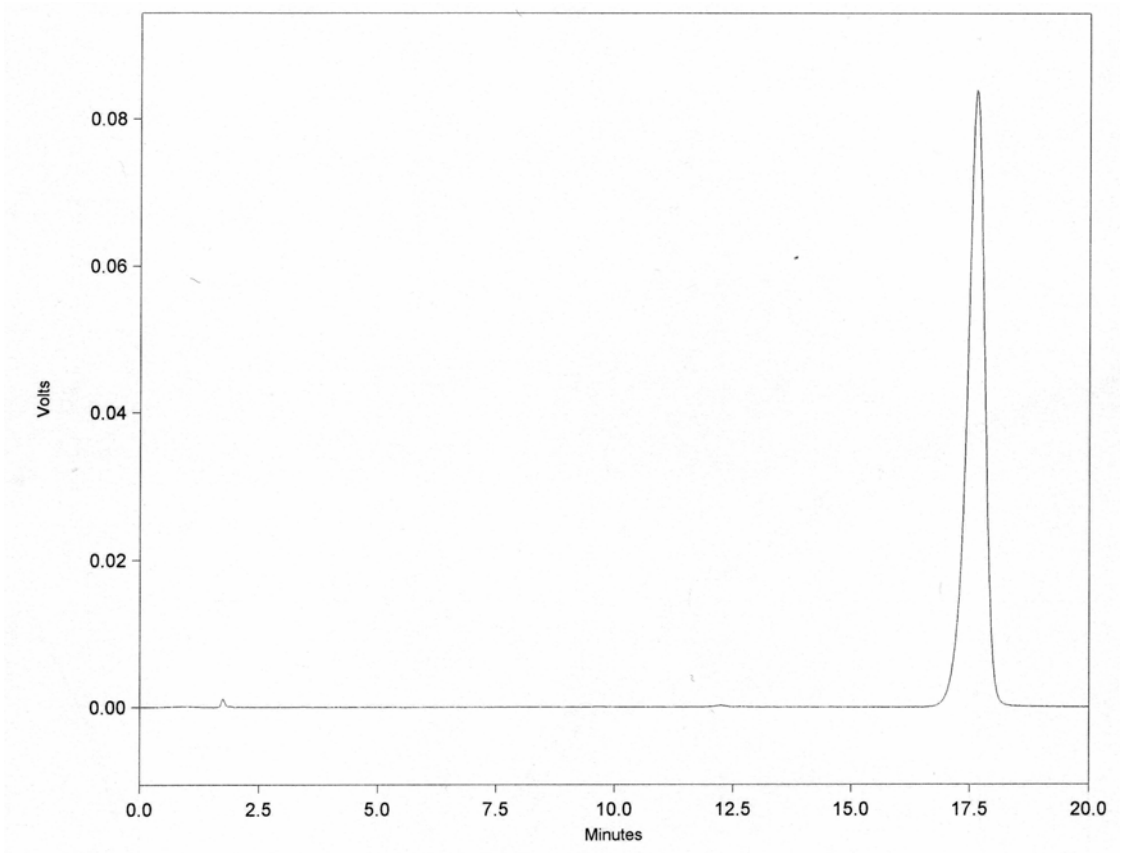

Figure 76. HPLC chromatogram of felodipine

Calibration curves of felodipine

Table 26. Peak area of felodipine assayed by HPLC method

Concentration (mg/L)	Peak area
5	119773.7
10	210048.2
20	411566.6
30	620667.0
40	841377.6

