PREPARATION AND APPLICATION OF CARBOXYMETHYL YAM (*DIOSCOREA ESCULENTA*) STARCH

By

Ornamphai Suwithayapan

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree
DOCTOR OF PHILOSOPHY
Program of Pharmaceutical Technology
Graduate School
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การเตรียมและการใช้ประโยชน์ของแป้งมันมือเสือดัดแปรด้วยหมู่คาร์บอกซีเมธิล

โดย
นางสาวอรอำไพ สุวิทยพันธุ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรดุษฎีบัณฑิต
สาขาวิชา เทคโนโลยีเภสัชกรรม
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The Graduate School, Silpakorn University accepted thesis entitled "Preparation and Application of Carboxymethyl Yam (*Dioscorea esculenta*) Starch" by Ornamphai Suwithayapan in partial fulfillment of the requirements for the degree of doctor of philosophy, program of pharmaceutical technology.

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ORNAMPHAI SUWITHATAPAN : PREPARATION AND APPLICATION OF CARBOXYMETHYL YAM (*DIOSCOREA ESCULENTA*) STARCH. THESIS ADVISORS : ASST. PROF. NATTAWAT NATTAPULWAT, Ph.D., AND NARUMOL PURKKAO, Ph.D. 187 pp.

Yam (*Dioscorea esculenta*) starch was extracted from yam tubers. The starch was modified in order to obtain some desired properties by a carboxymethylation. Box-Benkhen was used as an experimental design tool to investigate the influence of reaction variables and their interaction on the carboxymethyl yam starch (CMS) preparation. The effect of amount of sodium hydroxide (NaOH), amount of sodium monochloroacetate (SMCA) and reaction time on the degree of substitution (DS) of CMS was studied. Degrees of substitution, morphology, swelling power and viscosity of CMS were determined. Application of native yam starch and optimized CMS were studied, and their potential to use as tablet disintegrants and direct compressible fillers were evaluated. For direct compressible filler, spray dried yam starch with or without the addition of 0-1.5% CMS were prepared. The results showed that yam starch granules were polygonal with particle sizes of 2-20 μm. The tablets containing native yam starch disintegrated and allowed drug to release faster than that of tablets with corn, rice, and tapioca starches. With increasing native starch concentrations, the disintegration of the tablets was found to be faster, the result from regression analysis from the CMS preparation indicated that the most important factor in controlling DS was the amount of NaOH followed by SMCA content and reaction time, respectively. Interaction between NaOH and SMCA content showed negative effect at high concentration. The optimal condition to achieve CMS with the highest DS (0.19) was found to be at molar ratio of NaOH and SMCA to anhydrogluclose unit (AGU) of 1.80 and 2.35, respectively, and the reaction time of 4.8 hours. The swelling power and viscosity increased with an increase in the degree of modification. CMS showed satisfying properties to be a tablet disintegrant. DCP tablets containing 2% CMS disintegrated within 30 seconds. At higher concentrations of CMS, the disintegration and the dissolution of HCTZ tablet were prolonged. The scanning electron micrographs of spray dried yam starches (SDYS) revealed that the products were spherical agglomerated granules with the average particle sizes ranged from 84.43-104.35 μm. The SDYS tablets were stronger than the Era-Tab® tablet. Consequently, they disintegrated slower than the Era-Tab® tablet. CMS exhibited a powerful tablet disintegrating agent in SDYS when the CMS concentration was less than 0.5%. Incorporation with higher amount of CMS in SDYS retarded the tablet disintegration. Dilution capacity index (DCI) revealed that the products from SDYS possessed better carrying capacity. SDYS co-sprayed with 1.5% CMS governed the highest DCI value. The results from lubricant sensitivity showed that Era-tab® was the most sensitive to magnesium stearate. The disintegration of SDYS tablets seem to be more dependent on tablet hardness than the lubricant concentration. It can be concluded that SDYS co-sprayed with 0.5% CMS was a filler of choice for direct compression technique which had self disintegration property. CMS was an efficient disintegrant and the recommended concentration was not more than 2% w/w.

Program of Pharmaceutical Technology Graduate School, Silpakorn University Academic year 2008

Student's signature ....

Thesis Advisors' signature 1. .... 2. ....

