ROLE OF POLYACRYLIC ACID ON DRUG RELEASE FROM CONTROLLED POROSITY OSMOTIC PUMP USING CHITOSAN-POLYACRYLIC ACID COMPLEXES AS POLYMERIC OSMOGENTS

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ABSTRACT

The aim of this study is to evaluate the swelling properties of the type of polyacrylic acid (PAA) and various ratios of chitosan-polyacrylic acid (CS-PAA) interpolymer complexes by using swelling force, swelling ratio and Fourier transform infrared (FTIR) characterization. The best swelling interpolymer complexes will be used as osmotic agents for the development of controlled-porosity osmotic pump tablets (CPOPs). The FTIR results indicated that interpolymer complex was formed between CS and PAA through an electrostatic interaction of the protonated amine (NH_3^+) group of CS and the carboxylate (COO^-) group of PAA. The swelling force and swelling ratio of CS-PAA interpolymer complex using PAA 971P NF at the ratio of 2:1 showed the best swelling properties. Diclofenac sodium was used as a model drug for the CPOPs drug formulations containing the CS-PAA interpolymer complex and using PAA 971P NF at the ratio of 2:1. The core tablets were coated with a mixture of 4% w/v cellulose acetate in acetone solution containing PVP K90 (50% w/v with respect to cellulose acetate) as pore formers, using 25% w/w TEC as a plasticizer, to achieve 10% additional weight by using the perforated pan coater. Finally, CPOPs were coated with the mixture of 6% w/w Eudragit L 100-55 in 95% ethanol/acetone (3:1) solution containing 25% w/w PEG6000 of the film content as a plasticizer, to achieve 6% additional weight by using the perforated pan coater. The results showed that the more amount of CS-PAA in tablet formulation was added, the more drug release rate was also increased. The data of enteric coated tablet showed that there were no drug release into the acidic medium solution within 2 h. It was acceptable for the tablet, which was designed to release drug in the intestine. Only the formulation containing the ratio of CS-PAA00 gave the zero order kinetic condition, whereas the others were fitted to the Higuchi model. The properties of the polymer, the ratios and the amount of the composition were the important factors to formulate these osmotic tablet formulations. The amount of CS-PAA could effect the rate of drug release from the tablets. It might be the more swelling and greater force producing to push the drug through the pores on the cellulose acetate. In conclusion, the formulation with CS-PAA gave less zero order kinetics than the formulation without CS-PAA.

KEY WORDS: CONTROLLED-POROSITY OSMOTIC PUMP / CHITOSAN / POLYACRYLIC ACID / SWELLING PROPERTY / OSMOGENTS

149 pages

บทบาทของกรดโพลิอะไครลิคต่อการปลดปล่อยยาจากยาเม็ดออสโมติคชนิดควบคุมรูพรุนโดยใช้สารประกอบเชิงซ้อนของไคโตซาน-กรดโพลิอะไครลิคเป็นสารพอลิเมอร์ก่อแรงดัน

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อประเมินคุณสมบัติการพองตัวของชนิดของกรดโพลิอะไครลิคและอัตราส่วนระหว่างสารประกอบเชิงซ้อนของไคโตซาน-กรดโพลิอะไครลิคโดยใช้คุณสมบัติดังนี้คือ แรงในการพองตัว อัตราการพองตัว และการตรวจสอบโดย FTIR แล้วจึงเลือกสารประกอบที่มีการพองตัวดีที่สุดมาใช้เป็นสารพอลิเมอร์ก่อแรงดันสำหรับยาเม็ดออสโมติคปั๊มชนิดควบคุมรูพรุน ผลการศึกษา FTIR แสดงว่าสารประกอบเชิงซ้อนที่เกิดขึ้นนั้นเกิดจากปฏิกิริยาระหว่างประจุบวกจากหมู่ NH_3^+ ของไคโตซานและประจุลบจากหมู่ COO^- ของกรดโพลิอะไครลิค การวัดคุณสมบัติในการพองตัวในแง่ของแรงในการพองตัวและอัตราส่วนของ PAA ที่เปลี่ยนแปลงของสารประกอบเชิงซ้อนของไคโคซานและโพลีอะไครลิกแอซิดชนิด 971P NF ที่อัตราส่วน 2:1 แสดงให้เห็นคุณสมบัติการพองตัวที่ดีที่สุด ได้เลือกไดโครฟีแนคโซเดียมมาใช้เป็นยาต้นแบบของยาเม็ดออสโมติคปั๊มซึ่งประกอบด้วยสารประกอบเชิงซ้อนของไคโคซานและโพลีอะไครลิกแอซิดชนิด 971P NF ที่อัตราส่วน 2:1 ยาเม็ดถูกเคลือบด้วยส่วนผสมของเซลลูโลสอะซิเตทที่ประกอบด้วย พีวีพีเค90 (ปริมาณร้อยละ 50%ของเซลลูโลสอะซิเตท) เป็นสารก่อรูและ 25% ของทีอีซีเป็นพลาสติไซเซอร์เคลือบ โดยมีปริมาณน้ำหนักของเมมเบรนเพิ่มขึ้นร้อยละ 10 ด้วยเครื่องเคลือบฟิลม์ หลังจากนั้นยาเม็ดออสโมติคปั๊มก็ถูกเคลือบด้วยส่วนผสมของ 6% ของยูดราจิคแอล 100-55 ใน 95%เอทานอล/อะซีโตน (3:1) ที่ประกอบด้วย 25% ของพีอีจี 6000 เป็นพลาสติไซเซอร์ โดยยาเม็ดเคลือบมีปริมาณน้ำหนักของเมมเบรนเพิ่มขึ้นร้อยละ 6 ด้วยเครื่องเคลือบฟิลม์ ผลการศึกษาแสดงให้เห็นว่า ปริมาณของCS-PAA ที่มากขึ้นจะทำให้มีการปลดปล่อยยามากขึ้น ข้อมูลของยาเม็ดที่เคลือบเพื่อให้ออกฤทธิ์ที่ลำไส้อยู่ในช่วงที่ยอมรับได้และแสดงให้เห็นว่า ยาไม่มีการปลดปล่อยในมีเดียมที่มีฤทธิ์เป็นกรดภายในเวลา 2 ชม. ยาจึงเหมาะสมในการปลดปล่อยที่ลำไส้เล็ก รูปแบบการปลดปล่อยของยาสูตร CS-PPA00 ถือเป็นปฏิกิริยาอันดับศูนย์ ในขณะที่สูตรอื่นๆเป็นปฏิกิริยา Higuchi คุณสมบัติของโพลิเมอร์ อัตราส่วนและปริมาณของโพลิเมอร์ เป็นปัจจัยสำคัญในรูปแบบยาเม็ดออสโมติด ปริมาณของ CS-PPA มีผลในการปลดปล่อยยาจากยาเม็ดโดยอาจจะมีการพองตัวที่มากกว่าและแรงมากกว่าในการผลักดันยาออกมา ผ่านทางรูพรุนของเซลลูโลสอะซิเตท โดยสรุปรูปแบบที่ใช้ CS-PPA จะให้สมการปฏิกิริยาอันดับศูนย์ที่น้อยกว่ารูปแบบที่ไม่ใช้ CS-PPA

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LIST OF ABBREVIATION

%	percent
°C	degree Celsius
ANOVA	analysis of variance
BCS	Biopharmaceutics Classification System
BE	bioequivalence
CA	cellulose acetate
cm	centimeter
COO^-	carboxylic acid
CPOP	controlled-porosity osmotic pump
CS	chitosan
e.g.	*exmpli gratia*; for example
EOP	elementary osmotic pump
EOPT	effervescent osmotic pump tablet
Eq.	equation
et al.	*et alii*, and others
etc.	*et cetera*; other things
FTIR	fourier transform infrared
g	gram
GI	gastrointestinal
h	hour
H-CS	high molecular weight chitosan
HPLC	high performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
i.e.	id est, that is
IR	immediate release
IS	internal standard
IVIVC	*in vitro–in vivo* correlation

LIST OF ABBREVIATION (cont.)

L	liter
□g	microgram
μL	microliter
□m	micrometer
mg	milligram
min	minute
mL	milliliter
mm	millimeter
MW	molecular weight
N	Newton
ng	nanogram
nm	nanometer
no.	number
OCDDS	osmotically controlled drug delivery systems
p	p-value
PAA	polyacrylic acid
PEG	polyethylene glycol
pH	the negative logarithm of the hydrogen ion concentration
pKa	the negative logarithm of the dissociation constant
PPOP	push-pull osmotic pump
PPOT	push-pull osmotic pump tablet
PVP	polyvinylpyrrolidone
QC	quality control
R^2	coefficient of determination
rpm	revolutions per minute
RSD	relative standard deviation
s	second
SD	standard deviation

LIST OF ABBREVIATION (cont.)

SEM	scanning electron microscopy
SOTS	sandwiched osmotic tablet system
$t_{1/2}$	half-life
T_{max}	time to maximum observed plasma drug concentration
TA	triacetin
TEC	triethyl citrate
US FDA	the United State Food and Drug Administration
USP	the United State Pharmacopeia
w/w	by weight

CHAPTER I
INTRODUCTION

Osmotically controlled drug delivery system is the delivery of drug in a large extent. The release of the drug is independent of physiological factors in the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs (1). Various types of osmotically controlled drug delivery systems have been introduced and investigated; e.g., elementary osmotic pumps (EOP), push-pull osmotic pump (PPOP), and controlled-porosity osmotic pump (CPOP) (2). The development of osmotically drug delivery systems for CPOP and PPOP requires the use of an agent to push the drug from the tablet; this is an “osmotic agent”, e.g. sodium chloride (NaCl), potassium chloride (KCl), chitosan (CS), and polyacrylic acid (PAA). CS and PAA are widely used as osmopolymer for osmotic pump tablets. CS is used in the polymerization reaction with various types of PAA including PAA 934P NF, PAA 971P NF and PAA 974P NF to form the CS-PAA interpolymer complex. In this study, the CS-PAA interpolymer complexes are applied in CPOP as an osmotic agent. The preparation of CPOP is by incorporating the manufacture of the bilayered tablets with the drug layer (diclofenac sodium and KCl) and the polymer layer (CS-PAA interpolymer complexes and KCl). The semipermeable membrane is using cellulose acetate mixed with triethyl citrate (TEC) and polyvinylpyrrolidone K-90 (PVP K-90) as plasticizer and pore formers, respectively. Therefore, the performance in swelling property and characterization of CS-PAA interpolymer complexes was evaluated. The optimized CS-PAA interpolymer complex is expected to develop in osmotic controlled drug delivery systems.

The purpose of this study was:

1.1 To prepare complexes of various CS and PAA weight ratios to determine the suitable swelling properties.

1.2 To investigate the effect of PAA types, ratios of the CS-PAA, and proportion of PAA in the CS-PAA complexes.

1.3 To evalulate the selected PAA for CS-PAA as a polymeric osmogent for the development of the CPOP tablets.

CHAPTER II
LITERATURE REVIEW

2.1 Osmotic controlled-release drug delivery systems

Osmotically controlled drug delivery systems (OCDDS) utilize osmosis and the natural movement of water through a membrane to control the systemic delivery of drug within the body (3, 4). Drug release from these systems is independent of pH of the gastrointestinal (GI) tract and other physiological factors, for examples, gastric motility and the presence or absence of foods in the GI tract. The release characteristics can be predicted/ programmed from knowledges about the properties of the drug and the dosage form. OCDDS as one type of the controlled release systems provide a uniform amount of drug at the absorption site and thus, after absorption, allow maintenance of plasma concentration within a therapeutic range, which is able to minimize side effects, reduce the frequency of administration and increase patient compliances (3-7). The OCDDS are an interesting pump, different from others, in that they run by directly using different osmotic pressure as their energy sources. The comparison between the advantages and disadvantages of the osmotic pump tablet system for oral administration is shown in Table 2.1 (8, 9).

Various types of OCDDS have been introduced and investigated; e.g., an elementary osmotic pump (EOP), a push-pull osmotic pump (PPOP), and a controlled porosity osmotic pump (CPOP) (2). The development of osmotically drug delivery systems for CPOP and PPOP requires use of an agent to push the drug from the tablet; this is an “osmotic agent”, e.g. sodium chloride (NaCl), potassium chloride (KCl), Chitosan (CS), and polyacrylic acid (PAA).

The oral osmotic pumps have certainly come along way and the available products based on this technology and number of patents granted in the last few years make its presence felt in the market. They are also known as gastro-intestinal therapeutic system (GITS) and today, different types of osmotic pumps are available to meet variety of drug delivery demands (Table 2.2) (4).

Table 2.1 The advantages and disadvantages of OCDDS (adapted from reference No. 9)

Advantages	Disadvantages
1. Easy to formulate and simple in operation.	1. Dose dumping.
2. A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.	2. Rapid development of tolerance.
3. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.	3. Retrieval therapy is not possible in the case of unexpected adverse events.
4. They typically give a zero order release profile after an initial lag.	4. Expensive.
5. The rationale for this approach is that the presence of water in gastrointestinal tract is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.	5. If the coating process is not well controlled, there is a risk of film defects, which results in dose dumpling.
6. Drug release is independent of gastric pH and hydrodynamic condition.	6. Size hole is critical.
7. They are well characterized and understood.	
8. The release mechanisms are not dependent on drug.	
9. Improve patient compliance with reduced frequency.	
10. Deliveries may be delayed or pulsed if desired.	
11. Prolonged therapeutic effect with uniform blood concentration.	
12. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.	
13. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.	

Table 2.2 Different types of commercially available osmotic systems (adapted from reference No. 4)

(I) Osmotic pumps for experimental research	
- ALZET (Durect Corp., USA)	Miniature, implantable osmotic pumps for laboratory animals. Commonly implanted subcutaneously or intraperitoneally but, with the help of a catheter, can be used for intracerebral, intravenous, and intraarterial infusion. Different models having delivery rates from 0.25 to 10 μL/h and durations from 1 day to 4 weeks available. Delivery profile independent of drug formulation.
- OSMET (Durect Corp.)	Used as experimental tools for human pharmacological studies and can be used for oral, rectal, or vaginal administration. Delivery profile independent of drug formulation and it is available with release rates ranging from 8 to 120 μL/h
(II) Osmotic pumps for humans	
- Elementary osmotic pump (Alza Corp., USA)	Single layer tablet for delivery of drugs having moderate water solubility.
- Push-pull osmotic pump (Alza Corp.)	Bilayer tablet, used to deliver drugs having low to high water solubility. Products such as Ditropan XL (oxybutynin chloride), Procardia XL (nifedipine), and Glucotrol XL (glipizide) are based on this technology Number of modifications available such as delayed push-pull system, multi-layer push-pull system, and push-stick system.

Table 2.2 Different types of commercially available osmotic systems (cont.) (adapted from reference No. 4)

- L-OROS (Alza Corp.)	Designed to deliver lipophilic liquid formulations and is suitable for delivery of insoluble drugs.
- OROS-CT (Alza Corp.)	For targeted delivery to colon and can be used for local or systemic therapy.
- Portab System (Andrx Pharmaceuticals, USA)	Tablet core consist of soluble agent, which expands and create microporous channels for drug release.
- SCOT (single composition osmotic tablet, Andrx Pharmaceuticals)	Utilizes various osmotic modulating agents and polymer coatings to provide zero-order release.
- ENSOTROL drug delivery system (Shire Labs. Inc., USA)	Utilizes various solubilizing and wicking agents for delivery of poorly water soluble drugs.
- Zero-Os tablet technology (ADD Drug Delivery Technologies AG, Switzerland)	Specifically for delivery of lipophilic compounds. Consist of gel forming agents in the core that forms gel after coming in contact with water and drug is released as a fine dispersion.
- DUROS (Durect Corp.)	Miniature (4 x 45 mm), implantable osmotic pumps for long-term, parenteral, zero-order delivery of potent therapeutic agents. Deliver drugs at a precisely controlled and constant rate within therapeutic range for long periods. Viadur (leuprolide acetate), a successful product in the market, delivers leuprolide continuously at a nominal rate of 125 μg/day over 1 year for palliative treatment of prostate cancer. DUROS sufentanil (3 months continuous delivery for treatment of chronic pain) and DUROS hydromorphone (for continuous delivery to the spine) are in various developmental phases.

Table 2.2 Different types of commercially available osmotic systems (cont.) (adapted from reference No. 4)

(III) Osmotic pumps for veterinary use	
- VITS (veterinary implantable therapeutic system, Alza Corp.)	Designed to deliver drugs at a controlled rate in animals for a period of 1 day to 1 year and can be implanted subcutaneously or intraperitoneally in any ruminant, non-ruminant, companion, or production animals. Available in various sizes (2 – 10 mm in diameter) and can be designed to give delivery rates from μg/day to mg/day. Drug is kept isolated from body fluids and thus, can be used to delivery water-labile compounds, e.g. proteins and peptides.
- RUTS (ruminal therapeutic system, Alza Corp.)	For controlled delivery of drug can be administered. Generally 2 – 3 cm in diameter and up to 10 cm in length but larger dimensions are possible depending upon application. Can be designed for zero-order delivery of up to g/day for durations ranging from 1 day to 1 year. Ivomec SR (ivermectin) and Dura SE (sodium selenite) available commercially).

2.1.1 Historical background

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 semi-permeable 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 called the "osmotic pressure" (10).

OCDDS utilizes the principle of osmotic pressure for the controlled delivery of an active agent. Drug delivery systems based on the principle of osmosis presents a strong candidate for the controlled drug delivery with zero order rate. The release rates of the drugs from osmotic dispensing devices are dependent on the solubility and molecular weight and activity coefficient of drug (osmotic agent). The development of the controlled-release drug-delivery systems have been developed for a long time (11) as follows:

In 1748, Abbe Nollet (12) reported the first study of membrane phenomema appears. He placed spirit of wine in a vessel, the mount of which was closed with an animal bladder and immersed in water. Because it was more permeable to water than to wine, the bladder swelled and sometimes even burst, demonstrating semipermeability for the first time.

In 1820, Dutrechet (12) introduced the term "osmosis" to characterize the spontaneous flow of liquid across a permeable barrier.

In 1877, Pfeffer (13) performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature.

In 1884, Hugo de Vries (12) invoked osmotic concepts to understand the contraction of the contents of plant cells placed in solutions of high osmotic pressure, where the cell membrane acts as a semi-permeable membrane. The osmotic pressure difference between inside and outside environments causes osmotic water loss and results in plasmolysis.

In 1886, Van't Hoff (12,14) identified an underlying proportionality between osmotic pressure, concentration and temperature in Pfeffer's experiment. He revealed a relationship between osmotic pressure and solute concentration and

temperature that was similar to the ideal gas equation, can be described by the following equation.

$$V\pi = nRT \quad [2.1]$$

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:

$$\pi = (n/V)\,RT \quad [2.2]$$

or

$$\pi = cRT \quad [2.3]$$

Where, c is the concentration of the solute in mole per liter. The preceding equation can be applied satisfactorily to describe the osmotic pressure of dilute solutions of non-electrolytes 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 solutions is written as the following:

$$\pi = icRT \quad [2.4]$$

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus, a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of the drug.

Osmotic pressures for the concentrated solutions of the 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 flows across semi-permeable membranes. The osmotic water flow across a membrane is given by the equation.

$$dV/dt = (A\theta\Delta\pi) / l \quad [2.5]$$

Where dV/dt is the water flow across the membrane of area A, thickness l, and osmotic permeability θ in $cm^3 \cdot cm/cm^2 \cdot h \cdot atm$, and $\Delta\pi$ is the osmotic pressure difference between the two solutions on either side of the membrane. This equation is only strictly true for completely perm selective membranes: that is, membranes permeable to water but completely impermeable to the osmotic agent.

In 1955, Rose and Nelson developed an implantable pump. The first introduced use of an osmotic pump for controlling the drug delivery to the gut in sheep and cattle (15-17). Their pump consisted of three chambers as shown in Figure 2.l: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The salt and water chambers are separated by a rigid semi-permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. This water flow allows the increase in volume of the salt chamber, resulting distension of the latex diaphragm separated the salt and drug chamber, thereby pumping drug out of the device.

The pumping rate of Rose-Nelson pump is given by equation [2.6].

$$dM_t/dt = (dV/dt) \bullet c \qquad [2.6]$$

Where dM/dt = drug release rate

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

c = concentration of drug in drug chamber

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 semi-permeable membrane. This mean pumps had to be stored empty and loaded with water immediately prior to use, causing an inconvenient procedure. A Pharmetrix device (18) overcame this difficulty before administration of the pump.

In the early 1970s, the Higuchi-Leeper pump (19) 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 as shown in Figure 2.2. The device, containing a rigid housing and the semi-permeable membrane which is supported on a perforated frame, is activated by water imbibed from the surrounding environments. This makes the pump can be prepared loaded with drug and then stored for a long period prior to use.

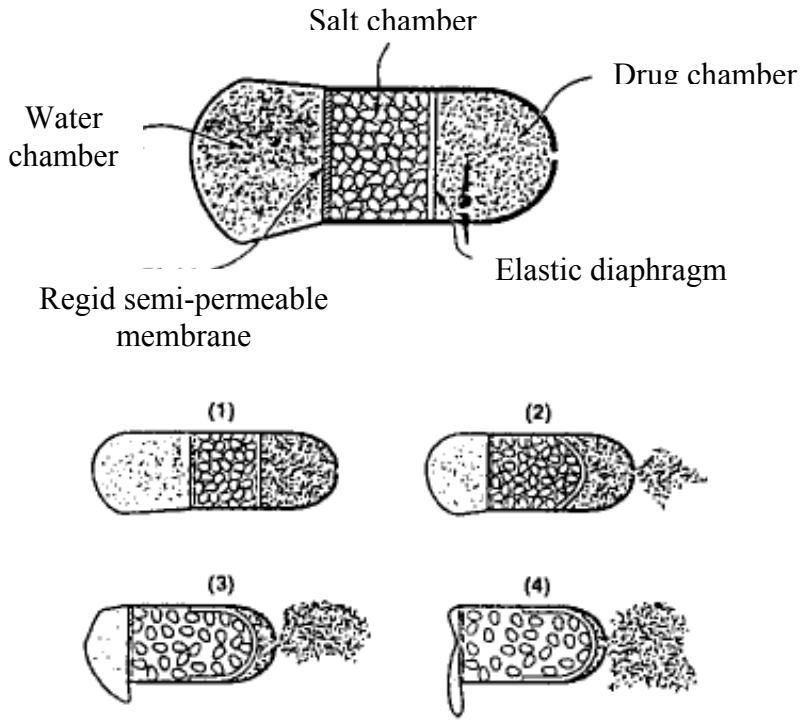


Figure 2.1 Principle of the three-chamber Rose-Nelson osmotic pump

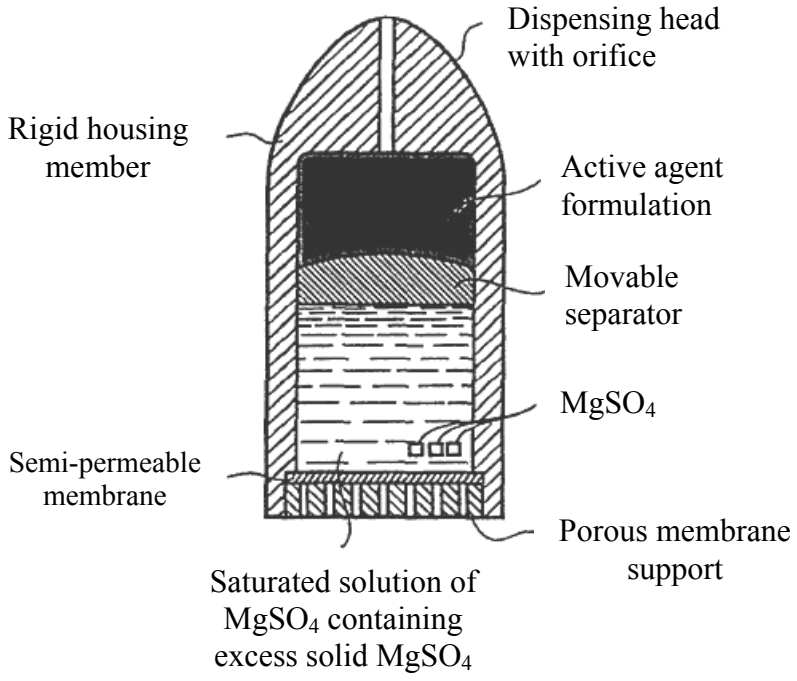


Figure 2.2 Higuchi-Leeper pump

In 1974, Higuchi and Theeuwes (20) applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems (Figure 2.3). In this system also, imbibition of the water from the surrounding environment activates the device. The desired agent is loaded to the device immediately prior to use. When the device is contacted with an aqueous environment, release of drug follows a time course set by the salt used in the salt coating layer and the permeability of the outer membrane casing. These forms are sold under the trade name Alzet (Alza Corp., CA) and are frequently used as implantable controlled-release delivery systems in experimental studies with animals.

In 1975, Theeuwes (21,22) pioneered the solid tablet osmotic dosage form. This system is known as the elementary osmotic pump (EOP) which is simplified and developed from the Rose-Nelson pump. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet. The tablet is then coated with a semi-permeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating as shown in Figure 2.4. After that seminal invention, Alza Corp. made osmotic delivery (the Oros® system) in various configurations of which have been marketed since 1983.

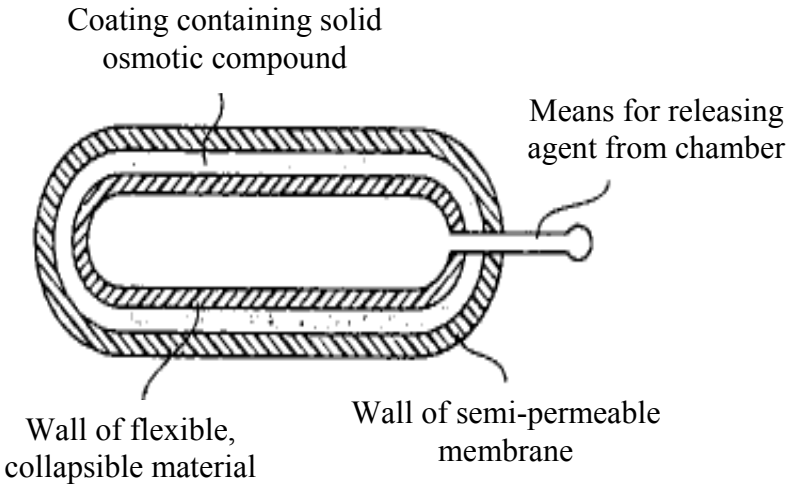


Figure 2.3 Higuchi-Theeuwes pump

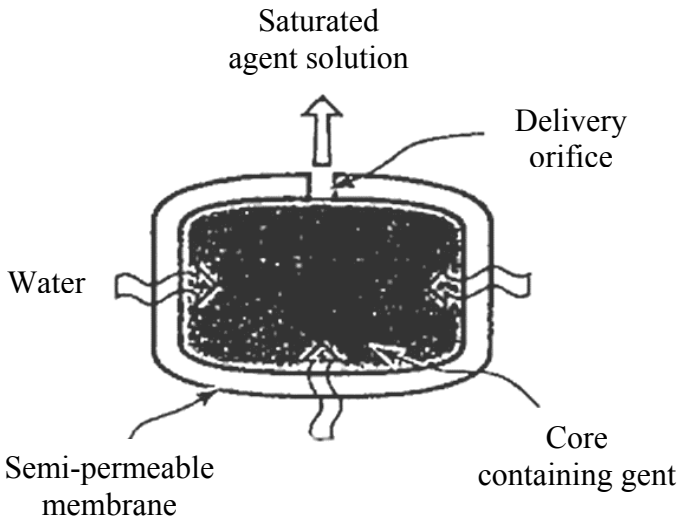


Figure 2.4 Elementary osmotic pump (EOP)

2.1.2 Theoretical aspects

Osmotically controlled release system required only osmotic pressure to be effective and is essentially independent of its environment. The delivery of agent from oral osmotic systems is controlled by the influx of solvent across the semi-permeable membrane, which in turn carries the agent to the outside environment. When an osmotic system is exposed to water or any body fluid, water will flow into core due to an osmotic pressure difference across the coating membrane. Under this osmotic pressure gradient, the volume flow of water into the core reservoir can be described by the following equation (4,23,24):

$$dv / dt = A / h \, Lp \, (\sigma\Delta\pi - \Delta p) \qquad [2.7]$$

Where dv / dt is water influx, A and h are the membrane area and membrane thickness, respectively; Lp is mechanical permeability; σ is the reflection coefficient; and $\Delta\pi$ and Δp are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system. The general expression for the solute delivery rate, dM / dt, obtained by pumping through the orifice is given by:

$$dM / dt = dv / dt \bullet C \qquad [2.8]$$

Where C is the concentration of compound in the dispensed fluid

Reflection coefficient takes into account the leakage of the solute through the membrane. A perfectly semi-permeable membrane is selectively permeable to water only and does not allow solute to pass through it. Thus, in case of a perfectly semi-permeable membrane, σ is close to unity. As size of the delivery orifice increases, hydrostatic pressure inside the system is minimized and $\Delta\pi >> \Delta p$. Since, Osmotic pressure of the gastrointestinal fluids is negligible as compared to that of core, π can be safely substituted for Δπ. By replacing the product $Lp\sigma$, in Equation [2.7], by a constant K and substituting Equation [2.7] in Equation [2.8], the following equation is obtained:

$$dM / dt = A K\pi C / h \qquad [2.9]$$

The best possible way to achieve a constant release from osmotic systems is through proper selection and optimization of the semi-permeable membrane (to maintain the first three terms on the right hand side of the equation constant) and maintaining a saturated solution of drug within the core. As long as excess solid agent is present inside the system, both π and C in Equation [2.9] can be maintained at constant levels. Therefore, it is possible to obtain constant zero-order release rates from osmotic system by maintaining the constant terms in Equation [2.9].