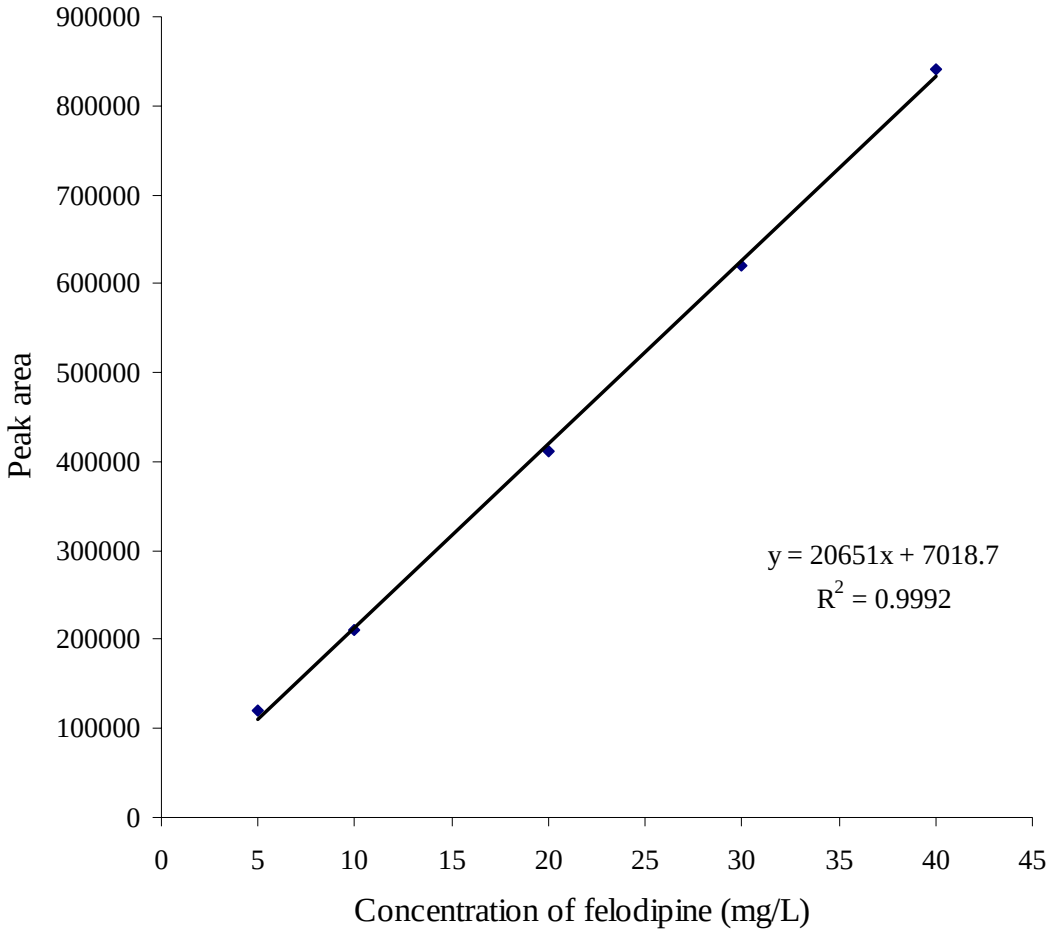

Figure 77. Calibration curve of felodipine by HPLC

Calibration curves of felodipine

Table 27. UV absorbance data of felodipine in 6.5 phosphate buffer at 362 nm

Concentration (mg/L)	Absorbance
6	0.109
10	0.177
20	0.356
30	0.530
40	0.708

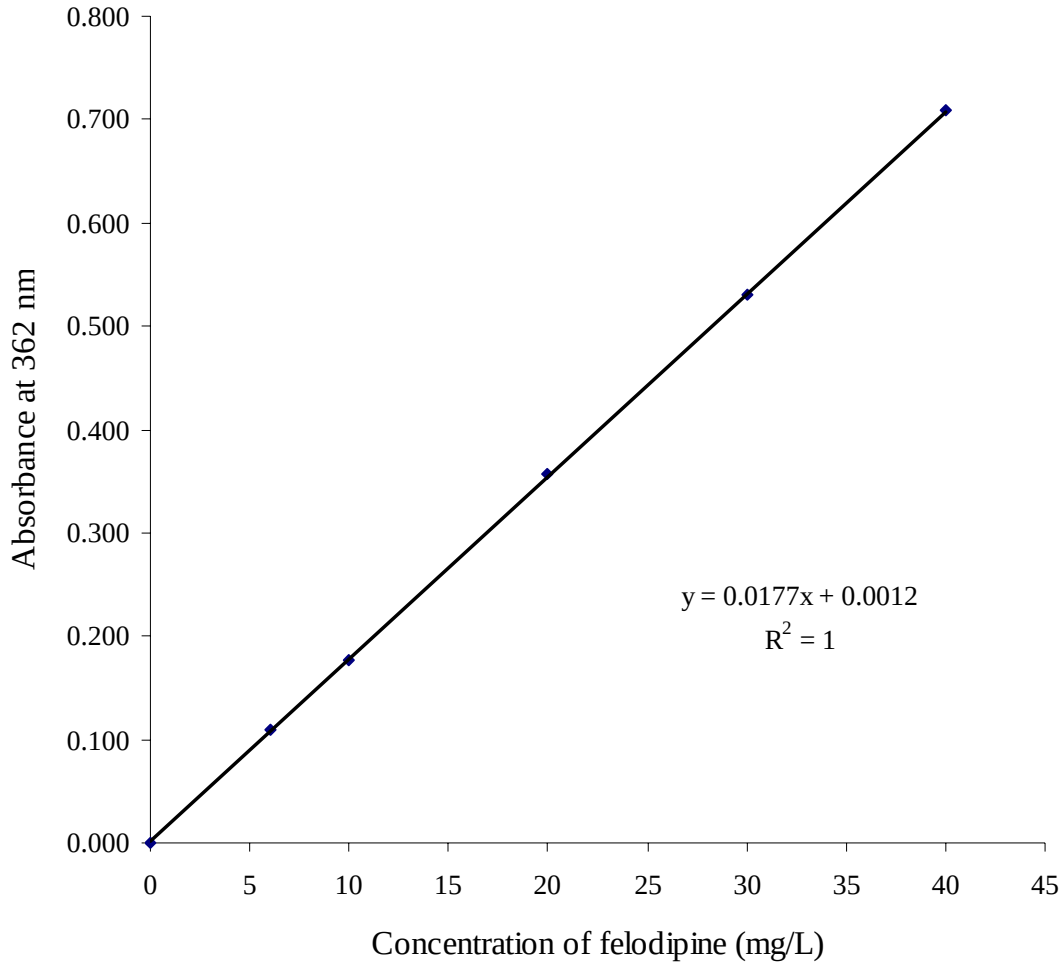

Figure 78. Calibration curve of felodipine in pH 6.5 phosphate at 362 nm

Table 28. Effect of various CS: PAA on the swelling force of complex

Time (min)	1:2	1:1	2:1
0	0.018	0.0196	0.0206
5	2.9017	4.3274	3.506
10	3.7497	5.4747	4.5395
15	4.3506	6.369	5.299
20	4.91	7.170	6.1956
25	5.4983	7.9482	7.1776
30	6.0322	8.7269	8.3918
35	6.6105	9.4897	9.2222
40	7.2179	10.23	10.063
45	7.7432	10.932	10.897
50	8.1627	11.943	11.687
55	8.6514	12.621	12.462
60	9.066	13.233	13.199
70	9.8921	13.759	14.636
80	10.496	14.578	15.981
90	11.314	15.262	17.246
100	11.754	15.842	18.389
110	12.064	16.311	19.413
120	12.313	16.811	20.329
130	12.629	17.282	21.103
140	12.857	17.683	21.849
150	13.118	18.031	22.507
160	13.356	18.353	23.148
170	13.666	18.621	23.727
180	13.887	18.822	24.191

Table 28. Effect of various CS: PAA ratios on the swelling force of complex (cont.)