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การศึกษานี้มีวัตถุประสงค์เพื่อนำแป้งมันมือเสือมาพัฒนาเป็นสารช่วยในการผลิตยาเม็ด ได้แก่ สารช่วยตอกโดยตรงและสารช่วยแตกตัว โดยทำการสกัดแป้งมันมือเสือจากหัวมันมือเสือ แล้วนำมาดัดแปรโดยการเติมหมู่คาร์บอกซีเมธิล ได้แป้งมันมือเสือดัดแปร (carboxymethyl yam starch, CMS) ออกแบบการทดลองโดยใช้วิธี Box-Benkhen เพื่อหาสภาวะที่เหมาะสมเพื่อให้ได้ระดับการแทนที่ของหมู่คาร์บอกซีเมธิล (DS) สูงสุด ในการศึกษานี้ได้ประเมินคุณสมบัติและความสามารถในการเป็นสารช่วยแตกตัวในยาเม็ดไดแคลเซียมฟอสเฟส (DCP) และศึกษาการปลดปล่อยยาไฮโดรคลอโรไทอะไซด์จากยาเม็ด โดยใช้ความเข้มข้นของแป้งมันมือเสือและ CMS ที่ความเข้มข้นต่างๆ จากนั้นยังได้พัฒนาแป้งมันมือเสือเป็นสารช่วยตอกโดยตรงด้วยวิธีพ่นแห้ง โดยใช้แป้งมันมือเสือผสมกับ CMS ในปริมาณร้อยละ 0 ถึงร้อยละ 1.5 โดยน้ำหนัก จากการศึกษาพบว่าแกรนูลแป้งมันมือเสือมีลักษณะเป็นรูปร่างหลายเหลี่ยม ขนาดประมาณ 2-20 ไมโครเมตร สภาวะที่เหมาะสมในการเตรียม CMS เพื่อให้ได้ค่า DS สูงสุดคือ อัตราส่วนโดยโมลของโซเดียมไฮดรอกไซด์ต่อแป้งมันมือเสือเป็น 1.8 และอัตราส่วนโดยโมลของโซเดียมโมโนคลอโรอะซีเตทต่อแป้งมันมือเสือเป็น 2.4 และเวลาทำปฏิกิริยา 4 ชั่วโมง 50 นาที ได้ CMS ที่มีค่า DS 0.19 โดยคุณสมบัติของ CMS มีดังนี้คือเป็นเจลได้ที่อุณหภูมิห้อง การพองตัวและความหนืด เพิ่มขึ้นตามค่า DS การใช้ CMS เป็นสารช่วยแตกตัวในยาเม็ดพบว่า CMS ร้อยละ 2 โดยน้ำหนัก ทำให้เม็ด DCP แตกตัวเร็วที่สุด และทำให้เม็ดยาไฮโดรคลอโรไทอะไซด์ปลดปล่อยยาเร็วที่สุด ในขณะที่ความเข้มข้นของ CMS มากกว่าร้อยละ 2 ทำให้การแตกตัวของเม็ด DCP และการปลดปล่อยยาจากเม็ดไฮโดรคลอโรไทอะไซด์ช้าลง จากการวิจัยครั้งนี้พบว่า แป้งมันมือเสือดัดแปรสามารถใช้เป็นสารช่วยตอกโดยตรงได้อย่างดี โดยแป้งมันมือเสือพ่นแห้งร่วมกับ CMS ร้อยละ 0.5 โดยน้ำหนัก เป็นสารช่วยตอกโดยตรงที่มีคุณสมบัติแตกตัวได้ด้วย สามารถใช้ CMS เป็นสารช่วยแตกตัวได้อย่างมีประสิทธิภาพ เมื่อใช้ในปริมาณที่เหมาะสม คือร้อยละ 0.5-2 โดยน้ำหนัก อนุภาคที่ได้จากการพ่นแห้งมีลักษณะเป็นก้อนกลม ขนาดอนุภาคประมาณ 84.43-104.35 ไมครอน มีคุณสมบัติการไหลและการตอกเป็นเม็ดที่ดี แป้งมันมือเสือพ่นแห้งร่วมกับ CMS ร้อยละ 1.5 โดยน้ำหนัก มีคุณสมบัติในการตอกเป็นเม็ดดีที่สุด มีความไวต่อแมกนีเซียมเสตียเรทน้อยที่สุด มีคุณสมบัติในการพาสารได้มากที่สุด แต่การแตกตัวและการปลดปล่อยยานานที่สุด ในขณะที่แป้งมันมือเสือพ่นแห้งร่วมกับ CMS ร้อยละ 0.5 โดยน้ำหนัก มีคุณสมบัติในการตอกเป็นเม็ดดีและมีความไวต่อแมกนีเซียมเสตียเรทน้อย แต่ทำให้การแตกตัวและการละลายยาเร็วที่สุด

สาขาวิชาเทคโนโลยีเภสัชกรรม บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร ปีการศึกษา 2551
ลายมือชื่อนักศึกษา ....
ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์ 1.............................. 2..............................