2.1.3 Classification of osmotic controlled systems

2.1.3.1 Elementary osmotic pump (EOP)

The elementary osmotic pump was first described by Theeuwes in 1975 (21). It consists of a drug-containing core (with or without an osmotic agent) coated with a semi-permeable membrane made of water-permeable cellulose polymers having an orifice for drug release as viewed in Figure 2.4. Water is drawn into the system by osmosis, driving drug in the core which is then released through the orifice. A lag time of 30 – 60 min is observed in most of the cases as the system hydrates before zero-order delivery from the system starts, about 60 – 80 % of drug is released at a constant rate from elementary osmotic pump (4). The release rate is determined by the fluid permeability of the membrane and osmotic pressure of core formulation. One of the limitations of these devices is the need for high water fluxes to achieve desirable drug release rates, which is usually achieved with very thin coatings that tend to rupture or by addition of the addition of plasticizers (17). A drug with poor

solubility, however, lacks the ability to create sufficient osmotic pressure, resulting moderate soluble drugs as the most appropriate for the elementary osmotic pump system (3). The other limitation of the elementary osmotic tablet is the decreasing release rate with time, particularly for very soluble drugs, for only 20% of the dose may be delivered as zero-order release. So, the elementary osmotic pump is very simple in preparation and can generally use for delivering of high to moderate water-soluble drug.

2.1.3.2 Push-pull osmotic pump (PPOP)

The push-pull osmotic pump uses a multi-compartment core to deliver drugs of a wide range of solubility. The basic push-pull osmotic pump system resembles a simple tablet in shape and has two layers as viewed in Figure 2.5. The bilayer core consists of a "drug layer" and a functional layer, called an "osmotic layer" or "push layer," and coated with a semi-permeable membrane. The second layer provides two functions: (1) to generate the osmotic potential within the tablet core and (2) to generate a hydrostatic pressure via a swelling force that "pushes" the extrudable material (drug layer) from the tablet. This layer primarily consists of a polymer that swells upon hydration (e.g., high molecular weight polyethylene oxide (PEO)) and an osmotic agent (e.g., sodium chloride). The "push" of the swelling layer against the drug layer forces the drug, which is suspended in the hydrated drug layer, through a delivery port that is formed into the membrane on the active layer side of the tablet (17). A number of modifications are available for this type of system such as delayed push-pull system (as used in Covera HS, extended release formulation for verapamil), multi-layer push-pull system (for pulsatile or delayed drug delivery), and push-stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned, or pulsatile release profile) (4). Adjustments to composition and thickness of the system's semi-permeable membrane are made to achieve a precise delivery rate that is independent of GI pH and external agitation.

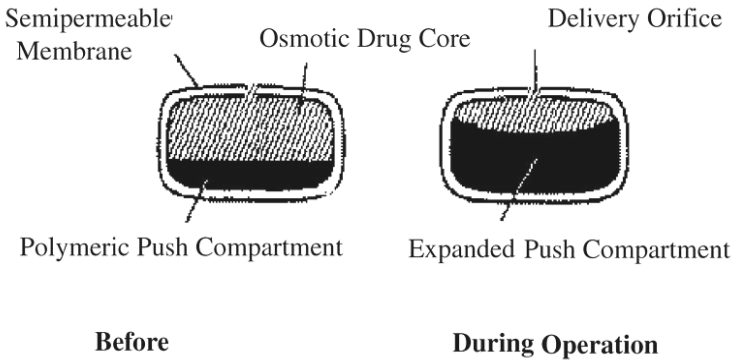


Figure 2.5 Push-pull osmotic pump (PPOP)

2.1.3.3 Controlled-porosity osmotic pump (CPOP)

The controlled-porosity osmotic pump contains water-soluble additives in the coating membrane, which dissolve after coming in contact with water, resulting in an in situ formation of a microporous membrane as viewed in Figure 2.6. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role (25). The interesting point of the controlled-porosity osmotic pump is the attempt to avoid the need of laser or mechanical drilling to create delivery orifice. The opening has formed by incorporation of a leachable component into the coating semi-permeable membrane coating solution (26).

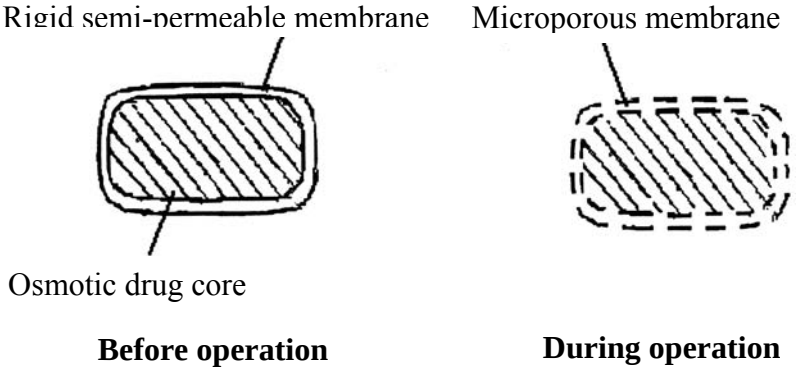


Figure 2.6 Controlled-porosity osmotic pump (CPOP)

2.1.3.4 Other types

The OROS-CT (Osmotic Controlled Drug Delivery in the Colon) used for colon-targeted drug delivery comprises of a single osmotic unit or as many as five to six push-pull osmotic units filled in a hard gelatin capsule as viewed in Figure 2.7 (4). After coming in contact with the gastrointestinal fluids, gelatin capsule dissolves and the enteric coating prevents entry of fluids from stomach to the system.

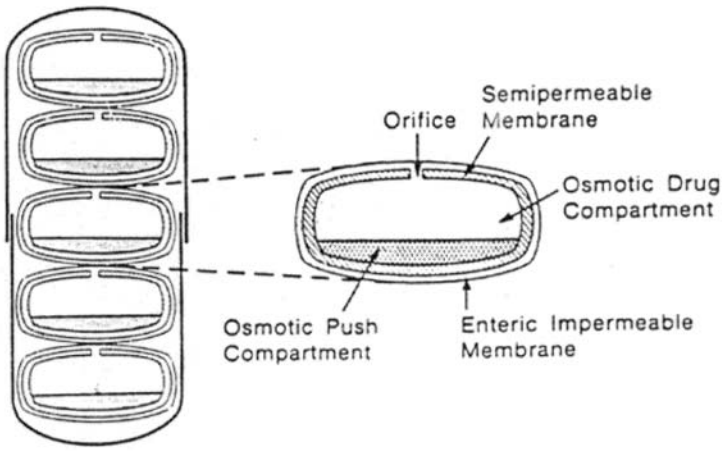


Figure 2.7 OROS-CT

When the system enters into a small intestine, the enteric coating dissolves and water is imbibed into the core, causing the push compartment to swell. Meanwhile, a flowable gel is formed in the drug compartment which is pushed out of the orifice at a rate which is precisely controlled by the rate of water transport across the semi-permeable membrane.

Liquid OROS controlled release systems are designed to deliver drugs as liquid formulations and combine the benefits of extended-release with high bioavailability. Figure 2.8 shows the cross-sectional diagram for L-OROS Softcap delivery system before and during operation (4). These systems are designed to deliver liquid-form drugs in extended-release manner with high bioavailability including lipophilic self-emulsifying formulation.

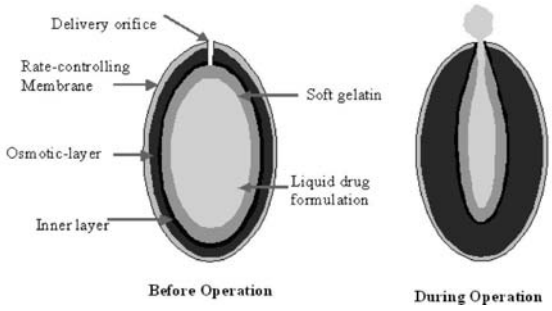


Figure 2.8 Liquid OROS systems

The sandwiched osmotic tablet system (SOTS), a tablet core consisting of a middle push layer and two attached drug layers, is coated with a semi-permeable membrane (4). As shown in Figure 2.9, both the drug layers are connected to the outside environment via two delivery orifices, one on each side. After coming in contact with the aqueous environment, the middle push layer containing swelling agents swells and pushes the drug layer released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa.

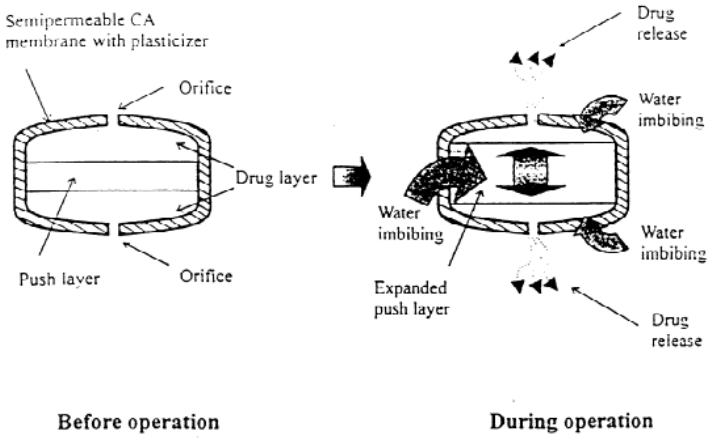


Figure 2.9 Sandwiched osmotic tablet system (SOTS)

2.1.4 Components of a bilayer osmotic tablet

The push-pull design of a drug containing layer paired with a swelling, push layer can accommodate drugs with a range of physical-chemical properties (i.e., solubility, log *P*, ionization) (27). A typical tablet core formulation for a bilayer osmotic tablet is shown in Table 2.3. The composition of the drug layer will depend mostly on the dose (drug loading) and the material properties of the drug. The composition of the swelling layer has some flexibility and can be standardized for most formulations. Typical ratios for drug layer:sweller layers are in the range from 1:2 to 1:3. The exact ratio will depend upon drug loading, tablet aspect ratios, and to some extent the rate of release. However, this ratio is not a critical parameter for typical bilayer osmotic pump tablet formulation described in Table 2.3. Some refinement in the ratio may be necessary once the tablets are compressed to ensure that the sweller layer extends into the tablet band upon compression (17).

Table 2.3 Typical tablet compositions for a bilayer osmotic tablet formulation (adapted from reference No.17)

Component	Weight percentage/ per layer
Drug layer components	
API	1 – 30
Solubilizer (e.g.,salts as buffers, cyclodextrin)	As needed
Entrainer, suspending agent (e.g., PEO MW 100,000 – 600,000)	40 – 90
Binder (e.g., hydroxypropyl cellulose)	0 – 5
Swelling/push layer components	
Swelling agent (e.g., PEO MW 4000-7000 K)	30 – 70
Osmotic agent (e.g., sodium chloride)	10 – 40
Binder (e.g., hydroxypropyl cellulose)	0 – 5
Drug layer:sweller layer ratio (by weight) : 2:1 – 3:1	

2.1.4.1 Tablet Core

(1) Drug Layer

The functional requirements of the drug layer include the ability to suspend drug particles and to be extruded through a delivery port as the tablet core becomes hydrated. The suspension of drug within the core as it is hydrated is achieved by formation of a concentrated polymer solution. The viscosity within the hydrating core is bound on the low side by the ability to suspend the drug and on the high side by the ability to flow through the delivery port. This viscosity range must be achieved with the addition of very small amount of water (0.5-2.0 mL) and in sufficient time so that relief of hydrostatic pressure from the influx of water and swelling of the functional layer is possible through extrusion of the drug layer. This functionality has been achieved by combining the drug with polyethylene oxide, a water-soluble polymer, and by limiting the amount of drug in this mixture so that the polymer dominates the hydration rate and viscosity of the layer.

Drug Properties: there are theorically few restrictions on the types of drugs that can be delivered in a controlled manner using bilayer osmotic tablets. Given the complexity and cost of manufacture of bilayer osmotic tablets, the use of this technology is usually justified only for poorly soluble drugs that require sustained delivery for greater than 6 h for these drugs. The use of simpler osmotic tablets (e.g., elementary, AMT) that require dissolution of drug within the core is prohibited by the drug solubility. Likewise, controlled delivery using matrix tablet technology is challenging due to erosion controlled release mechanism that predominates when drug solubility is low.

The ability to suspend and deliver an insoluble drug through a manufactured delivery port is one of the advantages of delivery using a bilayer osmotic tablet technology. There are a few considerations, however, for drug particle size, solubility, and mechanical properties that are important, particular for higher doses and hence higher drug loadings within the tablet core. The drug particle size is bound at one extreme by the ability to “fit” through the delivery port within the membrane coating, which is typically 500 – 1000 μm. Since the justification for this complex controlled release technology is usually low solubility, the drug particle size should be engineered toward the low end to promote dissolution (27, 28). Thus,

engineering of drug particle size to help in dissolution of the drug will ensure that delivery of suspended drug through the coating orifice is also possible.

Drug Entraining/Suspending Agent: The very specific requirements for hydration and viscosity in the drug layer of the tablet core have limited the choice of compendia excipients that can be used as the functional excipient in the drug layer. Water-soluble polymers such as polyethylene oxide, hydroxypropylmethylcellulose (HPMC), and polyvinylpyrrolidone (PVP) have been used for entrainment of drug; however, polyethylene oxide with average molecular weights ranging from 100,000 to 400,000 is most common (29). The nearly exclusive use of PEO is due to its ability to wet and hydrate to the appropriate viscosity range to suspend drug particles and flow through the delivery port. Also, the rate of hydration and viscosity drop in the PEO-based drug layer works well in combination with the hydration and swelling of PEO-based functional push layers. When PEO is used as the primary component in the drug containing layer, typical amounts range 40-90% by weight of the total drug layer. Maintaining a high concentration of PEO in the hydrating layer helps to achieve a cohesive layer that suspends drug and maintains a uniform composition as the layer is extruded from the tablet.

The compendia grades of polyethylene oxide currently supplied by Dow® (Polyox™ NF) are available in a number of different molecular weight grades and ranges of particle sizes. Generally, the Polyox™ grades of PEO are free flowing powders and are very compressible, making them very amenable to conventional blending and compression processes. Thus, the inclusion of fillers and/or binders to the drug layer to help in powder handling or to help produce a robust tablet is generally not required. The importance of the material properties of the Polyox™ grades of PEO are discussed later in the context of processing of the drug and swelling layers for compression.

(2) Granulation Aids and Binders

Even thought the Polyox™ grades PEO that comprise most of the tablet core have very good flow and compression properties, there are situations when it may be necessary to include binders or fillers in the drug layer. For example, for low dose, low drug loading, it may be necessary to use a granulation step to ensure that uniform distribution of drug is achieved and maintained during processing.

Alternatively, if the dose and drug loading are high, additional excipients may be required to improve flow or compression properties as a result of deficiencies in the material properties of the API. In these cases, the use of insoluble excipients should be minimized since they may cause delivery problems for the device. If insoluble excipients are required, they should be used in small amounts (e.g., <10% of formulation) to minimize the impact on the function of PEO in the drug layer.

2.1.4.2 Swelling Layer

The dual functionality required by the sweller layer is achieved by combining a component with a high osmotic potential with a high molecular weight water-soluble polymer that swells upon hydration. High molecular weight grades of PEO are very commonly used in bilayer osmotic tablets (30,31), but the use of other hydrogels and superdisintegrants (29) has also been reported. The rate of swelling achieved with the imbibition of small amounts of water is part of a balance that must be achieved to work in concert with the extruding sweller layer. The hydrostatic pressure generated by the swelling layer is dictated by the physical and mechanical properties of the functional (swelling) polymers and the hydrating drug layer that creates resistance to the flow through the delivery orifice. If this hydrostatic pressure exceeds the mechanical strength of the semi-permeable coating, a rupture of the coating membrane will occur. On the other hand, if the pressure is high enough to create a back pressure against the extruding drug layer, the “push-pull” mechanism of the two layers is lost, leading to entrapment of drug within the core and incomplete drug release.

(1) Osmotic agent

For controlling the drug release from these systems, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in compartment (4). If a drug does insufficient osmotic pressure, an osmotic agent or osmogen can be added in the formulation. Table 2.4 are listed some of the compounds that can be these form used as osmotic agents.

Polymeric osmotic agents are mainly used in the fabrication of PPOPs 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).

Table 2.4 The compounds can be used as osmotic agents (adapted from reference No.4)

Category	Examples
Water-soluble salts Of inorganic acids	Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate, etc.
Water-soluble salts Of organic acids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
Carbohydrates	Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc
Organic polymeric osmagents	Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, polyacrylamides, etc.

2.1.4.3 Membrane Coating

The function of the membrane coating is to isolate a highly water-soluble component that generates a high osmotic pressure and to create a rate-controlling barrier for diffusion for water into the core and delivery out of the pump. This barrier in an osmotic pump tablet is a semi-permeable film formed using a water-insoluble, film-forming polymer, in combination with a plasticizer or a pore former. Another requirement for the membrane coating is sufficient mechanical strength that it can resist the hydrostatic pressure that is created from the influx of water and due to swelling of the push layer. Cellulose acetate is commonly used as the basis for the semi-permeable membrane coating. The use of other water insoluble polymers (e.g.,

ethylcellulose) as the primary component in the membrane coating has been described in the literature (32-34). Enteric polymers have also been described for use as a membrane (35). However, enteric polymers only provide osmotic delivery in delivery in gastric media since dissolution of the membrane occurs once the tablet reaches the intestine.

The second component in an osmotic film coating is a water-soluble component (usually polyethylene glycol) for the primary purpose of increasing membrane porosity, water permeability, and release rate. In addition, PEG also acts as plasticizer to reduce the brittleness of the cellulose acetate film and to improve film robustness. The amount of PEG directly affects the drug delivery rate through its effect on the permeability of water into the tablet core and must be optimized for each formulation. The critical aspects of designing a membrane coating to achieve a target release rate include selection of the ratio of the insoluble and soluble components (e.g., cellulose acetate: PEG), the membrane thickness, and coating solution composition (solvent system, solid content) use for spraying the film onto the tablets (17).

2.1.4.4 Delivery Orifice

In bilayer osmotic tablets, drug is delivered through one or more delivery ports located on the face of the drug layer side of the tablet. The manufacture of a delivery orifice in a semi-permeable coating has been accomplished by a number of ways, including the intentional formation of defects in coatings. The most common way to manufacture delivery orifices in osmotic tablets is by using a laser to penetrate the semi-permeable coating on one or both sides of the tablet face. The disadvantage of this approach is that it is a costly and complex manufacturing step (16).

Generally speaking, the size and the number of holes are not critical to the delivery of drug in a bilayer osmotic tablet since the coating and the osmotic agent control the rate of release (27). Thus, the most important requirements for a delivery port are {1} that it is large enough to allow extrusion of the viscous drug layer that includes suspended drug particles that to be less than 100 μm; {2} that it is not too large (or too many), or the integrity of the membrane coating may be compromised as the hydrostatic forces increase due to tablet core hydration and swelling. These two requirements in combination with the preference to make the laser

drilling process as simple as possible usually result in a single hole that is on the order 500-1000 μm in diameter (17).

2.1.4.5 Other

(1) 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 a 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 (23).

(2) 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 polyethethylene glycols (300 to 6000 Da), polyhydricalcohols, 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 (23).

(3) Plasticizers

To give the semi-permeable membrane flexibility, plasticizers such as phthalates (dibenzyl, dihexyl, or butyl octyl), triacetin, expoxidized tallate, or tri-isoctyl trimellitate are added (23). In the design of osmotic controlled release systems, these plasticizers help to modulate and achieve the required release rate.

(4) 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 a multilayered reservoir, the water-permeable coat consists of hydrophilic polymers. In contrast, water-impermeable layers are formed from latex materials such polymethacrylates (Table 2.5). 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 (23).

Table 2.5 Materials Used in Different Layer Formulations (adapted from reference No.23)

Component	Example
Hydrophilic layer (water permeable)	Polysaccharides, hydroxypropymethyllcellulose, 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

2.1.5 Formulations aspects

Various factors that affect the drug release from OCDDS which should be considered in the formulation development are as follows.

2.1.5.1 Drug solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core as expressed in Equation [2.9]. Assuming a tablet core of pure drug, the fraction of core release with zero-order kinetics is given by the following equation (25,36):

$$F(z) = 1 - \frac{S}{\rho} \qquad [2.10]$$

where F(z) is the fraction released by a zero-order kinetic, S is the drug solubility (g/mL), and ρ is the density (g/mL) of the core tablet. Drugs with a solubility of ≤ 0.05 g/mL would be released with $\geq 95\%$ zero-order kinetics with respect to Equation [2.10]. However, the zero-order release rate would be slow according to Equation [2.9], due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-

order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. Though, it is possible to modulate the solubility of drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are:

(1) Use of cyclodextrin derivatives

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems. A CPOP has been developed for testosterone (solubility = 0.039 mg/mL at 37 °C), of which formed complexation with sulfobutyl ether-β-cyclodextrin sodium salt, $(SBE)_{7m}$-β-CD, the solubility was improved to 76.5 mg/mL (37). In a comparative study with hydroxypropyl-β-cyclodextrin (HP-β-CD) and a sugar mixture, it was found that testosterone release from the device in the presence of $(SBE)_{7m}$-β-CD was mainly due to osmotic pumping while for HP-β-CD, the major contribution was due to diffusion. In case of the sugar mixture, the drug was poorly released due to the absence of solubilizer. Similar results were obtained with prednisolone (38), and chlorpromazine (39,40). It was reported that several $(SBE)_{7m}$-β-CD salt forms could serve both as a solubilizer and osmotic agent (41). In addition, conventional β-CD was also used as a solubilizer in the development of EOP for glipizide (42).

(2) Resin modulation approach

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl pyridine) (25). Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to ensure that both the drug and resin carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained without chemical modification of the drug.

(3) Co-compression of drug with excipients

Incorporation of excipients that modulate the solubility of drug within the core can be one approach to control the release of drugs from the osmotic systems. McClelland and co-workers (25,36) reported CPOP of a highly water-soluble

drug, diltiazem hydrochloride (solubility more than 590 mg/mL at 37 °C). The majority of the drug fraction was release predominantly at a first-order rather than the desired zero-order rate, because of very high water-solubility. As a result of incorporation of sodium chloride (1 M) into the core tablet formulation, the solubility of diltiazem hydrochloride was reduced to 155 mg/mL. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14–16-h period.

In another study, doxazosin, which has pH-dependent solubility, was improved its solubility by organic acids (succinic and adipic acid) within the tablet cores coated with asymmetric membranes. The solubility of doxazosin was increased in the presence of organic acids and pH-independent release patterns were obtained (43).

As a similar approach, tromethamine was added in the core of OCDDS of glipizide, as a solubility modifier, to increase the microenvironmental pH of the core above the pKa of the drug (4). Glipizide is a weakly acidic drug that is practically insoluble in water and buffer media of acidic pH. Inclusion of tromethamine as alkalinizing agent in the developed formulations was clearly evident that the concentration of tromethamine had a direct effect on glipizide release. Tromethamine increased the solubility of glipizide and hence, its release from the developed systems.

(4) Use of effervescent mixtures

A controlled release effervescent osmotic pump tablet (EOPT) of Traditional Chinese Medicine Compound Recipe (TCMCR), named Fuzilizhong prescription which includes acidic drugs consisted of many known and unknown effective components, was prepared with sodium chloride, sodium hydrogen carbonate and hydroxypropyl methylcellulose (HPMC) as osmotic agents (44). The accumulative water-insoluble drug release was improved up to 96% at 14 h, since the osmotic pressure in EOPT with sodium chloride and sodium hydrogen carbonate increased greatly, which was induced mostly by carbon dioxide gas generating from the reaction of sodium hydrogen carbonate and the acidic drugs in TCMCR after the fluid being imbibed into the compartment through the semi-permeable membrane.

(5) Use of encapsulated excipients

Use of encapsulated excipients can be another approach to deliver poorly water-soluble drug from osmotic dosage forms. A capsule device coated with asymmetric membranes for the delivery of glipizide incorporated with encapsulated excipients (pH-controlling excipients) was described by Thombre et al. (45). The solubility modifier (meglumine) in the form of mini-tablets was coated with a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.

2.1.5.2 Osmotic pressure

For zero-order release, the π term in Equation [2.9] must keep a constant value. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment (46). In case of a drug does not possess sufficient osmotic pressure, an additional osmotic agent should be added to the core formulation. Some of the compounds that can be used as osmotic agents are listed in Table 2.6 (4). The osmotic pressure of the commonly used solutes in controlled-release formulations is particularly high, as described in Table 2.7 (47). In addition to these, potassium bicarbonate (48), cyclodextrin derivatives (49) have also been used as osmotic agents.

Polymeric osmogents are mainly use in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor water solubility. These are swellable and 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 (50).

2.1.5.3 Size of delivery orifice

Osmotic delivery systems have at least one delivery orifice in the membrane for drug release. 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 large, solute diffusion from orifice may take place. In contrast, size of delivery orifice should not also be too small otherwise; zero-order delivery will be affected because of development of hydrostatic pressure inside the system, resulting in unpredictable drug delivery. Mathematical calculations that can be used to calculate the optimum size of

the delivery orifice was reported in the literature (21), indicating that drug release from osmotic systems is not affected by the size of the delivery orifice within certain limits.

In a study by Theeuwes (21), a complete membrane controlled release of potassium chloride was obtained with orifice diameter in the range of 0.075–0.274 mm. At orifice size of 0.368 mm and above, control was lost because of significant contribution from diffusion. However, no systematic trends were observed within the orifice diameter between 0.075 and 0.274 mm.

Liu et al. (51) studied nifedipine release from osmotic pumps as a function of orifice diameter and no significant differences were found in the release profiles for orifice diameter ranging from 0.25 to 1.41 mm. However, the release was somewhat rapid with an orifice diameter of 2.0 mm probably because of significant diffusion. On the other hand, a longer lag time and uncontrollable/unpredictable and lower release rate were observed in the systems without any orifice.

Delivery orifices in the OCDDS can be created with use of a mechanical drill (52), but for commercial production scale, tablets need to be produced using a continuous process. Some of the reported processes to created delivery orifices in the OCDDS are as follows.

Table 2.6 Compounds that can be used as osmotic agents (adapted from reference No.4)

Category	Examples
Water-soluble salts of inorganic acids	magnesium chloride or sulfate lithium, sodium, or potassium chloride lithium, sodium, or potassium sulfate sodium or potassium hydrogen phosphate etc.
Water-soluble salts of organic acids	sodium or potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
Carbohydrates	arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc.
Water-soluble amino acids	glycine, leucine, alanine, methionine, etc.
Organic polymeric osmogents	sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, poly-acrylamides, etc.

Table 2.7 Osmotic pressure of saturated solutions of common pharmaceutical solutes (adapted from ref. No. 4)

Compound or mixture	Osmotic pressure (atm)
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	355
Lactose-sucrose	250
Potassium chloride	245
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-sucrose	190
Manitol-sucrose	170
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic 12.H_2O	36
Sodium phosphate dibasic 7.H_2O	31
Sodium phosphate dibasic 12.H_2O	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic H_2O	28

(1) Laser drilling

Laser drilling is one of the most commonly used techniques to create delivery orifice in OCDDS. Figure 2.10(a) showed the top view of the portion of the apparatus used to drill hole in the osmotic tablets (53). In simple words, the tablets in which holes are to be formed are charged in the hopper. The tablets drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station. At the passageway forming station, each tablet is tracked by an optical tracking system. If the speed of the moving tablets increases, the hole may become elliptical because of movement of tablets during the laser firing time. To avoid this problem, tracking velocity is synchronized with the velocity at which the tablets are moving. As shown in Figure 2.10(b), the tracking was carried out by the rotational oscillation of the mount and tracking mirror of the optical tracking system. During tracking, laser beam was fired in a pulse mode fashion and the beam was transmitted by the optical tracking mechanism onto the surface of the moving tablets and moves with the moving tablets as the mirror oscillates clockwise. The walls of the tablet adsorbed the energy of the beam and get heated ultimately causing piercing of the wall and, thus forming passageway. After completion, the tracking mirror oscillated counterclockwise back to its starting position to track the next tablet. It is possible to control the size of the orifice by varying the laser power, firing duration (pulse time), thickness of the wall, and the dimensions of the beam at the wall.

Sinchaipanid et al. (54) designed salbutamol EOP tablets and evaluated the fundamental variables affecting their release characteristics. A carbon dioxide laser beam was developed in order to deliver a power of 100 mJ and successfully used to make an opening of about 0.4 mm through the film. The intensity of the laser beam was high and instant enough to cut through the film without damaging the tablet surface. The release drug from the system was found to follow zero order kinetics.