Time (min)	1:2	1:1	2:1
190	14.052	19.015	24.557
200	14.246	19.178	24.942
210	14.42	19.316	25.239
220	14.478	19.538	25.479
230	14.54	19.783	25.754
240	14.65	19.849	26.067
250	14.74	20.07	26.263
260	14.841	20.274	26.357
270	14.947	20.325	26.562
280	14.977	20.328	26.75
290	14.996	20.355	26.818
300	15.117	20.455	26.934
310	15.262	20.511	27.087
320	15.33	20.582	27.272
330	15.378	20.637	27.355
340	15.436	20.680	27.386
350	15.469	20.776	27.458
360	15.49	20.793	27.598

Table 29. Effect of various CS: PAA ratios on the swelling ratio of complex

Time (min)	1:2	1:1	2:1
0	0.000	0	0.000
15	1.793	2.1	1.077
30	2.993	3.66	1.890
45	3.633	5.32	2.630
60	4.703	6.44	3.387
75	4.703	7.05	4.197
90	4.263	7.61	4.993
105	3.280	8.06	5.940
120	2.363	8.89	7.090
150	0.443	7.23	9.167
180	0.000	3.86	11.460
210			13.287
240			15.283
270			16.810
300			18.553
330			18.420
360			17.647

Table 30. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 150 mg of tablet weight using PEG 400 as plasticizer

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.73 (1.40)	0.51 (1.32)	2.63 (1.43)
3	9.69 (1.53)	10.16 (1.39)	12.64 (2.45)
4	20.47 (1.50)	20.82 (1.98)	24.38 (3.34)
5	31.45 (1.83)	32.84 (1.87)	36.03 (3.93)
6	42.41 (1.96)	43.60 (1.46)	46.94 (3.99)
7	53.13 (2.57)	54.23 (2.30)	58.52 (4.52)
8	61.43 (2.41)	63.44 (2.22)	68.66 (4.59)
9	67.76 (2.65)	71.33 (2.10)	76.35 (4.64)
10	73.49 (2.42)	77.92 (1.36)	82.26 (4.56)
11	77.90 (2.43)	83.72 (1.15)	86.55 (4.36)
12	82.03 (2.84)	87.55 (0.94)	88.98 (3.42)
13	84.38 (2.46)	89.91 (1.21)	89.80 (3.29)
14	85.63 (2.24)	91.42 (1.29)	90.52 (3.11)
15	86.37 (2.14)	92.97 (0.89)	90.84 (2.67)
16	86.78 (2.21)	92.97 (0.89)	91.20 (2.76)

Table 31. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 150 mg of tablet weight using DBS as plasticizer

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
3	0.12 (1.53)	0.57 (1.06)	0.28 (0.69)
4	2.30 (1.05)	3.05 (1.00)	4.98 (0.53)
5	7.64 (1.49)	8.88 (1.18)	11.31 (1.20)
6	13.64 (1.43)	14.22 (1.54)	17.44 (1.87)
7	19.39 (1.39)	19.73 (1.99)	23.86 (2.39)
8	24.13 (1.16)	25.06 (1.67)	29.65 (2.89)
9	29.07 (1.02)	30.59 (1.69)	34.86 (3.16)
10	35.47 (0.74)	36.38 (1.74)	41.81 (3.84)
11	42.23 (1.08)	42.12 (2.16)	47.96 (4.01)
12	49.14 (1.20)	48.34 (2.05)	53.87 (3.89)
13	54.00 (1.50)	54.48 (2.17)	59.15 (4.15)
14	58.93 (1.34)	58.78 (2.10)	63.59 (4.44)

Table 31. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 150 mg of tablet weight using DBS as plasticizer (cont.)

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
15	63.91 (1.30)	64.08 (1.72)	67.94 (4.33)
16	68.26 (1.41)	68.30 (1.79)	71.67 (4.22)
17	72.12 (1.38)	72.05 (1.75)	75.64 (4.25)
18	75.70 (1.26)	75.87 (1.62)	78.35 (4.26)
19	79.47 (1.24)	78.90 (1.60)	81.56 (3.94)
20	82.05 (0.98)	81.40 (1.79)	83.19 (3.41)
21	84.55 (1.09)	84.23 (1.46)	85.81 (2.63)
22	86.92 (1.25)	87.68 (1.46)	87.45 (2.01)
23	89.13 (1.28)	90.70 (1.38)	88.89 (1.68)
24	90.70 (0.90)	92.70 (1.16)	88.89 (1.68)

Table 32. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 130 mg of tablet weight using PEG 400 as plasticizer

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	3.82 (1.31)	3.33 (0.81)	2.84 (1.02)
3	11.53 (1.31)	12.80 (2.05)	12.99 (2.59)
4	21.43 (2.54)	24.21 (2.48)	25.28 (2.01)
5	31.51 (3.71)	34.86 (3.22)	37.14 (2.05)
6	42.32 (5.04)	45.56 (3.16)	48.32 (2.33)
7	50.54 (5.24)	55.90 (3.94)	58.89 (3.52)
8	60.24 (6.00)	65.75 (3.93)	67.78 (3.73)
9	68.49 (6.28)	73.41 (3.68)	75.25 (3.60)
10	76.17 (6.17)	80.18 (3.14)	80.85 (3.33)
11	81.96 (5.83)	84.88 (2.56)	85.49 (3.11)
12	86.53 (5.34)	88.14 (2.33)	88.76 (2.84)
13	89.38 (4.92)	90.18 (2.59)	91.04 (2.66)
14	91.33 (4.16)	90.69 (2.74)	92.09 (2.26)
15	92.54 (3.42)	91.58 (2.90)	92.95 (1.71)
16	93.26 (2.78)	92.46 (2.92)	93.50 (1.41)

Table 33. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 130 mg of tablet weight using DBS as plasticizer

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
3	3.06 (0.39)	2.84 (0.61)	3.22 (1.59)
4	9.19 (0.48)	8.93 (0.57)	9.46 (2.32)
5	15.89 (1.06)	15.83 (0.65)	16.36 (2.88)
6	22.83 (2.16)	23.24 (0.98)	24.28 (3.16)
7	29.98 (3.08)	30.55 (0.90)	32.01 (3.42)
8	38.20 (3.69)	37.75 (1.17)	39.85 (3.96)
9	45.32 (4.10)	44.77 (1.73)	47.74 (4.40)
10	53.43 (4.31)	51.74 (2.21)	56.03 (4.56)
11	60.62 (4.27)	58.87 (2.47)	63.23 (4.64)
12	66.62 (4.79)	64.83 (2.77)	69.41 (4.44)
13	72.14 (4.83)	70.44 (2.71)	74.74 (4.62)
14	77.03 (4.90)	75.47 (2.53)	79.49 (3.95)

Table 33. Effect of various CS: PAA ratios on drug release of felodipine push-pull osmotic tablets at 130 mg of tablet weight using DBS as plasticizer (cont.)

Time	% Dissolved (SD)		
(h)	1:2	1:1	2:1
15	81.08 (4.89)	79.65 (2.64)	82.69 (4.52)
16	84.31 (4.87)	83.37 (2.80)	86.31 (4.50)
17	87.74 (4.61)	86.57 (2.86)	89.27 (4.51)
18	90.54 (4.42)	89.13 (3.19)	91.33 (4.68)
19	92.51 (3.84)	91.43 (3.52)	92.94 (5.15)
20	93.29 (3.99)	92.36 (3.80)	94.42 (4.84)
21	93.97 (3.79)	92.49 (3.62)	95.39 (4.34)
22	94.13 (3.95)	92.80 (3.62)	95.97 (3.90)
23	94.22 (3.78)	93.38 (3.54)	96.70 (3.64)
24	94.22 (3.78)	93.25 (3.31)	96.70 (3.96)

Table 34. Effect of compression force on drug release of felodipine push-pull osmotic tablets at CS:PAA ratio of 1:1 and 150 mg of tablet weight, using PEG 400 as plasticizer.

Time	% Dissolved (SD)		
(h)	156 Mpa	234 Mpa	390 Mpa
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	3.45 (0.72)	3.23 (0.97)	5.32 (0.76)
3	16.45 (1.30)	12.80 (1.24)	18.60 (1.09)
4	33.72 (2.69)	32.82 (1.19)	34.91 (1.41)
5	50.22 (2.77)	48.76 (0.77)	51.48 (3.96)
6	64.35 (2.83)	61.81 (1.84)	65.52 (4.32)
7	74.38 (2.70)	72.03 (1.13)	75.49 (4.61)
8	82.03 (2.99)	78.98 (1.96)	82.41 (3.97)
9	86.13 (3.08)	84.42 (1.43)	86.07 (2.89)
10	87.83 (3.05)	86.77 (0.79)	87.52 (2.13)
11	88.32 (3.10)	87.81 (0.47)	88.61 (1.86)
12	88.39 (3.09)	87.97 (0.45)	89.10 (1.61)
13	88.43 (3.25)	88.15 (0.47)	89.92 (1.49)
14	88.46 (3.18)	88.15 (0.59)	89.92 (1.49)

Table 35. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-1	F-2	F-3	F-4
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	0.00 (0.00)	11.95 (0.89)	7.97 (1.76)	2.89 (0.57)
3	3.39 (1.43)	27.52 (1.88)	20.48 (3.38)	10.98 (0.53)
4	13.93 (1.57)	41.63 (2.03)	39.16 (2.29)	20.81 (2.11)
5	21.75 (1.19)	56.74 (2.15)	53.18 (2.87)	30.55 (2.65)
6	31.85 (1.15)	67.36 (2.48)	64.36 (1.92)	40.48 (3.24)
7	42.06 (0.55)	75.75 (2.96)	74.30 (1.58)	49.05 (3.02)
8	51.25 (0.78)	81.4 (2.50)	81.17 (1.83)	58.06 (2.40)
9	57.56 (0.40)	86.01 (2.90)	64.97 (1.88)	64.97 (2.61)
10	63.14 (1.19)	87.74 (3.01)	88.12 (1.22)	70.87 (1.87)
11	67.82 (0.80)	88.62 (3.04)	88.12 (1.23)	76.05 (2.04)
12	73.38 (1.15)	88.62 (3.07)	88.12 (1.24)	82.28 (1.06)

Table 36. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-5	F-6	F-7	F-8
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	7.40 (1.29)	1.77 (0.55)	1.07 (0.52)	11.82 (1.49)
3	22.80 (3.00)	9.74 (0.88)	8.38 (0.90)	28.55 (3.07)
4	41.50 (3.40)	21.06 (1.03)	20.65 (1.41)	45.44 (3.50)
5	55.50 (2.58)	27.61 (1.51)	30.41 (1.60)	60.38 (3.98)
6	66.70 (4.58)	37.69 (1.69)	40.93 (1.82)	75.41 (4.31)
7	76.00 (4.25)	46.11 (1.79)	54.29 (1.64)	84.48 (3.17)
8	79.70 (2.33)	56.42 (1.60)	65.67 (1.57)	88.40 (1.76)
9	80.50 (2.35)	64.61 (1.73)	74.33 (1.30)	90.04 (1.93)
10	81.20 (2.37)	70.65 (1.11)	80.52 (0.80)	90.04 (1.94)
11	82.00 (2.39)	76.42 (1.40)	85.62 (0.94)	90.04 (1.93)
12	82.80 (2.41)	80.06 (1.39)	89.75 (1.64)	90.04 (1.93)