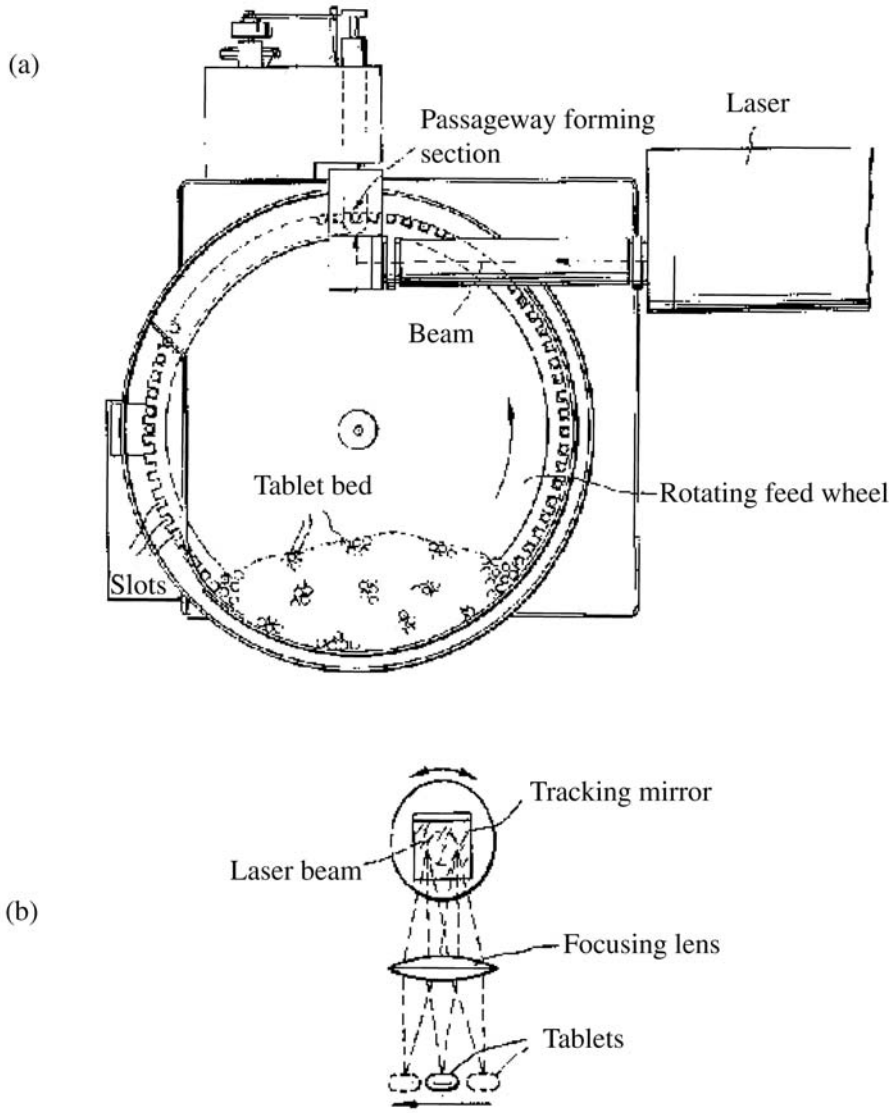


Figure 2.10 Top view of the laser hole-drilling system for osmotic dosage forms (a); and the pill tracking means (b) (adapted from ref. no. 53)

(2) Indentation that is not covered during the coating process

Coating the indented core tablet compressed by the punch with a needle is one approach to create the orifice in OCDDS. Liu et al. (55) prepared the osmotic formulation by coating the indented core tablet, using atenolol as a model drug; then optimized. The optimal osmotic tablet was found to be able to deliver atenolol at an approximately constant rate up to 24 h, independent of both release media and agitation rate. Indentation size of core tablet in the range of 1.00–1.14 mm hardly affected drug release. This method that is simply by coating the indented core tablet with the elimination of laser drilling may be promising in the field of the preparation of OCDDS.

(3) Use of pore forming agent

CPOPs are extension of EOPs and are essentially similar, except that there is no need to create a delivery orifice. Drug release from these types of system takes place through controlled porosity pores formed *in situ*. Incorporation of leachable substances in the coating membrane is the most widely reported method for the formation of pores in CPOP (25,56-58). These water-soluble additives dissolve on coming into contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from these types of system is independent of pH and has been shown to follow zero-order kinetics (56,57). Water soluble additives that can be used for this purpose consist of amino acid, sorbitol, mannitol, organic aliphatic and aromatic acid, including diols and polyols, as well as other water-soluble polymeric materials (59). Erodible material such as poly(glycolic), poly(lactic) acid or their combinations can also be used for this purpose (60).

These erodible or leachable materials produce one or more passageways with different geometrical shapes. The pores may also be formed in the membrane prior to the operation of the system by gas formation within curing polymer solutions, resulting in voids and pores in the final form of the membrane. The pores may also be formed in the membrane by the volatilization of components in the polymer solution leading to evolution of gases prior to application or during application of the solution to the core tablets resulting in the creation of the polymer foams serving as the porous membrane for drug release (59).

Zentner and co-workers (56, 57) determined drug release from CPOP as a function of water-soluble additive (sorbitol) in the coating membrane and reported that the release rate increased as the sorbitol content in the membrane increased from 10% to 50% w/w of cellulose acetate (CA).

In a similar study by Appel and Zentner (61) potassium chloride release from CPOP was found to increase with increasing pore-former (urea) concentration in the membrane. There was also a critical point (50% urea) above which there was a near-linear dependence of release rate on urea content. In device with less than 50% urea, swelling of the devices was observed; whereas devices with more than 50% urea retained their characteristic tablet shape. It was suggested that at lower urea concentration, the pores were not continuous and at higher concentrations greater fraction of the pores were continuous.

Okimoto et al. (40) defined the membrane controlling factors responsible for chlorpromazine release from a CPOP. The dosage form was spray coated with CA solutions varying the amount and size of micronized lactose (pore former). It was reported that the release rate of the drug increased with increasing amount of micronized lactose and decreasing lactose particle size in the membrane. The membrane surface area of the CPOPs were also measured by the gas absorption method and found that the membrane surface area of the CPOPs following release of membrane components had a linear relationship to the drug release rates from the CPOPs.

Kelbert et al. (62) prepared propranolol tablets coated with CA latex plasticized with either triethyl citrate (TEC) or triacetin (TA). Membrane permeability to the drug was increased by the addition of HPMC or sucrose. In case of TA plasticized films (at 150% w/w level), tablets with 15% w/w of HPMC had a tendency to swell and the film to rupture, showing insufficient porosity and/or film strength. Sucrose containing films showed a decrease in lag time with an increase in sucrose content. However, higher levels of sucrose (20% w/w and higher) caused rupturing of CA films. In case of TEC plasticized films (at 120% w/w level), higher levels of sucrose (50% w/w and higher) caused rupturing of CA films in the dissolution medium. It was concluded that the film plasticized with TEC and containing 40% sucrose and 10% PEG 8000 were found to provide the best release

characteristics in terms of small lag time and extended drug release profile for over 12 h. When sucrose was added to TA and TEC plasticized films, a macroporous membrane was created during exposure to the dissolution medium because of release of sucrose from the film. The mechanism of drug release was mainly a combination of molecular diffusion and osmosis.

In another study, the effect of level of pore former (PVP) in the membrane of OCDDS of glipizide was studied (63). Glipizide release was directly related to the initial level of PVP in the membrane. However, Burst strength decreased with an increase in the level of pore former. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane.

2.1.5.4 Semi-permeable membrane type and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of OCDDS. From Equation [2.9], the importance of rate-controlling membrane in the drug release can be easily recognized. Drug release from OCDDS is independent of the pH and agitational intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and effective isolation of dissolution process from the gut environment (21). To ensure that the coating is able to withstand the pressure within the device, the thickness of the semi-permeable membrane is usually kept between 200 and 300 μm (14). However, this may be problematic in cases where the drug is having low osmotic pressure because of incomplete/slow drug release may take place. Selecting membranes that have high water permeabilities can be a solution to this problem. One approach is by using composite wall (64). The tablet cores are coated with a membrane that has a passageway through the wall for releasing the agent. The wall is formed from a multiplicity of materials comprising a material permeable to an external fluid and substantially impermeable to agent (like CA) and at least one additional material selected from a group of materials that imparts stability to the wall and enhances the permeability of the wall to fluids (like HPMC and hydroxylbutyl methylcellulose).

Some of the membrane variables that are important in the design of OCDDS are as follows.

(1) Type and nature of polymer

Since the membrane in OCDDS is semi-permeable in nature, any polymer that is permeable to water but impermeable to solute can be used. Some of the polymers that can be selected for the above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, etc. (65); cellulose ethers like ethyl cellulose (61); and eudragits (66, 67).

Cellulose acetate (CA) has been widely used to form rate-controlling membranes for OCDDS. CA films are insoluble, yet semi-permeable to allow water to pass through the tablet coating. The water permeability of CA membranes 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. The permeabilities of these films can be further increased by the addition of hydrophilic flux enhancers. Incorporation of plasticizer in CA coating formulations generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility, and affects the permeability of the film (68).

(2) Membrane thickness

Thickness of the membrane has a profound effect on the drug release from OCDDS. It can be seen from Equation 2.9 that the release rate from OCDDS is inversely proportional to membrane thickness. Monolithic osmotic pump tablets of nifedipine coated with CA membrane were found to release the drug mainly through the mechanism of osmotic pumping (51). On studying the release as a function of coating thickness, it was found that as the coating thickness increased from 85 to 340 μm, the drug release decreased in an inversely proportional manner. An increased resistance of the membrane to water diffusion resulted in this effect.

On the other hand, thickness of asymmetric membrane was found to have insignificant effect on drug release. Herbig et al. (43) reported that release rates were unaffected by the overall membrane thickness in the range of 95–150 μm. One possible reason for this may be the unique structure of the asymmetric membrane coatings in which the porous substrate consists of open pores, void volume between 60–90%. Since most of resistance to the transport is the skin structure rather

than the porous substrate of the asymmetric membranes, the thickness of the porous substrate had only a slight effect on the release kinetics.

(3) Type and amount of plasticizer

Plasticizer can change viscoelastic behavior of polymers significantly. Particularly, 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 (61, 38, 69).

2.2 Chitosan-Polyacrylic Acid Interpolymer Complexes

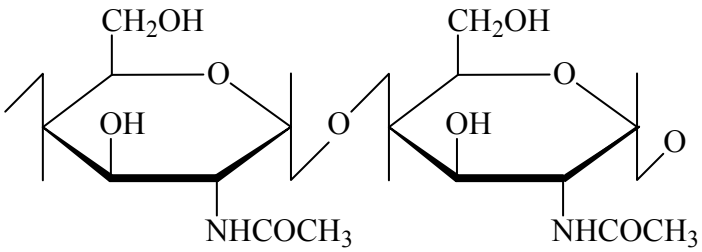
2.2.1 Chitosan

In 1859, Rouget (71) was discovered chitosan while he was experimenting with chemical and thermal manipulation of the natural fiber chitin. Since then, chitosan has been used as a pharmaceutical excipient in sustained release dosage forms, as an immunostimulant, and to promote wound healing (72). Chitosan's ability to bind to a variety of substances including acids, lipophilic substances, and minerals (73) has enabled it to be used for water purification for more than 30 yr. Chitosan has been sold in Europe and Japan for the past 20 years as a nonprescription product to inhibit fat absorption (71). Chitosan was first marketed as a dietary supplement in the United States in the late 1990s.

Chitosan (CS) is a copolymer of β-[1→4]-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose as a natural polymer obtained by alkaline deacetylation of chitin (Figure 2.11). It's non-toxic, biocompatible, and biodegradable. These properties make CS a good candidate for use in advanced drug delivery applications. CS has been investigated as an excipient in the pharmaceutical industry, to be used in direct tablet compression, as a tablet disintegrant, for the production of controlled release solid dosage forms of for the improvement of drug dissolution (Table 2.8) (74-77). The term CS refers to a group of polymers, which differ in their degree of N-deacetylation (40–98%) and molecular weight (50 – 2,000 kDa), viscosity (1% CS in 1% acetic acid, < 2000 mPaS). These two

characteristics are very important to the physico-chemical properties of the chitosans and hence, they have a major effect on the biological properties (75, 77).

(A)



(B)

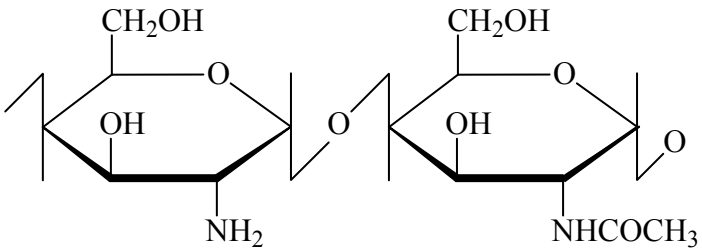


Figure 2.11 Structures of chitin (A) and chitosan (B)

Chitin is found in the exoskeleton of crustacea, insects, and some fungi. Chitosan has a rigid crystalline structure through inter- and intra-molecular hydrogen bonding. The main commercial sources of chitin are the shell wastes of shrimp, lobster, krill and crab (78,79). In terms of availability, chitin is next to cellulose, available to the extent of over 10 gigatons annually (80).

Chitosan is a weak base with a pKa value of the D-glucosamine residue of about 6.2–7.0, therefore, insoluble at neutral and alkaline pH values. However, it does make salts with inorganic and organic acid such as hydrochloric acid, acetic acid, glutamic acid, and lactic acid. In acidic media, the amine groups of the polymer are protonated resulting in a soluble, positively charged polysaccharide that has a high

charge density (one charge for each D-glucosamine unit). Chitosan can form gels by interacting with different types of divalent and polyvalent anions (81, 82).

A new form of chitosan has been extracted and purified. This electrostatically charged chitosan is poorly absorbed systemically but is able to bind lipids and prevent their digestion. The positively charged amino groups on the chitosan molecule bind to the negatively charged carboxylic groups of free fatty acids. This electromagnetic bond seems to be stronger than those observed in other dietary fibers. Additionally, hydrophobic bonds are also formed between chitosan and neutral fats such as cholesterol and triglycerides (83).

Table 2.8 Chitosan as a Pharmaceutical Excipient (adapted from reference No.77)

Conventional formulations	Novel applications
Direct compression tablets	Bioadhesion
Controlled release matrix tablets	Transmucosal drug transport
Wet granulation	Vaccine delivery
Gels	DNA delivery
Films	
Emulsions	
Wetting agent	
Coating agent	
Microspheres and microcapsules	

Chitosan exhibits a variety of physicochemical and biological properties resulting in numerous applications in fields such as waste water treatment, agriculture, fabric and textiles, cosmetics, nutritional enhancement and food processing. In addition to its lack of toxicity and allergenicity, its biocompatibility, biodegradability and bioactivity make it a very attractive substance for diverse applications as a biomaterial in the pharmaceutical and medical fields (81, 82, 84-90).

Chitosan has been extensively examined in the pharmaceutical industry for its potential in the development of controlled release drug delivery systems. This is

due to its unique polymeric cationic character and its gel and film forming properties. Such systems should allow the control of the rate of drug administration and prolong the duration of the therapeutic effect as well as perhaps the targeting of the drug to specific sites. Numerous systems have been described in the literature to include microgranulation systems, sustained release matrices, erodible matrices and controlled release gel systems (77).

2.2.2 Polyacrylic acid

Polyacrylic acid (PAA or Carbomer) is generic name for synthetic high molecular weight polymers of acrylic acid as shown in Figure 2.12. The main differences among the polymers are related to the crosslinker type and density, and presence of hydrophobic co-monomers.

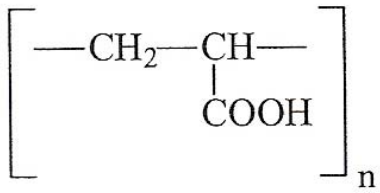


Figure 2.12 Structure of Poly(acrylic acid)

2.2.2.1 Typical properties of PAA polymers (91)

PAA polymers are flocculated powders averaging 2 to 7 microns in diameter, as determined by Coulter Counter. They are produced from primary polymer particles of about 0.2 micron average diameter. The flocculated agglomerates cannot be broken down into the ultimate particle once produced. Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. These linear polymers are soluble in a polar solvent, such as water. Crosslinked polymers swell in water up to 1,000 times their original volume (and ten times their original diameter) to form a gel when exposed to a pH environment above 4.0 - 6.0. Since the pKa of these polymers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone

ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer. Crosslinked polymers do not dissolve in water. The glass transition temperature of PAA polymer is 105°C (221°F) in powder form. However, the glass transition temperature drops dramatically as the polymer comes into contact with water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling. The molecular weight of these polymers is theoretically estimated to range from 700,000 to 3 or 4 billion. There are, however, no methods currently available to measure the actual molecular weight of a crosslinked (i.e. three-dimensional) polymer of this type.

2.2.2.2 PAA grades for Oral and Mucosal adhesive (91)

The PAA polymers which are recommended for oral and mucosal applications are designated by a "P" in the product trade name (i.e. Carbopol® 971P NF polymer).

(1) Carbopol® 934P NF Polymer

Carbopol® 934P NF polymer was designed especially for the pharmaceutical industry in the 1960s, as a high purity grade of Carbopol® 934 polymer. Some commercially available formulations contain Carbopol® 934P NF polymer, but this material is not recommended for new product development due to regulatory restrictions on benzene.

(2) Carbopol® 971P NF and Carbopol® 71G NF Polymers

Carbopol® 971P NF polymer is polymerized in ethyl acetate and is similar to Carbopol® 941 polymer (polymerized in benzene). Carbopol® 971P NF polymer was introduced specifically for use in oral and mucosal contact applications such as controlled release tablets, oral suspensions and bioadhesives. It is lightly crosslinked and therefore tends to be more efficient in controlling drug release than Carbopol® 974P NF polymer which is highly crosslinked. Typical usage levels in tablets for achieving extended release characteristics are 3 - 10 wt.%, depending on the drug properties, co-excipients and processing parameters.

Carbopol® 971P NF polymer also provides thickening, suspending and emulsion stabilizing properties to low viscosity systems for topical applications.

Carbopol® 71G NF polymer is a granular form of Carbopol® 971P NF polymer which is ideal for use in direct compression for tablets. It is the same chemical with no additives and improved flow properties.

(3) Carbopol® 974P NF Polymer

Carbopol® 974P NF polymer was introduced specifically for use in oral and mucoadhesive contact applications such as controlled release tablets, oral suspensions and bioadhesives. In addition, Carbopol® 974P NF polymer provides thickening, suspending and emulsion stabilizing properties to high viscosity systems for topical applications.

(4) Noveon® AA-1 Polycarbophil, USP

For bioadhesive applications, Noveon® AA-1 polycarbophil, USP is the industry standard and has been extensively formulated in a variety of drug delivery systems for mucosal applications. Buccal, intestinal, nasal, vaginal and rectal bioadhesive products can all be formulated with Noveon® AA-1 polycarbophil. The readily water-swellable PAA polymers are used in a diverse range of pharmaceutical applications to provide (92):

- Controlled release in tablets, PAA polymers offer consistent performance over a wide range of desired parameters (from pH-derived semi-enteric release to near zero-order drug dissolution kinetics) at lower concentrations than competitive systems.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications. Noveon AA-1 USP polycarbophil is the recognized industry standard for bioadhesion.
- Thickening at very low concentrations (less than 1%) to producr a wide range of viscosities and flow properties in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

2.2.3 Chitosan-polyacrylic acid interpolymer complexes

In 1996, Wang H and et al. (93) studied the behaviors of a mixture of water-soluble chitosan (CS) and polyacrylic acid (PAA) that showed the water-soluble CS may complex with PAA through electrostatic attraction. The polyelectrolyte complex exists steadily at about an equimolar unit composition. Although there are several kinds of groups in the CS chains including amino groups, hydroxyl groups, acetamido groups, etc., the electrostatic attraction between acrylate groups and protonated amino groups are the strongest interaction among all the possible secondary bonds between water-soluble CS and PAA. Therefore, the electrostatic attraction plays an predominant role during the formation of complex. But this does not mean that other interactions such as hydrogen bonding will not exist definitely; on the contrary, they may be beneficial to the stabilization of the complex.

Polymer complexes are formed by the association of two or more complementary polymers, and may arise from electrostatic forces, hydrophobic interactions, hydrogen bonding, van der Waals forces, or combination of these interactions. The formation of complexes may strongly affect the polymer solubility, rheology, conductivity, and turbidity of polymer solutions. Similarly, the mechanical properties, permeability, and electrical conductivity of the polymeric systems may be greatly affected by complexation (94).

Particularly, polyelectrolyte complexes are formed by the reaction of a polyelectrolyte with an oppositely charged polyelectrolyte in an aqueous solution. Electrostatic interactions are considerably stronger than most secondary binding interactions. Thus, electrostatic polyelectrolyte complexes exhibit unique physical and chemical properties with reasonable biocompatibility. Therefore, great attention has been focused on their application in biotechnology, pharmaceutics and medicine (95).

Ahn J-S, et al. (96) studied a mucoadhesive polymer by preparing a template polymerization of acrylic acid in the presence of CS as the matrix for transmucosal drug delivery system. The polymer complexes showed strong adhesive force and limited aqueous solubility. FT-IR results indicated that polymer complex was formed between PAA and CS through hydrogen bonding.

De la Torre, et al. (97) prepared a freeze-dried interpolymer complexes based on CS-PAA by developing amoxicillin delivery in an acidic environment. The

electrostatic polymer/polymer interactions generate polyionic complexes with different porous structures when indicated by scanning electron microscopy. In gastric simulated fluid (SGF), these kinds of interactions caused a greater swelling extent and a slower eroding rate of these interpolymer complexes, compared to freeze-dried hydrogel without PAA. The presence of higher CS content in the complexes generated a higher repulsion between the polymeric chains, therefore, a further increase in its maximum swelling ratio and a more sustained erosion profile were obtained in the SGF.

Torrado S, et al. (98) studied CS-PAA polyionic complexes to demonstrate prolonged gastric antibiotic delivery. Different polyioinic complexes of amoxicillin, CS and PAA were prepared and employing a non-invasive method; the gastric residence time of the formulations was evaluated by mean of ^{13}C-octanoic acid breath test. All the complexes showed extensive swelling, and diffusion of the antibiotic was controlled by the degree of polymer-drug interaction.

Rossi S, et al. (99) investigated the buccal delivery of acyclovir from films based on CS and PAA. The addition of PAA to CS produced a decrease in film hydration. Films based on CS-PAA weight ratio close to interaction product stoichiometry were characterized by higher rigidity and better wash away properties with respect to the other films and the commercial cream formulation. All the films examined promoted the permeation of acyclovir across epithelium when compared with acyclovir suspension and the commercial cream.

2.3 Diclofenac sodium as a model drug

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAIDs) with pronounced analgesic and antipyretic properties, is used in the long term treatment of rheumatoid arthritis and osteoarthritis. It produces a relatively high incidence of gastrointestinal side effects due to the physicochemical action on the gastric mucous and the inflammatory action on both small bowel and the colon. Its biological half-life has been reported as 1-2 h. Due to short biological half-life and associated adverse effects, it is an ideal candidate for controlled drug delivery in order

to achieve improved therapeutic efficacy and patient compliance (100,101). Its structural formula is given in Figure 2.13.

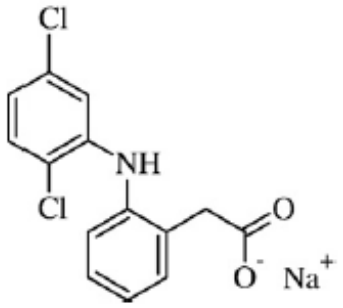


Figure 2.13 Structure of Diclofenac sodium

Diclofenac sodium has weak acidic properties (pKa about 4) and its solubility depends on the pH of the medium. It is slightly soluble in water, very slightly soluble in phosphate buffer at pH 6.8 and practically insoluble in hydrochloric acid at pH 1.1. Based on the Biopharmaceutics as a Class II drug. BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability, the main parameters for influencing rate and extent of absorption of a drug substances through gastrointestinal membranes and having significant influence on its bioavailability. Class II drugs are defined as those with high permeability but whose solubility in aqueous media is not sufficient for the whole does to be dissolved in the gastrointestinal tract. For these substances dissolution is therefore the rate limiting step to absorption. The choice of medium for in vitro dissolution tests is therefore expected to play a very important role in the dissolution of Class II drugs as it can depend on a wide variety of factors such as pH, ionic strength, buffer capacity, presence of surfactants, agitation and medium volume (100).

Diclofenac sodium in controlled-release delivery system

Very few investigations have been reported on the design and manufacture of diclofenac sodium controlled-release delivery system. Although several alternatives may be applied, tablet matrix seems to be the most popular delivery system because of its simplicity both in processing and instrumental requirement. In considering the potential of manufacturing a controlled-release dosage forms, several factors should be

taken into account. Such factors are the biological half-life of drug and its general degree of absorbability, the gastrointestinal site of absorption, the conventional dosage regimen, the frequency and types of toxicity encountered in the relation of peak to steady levels, the minimum effective concentration and the minimum toxic concentration.

There is probably no reason for formulating a drug having a biological half-life, $t_{1/2}$ of 8 hours or more into a controlled release preparation intended for peroral use. Usually drugs with half-life from 4 to 6 hours can readily be incorporated in such formulations while those having half-life of about 1 hour or less are not recommended to be formulated into this type of dosage form especially when their usual single doses are high, i.e., more than 50 mg. it is also important to know whether the prolonged release drug candidate can be absorbed from all regions of the gastrointestinal tract. Even if the drug is constantly released in vitro from the dosage form but not absorbed from deeper parts of the intestine, the prolonged release mechanism could be incompletely operative.

After oral administration diclofenac undergoes ‘first-pass’ metabolism with about 60% of drug reaching the systemic circulation in unchanged form. diclofenac sodium is almost totally absorbed because of its known pharmacokinetic properties, its effect of gastric irritation, its apparent plasma half-life, its efficient and complete absorption following oral administration, and its usual dose of 25 mg three times a day, diclofenac sodium becomes one of the most potential candidates for sustained release drug delivery system (102).

CHAPTER III
MATERIALS AND METHODS

3.1 Chemicals

3.1.1 Diclofenac sodium (Batch No. 20110128, Suzhou Ausun Chemical, China)

3.1.2 Potassium chloride (Batch No. 9A5472694, Carlo Erba Reagents SpA, Italy)

3.1.3 Magnesium stearate (Lot No. 9005511002, Unimer, Swizerland).

3.1.4 Pregelatinized starch (Starch 1500®, Lot No. 908030, Colorcon, West Point, USA)

3.1.5 Chitosan (High molecular weight, Batch No.BCBF5988V, Sigma-Aldrich, Japan)

3.1.6 Polyacrylic acid 934P NF (Carbopol 934P NF, Lot No. 0101068054, Lubrizol advance materials, Cleveland, USA)

3.1.7 Polyacrylic acid 971P NF (Carbopol 971P NF, Lot No. 0101136895, Lubrizol advance materials, Cleveland, USA)

3.1.8 Polyacrylic acid 974P NF (Carbopol 974P NF, Lot No. 0101006325, Lubrizol advance materials, Cleveland, USA)

3.1.9 Cellulose acetate (Batch No. MKBJ3010V, Aldrich, USA)

3.1.10 Polyvinylpyrrolidone K-30 (PVP K-30, Batch No. 03100271198, International Specialty Product, Wayne, USA)

3.1.11 Polyvinylpyrrolidone K-90 (PVP K-90, Batch No.03000250684, International Specialty Product, Wayne, USA)

3.1.12 Microcrystalline cellulose pH 101 (Ceolus™ pH 101, Batch No. 2092, Bag No.0182, Asahi Kasei Chemical corporation, Japan)

3.1.13 Microcrystalline cellulose pH 102 (Ceolus™ pH 102, Batch No. 1867, Bag No.0792, Asahi Kasei Chemical corporation, Japan)

3.1.14 Acetone (AR grade, lab-s, Thailand)

3.1.15 Polyethylene glycol 6000 (Namsiane International, Bangkok, Thailand)

3.1.16 Sodium hydroxide (Batch No. 802239, Ajax, Chemical, Auburn, Australia)

3.1.17 Ethanol 95% (Batch No. 8006-05, S.T. Baker, Malaysia)

3.1.18 Hydrochloride acid (Batch No. 01040121, Lab scan Asia, Bangkok, Thailand)

3.1.19 Acetic acid (Batch No. 01100156, Lab Scan Asia, Bangkok, Thailand)

3.1.20 Triethylamine (Batch No. 84289, Prolabo, Pavis, France)

3.1.21 Eudragit L 100-55 (Batch No. B111214555, Evonik Industries AG, Germany)

3.1.22 Phosphoric acid (Merck, Germany)

3.1.23 Monobasic sodium phosphate (Ajax Finechem Pty Ltd, Australia)

3.1.24 Methanol (HPLC grade) (Merck, Germany)

3.2 Equipments

3.2.1 Tumbling mixer (Rotomixer® Model BS 170, Foster Equipment, UK)

3.2.2 Single punch tablet machine (Model Exacta 1, Fette, Hamburg, Germany)

3.2.3 Analytical balance (Model A 200S, Sartorius, Goettingen, Germany)

3.2.4 Electronic precision balance (Model 1581 MP 8-1 , Sartorius, Goettingen, Germany)

3.2.5 Peristaltis pump (Watson-Marlow 505S, England)

3.2.6 Perforated pan coater (Thai Coater®, Model 15 L, Pharmaceutical and Medical supply LP., Thailand)

3.2.7 UV/Visible spectrophotometer (DU-650, Beckman Instruments, Fullerton, CA, USA)

3.2.8 High performance liquid chromatography

- High pressure pump (Model LC-10AT, Shimadzu, Japan)
- UV-detector (SPD-10VP, Shimadzu, Japan)
- System controller (SCL-10A VP, Shimadzu, Japan)

3.2.9 Dissolution test apparatus (SR8-plus Q-pak™, Hanson Research, Chatsworth, CA, USA)

3.2.10 Disintegration test apparatus (QC-21, Hanson Research, Chatsworth, CA, USA)

3.2.11 Electronic tablet hardness, diameter, thickness tester (Model PTB 311, Pharma Test, Hainburg, Germany)

3.2.12 Friabilator (Pharma Test® PTFR-A, D-63512, Germany)

3.2.13 Hot air oven (Kang Seng Lee Engineering, Thailand)

3.2.14 pH meter (Model MP 220, Mettler Toledo, Switzerland)

3.2.15 Sonicator (Model 2510 E – MT, Branson ultrasonic, Panbury, CT, USA)

3.2.16 Magnetic Stirrer (Pyru-Mac Stir Model L 344, Labinco BV, Breda, Netherland)

3.2.17 Fourier transform infrared spectrophotometer (Nicolet 6700, Thermo Fisher Scientific)

3.2.18 Scanning electron microscope (Model s-2360 N, Hitachi, Tokyo, Japan)

3.3 Methods

3.3.1 Preparation of CS-PAA interpolymer complexes

The polymer mixtures (3.3% w/v) of various CS-PAA weight ratios (1:2, 1:1, and 2:1) and various types of PAA 934P NF, PAA 971P NF and PAA 974P NF were prepared to form interpolymer complexes by separately dissolving CS and PAA in 1 M acetic acid and then mixing the solutions together. The mixture was neutralized with 3 M sodium hydroxide to achieve pH 5.0 and kept at room temperature (25 °C) overnight to allow complete precipitation of CS-PAA complexes. The complexes were

washed with distilled water. Thereafter, the wet masses were dried at 50 °C for 24 h and pulverized to fine powder by cutting mill (103).