Table 37. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-9	F-10	F-11	F-12
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.74 (0.59)	0.00 (0.00)	0.00 (0.00)	2.59 (0.71)
2	12.38 (1.12)	9.36 (0.84)	7.86 (1.36)	19.22 (3.54)
3	30.64 (3.71)	21.93 (1.19)	22.86 (1.35)	41.31 (1.37)
4	50.06 (1.36)	33.92 (1.95)	41.04 (1.11)	64.90 (0.85)
5	63.06 (2.41)	49.30 (1.80)	57.04 (2.11)	74.01 (2.13)
6	75.08 (3.51)	60.91 (1.74)	69.27 (1.86)	83.85 (1.75)
7	82.12 (2.63)	69.48 (1.29)	79.17 (2.12)	90.78 (1.25)
8	84.62 (2.10)	77.36 (1.52)	86.90 (1.58)	92.86 (1.22)
9	84.62 (2.10)	80.54 (1.60)	90.52 (1.19)	92.86 (1.23)
10	84.62 (2.10)	83.73 (1.45)	91.68 (0.80)	92.86 (1.24)
11	84.62 (2.10)	86.43 (1.49)	91.68 (0.60)	92.86 (1.24)
12	84.62 (2.10)	87.91 (0.82)	91.68 (0.60)	92.86 (1.24)

Table 38. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-13	F-14	F-15	F-16
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	2.41 (1.35)	2.00 (0.60)	0.00 (0.00)
2	8.38 (1.37)	17.87 (1.86)	17.04 (1.86)	12.93 (1.05)
3	22.00 (3.13)	39.48 (3.13)	34.91 (2.56)	29.26 (2.41)
4	36.13 (3.01)	57.85 (1.83)	52.35 (3.00)	44.89 (2.68)
5	50.17 (2.78)	73.50 (2.95)	69.37 (4.69)	59.98 (2.25)
6	62.16 (1.99)	81.69 (2.35)	80.46 (3.88)	73.90 (1.90)
7	70.38 (1.98)	85.94 (1.16)	87.25 (2.49)	84.48 (3.19)
8	77.13 (1.97)	85.94 (1.16)	88.75 (1.52)	88.73 (1.75)
9	79.57 (1.42)	85.94 (1.16)	89.27 (0.98)	90.82 (1.46)
10	81.40 (1.75)	85.94 (1.16)	89.27 (0.98)	92.14 (1.41)
11	81.40 (1.41)	85.94 (1.16)	89.27 (0.98)	92.14 (1.41)
12	81.40 (1.41)	85.94 (1.16)	89.27 (0.98)	92.14 (1.41)

Table 39. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-17	F-18	F-19	F-20
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.45 (0.00)
2	6.98 (0.15)	1.35 (0.77)	4.82 (0.79)	9.30 (1.19)
3	18.27 (2.20)	8.69 (1.12)	16.41 (2.64)	23.82 (1.43)
4	33.87 (3.83)	19.28 (1.40)	29.75 (2.04)	37.67 (2.57)
5	44.49 (3.82)	31.60 (3.22)	41.59 (1.66)	47.84 (4.26)
6	55.12 (4.05)	45.34 (2.89)	55.74 (2.41)	63.71 (3.56)
7	67.02 (4.03)	58.66 (4.33)	65.04 (1.77)	76.32 (4.07)
8	74.85 (3.28)	67.21 (4.04)	71.91 (2.26)	83.47 (3.87)
9	81.25 (2.91)	73.96 (2.90)	75.77 (2.28)	89.44 (2.74)
10	85.02 (2.54)	78.34 (2.05)	79.16 (2.25)	92.21 (2.36)
11	87.32 (1.96)	79.89 (1.41)	81.78 (1.73)	92.21 (2.36)
12	89.03 (1.130	79.89 (1.41)	81.78 (1.73)	92.21 (2.36)

Table 40. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-21	F-22	F-23	F-24
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.64 (0.58)
2	6.78 (1.38)	6.14 (0.89)	2.93 (1.19)	17.40 (1.80)
3	20.55 (1.98)	15.23 (1.08)	11.03 (1.66)	36.45 (2.48)
4	37.67 (2.76)	26.71 (1.60)	18.73 (1.97)	53.10 (2.91)
5	51.04 (2.98)	37.84 (1.52)	28.66 (2.66)	67.15 (4.55)
6	64.27 (3.94)	46.91 (1.67)	36.87 (2.72)	77.31 (3.13)
7	73.71 (3.14)	55.84 (1.31)	45.30 (3.62)	83.49 (1.47)
8	80.58 (2.90)	62.49 (1.34)	53.86 (3.88)	86.28 (1.30)
9	83.13 (2.73)	68.60 (1.11)	61.35 (3.82)	88.18 (1.76)
10	84.58 (3.25)	73.12 (1.63)	67.30 (3.72)	89.69 (1.56)
11	84.58 (3.03)	77.02 (1.30)	72.48 (3.82)	90.53 (1.30)
12	84.58 (3.03)	80.10 (1.72)	77.81 (3.24)	90.86 (1.30)

Table 41. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-25	F-26	F-27	F-28
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	15.91 (3.08)	2.72 (0.94)	7.44 (1.71)	7.71 (0.96)
3	33.83 (2.79)	11.91 (1.19)	20.32 (1.98)	20.45 (1.55)
4	53.84 (1.79)	23.16 (1.34)	33.27 (2.53)	33.59 (2.22)
5	71.09 (1.81)	33.46 (2.18)	47.70 (2.35)	48.18 (3.20)
6	83.29 (1.82)	44.54 (2.23)	62.76 (2.27)	61.95 (2.18)
7	89.99 (1.84)	55.53 (2.23)	70.12 (2.67	73.04 (2.26)
8	91.77 (1.86)	65.29 (3.09)	76.97 (2.80)	78.95 (2.03)
9	91.77 (1.86)	71.70 (3.46)	83.83 (2.90)	83.78 (1.89)
10	91.77 (1.86)	76.83 (2.88)	90.16 (1.97)	87.31 (2.07)
11	91.77 (1.86)	82.54 (3.72)	90.78 (1.13)	91.35 (2.03)
12	91.77 (1.86)	85.57 (3.16)	91.01 (1.13)	91.35 (2.05)

Table 42. Dissolution data of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

Time	% Dissolved (SD)			
(h)	F-29	F-30	F-31	F-32
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
2	7.06 (0.75)	8.01 (0.97)	7.13 (1.71)	7.58 (0.75)
3	20.09 (1.06)	20.87 (1.55)	19.85 (1.98)	20.61 (1.06)
4	35.11 (0.95)	34.02 (2.22)	32.79 (2.53)	35.64 (0.95)
5	50.41 (1.12)	48.62 (3.20)	47.22 (2.35)	50.95 (1.12)
6	63.45 (1.15)	63.70 (2.18)	64.07 (2.27)	62.62 (1.15)
7	72.55 (1.20)	73.93 (2.32)	71.46 (2.67)	72.12 (0.92)
8	79.60 (0.61)	79.85 (1.93)	78.32 (2.80)	79.01 (0.49)
9	84.75 (0.49)	84.25 (1.89)	83.92 (2.90)	84.12 (0.88)
10	90.19 (1.55)	90.20 (2.07)	89.95 (1.97)	90.20 (1.55)
11	90.19 (1.34)	90.20 (2.03)	90.65 (1.13)	90.20 (1.34)
12	90.19 (1.35)	90.20 (2.05)	91.01 (1.13)	90.20 (1.34)

Table 43. Dissolution data of optimized formulation of felodipine push-pull osmotic tablets and blank formulation.

Time	% Dissolved (SD)	
(h)	Optimized formulation	Blank formulation
0	0.00 (0.00)	0.00 (0.00)
1	0.00 (0.00)	0.00 (0.00)
2	10.70 (1.57)	5.90 (0.56)
3	26.23 (2.29)	22.34 (1.53)
4	40.38 (2.90)	38.26 (1.38)
5	53.77 (3.40)	53.05 (2.16)
6	65.66 (3.53)	63.04 (2.77)
7	74.39 (3.25)	69.37 (3.58)
8	80.99 (2.40)	73.47 (3.45)
9	85.50 (2.70)	76.20 (3.32)
10	88.49 (2.10)	78.47 (3.00)
11	89.92 (1.99)	79.71 (2.39)
12	90.43 (1.71)	80.00 (1.94)

Table 44 Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-1	F-2	F-3
0	0.0000	0.0000	0.0000
10	0.1056	0.0955	0.1304
20	0.1068	0.0990	0.1347
30	0.1080	0.1035	0.1385
40	0.1109	0.1065	0.1423
50	0.1124	0.1128	0.1462
60	0.1141	0.1153	0.1505
70	0.1160	0.1199	0.1523
80	0.1181	0.1199	0.1598
90	0.1194	0.1300	0.1632
100	0.1227	0.1361	0.1722
110	0.1261	0.1416	0.1837
120	0.1289	0.1513	0.1872
130	0.1316	0.1663	0.1906
140	0.1343	0.1712	0.1937
150	0.1370	0.1761	0.1974
160	0.1399	0.1790	0.2008
170	0.1442	0.1848	0.2039

Table 44. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.)

	Amount of water (g)		
Time (min)	F-1	F-2	F-3
180	0.1459	0.1892	0.2067
210	0.1558	0.2069	0.2130
240	0.1670	0.2217	0.2208
270	0.1884	0.2370	0.2279
300	0.1884	0.2478	0.2351
330	0.1961	0.2583	0.2421
360	0.2035	0.2644	0.2492
390	0.2146	0.2713	0.2554
420	0.2186	0.2789	0.2621
480	0.2322	0.2990	0.2737
510	0.2394	0.3037	0.2792
540	0.1131	0.3093	0.2853
570	0.1137	0.3166	0.2906
600	0.1141	0.3235	0.2968
630	0.2608	0.3301	0.3024
660	0.2678	0.3395	0.3082
690	0.2745	0.3451	0.3140
720	0.2818	0.3486	0.3199

Table 45. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-4	F-5	F-6
0	0.0000	0.0000	.00000
10	0.1143	0.1196	0.1053
20	0.1147	0.1229	0.1075
30	0.1169	0.1264	0.1096
40	0.1192	0.1300	0.1114
50	0.1230	0.1338	0.1133
60	0.1246	0.1379	0.1155
70	0.1274	0.1422	0.1182
80	0.1304	0.1448	0.1198
90	0.1322	0.1515	0.1242
100	0.1364	0.1579	0.1274
110	0.1396	0.1650	0.1306
120	0.1430	0.1759	0.1340
130	0.1465	0.1866	0.1372
140	0.1504	0.2037	0.1406
150	0.1544	0.2080	0.1440
160	0.1590	0.2159	0.1487
170	0.1636	0.2243	0.1512

Table 45. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-4	F-5	F-6
180	0.1685	0.2326	0.1551
210	0.1845	0.2596	0.1655
240	0.2020	0.2934	0.1816
270	0.2207	0.3143	0.1857
300	0.2276	0.3308	0.1899
330	0.2378	0.3484	0.1929
360	0.2416	0.3691	0.1994
390	0.2485	0.3819	0.2052
420	0.2552	0.3956	0.2087
480	0.2697	0.4111	0.2171
510	0.2789	0.4179	0.2218
540	0.2864	0.4245	0.2261
570	0.2939	0.4308	0.2307
600	0.3012	0.4374	0.2357
630	0.3079	0.4422	0.2401
660	0.3131	0.4455	0.2446
690	0.3217	0.4481	0.2486
720	0.3266	0.4499	0.2535