3.3.2 Physicochemical characterization

3.3.2.1 Fourier transform infrared (FTIR)

The potassium bromide (KBr) method was used. The CS-PAA interpolymer complexes were examined by FTIR spectroscopy to identify functional groups introduced into the polymer. One mg of CS-PAA interpolymer powder complexes were mixed with 1 g of KBr powder. The mixture was filled in a die and compressed at 5 kN for 1 min. The compressed disc was placed in a sample holder and scanned from 4000 to 400 cm^{-1}.

3.3.2.2 Swelling properties of CS-PAA hydrogel

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

- Swelling force

Comparison of swelling performance of PAA with different type of polymer mixture at different blend ratios was carried out using texture analyser TA-XT plus. The pre-test speed, the test speed and post-test speed were set up at 0.5, 0.5 and 10 mm/s respectively, at an acquisition rate of 0.1 point. The trigger force and distance were 5 g and 0.1 mm respectively. The swelling forces were investigated for 8 h; at least three repetitions were obtained for each formulation.

- Swelling ratio

The swelling ratio study was examined for 8 h using dissolution testing Apparatus II. The pre-weight tablets were immersed in 500 mL of deionized water at 37 °C; the paddle's rotation speed was set at 25 rpm. The samples were taken at 15-min time intervals; prior to weighing, the samples were removed from the swelling medium and blotted on a piece of filter paper to remove excess surface water. The swelling ratio (S_W) was determined according to the following expression:

$$S_W = W_S/W_D$$

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.

3.3.3 Preparation of diclofenac sodium core tablets

The optimized formulation of type of PAA was selected to develop an osmotic pump tablets by consider a swelling force and a swelling ratio. The bilayered tablets (drug layer and polymer layer) are prepared manually by double compression method. The basic formulation of sandwiched osmotic tablet core and the varying range of various chemicals were listed in Table 3.1. The compositions of CS-PAA interpolymer complexes various formulations were using diclofenac sodium as a model drug containing three ratio of the polymer mixture (CS:PAA; 1:2, 1:1, and 2:1) which were prepared and was kept constant dose of diclofenac sodium (75 mg). The drug layer (total weight, 200 mg) comprise diclofenac sodium as an active ingredient, potassium chloride as an osmotic agent, magnesium stearate as a lubricant, PVP K30 as a binder and Avicel pH 101: Starch 1500 mixture at 1:1 mass ratio as a filler. The polymer layer (total weight, 100 mg) comprise CS-PAA complex with different polymer weight as a polymeric osmogent, potassium chloride as an osmotic agent, magnesium stearate as a lubricant, Avicel pH 102: Starch 1500 mixture at 1:1 mass ratio as a filler and FD&C red NO.2 as a coloring agent. The ingredients of both layers were mixed separately in V-shape. The drug layer was prepared by wet granulation process and the polymer layer was prepared by direct compression process. Then, the granule was compressed on a single punch press using 9 mm punch and die tooling by following procedure. The polymer layer was first compressed into a soft slug. Then, the drug layer was added and compressed again to form the bilayer tablet. The tablet weight was set to be 300 mg and the hardness of approximately 80 N. The compressed tablets were stored in well-closed containers prior to coating.

Table 3.1 Formulation compositions of diclofenac sodium core tablets

Composition (mg)	Formulation				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA30**
Drug layer					
Diclofenac sodium	75	75	75	75	75
Potassium chloride	10	10	10	10	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
PVP K30	6	6	6	6	6
Filler [a]	107.5	107.5	107.5	107.5	107.5
Polymer layer					
CS-PAA interpolymer complex	-	5	10	20	30
Potassium chloride	10	10	10	10	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Filler [b]	88.5	83.5	78.5	68.5	58.5

Filler [a] is the mixture of Avicel pH 101:pregelatinized starch (1:1)

Filler [b] is the mixture of Avicel pH 102:pregelatinized starch (1:1)

3.3.4 Preparation of diclofenac sodium osmotic pump tablets

To determine the formulation which containing optimal amount of CS-PAA interpolymer complexes in polymer layer that exhibit a satisfactory drug release. The core tablets were coated with a mixture of 4% w/v cellulose acetate in acetone solution containing PVP K90 (50% w/v with respect to cellulose acetate) as pore formers, using 25% w/w TEC as a plasticizer, to achieve 10% additional weight using perforated pan coater. The coating conditions were shown in Table 3.2.

Table 3.2 Coating condition of the semi-permeable membrane were as follows

Condition	
Batch size	2 kg
Preheating time	30 min
Inlet air temperature	50-60 °C
Outlet air temperature	40-50 °C
Atomizing pressure	1.2 kgf/cm^2
Pan speed	10 rpm
Spray rate	4 ml/min
Drying air temperature	35 °C
Drying time	30 min

Diclofenac sodium core tablets were placed in the coating pan. Two kilograms filler tablets were added in order to achieve the appropriate batch size. Initially, the pan was rotated at low speed (1-2 rpm) and heated air was passed through the tablet bed. Coating process start once the outlet air temperature reach 35 °C and was maintained above this temperature by keeping the air temperature in the range of 50-60 °C. The revolution per minute of the pan, the rate of spraying of coating solution and the atomization pressure was kept as listed above. Coating was continued until the desired weight gain was obtained. Finally, coated tablets were dried at 35 °C for 12 h before analysis.

3.3.5 Preparation of diclofenac sodium extended release tablets

The diclofenac sodium osmotic pump tablets were coated with a mixture of 6% w/w Eudragit L 100-55 in 95% ethanol/acetone (3:1) solution containing 25% w/w PEG6000 of film content as a plasticizer, to achieve 6% additional weight using perforated pan coater. The coating conditions were shown in Table 3.3.

Table 3.3 Coating condition of the extended release tablets

Condition	
Batch size	2 kg
Preheating time	30 min
Inlet air temperature	40-45 °C
Outlet air temperature	35-40 °C
Atomizing pressure	1.2 kgf/cm^2
Pan speed	10 rpm
Spray rate	2 ml/min
Drying air temperature	35 °C
Drying time	30 min

3.3.6 Evaluation of diclofenac sodium core tablets

Diclofenac sodium core tablets were examined for their physical properties, i.e., average weight, hardness and friability. The hardness and friability of core tablets were considered critical parameters since the core tablets had to withstand the tumbling motion of tablet beds in the pan coater. Disintegration time, drug dissolution and content were determined to ascertain that they had appropriate properties for the further study.

3.3.6.1 Weight variation

Weight variation was determined by weighing 10 tablets individually. The average weight and their standard deviation were calculated.

3.3.6.2 Thickness, diameter, and hardness

Ten tablets were randomly sampled and individually measured their thickness, diameter and hardness using an electronic tablet hardness, diameter, thickness tester (Pharma Test® Model PTB 311). Their means and standard deviations were reported.

3.3.6.3 Friability

Approximately 6.5 g of tablets were accurately weighed and then loaded into a Roche type friabilator. The drum was rotated at 25 rpm for 4 min. Loss of weight with respect to the initial value was calculated as percent friability.

3.3.6.4 Disintegration test

The determination is based on USP 36 method for the uncoated tablets using disintegration apparatus USP type. Six tablets from each preparation were tested for their disintegration time using water as disintegration medium at the temperature of 37 ± 2 °C. Means and standard deviations of six tablets were calculated.

3.3.6.5 Content uniformity

Content uniformity of diclofenac sodium core tablets was determined by the assay of ten tablets individually. Each tablet was transferred into a 100-mL volumetric flask. The assay method was followed under the content uniformity in diclofenac sodium extended release tablets as directed in assay of USP 36 by HPLC method.

- High performance liquid chromatography (HPLC)

A High performance liquid chromatography equipped with an UV-detector and computerized recorder was used. A C8 column (25 × 4.6 mm internal diameter) packed with porous silica (5 µm particles) was stationary phase. The flow rate was 1.0 mL/min and the detector was set at the wavelength of 254 nm.

Mobile phase: The mobile phase was composed of 70% v/v of methanol and 30% v/v of buffer (0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. Adjust with appropriate component to a pH of 2.5)

Standard preparation: An accurate weight about 50 mg of standard diclofenac sodium was dissolved and adjusted to 100 mL of methanol and water (7:3) solution in volumetric flask. Appropriate dilutions were made to obtain diclofenac sodium standard solutions of 5, 10, 20, 30, 40 mg/mL. The solution was filtered through a 0.45 µm polyamine membrane filter. A portion of each standard solution was injected into HPLC column. The peak areas of drug were plotted against the concentrations of drug.

Sample preparation: To prepare a sample solution, diclofenac sodium powder (not less than 10 tablets), equivalent to about 100 mg of diclofenac sodium, was transferred to a 200- mL volumetric flask and added with 150 mL of methanol and water (7:3) solution. Heated on a steam bath for 3-5 min, and sonicated for 20 min. The sample were cooled to room temperature, and diluted with methanol

and water (7:3) solution to volume. The flask was placed in an ice bath for 45 min, shaked occasionally to precipitate out any undissolved waxy material. A portion of the chilled solution was passed through a filter of 0.45-µm or finer pore size. Allow the filtrate to reach room temperature before using.

3.3.7 *In vitro* dissolution of diclofenac sodium core tablets

3.3.7.1 Calibration curve

An accurate weight of 10 mg of diclofenac sodium was transferred to a volumetric flask and dissolved in phosphate buffer (pH 7.5) to achieve the concentration of 10 mg%. Appropriate dilution with phosphate buffer (pH 7.5) was made to obtain series of standard solution between 0.5 to 3.0 mg%. An absorbance of each standard solution was determined by a UV spectrophotometer at the maximum absorption wavelength of 276 nm. The phosphate buffer (pH 7.5) was used as a blank.

3.3.7.2 Dissolution test

The drug release from diclofenac sodium core tablets was determined using USP 36 dissolution test for diclofenac sodium extended release tablets. The dissolution test was performed by a USP Apparatus II (paddle method) connecting with a UV/visible spectrophotometer equipped with six 1-cm flow cells and six-channel peristaltic pump. The temperature of medium was maintained at 37 ± 0.5 °C. A 900 mL of 0.05 M phosphate buffer (pH 7.5) was used as a dissolution medium. The rotation speed of paddle was 50 rpm. The samples were collected every 5 min for 1 h to determine the released amount of diclofenac sodium by UV/visible spectrophotometry. The absorbance of samples was detected at the wavelength of 276 nm. The percentages of drug release were calculated by comparing to the standard curve of diclofenac sodium in phosphate buffer (pH 7.5).

3.3.8 Evaluation of diclofenac sodium osmotic pump tablets and diclofenac sodium extended release tablets

Weight variation, thickness, diameter, and hardness of diclofenac sodium osmotic pump tablet and diclofenac sodium extended release tablets were examined with the method as described in the section 3.3.5.1 and 3.3.5.2.

3.3.9 *In vitro* dissolution test of diclofenac sodium osmotic pump tablets and diclofenac sodium extended release tablets.

3.3.9.1 Calibration curve

The calibration curve of diclofenac sodium in phosphate buffer pH 7.5 was prepared as described in the section 3.3.6.

3.3.9.2 Determination of drug release from diclofenac sodium osmotic pump tablets.

The dissolution test was performed as described in the section 3.3.6.2. The procedure and criterion employed for the drug release was based on USP 36, according to diclofenac sodium extended release tablet as described in Tables 3.4 and 3.5. The dissolution profiles were constructed by plotting the average percent release of diclofenac sodium against time. Six tablets of each formulation were determined. The mean and SD of percentages of the drug dissolved were calculated.

Table 3.4 Dissolution procedures for diclofenac sodium osmotically controlled release tablets

	24 h-diclofenac CPOP	**10 h-diclofenac CPOP**
Drug Release (USP36)	Test 1	Test 2
The rotation speed of paddle	50 rpm	50 rpm
Wavelength	276 nm	276 nm

Table 3.5 Acceptance criteria of drug dissolved for diclofenac sodium osmotically controlled release tablets

	Time (h)	Drug dissolved (%)
For 24 h of	1	between 15% and 35%
diclofenac CPOP	5	between 45% and 65%
	10	between 65% and 85%
	16	between 75% and 95%
	24	not less than 80%
For 10 h of	1	not more than 28%
diclofenac CPOP	2	between 20% and 40%
	4	between 35% and 60%
	6	between 50% and 80%
	10	not less than 65%

3.3.10 Scanning electron microscopy (SEM) of coating membranes

In order to evaluate the surface morphology of the optimized formulation diclofenac sodium osmotic pump tablet, the surface of the tablet both before and after the dissolution test was studied by SEM. Surface pore diameters were measured by visual inspection of SEM pictures which were generated by a nanoscope's image processing program.

3.3.11 Statistical analysis

The result of osmotic pump tablets was expressed as mean ± SD values. The statistical significance was performed by using one-way analysis of variance test (ANOVA) and a value of $P < 0.05$ was statistically significant.

CHAPTER IV
RESULTS AND DISCUSSION

4.1 Preparation of CS-PAA interpolymer complexes

4.1.1 Quantitative analysis of CS-PAA interpolymer complex from polymerization reaction

CS-PAA interpolymer complex was formed by polymer blending of polyelectrolyte complexes containing CS (polycations polymer) and PAA (polyanions polymer) at various ratios. The powder of polymer was dissolved in acetic acid and mixed together. Then, the mixture was added with sodium hydroxide to neutralize and achieve pH at 5.0, the mixture appeared as white gel-like precipitates and became more viscous after standing overnight. After drying at 50 ºC, a golden-yellow membrane was obtained. The color change after drying could be due to the oriented polymer chains of CS and PAA, which altered light reflection as reported previously. The preparation of CS-PAA at the ratio of 1:2 provided the highest yield of CS-PAA 971P NF of 87.21%, whereas the yields of CS-PAA 974P NF and CS-PAA 934P NF were 86.12% and 84.55%, respectively. At the ratio of 1:1, the yield of CS-PAA 971P NF, CS-PAA 974P NF and CS-PAA 934P NF were 77.03%, 76.36% and 74.18%, respectively. Finally, at the ratio of 2:1, the provided yield of CS-PAA 971P NF, CS-PAA 974P NF and CS-PAA 934P NF were 75.82%, 73.91% and 72.39%, respectively (Figure 4.1).

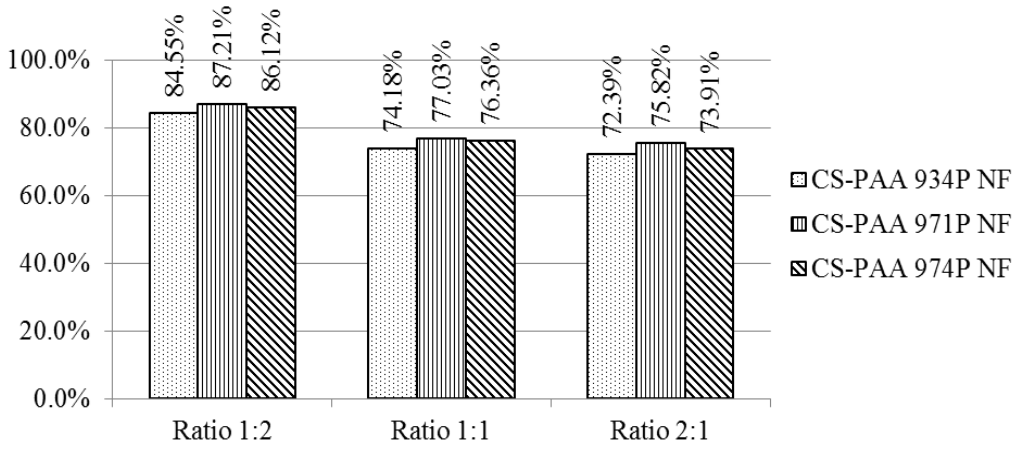


Figure 4.1 Percent yield of the CS-PAA complex production

4.1.2 Fourier transform infrared spectroscopy (FTIR)

In this work, the range of 1400–1800 cm^{-1} was used in all spectra as it is a suitable region to examine the effect on the vibration modes of carbonyl groups and carboxylate groups due to possible hydrogen bonding interactions in the CS-PAA complex (103).

FTIR spectra of chitosan, PAA 934P NF, PAA 971P NF, and PAA 974P NF were shown in Figure 4.2. For the IR spectrum of chitosan, the characteristic absorption bands appeared at 1650 cm^{-1} (amide I), 1600 cm^{-1} (amide II) and 1383 cm^{-1} (amide III). The absorption bands of the carboxyl groups of PAA 934P NF, PAA 971P NF and PAA 974P NF can be observed at 1717, 1715 and 1710 cm^{-1}, respectively.

Figure 4.3 demonstrated the absorption peaks for the CS-PAA ratio of 1:2 at 1645 (–C=C–, alkenes), 1550 (C–C stretch, aromatic), and 1408 cm^{-1} (C–C stretch, aromatic), the CS-PAA ratio of 1:1 at 1640 (–C=C–, alkenes), 1550 (C–C stretch, aromatic), and 1408 cm^{-1} (C–C stretch, aromatic), and the CS-PAA ratio of 2:1 at 1717 (C=O, unsaturated esters), 1665 cm-1 (C=O, unsaturated aldehydes or ketones). Figure 4.4 shows absorption peaks for the CS-PAA ratio of 1:2 at 1650 (–C=C–, alkenes), and 1410 cm^{-1} (C–C stretch, aromatic), the CS-PAA ratio of 1:1 at 1640 (–C=C–, alkenes) and 1410 cm^{-1} (C–C stretch, aromatic), and the CS-PAA ratio of 2:1 at 1715 (C=O, unsaturated esters), 1670 (–C=C–, alkenes), 1560 (C–C stretch, aromatic) and 1425 cm^{-1} (C–C stretch, aromatic). These results indicated that the carboxylic

groups of PAA were dissociated into COO− groups which complexed with the protonated amino groups of chitosan through electrostatic interaction to form polyelectrolyte complex during the polymerization procedure. Figure 4.5 showed absorption peaks for the CS-PAA ratio of 1:2 at 1750 (C=O, esters, saturated aliphatic), 1710 (C=O, unsaturated aldehydes or ketones), and 1450 cm^{-1} (C–C stretch), the CS-PAA ratio of 1:1 at 1760 (COOH, carboxylic acids), 1680 (–C=C–, alkenes), and 1410 cm^{-1} (C–C stretch, aromatic), and the CS-PAA ratio of 2:1 at 1745 (COOH, carboxylic acids), 1680 (–C=C–, alkenes), and 1445 cm^{-1} (C–C stretch, aromatic). The FTIR results indicated that interpolymer complex was formed between CS and PAA through an electrostatic interaction of the protonated amine (NH_3^+) group of CS and the carboxylate (COO^-) group of PAA.

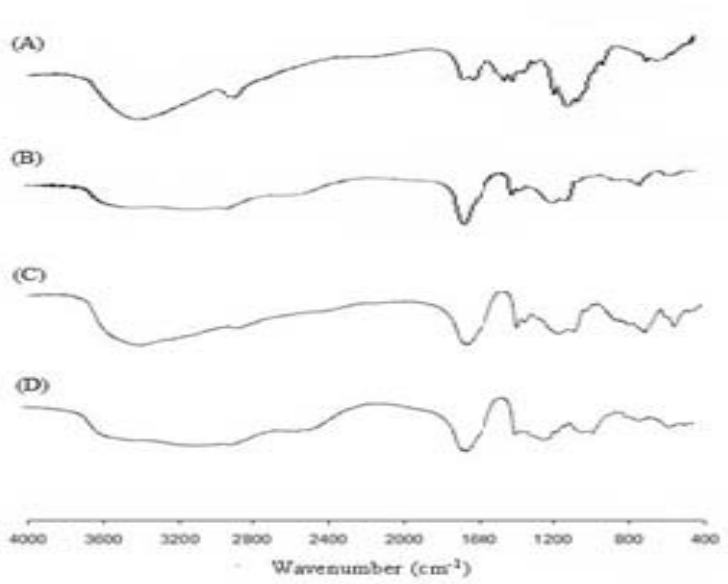


Figure 4.2 FTIR spectra of pure sample: (A) CS; (B) PAA 934P NF; (C) PAA 971P NF; (D) PAA 974P NF

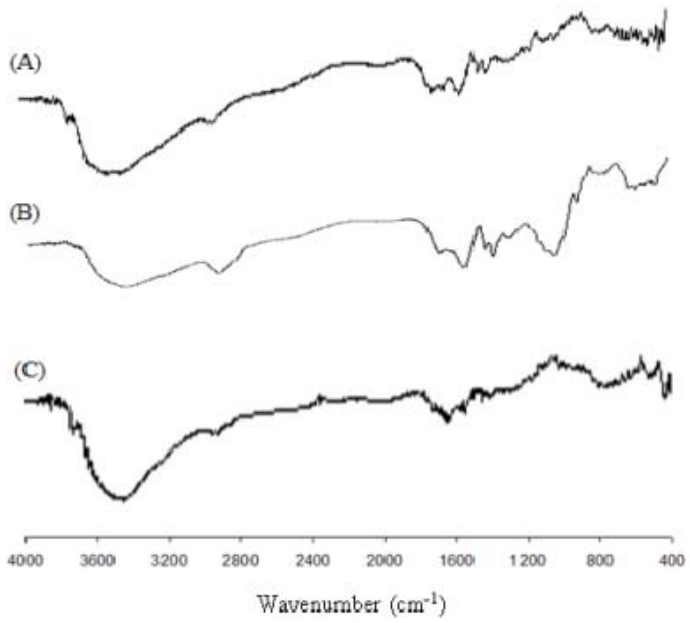


Figure 4.3 FTIR spectra of CS-PAA 934P NF interpolymer complex at different ratios: (A) the ratio of 1:2, (B) the ratio of 1:1, (C) the ratio of 2:1

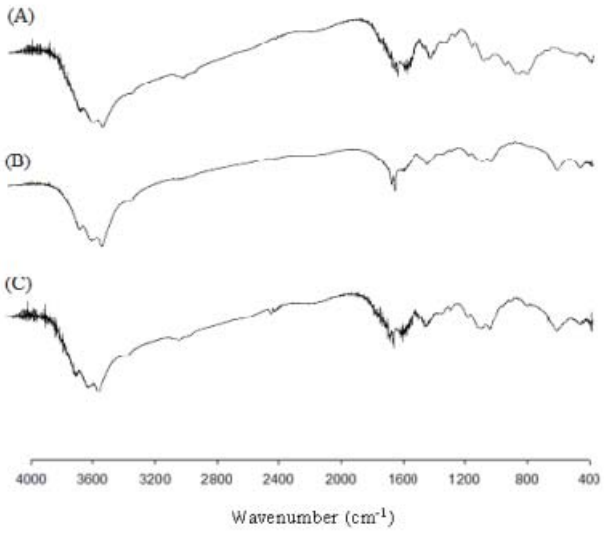


Figure 4.4 FTIR spectra of CS- PAA 971P NF interpolymer complex at different ratios: (A) the ratio of 1:2, (B) the ratio of 1:1, (C) the ratio of 2:1

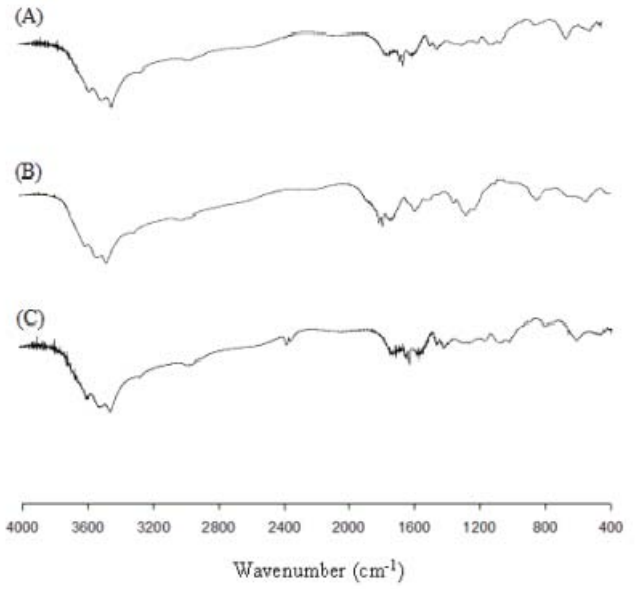


Figure 4.5 FTIR spectra of CS- PAA 974P NF interpolymer complex at different ratios: (A) the ratio of 1:2, (B) the ratio of 1:1, (C) the ratio of 2:1

4.1.3 Swelling properties

4.1.3.1 Swelling forces

Experiments were performed to determine the forces that exerted on the CS-PAA interpolymer complex hydrogels when they were swollen under the study condition. Figure 4.6 and 4.7 showed the swelling behaviours of the CS-PAA interpolymer complexes in water with various type of PAA (PAA 934P NF, PAA 971P NF, and PAA 974P NF) and various ratios of CS-PAA (1:2, 1:1, 2:1). CS-PAA complexes with the type of PAA 934P NF at the ratios of 1:2, 1:1, and 2:1 exhibited maximum swelling force at 23.62, 25.05 and 31.63 N, respectively. The type of PAA 971P NF at the ratios of 1:2, 1:1, and 2:1, showed maximum swelling forces of 20.56, 28.88 and 36.79 N respectively. The type of PAA 974P NF at the ratios of 1:2, 1:1 and 2:1 showed maximum swelling forces of 15.93, 27.73 and 34.01 N respectively. It was found that CS-PAA interpolymer complex from PAA 971P NF at the ratio of 2:1 showed maximum swelling force.

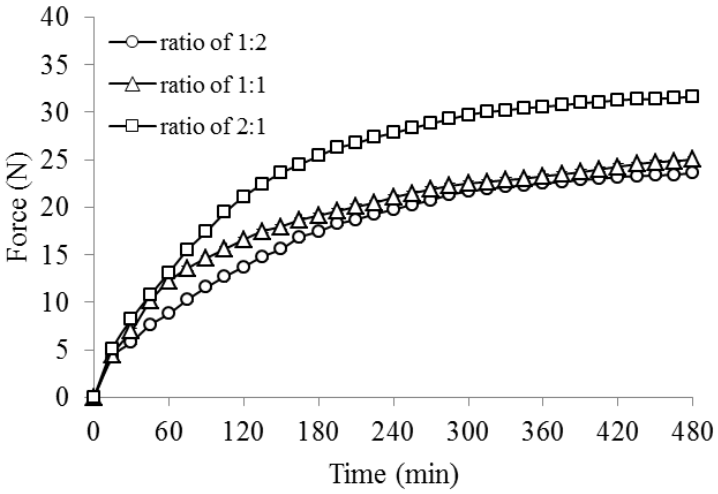
The results indicated that the swelling force increased with the increased ratio of CS. Moreover, PAA 971P NF is lightly crosslinked and therefore tends to be more porous in hydrogel than PAA 934P NF and PAA 974P NF polymer

which is highly crosslinked. Also, the diffusion coefficients of water penetrating into the gels increased with increasing pore volume of the gels (91,105) that may affect the increase of the swelling force.

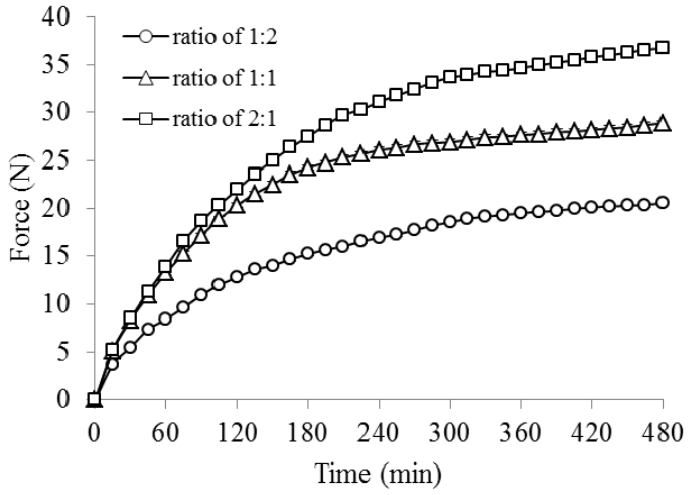
4.1.3.2 Swelling ratios

Figure 4.8 and 4.9 showed the swelling ratios of CS-PAA interpolymer complexes at various types of PAA and various ratios. The swelling ratios obtained from CS-PAA 934P NF at the proportion of 1:2, 1:1 and 2:1 were 15.47, 17.63 and 22.95, respectively. The CS-PAA complexes using PAA 971P NF at the ratios of 1:2, 1:1 and 2:1 showed the swelling ratios of 13.42, 20.53 and 23.40, respectively. The CS-PAA complexes using PAA 974P NF at the ratios of 1:2, 1:1 and 2:1 provided the swelling ratios of 11.70, 19.57 and 21.53, respectively. CS-PAA interpolymer complexes were found to increase swelling ratios when the proportion of CS increased. The maximum swelling force of 23.40 N was obtained with PAA 971P NF at the ratio of 2:1. For the further study, the ratio of CS-PAA 971P NF at 2:1 was selected based on the good swelling characteristics.

(A)



(B)



(C)

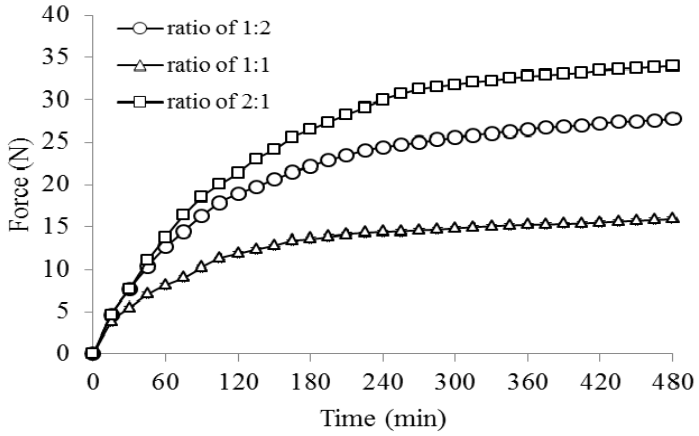
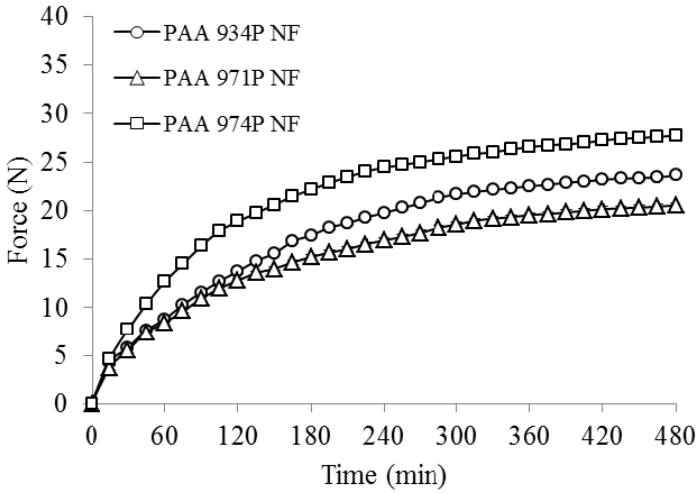
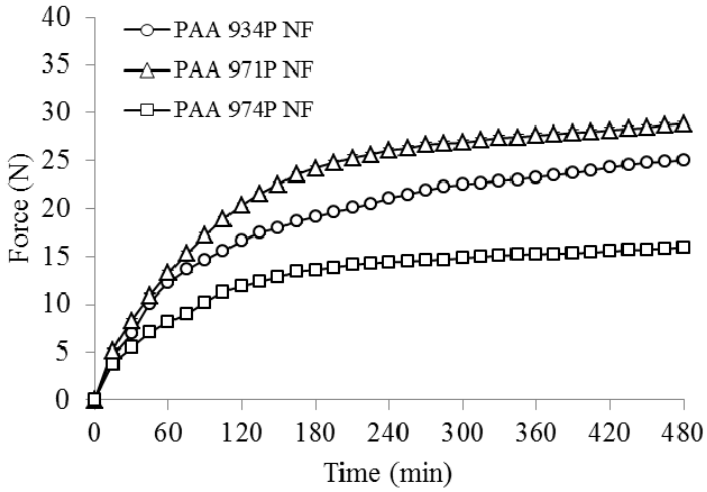


Figure 4.6 Swelling forces (N) of CS-PAA interpolymer complexes at various types of PAA: (A) PAA 934P NF, (B) PAA 971P NF, and (C) PAA 974P NF

(A)



(B)



(C)

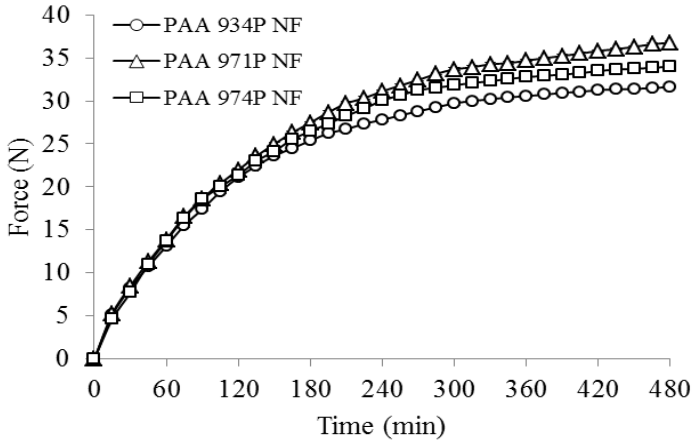
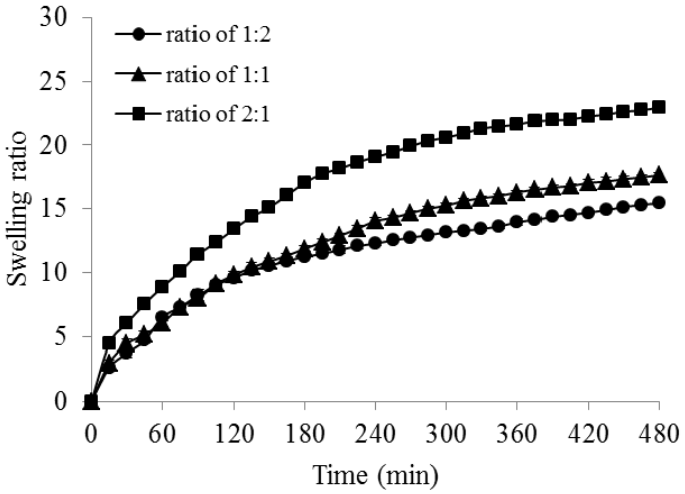
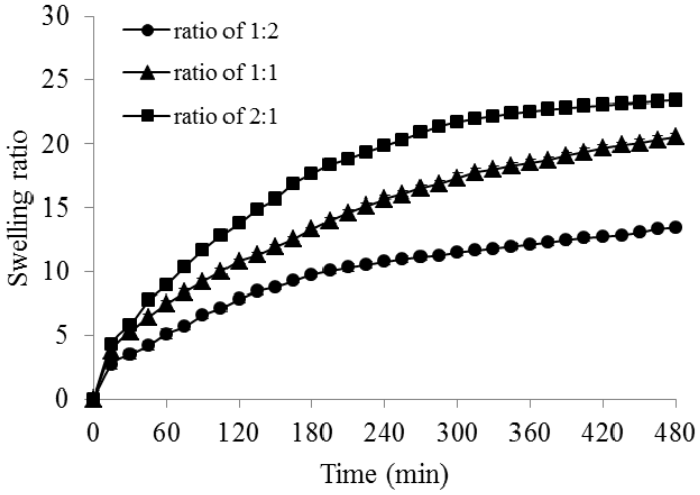


Figure 4.7 Swelling forces (N) of CS-PAA interpolymer complexes at various ratios of CS-PAA: (A) ratio of 1:2, (B) ratio of 1:1, and (C) ratio of 2:1

(A)



(B)



(C)

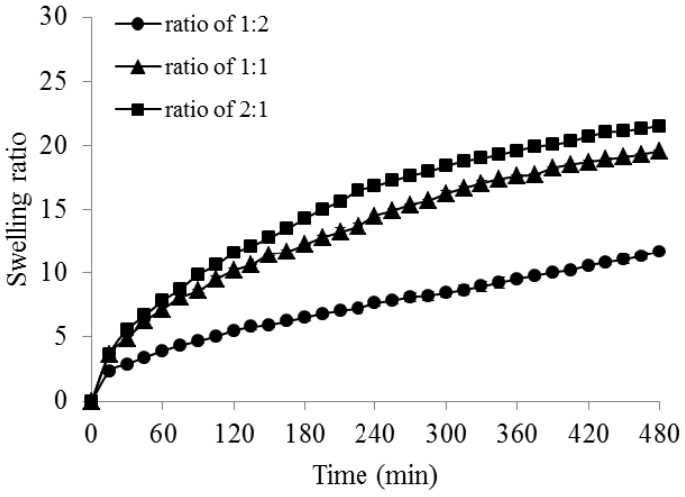
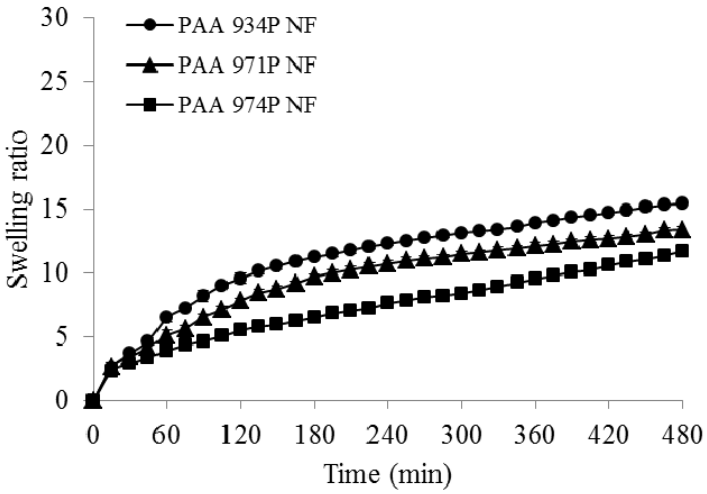
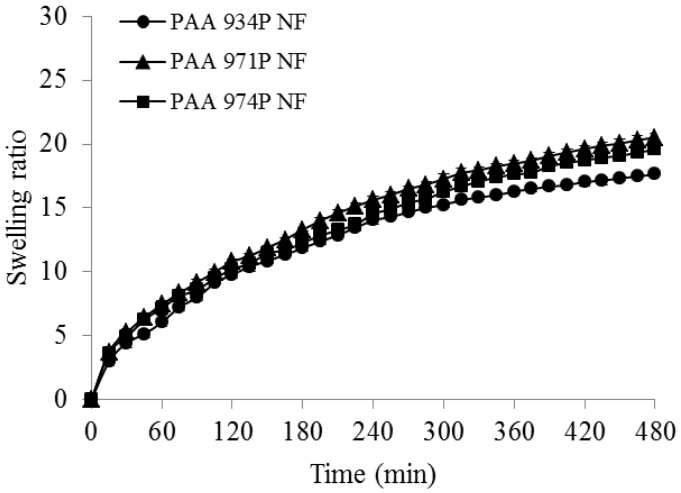


Figure 4.8 Swelling ratios of CS-PAA interpolymer complexes at various types of PAA: (A) PAA 934P NF, (B) PAA 971P NF, and (C) PAA 974P NF

(A)



(B)



(C)

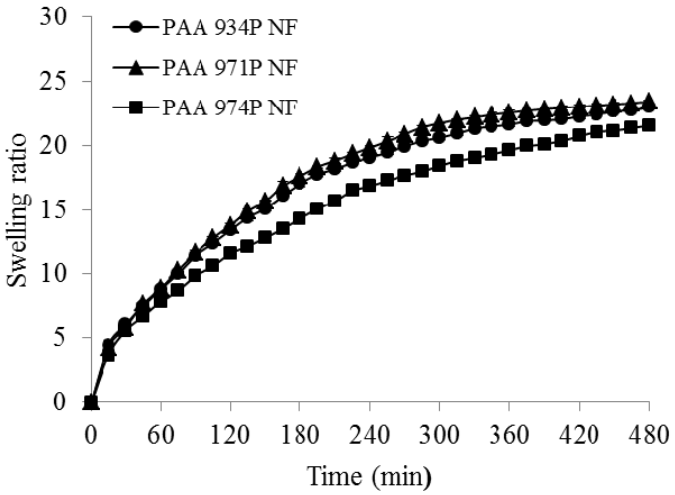


Figure 4.9 Swelling ratios of CS-PAA interpolymer complexes at various ratios of CS-PAA: (A) ratio of 1:2, (B) ratio of 1:1, and (C) ratio of 2:1

4.2 Evaluation of diclofenac sodium core tablets

Diclofenac sodium core tablets were prepared by a wet granulation method. The bilayer tablet contained drug layer and polymer layer. Drug layer comprises diclofenac sodium as an active ingredient, potassium chloride as an osmotic agent, PVP K30 as a binder, magnesium stearate as a lubricant, and the mixture of Avicel pH 101: Starch 1500 (1:1) as a filler. Polymer layer contained potassium chloride as an osmotic agent, magnesium stearate as a lubricant, the mixture of Avicel pH 102: Starch 1500 (1:1) as a filler and various amounts of CS:PAA interpolymer complexes as osmotic agents. It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for the release of water-insoluble drug. The hydration and gel formulation of chitosan are very much dependent on pH of the surroundings. It is insoluble at an alkaline and neutral pH but soluble in the acid condition. Upon dissolution, amine groups of the polymer become protonated, forming a resultant viscous and soluble polysaccharide. Inclusion of citric acid as pH- regulating excipient in the developed formulations was expected to decrease the microenvironmental pH of the core to a suitable level at which chitosan could form appropriate viscous gelling solution and hence, to enhance the osmotic pressure of the core tablets (104).

The core tablets of diclofenac sodium were evaluated for the physical properties of the tablets including weight variation, thickness, diameter, hardness, friability, and disintegration time, to ascertain that they had properties appropriate for the further study.

4.2.1 Weight variation

The core tablets were produced in different amounts of the CS-PAA interpolymer complexes. Their average and standard deviation were shown in Table 4.1. All formulations met the USP36 requirements on weight variation test.

4.2.2 Hardness, thickness, and diameter

Hardness, thickness and diameter of 20 tablets were monitored by using a multipurpose measuring device (Pharma Test® PTB311, Germany). Their means and standard deviation were shown in Table 4.1.

4.2.3 Friability

The friability increased with an increased amount of CS-PAA interpolymer complexes in the formulation. Their means and standard deviation were shown in Table 4.1. The CS-PAA30 formulation showed the friability of more than 1%. Therefore, that formulation was disregarded.

4.2.4 Disintegration time

The results for evaluation of all tablet formulations prepared by double compression method were shown in Table 4.1. The disintegration time of all tablet formulations was disintegrated in less than 16 min.

4.3 Evaluation of diclofenac sodium osmotic pump tablets

The core tablets of diclofenac sodium were coated with a mixture of 4% w/v cellulose acetate, to achieve 10% additional weight. The physical properties of the tablets were evaluated weight variation, thickness, diameter, hardness, and friability, to ascertain that they had properties appropriate for further study.

4.3.1 Weight variation

The semi-permeable membrane of osmotic pump tablets were produced in different amount of CS-PAA interpolymer complexes. Their average and standard deviation were shown in Table 4.2. All formulations met the USP36 requirements on weight variation test.

4.3.2 Hardness, thickness, and diameter

Hardness, thickness and diameter of 20 tablets were monitored by using a multipurpose measuring device (Pharma Test® PTB311, Germany). Their means and standard deviation are shown in Table 4.2.

4.3.3 Friability

The friability of all formulation didn’t erode. Their means and standard deviation are shown in Table 4.2.

Table 4.1 The physical properties of diclofenac sodium core tablets

Properties	Mean (SD)				
	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20	CS-PAA30
Weight, (mg)	300.85 (2.20)	299.75 (1.29)	302.25 (2.10)	301.30 (2.05)	300.00 (2.47)
Thickness, (mm)	4.03 (0.01)	4.05 (0.01)	4.04 (0.02)	4.03 (0.01)	4.04 (0.01)
Diameter, (mm)	8.97 (0.01)	8.96 (0.01)	8.98 (0.01)	8.97 (0.01)	8.97 (0.01)
Hardness, (kg)	8.76 (0.82)	8.46 (0.93)	9.48 (0.80)	9.03 (0.73)	8.75 (0.90)
Disintegration time (min)	14.18 (0.70)	10.70 (0.80)	15.65 (0.75)	15.20 (0.58)	13.13 (0.83)
Content uniformity (%)	99.99 (0.80)	99.76 (0.47)	100.60 (0.82)	100.13 (0.67)	99.93 (0.75)
Friability, (%)	0.14	0.17	0.27	0.35	2.96

Table 4.2 The physical properties of diclofenac sodium tablets with semi-permeable membrane (10%)

Properties	Mean (SD)			
	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20
Weight, (mg)	331.45 (3.35)	331.95 (3.38)	333.80 (3.31)	331.45 (3.45)
Thickness, (mm)	4.26 (0.01)	4.27 (0.01)	4.28 (0.01)	4.27 (0.01)
Diameter, (mm)	9.27 (0.01)	9.27 (0.01)	9.29 (0.01)	9.27 (0.01)
Hardness, (kg)	11.08 (1.03)	11.04 (1.04)	12.56 (1.08)	12.16 (1.34)
Friability, (%)	0.00	0.00	0.00	0.00

4.4 Evaluation of diclofenac sodium osmotic pump tablets coated with Eudragit L.

The diclofenac sodium osmotic pump tablets were coated with a mixture of 6% w/w Eudragit L 100-55 in 95% ethanol : acetone (3:1) solution, to achieve 6% additional weight. The physical properties of the tablets were evaluated weight variation, thickness, diameter, hardness, and friability, to ascertain that they had properties appropriate for further study.

4.4.1 Weight variation

The diclofenac sodium osmotic pump tablets were produced in different amount of CS-PAA interpolymer complexes. Their average and standard deviation were shown in Table 4.3. All formulations met the USP36 requirements on weight variation test.

4.4.2 Hardness, thickness, and diameter

Hardness, thickness and diameter of 20 tablets were monitored by using a multipurpose measuring device (Pharma Test® PTB311, Germany). Their means and standard deviation are shown in Table 4.3.

4.4.3 Friability

The friability of all formulation didn't erode. Their means and standard deviation are shown in Table 4.3.

Table 4.3 The physical properties of semi-permeable membrane of diclofenac sodium tablets with Eudragit L (6%).

Properties	Mean (SD)			
	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20
Weight, (mg)	351.45 (2.58)	350.00 (2.05)	353.15 (2.80)	352.75 (2.90)
Thickness, (mm)	4.46 (0.02)	4.44 (0.02)	4.46 (0.02)	4.45 (0.01)
Diameter, (mm)	9.45 (0.01)	9.44 (0.02)	9.46 (0.02)	9.46 (0.02)
Hardness, (kg)	16.88 (0.99)	16.44 (1.50)	18.36 (1.13)	17.39 (1.23)
Friability, (%)	0.00	0.00	0.00	0.00

4.5 Drug release studies and mechanism

4.5.1 Drug release studies

Table 4.4 and Figure 4.10 showed the dissolution profiles of core tablet containing diclofenac sodium and various excipients in pH 7.5 phosphate buffer solutions. The rate of drug dissolution from core tablet was slow release from the tablets. This might be due to the gel forming ability of PAA at pH 7.5, which retards the rate of drug release from the tablet. Almost all carboxyl groups dissociated at pH 7.5 resulting in the formation of a swollen gel. Therefore, the dissolution profile of diclofenac sodium from double layer of core tablet in all formulations was similar the slow release from the dissolution medium at pH 7.5.

Table 4.5 and Figure 4.11 showed the dissolution profiles of osmotic pump tablet coated with semi-permeable membrane containing diclofenac sodium and various excipients in pH 7.5 phosphate buffer solutions. Drug release of all formulations was found to range from 51.01 to 79.01% in 10 h and 89.98 to 95.80% in 24 h. The release rate depended on the amount of the osmotic agent. The amount of the osmotic agent increased then the osmotic pressure created inside the tablet also increased, the core compartment imbibed aqueous fluids from the surrounding environment across the membrane and dissolved the drug, so the release of the drug also increased.

Table 4.6 and Figure 4.12 showed the dissolution profiles of osmotic pump tablet coated with semi-permeable membrane, coated with Eudragit L containing diclofenac sodium and various excipients in pH 1.2 hydrochloric acid solutions at 2 h and pH 7.5 phosphate buffer solutions at 24 h. The release rate was not drug release through medium solution within 2 h in pH 1.2 hydrochloric acid solutions. Drug release of all formulations was found to range from 50.87 to 79.24% at 10 h and 90.15 to 96.11% at 24 h in pH 7.5 phosphate buffer solutions. The release rate also depended on the amount of the osmotic agent.

4.5.2 Drug release mechanism

The release studies of drug formulation from all formulations were examined for the kinetic drug releases by plotting in the mode of data treatments. The

drug released model that used in this thesis, Higuchi's model of diffusion of time which were of plotted cumulative percentage drug released versus square root of time, Zero-order kinetics were plotted between the cumulative drug released and times and First-order kinetics were plotted of Log % drug released versus times.

The result showed that the core tablet contained higher amount of CS-PPA following the Higuchi model. This was due to the property of the CS-PPA complex. The higher amount of the polymer complex could have the greater swelling than the less amount of the polymer complex. The drug from the drug layer side that was close to the polymer layer diffused through the polymer.

The core tablet coated with cellulose acetate contained PVP K90 for semipermeable membrane showed the tendency as followed in the core tablet formulations.

The data of the enteric coated tablet showed that there was no drug release through the medium solution within 2 h. Thus, this will be suitable for the tablet which needed the drug to be released in the intestine. Only the CS-PAA00 formulation gave the zero-order kinetic, whereas the others were fitted to the Higuchi model. When increased the amount of polymer, the R^2 value of the graph which plotted between the cumulative percentage drug released and the square root was close to 1. The properties and amount of the polymer were important factors to formulate this osmotic tablet formulation. The higher amount of CS-PAA could have an effect on the rate of drug release from the tablets. This might be due to the more swelling and the greater force to push drug through the pore on the cellulose acetate (Table 4.7-4.8 and Figure 4.13-4.20).

Table 4.4 The % drug release at various time intervals

Time	% drug release				
	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20	CS-PAA30
5	13.38	15.48	16.59	18.80	19.58
10	31.47	31.19	32.91	32.93	31.49
15	44.03	45.81	46.13	47.15	49.94
20	57.33	60.06	60.52	61.82	62.22
25	69.07	70.41	71.02	71.79	74.69
30	77.78	79.13	79.26	80.43	84.85
35	84.60	85.37	84.95	86.81	91.01
40	89.34	91.24	88.99	90.38	93.61
45	93.43	94.37	93.18	94.21	95.57
50	96.69	96.45	95.78	96.20	97.39
55	98.88	98.12	98.03	98.38	98.61
60	100.00	99.59	99.92	100.05	99.92

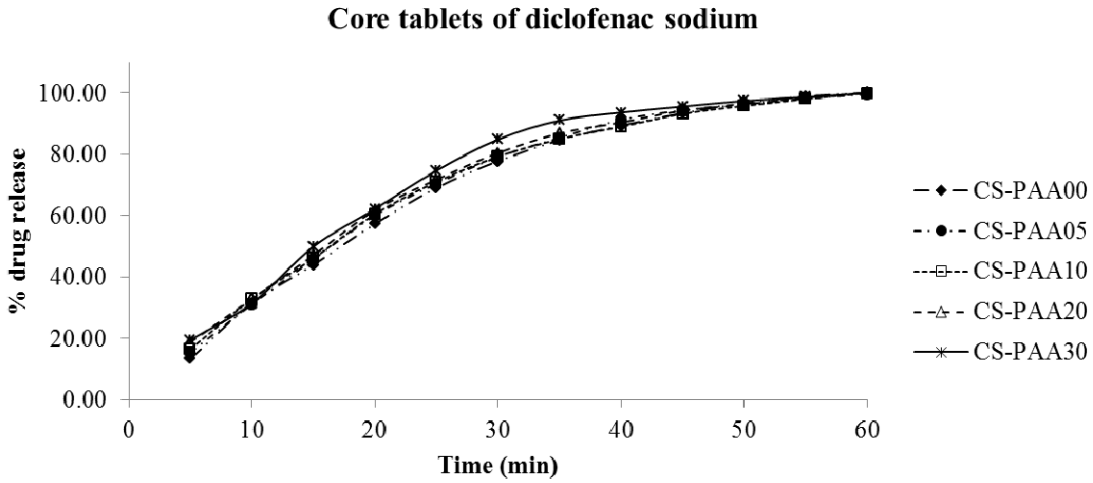


Figure 4.10 The release profile of diclofenac sodium from the core tablets

Table 4.5 The drug release study of various formulations from the semi-permeable membrane osmotic pump tablets

Time (h)	Mean (SD)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1	4.02 (0.50)	11.59 (0.35)	15.72 (2.30)	22.40 (1.35)
2	12.01 (0.47)	24.14 (0.44)	28.57 (0.74)	31.00 (1.49)
3	18.13 (0.46)	31.33 (0.57)	38.24 (0.74)	38.68 (1.59)
4	25.70 (0.64)	39.05 (0.41)	43.50 (0.66)	46.35 (1.67)
5	31.88 (1.71)	44.48 (0.35)	48.00 (0.80)	54.56 (1.74)
6	35.10 (1.66)	51.11 (0.20)	53.80 (1.10)	61.69 (1.79)
7	39.54 (1.85)	55.01 (0.29)	58.28 (0.80)	68.19 (1.83)
8	43.30 (1.56)	57.81 (0.71)	62.48 (0.60)	72.12 (1.86)
9	47.77 (1.57)	61.23 (0.42)	66.08 (1.20)	75.60 (1.88)
10	51.01 (1.89)	65.10 (0.36)	70.30 (0.91)	79.01 (1.90)
11	54.77 (2.16)	66.10 (0.40)	73.47 (0.67)	81.04 (1.91)
12	57.94 (1.57)	68.43 (0.86)	77.92 (0.86)	83.41 (1.92)
13	61.79 (1.45)	70.57 (1.30)	80.30 (1.02)	85.54 (1.93)
14	64.57 (1.55)	72.64 (1.74)	82.05 (1.22)	86.81 (1.94)
15	68.53 (2.01)	75.44 (1.90)	84.23 (1.46)	88.31 (1.95)
16	71.26 (1.52)	78.61 (2.91)	85.59 (1.41)	89.46 (1.95)
17	74.27 (1.70)	82.01 (2.57)	87.19 (2.01)	90.48 (1.96)
18	78.14 (1.99)	83.98 (1.75)	88.75 (2.45)	91.48 (1.96)
19	82.28 (1.32)	85.84 (1.35)	89.81 (2.30)	92.21 (1.96)
20	84.50 (0.64)	87.16 (1.31)	90.85 (2.44)	92.99 (1.97)
21	85.89 (0.61)	88.01 (1.22)	91.86 (2.58)	93.77 (1.97)
22	87.57 (1.14)	89.42 (1.41)	92.64 (2.54)	94.51 (1.98)
23	89.07 (1.93)	90.21 (1.26)	93.35 (2.43)	95.17 (1.98)
24	89.98 (1.64)	90.91 (1.21)	93.91 (2.38)	95.80 (1.98)

Table 4.6 The drug release study of various formulations from the osmotic pump tablets coated with Eudragit L

Time (h)	Mean (SD)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
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)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
3	4.42 (0.74)	15.60 (0.91)	17.07 (0.84)	22.67 (1.22)
4	12.28 (0.59)	23.84 (0.56)	28.75 (0.85)	31.28 (1.04)
5	18.33 (0.59)	31.27 (1.02)	38.41 (0.88)	39.01 (1.09)
6	25.76 (1.12)	38.78 (0.64)	43.68 (0.92)	46.69 (1.87)
7	31.59 (1.55)	45.24 (0.72)	48.08 (1.00)	54.94 (2.79)
8	35.53 (1.87)	51.09 (0.67)	53.88 (1.24)	62.05 (1.90)
9	40.18 (1.55)	54.85 (1.30)	58.42 (0.97)	68.42 (2.34)
10	43.57 (0.89)	56.87 (1.33)	62.67 (0.82)	72.36 (1.95)
11	47.51 (1.19)	61.05 (1.51)	66.73 (0.81)	75.93 (1.90)
12	50.87 (1.14)	65.50 (0.40)	70.59 (1.10)	79.24 (1.07)
13	54.43 (1.42)	67.36 (1.26)	73.70 (0.91)	81.44 (2.02)
14	57.82 (1.02)	69.42 (1.49)	78.09 (0.91)	83.76 (2.23)
15	61.78 (0.93)	72.09 (2.17)	80.44 (1.07)	85.81 (2.71)
16	64.70 (0.96)	74.73 (2.85)	82.16 (1.23)	87.04 (2.44)
17	68.95 (1.47)	77.51 (3.55)	84.21 (1.59)	88.62 (2.17)
18	72.18 (0.95)	79.88 (3.56)	85.60 (1.55)	89.76 (1.89)
19	75.67 (1.17)	81.49 (3.65)	87.08 (1.96)	90.76 (1.64)
20	79.11 (1.62)	83.62 (3.08)	88.47 (2.45)	91.75 (1.29)
21	82.90 (1.04)	85.64 (2.97)	89.70 (2.36)	92.44 (1.41)
22	84.99 (0.35)	87.30 (3.18)	90.60 (2.45)	93.20 (1.45)
23	86.32 (0.81)	88.91 (3.34)	91.40 (2.60)	94.02 (1.50)
24	87.77 (1.31)	90.15 (3.64)	92.06 (2.53)	94.75 (1.62)
25	89.09 (1.60)	91.01 (3.49)	92.71 (2.40)	95.42 (1.67)
26	90.15 (2.03)	91.68 (3.33)	93.28 (2.34)	96.11 (1.74)

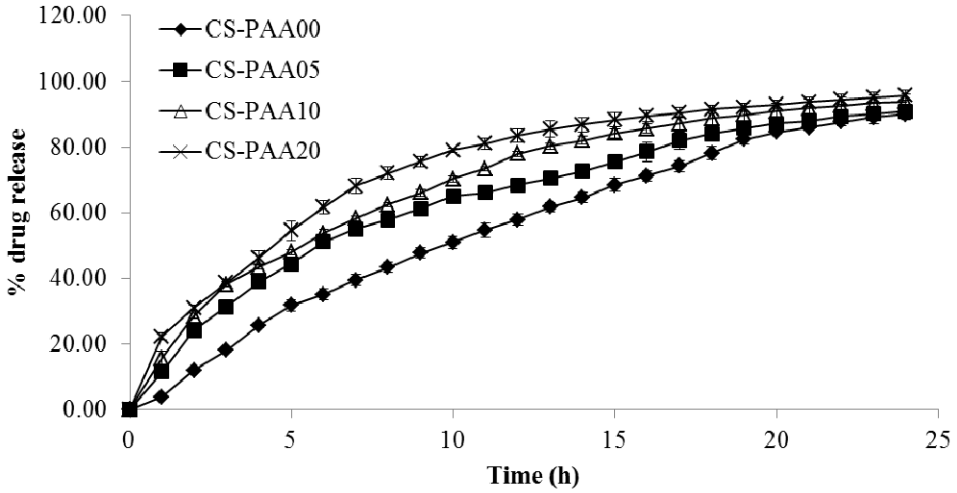


Figure 4.11 Drug release profiles of various formulation from the semi-permeable membrane osmotic pump tablets with various amount of CS-PAA