Table 46. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-7	F-8	F-9
0	0.0000	0.0000	0.0000
10	0.1032	0.1227	0.1130
20	0.1040	0.1261	0.1162
30	0.1061	0.1299	0.1203
40	0.1077	0.1342	0.1247
50	0.1101	0.1395	0.1277
60	0.1142	0.1454	0.1304
70	0.1154	0.1525	0.1369
80	0.1186	0.1616	0.1419
90	0.1217	0.1711	0.1608
100	0.1251	0.1857	0.1669
110	0.1289	0.1930	0.1725
120	0.1318	0.1957	0.1765
130	0.1370	0.1963	0.1813
140	0.1409	0.1993	0.1889
150	0.1454	0.2057	0.1909
160	0.1500	0.2085	0.1953
170	0.1550	0.2128	0.1989

Table 46. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont).

	Amount of water (g)		
Time (min)	F-7	F-8	F-9
180	0.1634	0.2158	0.2000
210	0.1777	0.2210	0.2138
240	0.1984	0.2307	0.2238
270	0.2120	0.2398	0.2339
300	0.2257	0.2507	0.2427
330	0.2406	0.2542	0.2524
360	0.2535	0.2621	0.2597
390	0.2645	0.2693	0.2683
420	0.2724	0.2753	0.2757
480	0.2948	0.2872	0.2947
510	0.3018	0.2922	0.3019
540	0.3096	0.2989	0.3102
570	0.3163	0.3026	0.3158
600	0.3259	0.3084	0.3228
630	0.3342	0.3137	0.3271
660	0.3435	0.3179	0.3314
690	0.3525	0.3240	0.3337
720	0.3611	0.3290	0.3369

Table 47. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-10	F-11	F-12
0	0.0000	0.0000	0.0000
10	0.0854	0.0953	0.1450
20	0.0889	0.0993	0.1430
30	0.0923	0.1020	0.1467
40	0.0961	0.1052	0.1514
50	0.1002	0.1088	0.1564
60	0.1041	0.1147	0.1618
70	0.1078	0.1165	0.1691
80	0.1116	0.1206	0.1786
90	0.1155	0.1249	0.1910
100	0.1195	0.1297	0.1962
110	0.1240	0.1351	0.2022
120	0.1291	0.1414	0.2067
130	0.1357	0.1483	0.2114
140	0.1440	0.1604	0.2169
150	0.1589	0.1695	0.2228
160	0.1630	0.1739	0.2287
170	0.1658	0.1795	0.2345

Table 47. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-10	F-11	F-12
180	0.1707	0.1832	0.2407
210	0.1883	0.1905	0.2570
240	0.1996	0.2012	0.2732
270	0.2103	0.2172	0.2888
300	0.2212	0.2272	0.3007
330	0.2304	0.2359	0.3140
360	0.2415	0.2417	0.3262
390	0.2504	0.2543	0.3361
420	0.2594	0.2650	0.3441
480	0.2759	0.2859	0.3598
510	0.2831	0.2964	0.3657
540	0.2896	0.3058	0.3712
570	0.2955	0.3149	0.3765
600	0.3010	0.3192	0.3836
630	0.3056	0.3256	0.3860
660	0.3096	0.3317	0.3892
690	0.3136	0.3373	0.3918
720	0.3173	0.3414	0.3943

Table 48. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-13	F-14	F-15
0	0.0000	0.0000	0.0000
10	0.0962	0.1477	0.1295
20	0.0990	0.1506	0.1324
30	0.1017	0.1543	0.1425
40	0.1052	0.1587	0.1460
50	0.1090	0.1641	0.1502
60	0.1129	0.1714	0.1569
70	0.1171	0.1853	0.1655
80	0.1220	0.1917	0.1743
90	0.1277	0.1941	0.1877
100	0.1343	0.1977	0.1941
110	0.1421	0.2021	0.1973
120	0.1516	0.2069	0.2036
130	0.1600	0.2109	0.2096
140	0.1696	0.2143	0.2157
150	0.1950	0.2184	0.2225
160	0.2000	0.2208	0.2290
170	0.2068	0.2220	0.2349

Table 48. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-13	F-14	F-15
180	0.2147	0.2235	0.2421
210	0.2279	0.2308	0.2585
240	0.2409	0.2390	0.2744
270	0.2608	0.2474	0.2878
300	0.2780	0.2558	0.2974
330	0.2963	0.2640	0.3019
360	0.3151	0.2728	0.3089
390	0.3278	0.2761	0.3156
420	0.3381	0.2816	0.3260
480	0.3529	0.2926	0.3431
510	0.3607	0.2982	0.3509
540	0.3698	0.3035	0.3577
570	0.3779	0.3084	0.3641
600	0.3859	0.3136	0.3716
630	0.3920	0.3183	0.3761
660	0.3969	0.3221	0.3805
690	0.4013	0.3272	0.3830
720	0.4051	0.3494	0.3846

Table 49. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-16	F-17	F-18
0	0.0000	0.0000	0.0000
10	0.1350	0.1068	0.0991
20	0.1392	0.1109	0.1008
30	0.1425	0.1145	0.1031
40	0.1459	0.1200	0.1061
50	0.1497	0.1226	0.1091
60	0.1538	0.1279	0.1141
70	0.1582	0.1326	0.1157
80	0.1609	0.1381	0.1193
90	0.1689	0.1441	0.1236
100	0.1763	0.1492	0.1280
110	0.1831	0.1640	0.1326
120	0.1950	0.1705	0.1376
130	0.1996	0.1727	0.1430
140	0.2019	0.1762	0.1493
150	0.2062	0.1812	0.1568
160	0.2115	0.1851	0.1645
170	0.2146	0.1888	0.1723

Table 49. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-16	F-17	F-18
180	0.2189	0.1926	0.1805
210	0.2337	0.2005	0.2083
240	0.2456	0.2090	0.2253
270	0.2568	0.2166	0.2449
300	0.2669	0.2252	0.2569
330	0.2769	0.2339	0.2684
360	0.2852	0.2424	0.2823
390	0.2931	0.2506	0.2963
420	0.3018	0.2577	0.3069
480	0.3130	0.2710	0.3287
510	0.3187	0.2772	0.3378
540	0.3228	0.2835	0.3478
570	0.3272	0.2898	0.3600
600	0.3314	0.2955	0.3738
630	0.3365	0.3009	0.3864
660	0.3397	0.3052	0.3955
690	0.3458	0.3116	0.4029
720	0.3502	0.3195	0.4092

Table 50. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-19	F-20	F-21
0	0.0000	0.0000	0.0000
10	0.0925	0.0970	0.0883
20	0.0952	0.1028	0.0930
30	0.0981	0.1079	0.0967
40	0.1009	0.1108	0.1019
50	0.1052	0.1145	0.1045
60	0.1069	0.1188	0.1087
70	0.1102	0.1247	0.1132
80	0.1135	0.1316	0.1160
90	0.1169	0.1356	0.1230
100	0.1204	0.1459	0.1286
110	0.1240	0.1540	0.1351
120	0.1280	0.1620	0.1423
130	0.1329	0.1771	0.1501
140	0.1389	0.1887	0.1664
150	0.1456	0.2008	0.1722
160	0.1519	0.2097	0.1762
170	0.1623	0.2255	0.1837

Table 50. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-19	F-20	F-21
180	0.1660	0.2317	0.1850
210	0.1819	0.2432	0.1962
240	0.1889	0.2576	0.2069
270	0.1996	0.2701	0.2140
300	0.2115	0.2836	0.2234
330	0.2205	0.2967	0.2329
360	0.2319	0.3107	0.2452
390	0.2421	0.3217	0.2549
420	0.2549	0.3318	0.2655
480	0.2735	0.3493	0.2820
510	0.2832	0.3580	0.2901
540	0.2938	0.3666	0.2975
570	0.2999	0.3743	0.3055
600	0.3084	0.3823	0.3151
630	0.3151	0.3899	0.3210
660	0.3199	0.3960	0.3245
690	0.3231	0.4076	0.3286
720	0.3258	0.4118	0.3329

Table 51. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-22	F-23	F-24
0	0.0000	0.0000	0.0000
10	0.0857	0.0945	0.0962
20	0.0885	0.0974	0.0991
30	0.0907	0.1001	0.1017
40	0.0934	0.1027	0.1052
50	0.0964	0.1053	0.1090
60	0.0996	0.1081	0.1129
70	0.1028	0.1109	0.1171
80	0.1048	0.1137	0.1221
90	0.1095	0.1165	0.1277
100	0.1132	0.1196	0.1343
110	0.1173	0.1226	0.1421
120	0.1214	0.1256	0.1517
130	0.1260	0.1287	0.1600
140	0.1309	0.1318	0.1696
150	0.1399	0.1350	0.1950
160	0.1447	0.1383	0.2000
170	0.1508	0.1419	0.2068

Table 51. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-22	F-23	F-24
180	0.1526	0.1458	0.2147
210	0.1604	0.1585	0.2279
240	0.1696	0.1709	0.2409
270	0.1848	0.1875	0.2607
300	0.1956	0.1936	0.2780
330	0.2012	0.1970	0.2963
360	0.2061	0.2003	0.3151
390	0.2120	0.2072	0.3270
420	0.2187	0.2153	0.3376
480	0.2327	0.2245	0.3529
510	0.2396	0.2294	0.3607
540	0.2474	0.2357	0.3698
570	0.2518	0.2407	0.3779
600	0.2575	0.2441	0.3859
630	0.2628	0.2472	0.3920
660	0.2699	0.2517	0.3969
690	0.2758	0.2550	0.4013
720	0.2792	0.2591	0.4051

Table 52. Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study.

	Amount of water (g)		
Time (min)	F-25	F-26	F-27
0	0.0000	0.0000	0.0000
10	0.1257	0.0971	0.1242
20	0.1280	0.0993	0.1257
30	0.1322	0.1005	0.1275
40	0.1353	0.1025	0.1294
50	0.1402	0.1038	0.1318
60	0.1457	0.1052	0.1348
70	0.1533	0.1068	0.1403
80	0.1636	0.1094	0.1418
90	0.1825	0.1125	0.1456
100	0.1881	0.1150	0.1504
110	0.1927	0.1188	0.1563
120	0.1996	0.1221	0.1626
130	0.2039	0.1259	0.1725
140	0.2087	0.1298	0.1784
150	0.2170	0.1341	0.1833
160	0.2206	0.1407	0.1867
170	0.2256	0.1439	0.1916

Table 52 Water uptake of felodipine push-pull osmotic pump tablets in central composite design for optimization study (cont.).

	Amount of water (g)		
Time (min)	F-25	F-26	F-27
180	0.2278	0.1490	0.1939
210	0.2371	0.1650	0.2041
240	0.2459	0.1723	0.2168
270	0.2544	0.1795	0.2263
300	0.2602	0.1874	0.2367
330	0.2685	0.1935	0.2450
360	0.2757	0.2010	0.2534
390	0.2841	0.2085	0.2617
420	0.2928	0.2171	0.2714
480	0.3076	0.2311	0.2922
510	0.3157	0.2389	0.2966
540	0.3232	0.2464	0.3027
570	0.3296	0.2535	0.3091
600	0.3339	0.2596	0.3152
630	0.3372	0.2662	0.3216
660	0.3411	0.2719	0.3266
690	0.3439	0.2774	0.3346
720	0.3473	0.2829	0.3391

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