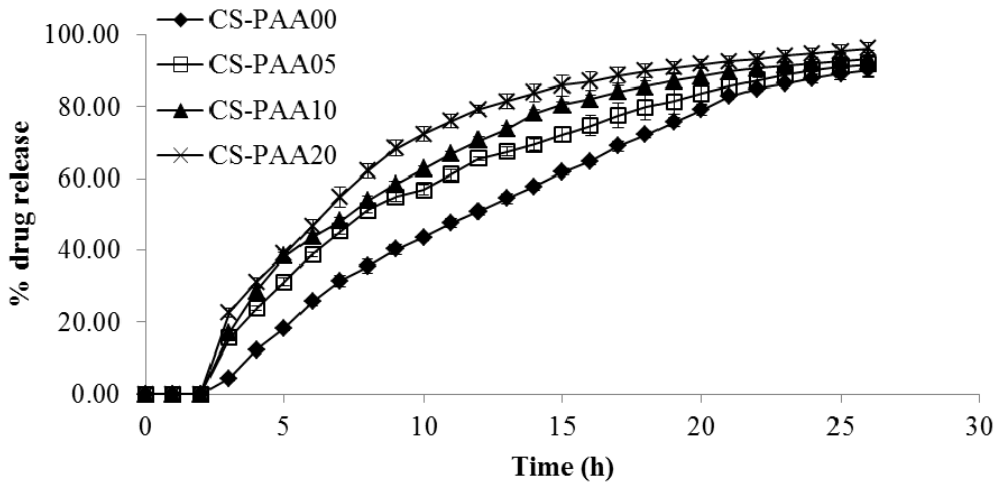


Figure 4.12 Drug release profiles of various formulation from the osmotic pump tablets coated by Eudragit L with various amount of CS-PAA

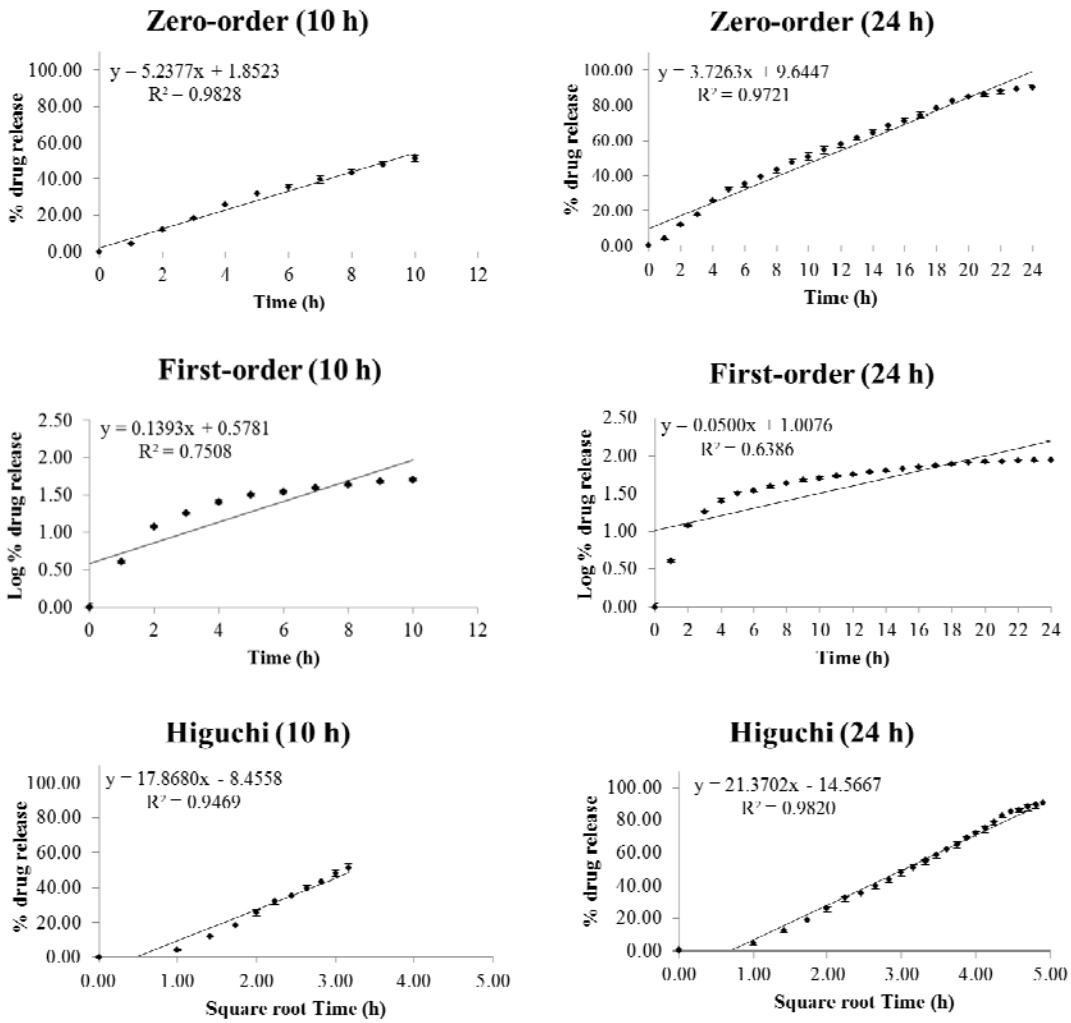


Figure 4.13 The drug release study of the CS-PAA00 formulation from the semi-permeable membrane osmotic pump tablets

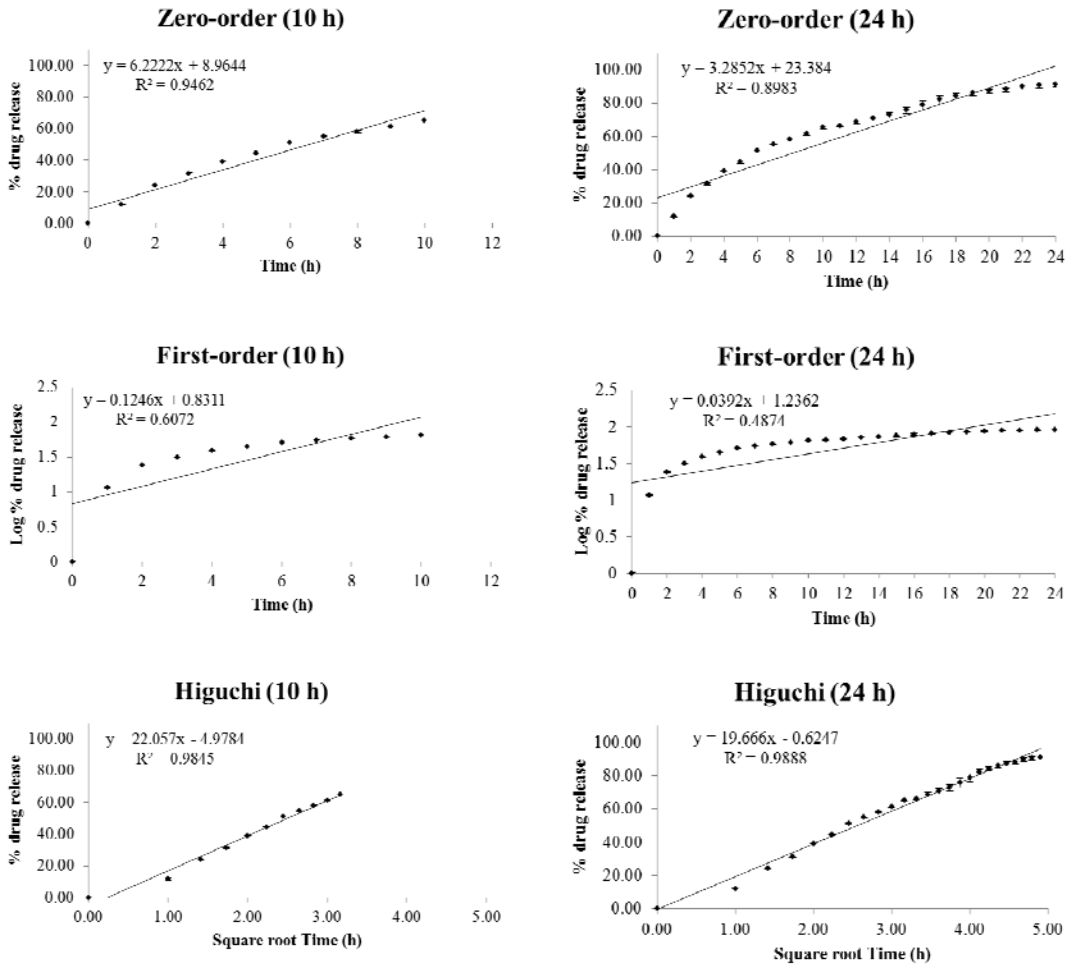


Figure 4.14 The drug release study of the CS-PAA05 formulation from the semi-permeable membrane osmotic pump tablets

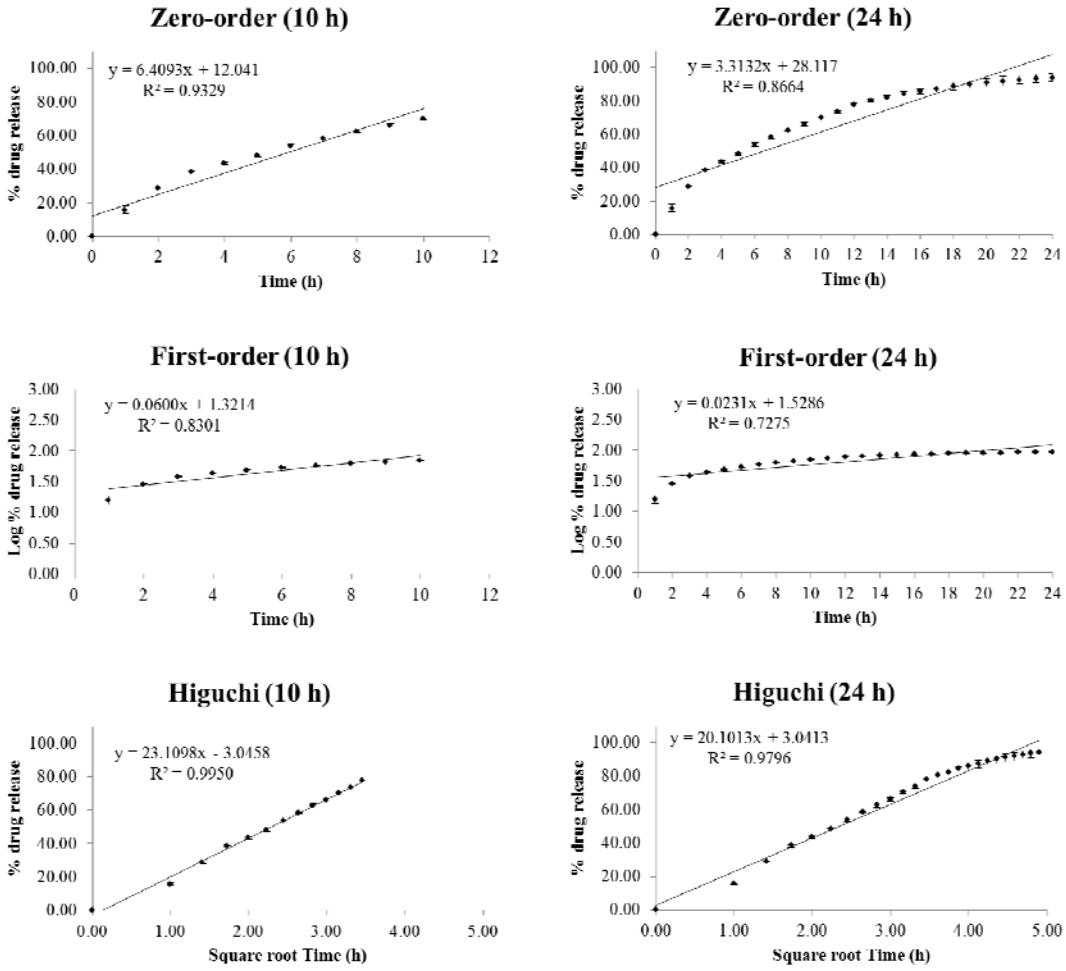


Figure 4.15 The drug release study of the CS-PAA10 formulation from the semi-permeable membrane osmotic pump tablets

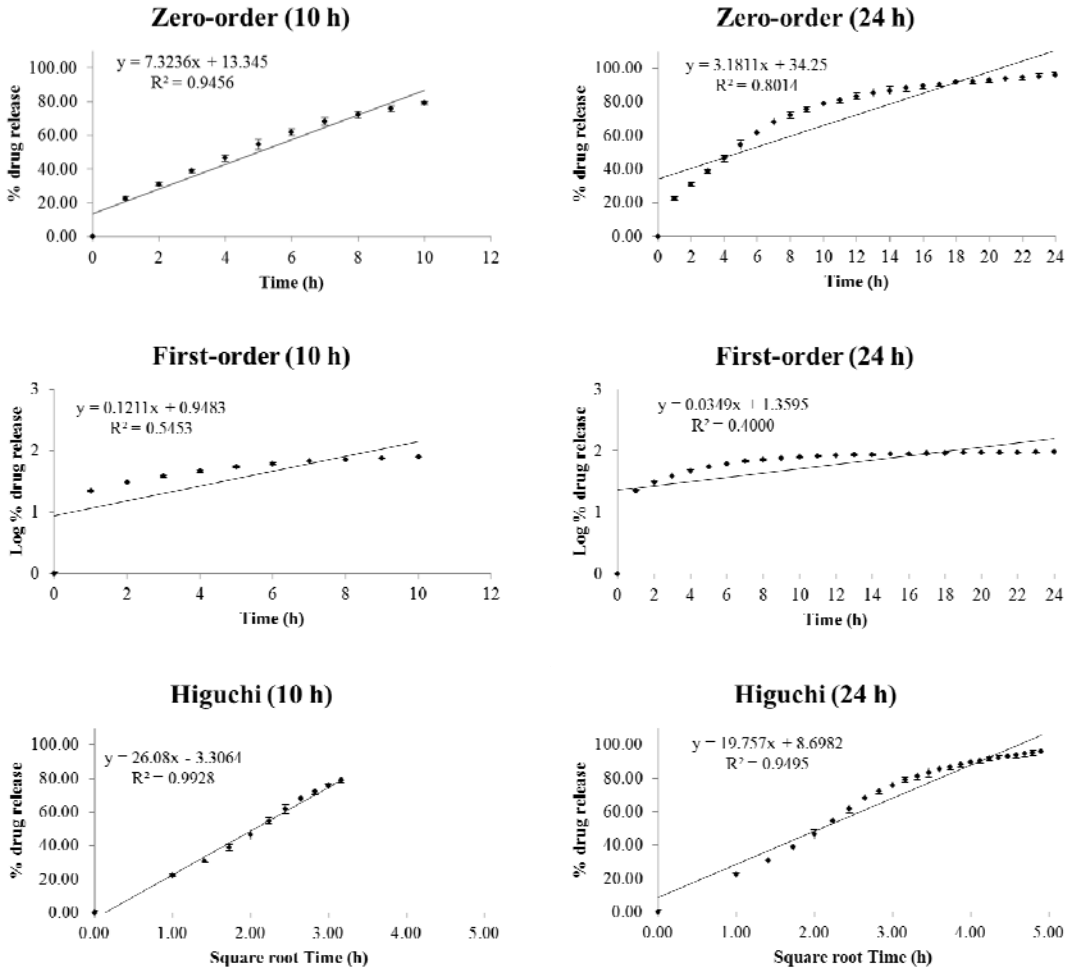


Figure 4.16 The drug release study of the CS-PAA20 formulation from the semi-permeable membrane osmotic pump tablets

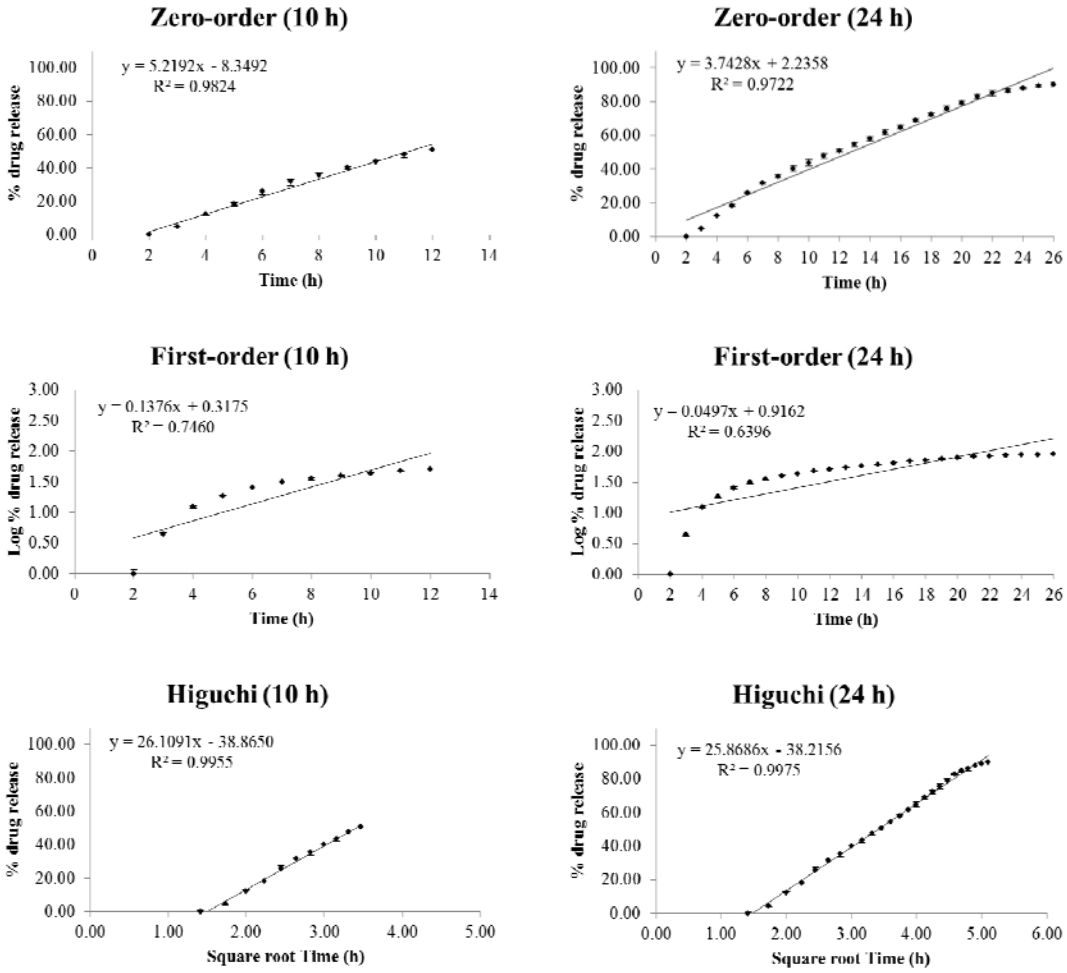


Figure 4.17 The drug release study of the CS-PAA00 formulation from the osmotic pump tablets coated with Eudragit L

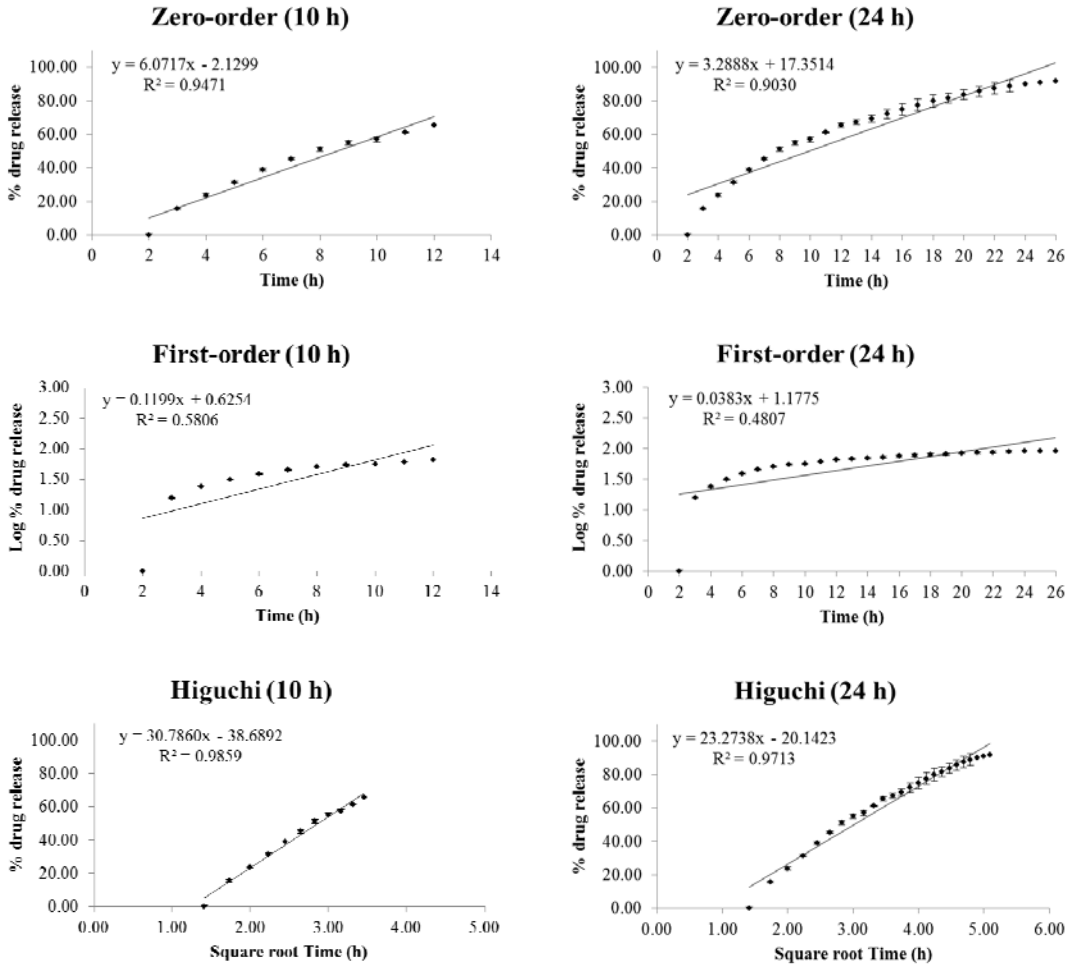


Figure 4.18 The drug release study of the CS-PAA05 formulation from the osmotic pump tablets coated with Eudragit L

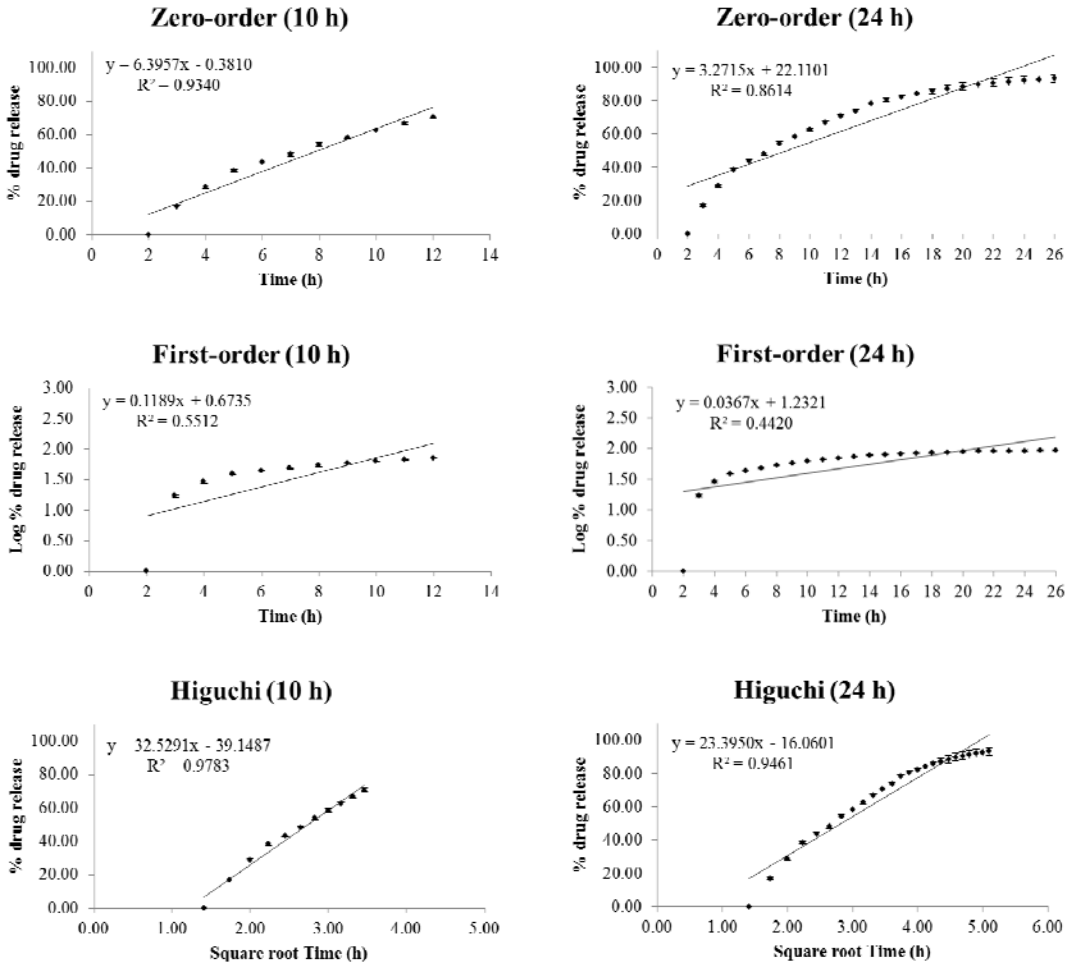


Figure 4.19 The drug release study of the CS-PAA10 formulation from the osmotic pump tablets coated with Eudragit L

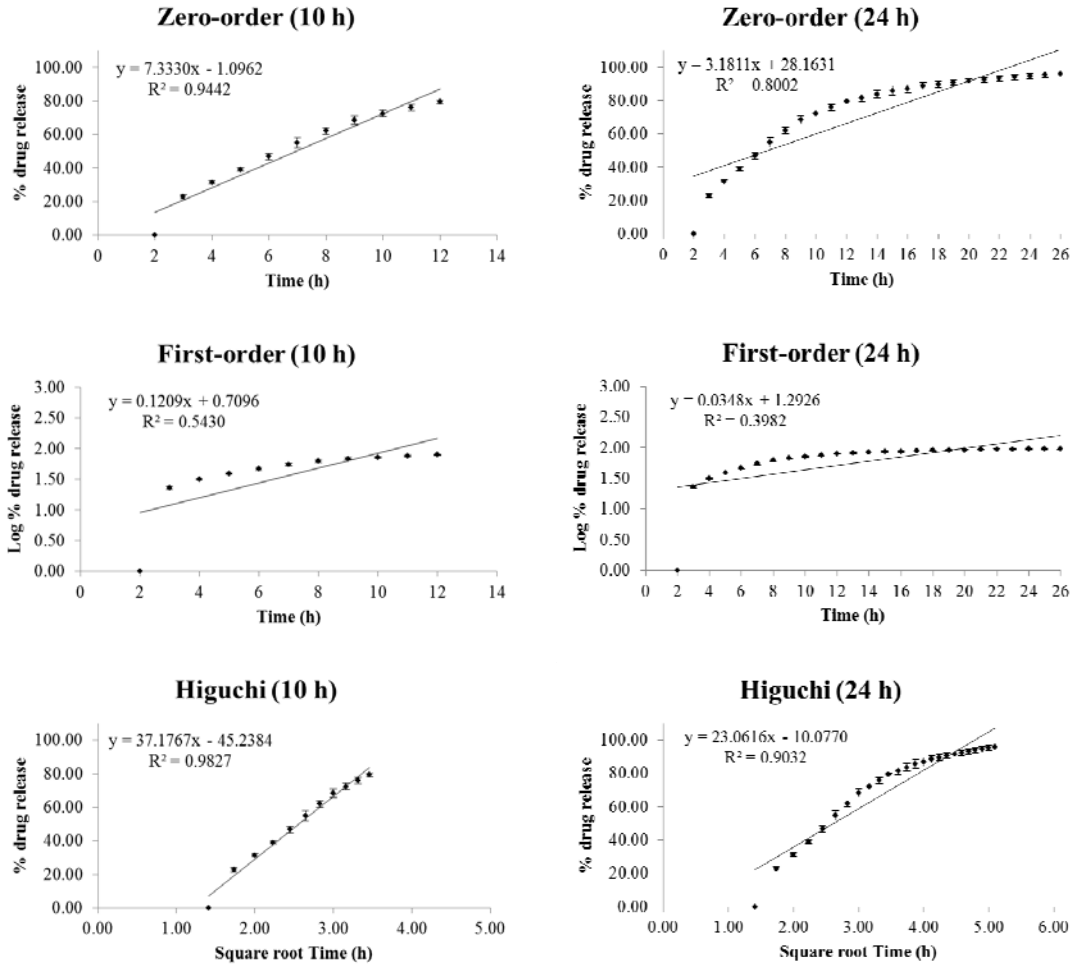


Figure 4.20 The drug release study of the CS-PAA20 formulation from the osmotic pump tablets coated with Eudragit L

Table 4.7 Model fitting of drug release data of the osmotic pump tablet with semi-permeable membrane based on the mathematical models

Formulations	Model	R^2		R	
		10 h	24 h	10 h	24 h
CS-PAA00	Zero-order	0.9828	0.9721	0.9914	0.9860
	First-order	0.7508	0.6386	0.8665	0.7991
	Higuchi	0.9469	0.9820	0.9731	0.9910
CS-PAA05	Zero-order	0.9462	0.8983	0.9727	0.9478
	First-order	0.6072	0.4874	0.7792	0.6981
	Higuchi	0.9845	0.9888	0.9922	0.9944
CS-PAA10	Zero-order	0.9329	0.8664	0.9659	0.9308
	First-order	0.8301	0.7275	0.9111	0.8529
	Higuchi	0.9950	0.9796	0.9975	0.9897
CS-PAA20	Zero-order	0.9456	0.8014	0.9724	0.8952
	First-order	0.5453	0.4000	0.7384	0.6325
	Higuchi	0.9928	0.9495	0.9964	0.9744

Table 4.8 Model fitting of drug release data of the osmotic pump tablet coated with Eudragit L based on the mathematical models

Formulations	Model	R^2		R	
		10 h	24 h	10 h	24 h
CS-PAA00	Zero-order	0.9824	0.9722	0.9912	0.9860
	First-order	0.7460	0.6396	0.8637	0.7997
	Higuchi	0.9955	0.9975	0.9977	0.9987
CS-PAA05	Zero-order	0.9471	0.9030	0.9732	0.9503
	First-order	0.5806	0.4807	0.7620	0.6933
	Higuchi	0.9859	0.9713	0.9929	0.9855
CS-PAA10	Zero-order	0.9340	0.8614	0.9664	0.9281
	First-order	0.5512	0.4420	0.7424	0.6648
	Higuchi	0.9783	0.9461	0.9891	0.9727
CS-PAA20	Zero-order	0.9442	0.8002	0.9717	0.8945
	First-order	0.5430	0.3982	0.7369	0.6310
	Higuchi	0.9827	0.9032	0.9913	0.9504

4.5.3 Scanning electron microscopy (SEM) of the coating membranes

Figure 4.21 showed the SEM micrographs of the porous films for the optimized CS-PAA05 coating membranes of CPOP osmotic pump tablets, before and after the dissolution test, in order to explain the mechanism of the drug release. The surface morphology of the coating membranes displayed before the dissolution test did not have any porous on the film coating membrane. But, after the dissolution test, there were many porous appearances on the film coating membrane. The pore sizes of the film coating membrane after dissolution test was varied between 1 and 10 μm.

(A) (B)

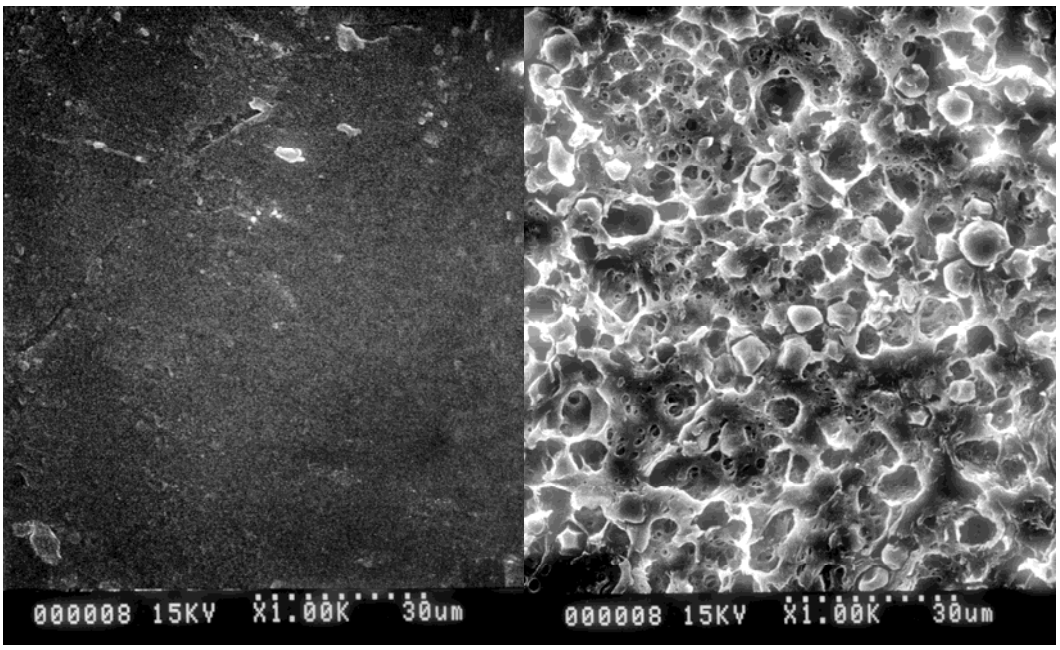


Figure 4.21 Scanning Electron microscopy (SEM) studies before (A) and after (B) the dissolution test

CHAPTER V
CONCLUSION

5.1 Preparation of CS-PAA interpolymer complexes

5.1.1 Quantitative analysis of CS-PAA interpolymer complex from the polymerization reaction

The CS-PAA interpolymer complex was formed by polymer blending of polyelectrolyte complexes containing CS (polycations polymer) and PAA (polyanions polymer) at various ratios. The preparation of CS-PAA at the ratio of 1:2 provided the highest yield of CS-PAA 971P NF at 87.21%, whereas the yields of CS-PAA 974P NF and CS-PAA 934P NF were 86.12 and 84.55%, respectively. At the ratio of 1:1, it provided the yield of CS-PAA 971P NF, CS-PAA 974P NF and CS-PAA 934P NF at 77.03, 76.36 and 74.18%, respectively. Finally, at the ratio of 2:1, it provided the yield of CS-PAA 971P NF, CS-PAA 974P NF and CS-PAA 934P NF at 75.82, 73.91 and 72.39%, respectively.

5.1.2 Swelling properties

5.1.3.1 Swelling forces

All formulations were found that CS-PAA interpolymer complex from PAA 971P NF at the ratio of 2:1 showed the maximum swelling force. The results indicated that the swelling force increased with an increase of the ratio of CS. Moreover, PAA 971P NF is lightly crosslinked and therefore tends to be more porous in the hydrogel than PAA 934P NF and PAA 974P NF polymer which are highly crosslinked. Also, the diffusion coefficients of water penetrating into the gels increased with increasing pore volume of the gels (91,105) which can affect the increase of the swelling force.

5.1.3.2 Swelling ratios

The maximum swelling force of 23.40 N was obtained with PAA 971P NF at the ratio of 2:1. The results demonstrated the swelling ratios increased when the proportion of CS increased.

Therefore, the good swelling characteristics of the ratio of CS-PAA 971P NF at 2:1 was selected to develop the osmotic tablet formulation.

5.2 Evaluation of osmotic tablet formulation

In this study, a controlled-porosity osmotic pump tablet (CPOP) using CS-PAA as an osmotic agent was developed. Diclofenac sodium, a non-steroidal anti-inflammatories (NSAIDs), was used as a model drug. The CPOP can be prepared by double compression of drug and polymer layer to obtain a bilayer tablet. Drug layer comprised diclofenac sodium as an active ingredient, potassium chloride as osmotic agent, PVP K30 as a binder, magnesium stearate as a lubricant, and the mixture of Avicel pH 101: Starch 1500 (1:1) as a filler. Polymer layer contained potassium chloride as osmotic agent, magnesium stearate as a lubricant, the mixture of avicel pH 102: starch 1500 (1:1) as filler and various amount of CS-PAA interpolymer complex as osmotic agent (0%, 5%, 10%, 20%, and 30%). The CS-PAA30 formulation showed the friability of more than 1%. Therefore, this formulation was disregarded.

The rate of drug dissolution from all osmotic tablet formulations was the slow release from the tablets. This might be due to the gel forming ability of PAA at pH 7.5, which retarded the rate of drug release from the tablet. Almost all carboxyl groups dissociated at pH 7.5 resulting in the formation of a swollen gel. The release rate of osmotic tablets depended on the amount of the osmotic agent. The amount of the osmotic agent increased then the osmotic pressure created inside the tablet also increased, the core compartment imbibed aqueous fluids from the surrounding environment across the membrane and dissolved the drug. So, the release of the drug also increased.

The drug released model that used in this thesis, the Higuchi’s model of diffusion of time was plotted between the cumulative percentage drug released versus

the square root of time. The zero-order kinetics were plotted between the cumulative drug released and time and the first-order kinetics were plotted between Log % drug released versus time. The result showed that the core tablet contained higher amount of CS-PPA following the Higuchi model. The data of the enteric coated tablet showed that there were no drug release through the medium solution within 2 h. Therefore, it was suitable for the tablet which needed to release the drug in the intestine. Only the CS-PAA00 formulation gave the zero-order kinetic, whereas the others were fitted to the Higuchi model. When increased the amount of the polymer, the R^2 value of the graph which plotted between the cumulative percentage drug released and the square root was close to 1. The property and the amount of the polymer were the important factors to formulate this osmotic tablet formulation. The higher amount of CS-PAA could affect the rate of the drug release from the tablets. This might be due to the more swelling and greater force to push the drug through the pore on cellulose acetate.

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APPENDIX

Calibration curve for assay preparation by HPLC

Table A.1 Peak area of diclofenac sodium assayed by HPLC at UV 254 nm (n = 5)

Concentration (µg/mL)	Mean Peak area (Au)
200.0000	2041004
400.0000	4053146
600.0000	6016050
800.0000	8037042
1000.0000	9976935

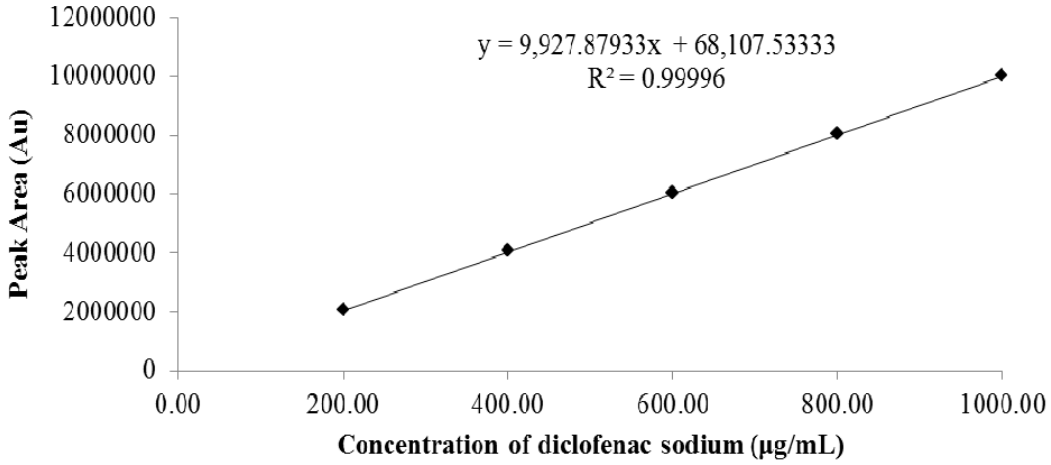

Figure A.1 Calibration curve of diclofenac sodium determined by HPLC at UV 254 nm (n = 5)

Calibration curve for dissolution testing by UV spectrophotometry

Table A.2 UV absorbance of diclofenac sodium in 0.05 M phosphate buffer pH 7.5 at 276 nm (n = 5)

Concentration (mg/mL)	Absorbance
0.5	0.1612
1.0	0.3332
1.5	0.4934
2.0	0.6573
2.5	0.8216
3.0	0.9962

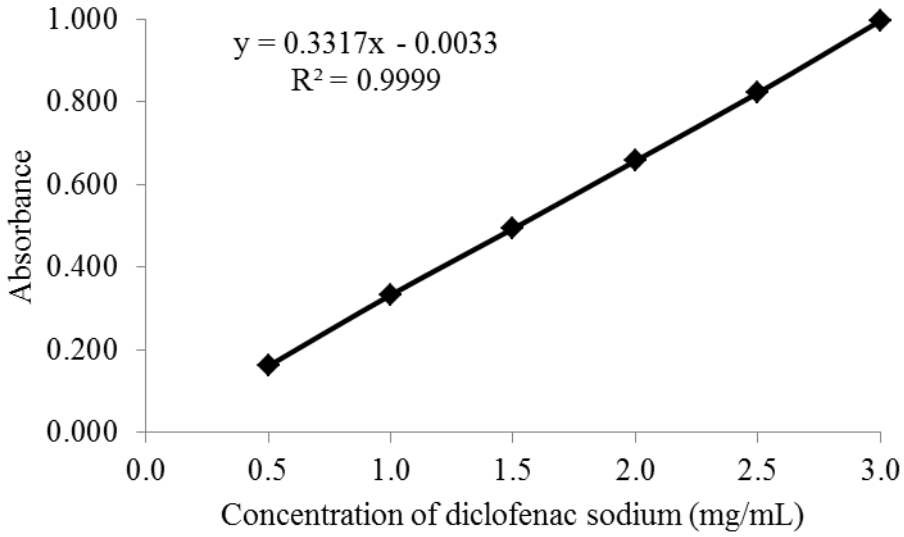

Figure A.2 Calibration curve of diclofenac sodium in 0.05 M phosphate buffer pH 7.5 at 276 nm (n = 5)

Evaluation of Tablets

Content uniformity of dosage unit by weight variation

Table A.3 Weight and weight variation of diclofenac core tablets containing different amount of CS-PAA complexes

No.	Weight (mg)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA30**
1	303	303	303	301	300
2	302	301	304	301	301
3	301	300	304	302	302
4	297	299	302	297	299
5	298	300	300	299	298
6	300	299	300	300	296
7	301	298	299	302	304
8	303	299	305	303	300
9	306	299	300	304	302
10	297	300	306	300	301
11	301	301	303	301	300
12	299	302	300	305	296
13	300	300	303	300	298
14	302	300	301	302	304
15	303	298	300	302	302
16	302	299	301	303	303
17	301	298	302	299	300
18	300	299	303	300	296
19	299	300	306	305	298
20	302	300	303	300	300
Min	**297**	**298**	**299**	**297**	**296**
Max	**306**	**303**	**306**	**305**	**304**
Mean	**300.85**	**299.75**	**302.25**	**301.3**	**300.00**
SD	**2.20**	**1.29**	**2.10**	**2.05**	**2.47**
%CV	**0.73**	**0.43**	**0.69**	**0.68**	**0.82**

Table A.4 Weight and weight variation of diclofenac osmotic pump tablets with semipermeable membrane

No.	Weight (mg)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	330	332	335	330
2	336	331	332	333
3	335	328	331	338
4	331	327	330	336
5	327	328	329	335
6	330	333	330	337
7	332	329	331	335
8	334	330	336	332
9	337	336	332	327
10	330	334	340	329
11	329	337	339	337
12	328	335	337	335
13	337	334	336	334
14	327	331	336	337
15	329	330	338	334
16	334	338	330	337
17	327	337	334	334
18	330	330	332	330
19	331	331	336	329
20	335	328	332	330
Min	**327**	**327**	**329**	**327**
Max	**337**	**338**	**340**	**338**
Mean	**331.45**	**331.95**	**333.80**	**333.45**
SD	**3.35**	**3.38**	**3.31**	**3.28**
%CV	**1.01**	**1.02**	**0.99**	**0.98**

Table A.5 Weight and weight variation of diclofenac osmotic pump tablets with semipermeable membrane plus enteric-coating membrane

No.	Weight (mg)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	350	349	355	356
2	352	350	354	349
3	352	350	354	349
4	349	346	349	355
5	355	347	357	350
6	355	347	357	349
7	351	350	350	350
8	347	352	350	356
9	352	353	349	356
10	351	350	355	355
11	355	348	353	354
12	354	349	352	354
13	354	349	352	354
14	351	350	356	356
15	349	350	351	350
16	349	353	350	349
17	351	353	351	350
18	347	350	357	356
19	350	352	356	355
20	355	352	355	352
Min	**347**	**346**	**349**	**349**
Max	**355**	**353**	**357**	**356**
Mean	**351.45**	**350.00**	**353.15**	**352.75**
SD	**2.58**	**2.05**	**2.80**	**2.90**
%CV	**0.73**	**0.59**	**0.80**	**0.82**

Table A.6 Diameter of diclofenac core tablets containing different amount of CS-PAA complexes

No.	Diameter (mm)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA00**
1	8.96	8.98	8.96	8.96	8.98
2	8.99	8.97	8.96	8.98	8.96
3	8.98	8.96	8.98	8.96	8.97
4	8.97	8.95	8.99	8.97	8.99
5	8.98	8.96	8.99	8.97	8.96
6	8.98	8.98	8.97	8.98	8.97
7	8.97	8.98	8.97	8.96	8.96
8	8.96	8.96	8.99	8.98	8.99
9	8.95	8.96	8.99	8.98	8.97
10	8.98	8.96	8.99	8.96	8.98
Min	**8.95**	**8.95**	**8.96**	**8.96**	**8.96**
Max	**8.99**	**8.98**	**8.99**	**8.98**	**8.99**
Mean	**8.97**	**8.96**	**8.98**	**8.97**	**8.97**
SD	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**
%CV	**0.11**	**0.11**	**0.11**	**0.11**	**0.11**

Table A.7 Diameter of diclofenac osmotic pump tablets with semipermeable membrane

No.	Diameter (mm)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	9.26	9.28	9.26	9.26
2	9.29	9.27	9.26	9.28
3	9.28	9.26	9.28	9.26
4	9.27	9.25	9.29	9.27
5	9.28	9.26	9.29	9.27
6	9.28	9.28	9.27	9.28
7	9.27	9.28	9.27	9.26
8	9.26	9.26	9.29	9.28
9	9.25	9.26	9.29	9.28
10	9.28	9.26	9.29	9.26
Min	**9.25**	**9.25**	**9.26**	**9.26**
Max	**9.29**	**9.28**	**9.29**	**9.28**
Mean	**9.27**	**9.27**	**9.28**	**9.27**
SD	**0.01**	**0.01**	**0.01**	**0.01**
%CV	**0.11**	**0.11**	**0.11**	**0.11**

Table A.8 Diameter of diclofenac osmotic pump tablets with semipermeable membrane plus enteric-coating membrane

No.	Diameter (mm)			
	CS-PAA00	**CS-PAA05**	**CS-PAA-10**	**CS-PAA20**
1	9.45	9.44	9.44	9.44
2	9.44	9.45	9.45	9.44
3	9.43	9.45	9.45	9.47
4	9.43	9.43	9.49	9.46
5	9.45	9.42	9.46	9.45
6	9.45	9.45	9.45	9.45
7	9.48	9.46	9.49	9.49
8	9.46	9.42	9.47	9.47
9	9.44	9.48	9.47	9.46
10	9.45	9.42	9.46	9.46
Min	**9.43**	**9.42**	**9.44**	**9.44**
Max	**9.48**	**9.48**	**9.49**	**9.49**
Mean	**9.45**	**9.44**	**9.46**	**9.46**
SD	**0.01**	**0.02**	**0.02**	**0.02**
%CV	**0.11**	**0.21**	**0.21**	**0.21**

Table A.9 Thickness of diclofenac core tablets containing different amount of CS-PAA complexes

No.	Diameter (mm)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA00**
1	4.01	4.03	4.04	4.01	4.04
2	4.03	4.03	4.02	4.03	4.03
3	4.03	4.06	4.06	4.05	4.06
4	4.04	4.04	4.04	4.05	4.02
5	4.05	4.04	4.07	4.02	4.03
6	4.03	4.02	4.07	4.02	4.03
7	4.06	4.05	4.02	4.01	4.02
8	4.02	4.06	4.02	4.03	4.06
9	4.03	4.04	4.07	4.02	4.03
10	4.04	4.03	4.03	4.02	4.04
Min	**4.01**	**4.02**	**4.02**	**4.01**	**4.02**
Max	**4.06**	**4.06**	**4.07**	**4.05**	**4.06**
Mean	**4.03**	**4.04**	**4.04**	**4.03**	**4.04**
SD	**0.01**	**0.01**	**0.02**	**0.01**	**0.01**
%CV	**0.25**	**0.25**	**0.50**	**0.25**	**0.25**

Table A.10 Thickness of diclofenac osmotic pump tablets with semipermeable membrane

No.	Diameter (mm)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	4.26	4.26	4.26	4.27
2	4.28	4.27	4.26	4.28
3	4.26	4.28	4.26	4.26
4	4.28	4.29	4.29	4.26
5	4.26	4.28	4.29	4.27
6	4.27	4.27	4.27	4.28
7	4.28	4.28	4.29	4.26
8	4.26	4.26	4.29	4.28
9	4.25	4.28	4.27	4.26
10	4.26	4.25	4.29	4.28
Min	**4.25**	**4.25**	**9.26**	**4.26**
Max	**4.28**	**4.29**	**9.29**	**4.28**
Mean	**4.26**	**4.27**	**4.28**	**4.27**
SD	**0.01**	**0.01**	**0.01**	**0.01**
%CV	**0.23**	**0.23**	**0.23**	**0.23**

Table A.11 Thickness of diclofenac osmotic pump tablets with semipermeable membrane plus enteric-coating membrane

No.	Diameter (mm)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	4.44	4.45	4.47	4.44
2	4.47	4.44	4.45	4.45
3	4.46	4.43	4.46	4.43
4	4.45	4.42	4.49	4.43
5	4.46	4.42	4.46	4.45
6	4.45	4.45	4.45	4.48
7	4.49	4.46	4.49	4.45
8	4.47	4.48	4.44	4.46
9	4.44	4.42	4.47	4.45
10	4.46	4.45	4.45	4.44
Min	**4.44**	**4.42**	**4.44**	**4.43**
Max	**4.49**	**4.48**	**4.49**	**4.48**
Mean	**4.46**	**4.44**	**4.46**	**4.45**
SD	**0.02**	**0.02**	**0.02**	**0.01**
%CV	**0.45**	**0.45**	**0.45**	**0.22**

Table A.12 Hardness of diclofenac core tablets containing different amount of CS-PAA complexes

No.	Hardness (kg)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA00**
1	7.9	8.1	10.6	8.1	9.5
2	8.2	9.3	9.9	9.9	9.7
3	8.5	9.7	8.2	9.1	7.2
4	8.9	7.1	8.8	9.5	8.4
5	10.1	7.5	9.3	8.4	8.2
6	9.3	8.4	9.1	8.3	8.4
7	9.2	9.2	8.6	8.9	10.2
8	9.5	9.4	9.8	10.2	9.3
9	7.3	7.3	10.2	8.4	8.2
10	8.7	8.6	10.3	9.5	8.4
Min	**7.3**	**7.1**	**8.2**	**8.1**	**7.5**
Max	**10.1**	**9.4**	**10.6**	**10.2**	**10.4**
Mean	**8.76**	**8.46**	**9.48**	**9.03**	**8.75**
SD	**0.82**	**0.93**	**0.80**	**0.73**	**0.90**
%CV	**9.36**	**11.00**	**8.44**	**8.08**	**10.29**

Table A.13 Hardness of diclofenac osmotic pump tablets with semipermeable membrane

No.	Hardness (kg)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	10.1	11.7	11.2	10.3
2	12.2	10.2	10.5	13.8
3	12.5	9.9	12.3	11.4
4	12.8	10.1	13.2	11.9
5	12.2	10.4	14.1	12.3
6	10.3	11.9	13.4	12.4
7	11.4	12.3	12.8	9.9
8	11.5	12.1	12.9	13.7
9	12.8	9.8	12.0	13.5
10	13.0	12.0	13.2	12.4
Min	**10.2**	**9.8**	**10.5**	**9.9**
Max	**13.0**	**12.3**	**14.1**	**13.7**
Mean	**11.88**	**11.04**	**12.56**	**12.16**
SD	**1.03**	**1.04**	**1.08**	**1.34**
%CV	**8.70**	**9.42**	**8.60**	**11.02**

Table A.14 Hardness of diclofenac osmotic pump tablets with semipermeable membrane plus enteric-coating membrane

No.	Hardness (kg)			
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**
1	15.8	17.1	17.6	18.1
2	16.3	17.5	17.4	18.4
3	16.9	18.2	18.6	15.3
4	18.4	18.5	19.2	15.9
5	18.1	14.8	17.1	16.4
6	17.7	14.5	19.9	17.4
7	15.6	15.0	20.4	17.0
8	15.9	15.4	18.1	17.9
9	16.8	15.9	17.7	19.2
10	17.3	17.5	17.6	18.3
Min	**14.8**	**14.5**	**17.1**	**15.3**
Max	**18.4**	**18.7**	**20.4**	**19.2**
Mean	**16.88**	**16.44**	**18.36**	**17.39**
SD	**0.99**	**1.50**	**1.13**	**1.23**
%CV	**5.86**	**9.12**	**6.15**	**7.07**

Table A.15 Friability of diclofenac core tablets containing different amount of CS-PAA complexes

	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20	CS-PAA30
Before	6.624	6.608	6.641	6.635	6.589
After	6.615	6.597	6.623	6.612	6.394
% Friability	0.14	0.17	0.27	0.35	2.96

Table A.16 Friability of diclofenac osmotic pump tablet with semipermeable membrane

	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20
Before	6.630	6.639	6.677	6.628
After	6.630	6.639	6.677	6.628
% Friability	0.00	0.00	0.00	0.00

Table A.17 Friability of diclofenac osmotic pump tablets with semipermeable membrane plus enteric-coating membrane

	CS-PAA00	CS-PAA05	CS-PAA10	CS-PAA20
Before	6.665	6.654	6.713	6.702
After	6.665	6.654	6.723	6.702
% Friability	0.00	0.00	0.00	0.00

Table A.18 Disintegration time of diclofenac core tablets containing different amount of CS-PAA complexes

No.	Disintegration time (min)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA30**
1	14.28	10.11	14.78	15.34	11.86
2	15.20	10.34	15.89	14.95	12.54
3	14.19	9.93	14.69	14.28	13.96
4	14.37	10.50	16.01	15.36	12.98
5	14.03	11.25	15.97	16.04	13.57
6	13.01	12.03	16.56	15.24	13.89
Min	**13.01**	**9.93**	**14.69**	**14.28**	**11.86**
Max	**15.20**	**12.03**	**16.01**	**16.04**	**13.96**
Mean	**14.18**	**10.70**	**15.65**	**15.20**	**13.13**
SD	**0.70**	**0.80**	**0.75**	**0.58**	**0.83**
%CV	**4.94**	**7.48**	**4.80**	**3.82**	**6.32**

Table A.19 Content uniformity of diclofenac core tablet containing different amount of CS-PAA complexes

No.	Content uniformity (%)				
	CS-PAA00	**CS-PAA05**	**CS-PAA10**	**CS-PAA20**	**CS-PAA30**
1	100.82	100.83	100.83	100.16	99.83
2	100.49	100.16	101.17	100.16	100.16
3	100.16	99.83	101.17	100.50	100.49
4	98.83	99.49	100.50	98.83	99.49
5	99.16	99.83	99.83	99.50	99.16
6	99.82	99.49	99.83	99.83	98.50
7	100.16	99.16	99.50	100.50	101.16
8	100.82	99.49	101.50	100.83	99.83
9	100.82	99.49	99.83	101.16	100.49
10	98.83	99.83	101.83	99.83	100.16
Mean	**99.99**	**99.76**	**100.60**	**100.13**	**99.93**
SD	**0.802**	**0.468**	**0.818**	**0.674**	**0.753**
%CV	**0.802**	**0.469**	**0.813**	**0.674**	**0.753**

Swelling Characteristic Data

- **Swelling force**

Table A.20 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 934P NF at different ratios

Time (min)	PAA 934P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	4.21±0.22	4.49±0.25	5.12±0.19
30	5.79±0.22	6.98±0.27	8.23±0.16
45	7.60±0.24	10.12±0.23	10.76±0.18
60	8.80±0.22	12.18±0.26	13.11±0.19
75	10.28±0.22	13.60±0.27	15.52±0.21
90	11.57±0.22	14.65±0.22	17.41±0.24
105	12.73±0.21	15.61±0.27	19.45±0.21
120	13.73±0.23	16.60±0.26	21.11±0.21
135	14.81±0.22	17.48±0.19	22.45±0.20
150	15.60±0.17	17.97±0.26	23.63±0.21
165	16.84±0.22	18.67±0.25	24.49±0.20
180	17.45±0.22	19.13±0.26	25.38±0.19
195	18.24±0.23	19.60±0.23	26.24±0.20
210	18.70±0.20	20.05±0.26	26.71±0.21
225	19.29±0.22	20.48±0.27	27.35±0.21
240	19.76±0.22	21.05±0.26	27.80±0.19
255	20.27±0.22	21.48±0.25	28.32±0.19
270	20.75±0.24	21.88±0.27	28.80±0.20
285	21.32±0.21	22.25±0.26	29.26±0.20
300	21.66±0.26	22.51±0.25	29.73±0.25
315	21.91±0.24	22.68±0.27	30.00±0.21
330	22.14±0.22	22.87±0.26	30.21±0.21

[a]Mean±SD, n=3

Table A.20 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 934P NF at different ratios (Cont.)

Time (min)	PAA 934P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
345	22.31±0.22	23.03±0.26	30.42±0.20
360	22.52±0.21	23.03±0.25	30.58±0.19
375	22.66±0.25	23.47±0.28	30.73±0.20
390	22.88±0.23	23.69±0.27	30.95±0.21
405	22.98±0.24	23.98±0.24	31.07±0.20
420	23.19±0.21	24.27±0.27	31.27±0.20
435	23.29±0.26	24.54±0.23	31.34±0.21
450	23.34±0.24	24.76±0.24	31.40±0.20
465	23.42±0.22	24.85±0.16	31.50±0.22
480	23.62±0.28	25.05±0.25	31.63±0.20

[a]Mean±SD, n=3

Table A.21 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 971P NF at different ratios

Time (min)	PAA 971P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	3.71±0.23	5.16±0.27	5.25±0.14
30	5.52±0.22	8.32±0.22	8.49±0.14
45	7.40±0.20	10.92±0.26	11.31±0.12
60	8.42±0.21	13.24±0.24	13.89±0.14
75	9.63±0.21	15.29±0.27	16.55±0.13
90	10.91±0.22	17.18±0.27	18.65±0.14
105	11.99±0.22	18.93±0.26	20.41±0.13
120	12.79±0.24	20.36±0.28	21.98±0.20
135	13.57±0.21	21.56±0.26	23.59±0.12
150	14.02±0.22	22.54±0.26	24.98±0.14
165	14.67±0.22	23.56±0.31	26.33±0.12
180	15.23±0.20	24.23±0.24	27.46±0.14
195	15.67±0.21	24.77±0.26	28.68±0.14
210	16.04±0.22	25.28±0.27	29.72±0.20
225	16.55±0.21	25.64±0.25	30.34±0.18
240	16.93±0.23	26.08±0.27	31.12±0.14
255	17.29±0.24	26.29±0.27	31.79±0.15
270	17.71±0.24	26.66±0.26	32.45±0.13
285	18.23±0.23	26.79±0.27	33.16±0.12
300	18.55±0.23	26.89±0.27	33.68±0.16
315	18.95±0.22	27.12±0.31	33.93±0.14
330	19.18±0.22	27.37±0.28	34.28±0.15
345	19.31±0.24	27.46±0.27	34.39±0.18
360	19.55±0.24	27.63±0.28	34.70±0.14

[a]Mean±SD, n=3

Table A.21 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 971P NF at different ratios (Cont.)

Time (min)	PAA 971P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
75	19.64±0.25	27.74±0.26	34.98±0.15
390	19.80±0.31	27.93±0.29	35.25±0.14
405	19.98±0.27	27.99±0.28	35.51±0.13
420	20.14±0.27	28.17±0.28	35.83±0.14
435	20.24±0.23	28.32±0.29	36.03±0.11
450	20.31±0.22	28.44±0.32	36.30±0.14
465	20.40±0.24	28.69±0.26	36.60±0.13
480	20.56±0.23	28.88±0.21	36.79±0.14

Table A.22 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 974P NF at different ratios

Time (min)	PAA 974P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	3.72±0.23	4.61±0.23	4.63±0.27
30	5.48±0.23	7.69±0.28	7.70±0.31
45	7.02±0.25	10.33±0.23	11.02±0.27
60	8.13±0.21	12.65±0.20	13.76±0.25
75	9.01±0.24	14.49±0.23	16.40±0.28
90	10.24±0.23	16.35±0.23	18.56±0.31
105	11.28±0.10	17.89±0.27	20.02±0.28
120	11.83±0.23	18.88±0.24	21.38±0.28
135	12.34±0.21	19.73±0.21	23.02±0.32
150	12.80±0.13	20.60±0.18	24.14±0.27
165	13.38±0.14	21.46±0.21	25.56±0.27
180	13.57±0.24	22.18±0.20	26.45±0.19
195	13.82±0.23	22.86±0.19	27.38±0.28
210	14.12±0.15	23.46±0.22	28.26±0.23
225	14.26±0.09	24.03±0.22	29.12±0.28
240	14.38±0.23	24.43±0.20	30.06±0.28
255	14.45±0.23	24.71±0.24	30.67±0.11
270	14.58±0.25	24.99±0.23	31.25±0.28
285	14.65±0.23	25.29±0.24	31.55±0.27
300	14.82±0.23	25.57±0.22	31.82±0.27
315	14.94±0.25	25.83±0.23	32.11±0.19
330	15.07±0.24	26.01±0.23	32.29±0.28
345	15.15±0.23	26.31±0.13	32.56±0.29
360	15.21±0.22	26.54±0.15	32.78±0.16

[a]Mean±SD, n=3

Table A.22 Swelling force[a] (N) of CS-PAA interpolymer complexes of PAA 974P NF at different ratios (Cont.)

Time (min)	PAA 974P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
375	15.26±0.22	26.72±0.20	32.92±0.17
390	15.32±0.23	26.83±0.19	33.09±0.17
405	15.39±0.22	26.97±0.21	33.23±0.27
420	15.51±0.24	27.23±0.20	33.50±0.23
435	15.63±0.23	27.40±0.19	33.66±0.27
450	15.72±0.22	27.47±0.21	33.74±0.26
465	15.81±0.24	27.59±0.19	33.85±0.30
480	15.93±0.22	27.73±0.19	34.01±0.27

[a]Mean±SD, n=3

- **Swelling ratio**

Table A.23 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 934P NF at different ratios

Time (min)	PAA 934P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	2.60±0.28	2.96±0.28	4.43±0.21
30	3.72±0.30	4.44±0.35	6.04±0.15
45	4.68±0.25	5.13±0.33	7.53±0.17
60	6.50±0.31	6.05±0.31	8.86±0.07
75	7.27±0.16	7.24±0.29	10.05±0.14
90	8.20±0.44	8.00±0.27	11.42±0.20
105	9.04±0.25	9.11±0.26	12.38±0.17
120	9.58±0.37	9.79±0.28	13.40±0.13
135	10.16±0.24	10.41±0.34	14.38±0.24
150	10.53±0.28	10.80±0.25	15.09±0.23
165	10.93±0.20	11.33±0.14	16.07±0.17
180	11.24±0.10	11.87±0.22	17.03±0.26
195	11.47±0.21	12.38±0.23	17.75±0.16
210	11.78±0.29	12.88±0.23	18.15±0.17
225	12.08±0.22	13.45±0.23	18.66±0.18
240	12.28±0.19	14.03±0.30	19.06±0.16
255	12.53±0.16	14.30±0.18	19.44±0.14
270	12.74±0.16	14.67±0.20	19.91±0.12
285	12.94±0.14	15.01±0.22	20.33±0.22
300	13.15±0.10	15.25±0.20	20.58±0.21
315	13.29±0.19	15.61±0.22	20.91±0.13
330	13.41±0.17	15.83±0.19	21.29±0.25

[a]Mean±SD, n=3

Table A.23 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 934P NF at different ratios (Cont.)

Time (min)	PAA 934P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
345	13.62±0.21	16.00±0.19	21.46±0.14
360	13.94±0.28	16.29±0.17	21.60±0.15
375	14.13±0.17	16.49±0.23	21.86±0.12
390	14.37±0.06	16.67±0.22	21.93±0.07
405	14.53±0.12	16.79±0.18	22.01±0.08
420	14.70±0.16	17.04±0.30	22.25±0.20
435	14.90±0.21	17.14±0.31	22.39±0.21
450	15.14±0.14	17.33±0.21	22.62±0.13
465	15.32±0.15	17.47±0.18	22.72±0.11
480	15.43±0.18	17.63±0.18	22.95±0.17

[a]Mean±SD, n=3

Table A.24 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 971P NF at different ratios

Time (min)	PAA 971P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	2.66±0.35	3.72±0.39	4.25±0.28
30	3.47±0.37	5.25±0.31	5.81±0.39
45	4.17±0.35	6.43±0.27	7.69±0.15
60	5.10±0.40	7.45±0.26	8.91±0.10
75	5.66±0.27	8.34±0.24	10.32±0.09
90	6.55±0.23	9.18±0.27	11.64±0.22
105	7.12±0.27	9.98±0.24	12.79±0.07
120	7.83±0.24	10.79±0.18	13.77±0.12
135	8.44±0.30	11.25±0.18	14.87±0.18
150	8.75±0.24	11.91±0.17	15.67±0.06
165	9.21±0.18	12.53±0.16	16.84±0.36
180	9.71±0.22	13.31±0.14	17.60±0.20
195	10.01±0.25	14.00±0.25	18.33±0.05
210	10.27±0.30	14.62±0.26	18.80±0.24
225	10.49±0.29	15.14±0.26	19.33±0.10
240	10.72±0.25	15.63±0.27	19.82±0.18
255	10.93±0.29	16.03±0.21	20.31±0.33
270	11.11±0.22	16.49±0.23	20.86±0.12
285	11.23±0.22	16.83±0.25	21.39±0.12
300	11.47±0.23	17.27±0.39	21.71±0.05
315	11.61±0.19	17.73±0.34	21.99±0.08
330	11.78±0.23	17.96±0.25	22.17±0.11
345	11.94±0.21	18.26±0.24	22.39±0.15
360	12.10±0.26	18.48±0.26	22.54±0.21

[a]Mean±SD, n=3

Table A.24 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 971P NF at different ratios (Cont.)

Time (min)	PAA 971P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
375	12.25±0.25	18.71±0.23	22.69±0.27
390	12.46±0.23	19.07±0.26	22.81±0.20
405	12.62±0.25	19.34±0.28	22.92±0.15
420	12.70±0.23	19.64±0.26	23.02±0.16
435	12.85±0.18	19.88±0.26	23.10±0.16
450	13.03±0.19	20.05±0.35	23.19±0.11
465	13.34±0.22	20.31±0.34	23.29±0.08
480	13.42±0.22	20.53±0.28	23.40±0.10

[a]Mean±SD, n=3

Table A.25 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 974P NF at different ratios

Time (min)	PAA 974P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
0	0.00±0.00	0.00±0.00	0.00±0.00
15	2.32±0.05	3.64±0.11	3.66±0.26
30	2.90±0.09	4.90±0.11	5.57±0.29
45	3.42±0.09	6.23±0.44	6.68±0.30
60	3.93±0.11	7.17±0.54	7.83±0.29
75	4.36±0.08	8.09±0.33	8.75±0.31
90	4.67±0.13	8.59±0.13	9.87±0.36
105	5.05±0.15	9.49±0.32	10.61±0.31
120	5.50±0.22	10.20±0.16	11.59±0.36
135	5.80±0.20	10.67±0.07	12.15±0.29
150	5.94±0.16	11.44±0.12	12.81±0.31
165	6.23±0.18	11.71±0.13	13.51±0.24
180	6.52±0.21	12.28±0.04	14.31±0.24
195	6.83±0.18	12.84±0.20	15.05±0.29
210	7.05±0.18	13.26±0.35	15.67±0.36
225	7.24±0.17	13.71±0.23	16.48±0.30
240	7.63±0.24	14.53±0.13	16.84±0.35
255	7.85±0.26	14.91±0.20	17.26±0.29
270	8.11±0.32	15.41±0.08	17.66±0.31
285	8.23±0.35	15.71±0.13	17.97±0.32
300	8.43±0.33	16.26±0.22	18.41±0.34
315	8.67±0.36	16.67±0.14	18.79±0.31
330	8.94±0.42	17.07±0.21	19.01±0.28
345	9.24±0.41	17.40±0.08	19.30±0.29
360	9.53±0.20	17.63±0.06	19.60±0.28

[a]Mean±SD, n=3

Table A.25 Swelling ratios[a] of CS-PAA interpolymer complexes of PAA 974P NF at different ratios (Cont.)

Time (min)	PAA 974P NF		
	CS:PAA 1:2	CS:PAA 1:1	CS:PAA 2:1
375	9.79±0.17	17.76±0.05	19.93±0.29
390	10.05±0.13	18.26±0.07	20.07±0.31
405	10.24±0.15	18.53±0.08	20.33±0.36
420	10.59±0.24	18.73±0.13	20.71±0.32
435	10.86±0.26	18.94±0.08	21.04±0.29
450	11.06±0.34	19.09±0.13	21.13±0.29
465	11.36±0.30	19.33±0.08	21.33±0.28
480	11.70±0.13	19.57±0.09	21.53±0.29

[a]Mean±SD, n=3

In vitro dissolution testing

Table A.26 The release studies of core tablet of CS-PAA00 (n = 6)

Time	% drug release						
(min)	1	2	3	4	5	6	Mean
5	14.18	13.01	12.82	15.48	12.46	12.30	13.38
10	32.08	31.58	31.55	30.88	31.78	30.96	31.47
15	45.91	43.89	43.5	43.36	43.64	43.86	44.03
20	62.94	56.43	54.82	59.95	53.75	56.11	57.33
25	70.52	65.21	68.9	70.18	69.73	69.89	69.07
30	81.35	76.37	76.42	77.67	77.36	77.53	77.78
35	87.86	83.95	83.92	84.39	83.65	83.80	84.60
40	94.23	87.72	88.04	88.95	88.49	88.62	89.34
45	97.37	92.62	93.89	92.00	92.37	92.34	93.43
50	99.65	96.92	96.95	93.42	96.60	96.60	96.69
55	101.14	98.22	98.32	98.03	99.62	97.96	98.88
60	101.18	99.38	100.04	99.73	100.68	98.99	100.00

Table A.27 The release studies of core tablet of CS-PAA05 (n = 6)

Time	% drug release						
(min)	1	2	3	4	5	6	Mean
5	17.13	15.32	15.15	15.33	14.20	15.74	15.48
10	29.05	27.21	33.76	33.74	32.45	30.93	31.19
15	48.17	46.30	45.75	45.83	45.55	43.27	45.81
20	63.05	61.91	57.12	57.14	61.08	60.04	60.06
25	70.44	69.26	71.25	71.30	70.62	69.57	70.41
30	79.59	77.98	78.86	78.88	81.48	77.97	79.13
35	85.19	83.87	85.01	85.04	86.71	86.42	85.37
40	89.34	88.24	91.59	91.64	92.55	94.06	91.24
45	91.44	91.32	95.06	95.07	97.18	96.15	94.37
50	93.90	93.04	97.66	97.69	98.98	97.41	96.45
55	95.84	96.69	98.85	98.88	100.02	98.44	98.12
60	97.31	99.51	100.06	100.08	101.06	99.50	99.59

Table A.28 The release studies of core tablet of CS-PAA10 (n = 6)

Time	% drug release						
(min)	1	2	3	4	5	6	Mean
5	18.98	18.44	12.98	14.07	17.53	17.52	16.59
10	32.95	35.06	31.58	32.74	32.55	32.60	32.91
15	47.81	50.44	43.55	44.72	45.22	45.01	46.13
20	62.57	66.26	54.89	56.11	61.68	61.63	60.52
25	70.66	72.58	68.97	70.19	72.23	71.46	71.02
30	82.31	79.82	76.55	77.74	79.64	79.51	79.26
35	83.92	84.93	83.96	85.10	86.17	85.64	84.95
40	88.69	86.80	88.09	89.31	90.51	90.56	88.99
45	93.28	89.74	93.97	95.13	93.49	93.46	93.18
50	96.50	92.97	97.20	98.38	94.96	94.65	95.78
55	97.60	94.63	98.39	99.76	99.17	98.65	98.03
60	98.88	96.97	100.21	101.44	101.17	100.82	99.92

Table A.29 The release studies of core tablet of CS-PAA20 (n = 6)

Time	% drug release						
(min)	1	2	3	4	5	6	Mean
5	19.96	21.20	19.09	18.25	17.18	17.13	18.80
10	33.89	38.00	30.36	30.06	32.69	32.55	32.93
15	48.72	53.46	42.31	48.46	45.04	44.93	47.15
20	63.21	69.31	54.56	60.46	61.84	61.55	61.82
25	71.37	75.63	66.49	73.57	71.95	71.70	71.79
30	82.91	82.89	73.62	84.27	79.52	79.36	80.43
35	84.89	88.05	84.89	90.86	86.19	85.95	86.81
40	89.38	89.88	89.12	93.22	90.43	90.27	90.38
45	94.37	92.90	96.10	95.04	93.47	93.39	94.21
50	97.33	96.17	97.62	96.43	94.92	94.74	96.20
55	98.39	97.93	98.72	97.54	98.92	98.80	98.38
60	99.94	100.22	99.74	98.60	101.08	100.69	100.05

Table A.30 The release studies of core tablet of CS-PAA30 (n = 6)

Time	% drug release						
(min)	1	2	3	4	5	6	Mean
5	20.78	20.41	19.39	20.31	17.39	19.20	19.58
10	32.74	32.37	31.45	32.14	29.20	31.04	31.49
15	51.9	50.79	50.07	50.14	47.42	49.29	49.94
20	66.81	62.65	61.80	62.11	58.97	60.98	62.22
25	74.25	76.12	75.11	75.61	72.57	74.48	74.69
30	83.45	87.11	84.17	86.19	83.11	85.04	84.85
35	89.08	93.62	88.96	92.89	89.76	91.72	91.01
40	93.26	96.28	93.17	95.39	90.80	92.76	93.61
45	95.42	97.35	95.08	97.18	93.16	95.20	95.57
50	97.47	99.43	97.59	98.37	94.50	96.97	97.39
55	99.05	100.81	98.74	99.40	95.67	97.99	98.61
60	100.08	102.95	100.11	100.43	96.91	99.01	99.92

Table A.31 The release studies of core tablets of CS-PAA00 after coating with semi-permeable membrane (n = 6)

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	3.84	4.11	3.34	4.87	4.11	3.82	4.02
2	11.76	12.06	11.53	12.84	12.13	11.71	12.01
3	18.16	17.74	17.62	18.84	18.47	17.97	18.13
4	25.67	25.31	24.94	26.78	26.01	25.48	25.70
5	31.02	34.49	33.41	31.21	29.92	31.24	31.88
6	33.74	38.30	35.31	34.65	34.69	33.94	35.11
7	38.74	42.15	37.95	37.78	41.50	39.11	39.54
8	42.84	44.60	42.80	40.92	45.39	43.29	43.31
9	46.69	49.60	47.00	46.72	49.96	46.64	47.77
10	50.43	52.29	50.22	48.63	54.06	50.41	51.01
11	54.55	56.02	53.01	52.37	58.33	54.30	54.76
12	57.14	59.75	57.01	56.36	60.10	57.29	57.94
13	62.12	62.44	60.31	59.90	63.80	62.17	61.79
14	64.30	64.18	64.16	62.69	67.42	64.67	64.57
15	67.66	65.97	69.88	67.76	71.74	68.15	68.53
16	70.89	68.49	71.91	72.16	72.85	71.23	71.26
17	73.41	73.14	72.57	76.67	76.15	73.67	74.27
18	77.49	77.18	77.05	82.18	77.28	77.69	78.14
19	82.61	83.48	80.72	83.42	80.54	82.92	82.28
20	84.75	84.75	84.54	84.57	83.27	85.14	84.50
21	85.73	85.70	87.05	85.79	85.26	85.80	85.89
22	86.59	86.89	89.17	87.17	88.87	86.74	87.57
23	87.44	87.52	91.34	89.19	91.50	87.47	89.08
24	88.54	88.63	91.82	90.22	92.04	88.61	89.98

Table A.32 The release studies of core tablets of CS-PAA05 after coating with semi-permeable membrane (n = 6)

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	11.03	11.75	11.51	11.59	12.12	11.54	11.59
2	23.76	24.24	24.02	23.77	24.96	24.11	24.14
3	30.75	31.50	31.98	30.96	31.96	30.80	31.33
4	38.77	39.27	39.01	38.93	39.74	38.57	39.05
5	44.16	44.32	44.76	44.29	45.07	44.29	44.48
6	51.04	51.40	50.93	50.93	51.30	51.04	51.11
7	54.72	55.23	55.26	54.65	55.28	54.89	55.01
8	57.51	58.27	56.80	58.31	58.65	57.29	57.81
9	60.60	61.49	61.74	61.16	61.47	60.89	61.23
10	65.06	65.58	65.12	64.77	64.64	65.43	65.10
11	65.68	66.31	66.19	65.79	66.75	65.87	66.10
12	67.92	69.81	68.92	68.05	68.55	67.35	68.43
13	69.24	72.09	70.40	72.16	70.26	69.28	70.57
14	70.43	74.97	72.08	74.47	71.69	72.18	72.64
15	72.75	78.53	75.12	76.28	74.74	75.20	75.44
16	74.33	83.30	78.88	78.93	78.93	77.29	78.61
17	78.09	84.55	84.79	82.89	81.18	80.55	82.01
18	82.87	85.89	85.84	84.21	83.70	81.37	83.98
19	85.20	87.13	87.31	85.97	85.81	83.63	85.84
20	86.35	87.99	89.27	87.03	86.80	85.52	87.16
21	87.19	88.85	90.00	87.73	87.62	86.65	88.01
22	88.05	89.81	92.05	88.80	88.79	89.02	89.42
23	89.07	90.45	92.53	89.55	89.32	90.34	90.21
24	89.57	90.94	93.07	90.38	90.24	91.27	90.91

Table A.33 The release studies of core tablets of CS-PAA10 after coating with semi-permeable membrane (n = 6).

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	16.8	17.18	16.46	14.64	17.72	11.54	15.72
2	28.61	29.21	28.24	27.27	29.21	28.86	28.57
3	38.06	39.00	37.83	37.09	39.04	38.39	38.24
4	43.48	44.04	43.20	42.38	44.21	43.70	43.50
5	48.20	48.79	47.65	46.55	48.43	48.39	48.00
6	54.26	54.59	53.36	51.75	54.51	54.34	53.80
7	58.48	58.94	57.89	56.85	58.93	58.58	58.28
8	62.65	62.95	62.18	61.38	62.83	62.87	62.48
9	66.45	67.22	66.51	65.53	63.91	66.86	66.08
10	70.44	70.89	70.05	68.58	70.98	70.84	70.30
11	73.63	74.13	73.03	72.33	73.91	73.76	73.47
12	78.39	78.87	77.00	77.08	78.78	77.38	77.92
13	80.85	81.85	80.13	79.16	80.55	79.27	80.30
14	82.92	84.03	81.13	81.05	82.05	81.10	82.05
15	85.55	86.32	82.43	84.13	83.80	83.15	84.23
16	87.09	87.24	83.59	85.35	85.64	84.64	85.59
17	89.87	88.44	84.47	88.10	86.83	85.45	87.19
18	92.50	89.86	85.35	89.46	88.01	87.32	88.75
19	93.18	90.64	86.30	90.67	89.27	88.78	89.81
20	94.40	91.53	87.16	92.11	90.00	89.92	90.85
21	95.56	92.39	87.97	93.37	90.61	91.26	91.86
22	96.18	93.23	88.91	94.37	91.24	91.89	92.64
23	96.85	93.98	89.93	94.88	91.88	92.58	93.35
24	97.39	94.49	90.60	95.38	92.46	93.14	93.91

Table A.34 The release studies of core tablets of CS-PAA20 after coating with semi-permeable membrane (n = 6).

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	22.35	23.01	22.93	22.86	20.27	22.95	22.40
2	30.08	32.13	31.41	30.33	30.00	32.04	31.00
3	37.50	40.31	38.57	37.88	37.86	39.95	38.68
4	44.59	48.83	46.64	44.96	44.48	48.61	46.35
5	52.10	58.28	54.89	52.34	52.00	57.76	54.56
6	59.90	64.01	62.42	60.35	59.83	63.65	61.69
7	66.05	71.22	68.62	66.33	66.06	70.84	68.19
8	70.30	73.66	74.59	70.80	70.06	73.32	72.12
9	74.17	76.85	78.02	74.31	74.00	76.22	75.60
10	78.79	78.72	80.33	79.17	78.52	78.55	79.01
11	82.24	79.73	82.81	82.38	79.35	79.74	81.04
12	85.90	81.87	83.76	85.68	81.32	81.93	83.41
13	88.79	83.39	86.03	88.30	82.84	83.86	85.54
14	89.48	84.48	87.03	89.17	84.01	86.68	86.81
15	90.35	86.01	88.26	89.93	85.63	89.70	88.31
16	91.10	87.54	89.45	90.97	87.04	90.66	89.46
17	91.82	88.89	90.61	91.75	88.32	91.49	90.48
18	92.58	90.31	91.33	92.61	89.86	92.17	91.48
19	93.37	91.04	91.93	93.35	90.45	93.12	92.21
20	94.22	91.72	92.64	94.17	91.20	93.97	92.99
21	95.15	92.39	93.25	95.17	91.82	94.84	93.77
22	95.92	93.16	93.90	95.94	92.43	95.70	94.51
23	96.76	93.75	94.49	96.60	93.02	96.37	95.17
24	97.48	94.28	95.21	97.22	93.59	97.02	95.80

Table A.35 The release studies of CS-PAA00 osmotic pump tablets after coating with eudragit L (n = 6).

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	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
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	3.87	5.04	3.69	5.51	4.51	3.87	4.42
4	11.89	12.30	12.29	13.35	12.18	11.64	12.28
5	17.99	17.67	18.36	19.21	18.84	17.91	18.33
6	26.20	25.69	25.70	27.17	26.03	23.76	25.76
7	31.05	34.52	31.04	31.77	29.94	31.24	31.59
8	33.75	38.88	35.73	36.05	34.73	34.05	35.53
9	38.66	42.74	40.70	38.80	40.77	39.40	40.18
10	42.98	44.71	43.00	42.62	44.62	43.51	43.57
11	46.72	49.66	46.46	47.41	48.01	46.82	47.51
12	50.69	52.31	50.74	49.23	52.00	50.26	50.87
13	54.33	55.85	53.23	52.52	56.15	54.47	54.43
14	57.18	58.43	57.46	57.01	59.63	57.19	57.82
15	62.13	62.34	60.91	60.35	62.19	62.73	61.78
16	64.43	64.40	64.76	63.45	66.39	64.78	64.70
17	67.55	68.10	70.38	68.24	71.19	68.23	68.95
18	70.88	72.81	72.46	71.86	73.54	71.52	72.18
19	74.28	76.92	75.79	76.01	76.78	74.25	75.67
20	77.47	79.99	77.51	81.08	80.56	78.06	79.11
21	82.72	83.43	81.29	84.40	82.47	83.06	82.90
22	84.66	84.95	84.93	85.25	84.60	85.52	84.99
23	85.58	85.86	87.77	86.45	85.73	86.55	86.32
24	86.42	86.80	90.07	87.40	88.35	87.56	87.77
25	87.38	87.85	91.86	89.30	89.62	88.50	89.09
26	88.36	88.76	93.90	90.63	90.22	89.03	90.15

Table A.36 The release studies of CS-PAA05 osmotic pump tablets after coating with eudragit L (n = 6).

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	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
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	16.72	16.83	15.01	15.05	15.03	14.97	15.60
4	23.82	22.82	23.66	24.24	24.08	24.39	23.84
5	31.88	29.34	31.86	30.90	32.01	31.62	31.27
6	39.29	37.60	38.91	38.55	39.06	39.28	38.78
7	46.60	45.06	44.86	44.66	44.82	45.46	45.24
8	51.09	49.89	51.06	51.82	51.06	51.61	51.09
9	55.59	52.25	55.66	54.92	55.37	55.30	54.85
10	56.98	54.44	56.95	57.59	56.86	58.42	56.87
11	61.75	58.06	62.09	61.04	61.83	61.55	61.05
12	65.25	65.01	65.37	65.56	65.65	66.16	65.50
13	66.75	66.47	66.28	66.78	68.56	69.33	67.36
14	69.74	68.81	68.18	67.80	70.09	71.88	69.42
15	72.10	73.91	70.11	69.30	72.08	75.01	72.09
16	76.63	76.45	71.72	70.90	74.75	77.94	74.73
17	79.67	80.52	73.65	72.42	78.52	80.27	77.51
18	82.61	82.88	75.37	75.61	80.06	82.74	79.88
19	85.10	84.49	76.59	77.78	80.93	84.03	81.49
20	85.88	87.37	79.21	81.11	83.07	85.06	83.62
21	87.55	89.49	81.04	84.29	84.57	86.87	85.64
22	89.56	91.92	82.87	85.84	85.84	87.77	87.30
23	91.68	93.58	84.49	86.69	87.66	89.33	88.91
24	92.62	95.87	85.82	87.69	88.50	90.42	90.15
25	93.40	96.63	87.08	88.75	89.26	90.95	91.01
26	93.92	97.17	88.14	89.67	89.78	91.42	91.68

Table A.37 The release studies of CS-PAA10 osmotic pump tablets after coating with eudragit L (n = 6)

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	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
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	17.75	17.17	16.11	17.43	17.58	15.73	16.96
4	29.24	28.27	28.65	29.32	29.36	27.17	28.67
5	38.91	38.20	37.45	39.15	39.13	37.14	38.33
6	44.13	43.51	42.63	44.57	44.39	42.40	43.61
7	48.51	48.09	47.17	48.80	49.01	46.47	48.01
8	54.38	53.99	52.89	54.71	55.03	51.76	53.79
9	58.98	58.24	57.67	59.02	59.27	56.76	58.32
10	62.84	62.53	62.15	63.29	63.66	61.38	62.64
11	66.91	66.52	66.13	67.60	67.50	65.51	66.70
12	71.36	70.46	69.75	71.22	71.36	68.63	70.46
13	74.28	73.40	72.74	74.36	74.51	72.36	73.61
14	78.87	78.11	76.75	79.00	77.97	77.08	77.96
15	80.66	80.85	79.71	82.20	79.81	79.20	80.41
16	82.23	83.02	80.82	84.05	81.68	81.06	82.14
17	83.92	85.62	82.02	86.48	83.42	84.12	84.26
18	85.81	87.12	83.14	87.27	84.75	85.32	85.57
19	86.94	89.71	84.11	88.50	85.94	87.42	87.25
20	88.02	92.35	85.01	89.16	87.28	89.47	88.70
21	89.64	93.18	85.93	90.38	88.82	90.32	89.87
22	90.15	94.40	86.87	91.32	89.95	91.34	90.79
23	90.75	95.58	87.55	92.02	90.97	92.15	91.63
24	91.31	96.15	88.32	92.67	91.90	92.79	92.35
25	91.93	96.65	89.25	93.24	92.60	93.39	92.95
26	92.50	97.16	89.91	93.74	93.28	93.87	94.11

Table A.38 The release studies of CS-PAA20 osmotic pump tablets after coating with eudragit L (n = 6).

Time	% drug release						
(h)	1	2	3	4	5	6	Mean
0	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
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	23.33	23.69	23.33	22.76	22.60	20.32	22.67
4	31.06	32.13	32.54	30.11	31.78	30.07	31.28
5	38.46	39.29	40.78	38.09	39.55	37.87	39.01
6	45.53	47.49	49.19	45.14	48.22	44.58	46.69
7	53.20	55.56	58.54	52.48	57.80	52.07	54.94
8	60.96	63.20	64.42	60.22	63.52	59.95	62.05
9	67.20	69.30	71.48	66.12	70.50	65.92	68.42
10	71.39	75.08	73.93	70.64	72.95	70.16	72.36
11	75.19	78.92	77.25	74.27	76.00	73.93	75.93
12	79.90	81.08	78.87	78.96	78.21	78.42	79.24
13	83.29	83.54	80.12	82.96	79.35	79.39	81.44
14	86.56	84.54	82.22	85.96	81.78	81.48	83.76
15	89.08	86.66	83.88	88.70	83.64	82.91	85.81
16	89.91	87.82	84.69	89.47	86.30	84.04	87.04
17	90.70	89.01	86.21	90.49	89.65	85.66	88.62
18	91.70	90.36	87.76	91.13	90.53	87.08	89.76
19	92.43	91.44	89.05	91.91	91.35	88.39	90.76
20	93.27	92.11	90.46	92.65	92.08	89.95	91.75
21	94.25	92.72	91.09	93.45	92.63	90.51	92.44
22	94.96	93.37	91.76	94.38	93.47	91.24	93.20
23	95.82	94.14	92.61	95.18	94.45	91.89	94.02
24	96.83	94.71	93.27	95.87	95.31	92.51	94.75
25	97.42	95.35	93.79	96.68	96.14	93.13	95.42
26	98.00	95.84	94.54	97.46	97.17	93.63	96.11

BIOGRAPHY

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