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Ornamphai Suwithayapan

CONTENTS

Page

LIST OF TABLES

Table Page

Table Page

Table Page

LIST OF FIGURES

Figure Page

Figure Page

LIST OF ABBREVIATIONS

CP	compression pressure
CMS	carboxymethyl yam starch
e.g.	exempli gratia, for example
et al.	et alii, and others
DT	disintegration time
g	gram
i.e.	id est, that is
kg	kilogram
kN	kilo Newton
mg	milligram
min	minute
mL	milliliter
MPa	Mega Pascal
pH	the negative logarithm of the hydrogen ion concentration
R^2	coefficient of determination
SD	standard deviation
SDYS+CMS0%	spray dried yam starch
SDYS+CMS0.5%	co-spray dried yam starch with CMS 0.5% w/w
SDYS+CMS1.0%	co-spray dried yam starch with CMS 1.0% w/w
SDYS+CMS1.5%	co-spray dried yam starch with CMS 1.5% w/w
USP	United State Pharmacopoiea
w/w	weight by weight

CHAPTER I

INTRODUCTION

Starches from various natural origins are well-known, safe, and have been extensively investigated in pharmaceutical industry. They are mainly used in oral solid dosage forms as fillers, binders or disintegrants. Since starches have some limitation properties. To improve their properties such as flowability, gelatinizing temperature, paste or gel viscosity, hydrophillicity, or swelling characteristic, starches have been modified. Modifications are including physical modification, chemical modification and genetic modification. For example spray dried rice starches (Era-Tab®, Primotab®) were introduced as direct compression fillers. Rice starch was physically modified by spraying and drying starch slurry to form a round agglomerated particle. Consequently, it has excellent flow and binding properties (Bos et al. 1992 : 93-106). Some desirous properties were obtained by chemical modification. Korhonen (Korhonen et al. 2000 : 1138-1143) and Silvennoinen R. (Silvennoinen et al. 1999 : 213–220) modified barley starch by acetylation. The starch acetate properties were depending on degree of substitution and it showed potentially useful as direct compression excipient. Carboxymethyl starch is another examples of chemically modified starch. It was prepared by a reaction of starch (St-OH) and sodium monochloroacetate ($ClCH_2COO^-Na^+$) in the presence of sodium hydroxide (NaOH). The efficiency of reaction was determined by the degree of substitution. Carboxymethyl starch has been used as a tablet disintegrant.

Carboxymethyl starch acts as an anionic polyelectrolyte in aqueous slurry or paste. It increased rate of swelling to reach higher peak viscosity, and has a higher cooked out viscosity than unmodified starch. Carboxymethyl potato starch is an official ingredient in pharmacopoeias in the name of sodium starch glycolate.

The Yam (Dioscorea sp.) is a local plant of many countries, i.e., Nigeria, Jamica, Brazil, China, and Thailand (Yu et al. 1999 : 5-10 ; Alves et al. 2002 : 476-481 ; Riley et al. 2004 : 69-73 ; Shujun et al. 2006 : 30-37). The nutrient content of yam tuber has been determined (Vorasuntharosoj 2001 : 124-127). The main use of yam is as food, usually eaten boiled or roasted. Yam (*D. alata*) is a food crop of economic value in southern Brazil. The yam flour has been used in bread products and snacks (Alves et al. 2002 : 476-481). Furthermore, it is believed that the mixture of yam flour, rice flour and some nutrients is beneficial to infant health (Yu et al. 1999 : 5-10). In traditional Chinese medicine, yam (*D. opposita*) tuber has been used as an important invigorant. It can invigorate the spleen, stomach, and kidney. Promotion of the body fluids has also been reported (Shujun et al. 2006 : 30-37). In Thailand, the most common yam specie is *Dioscorea esculenta* (Vorasuntharosoj 2001 : 124-127). The applications of this yam starch in food industry and pharmaceutics have not been reported. This study was designed to modify yam starch (*D. esculenta*) by carboxymethylation and study the properties of modified yam starch. The efficacy of yam starch and carboxymethyl yam starch (*D. esculenta*) as a tablet disintegrant and a tablet filler were also be evaluated in this study. The objectives of this study are as follows:

1. Preparation of carboxymethyl yam starch by using optimization technique.

2. Evaluation of the properties of carboxymethyl yam starch.

3. Evaluation of carboxymethyl yam starch as a tablet disintegrant compared with other commercial carboxymethyl starch.

4. Evaluation of carboxymethyl yam starch as direct compressible filler

    4.1 Preparation of spray dried yam starch with various concentration of carboxymethyl yam starch.

    4.2 Evaluation of the tableting properties of spray dried yam starch compared with other commercial spray dried starches.

CHAPTER II

LITERATURE REVIEW

Starch is a reserve carbohydrate in the plant kingdom. It is the major source of carbohydrate for humans. Starch is deposited in plants in form of microscopic granules ranging from 1 to 100 μm or more in diameter.

Chemically, Starch is polysaccharide consisting of anhydroglucose units linked through α-D (1→4) glucosidic bonds. A schematic diagram of anhydroglucose unit is shown in Figure 1.

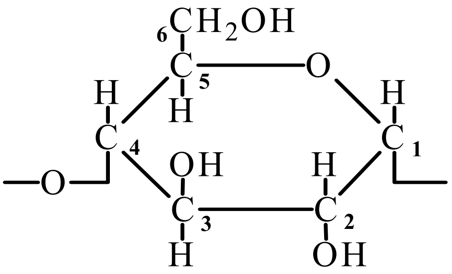


Figure 1 Schematic diagram of anhydroglucose unit.

Starch is composed of two major polysaccharides called amylose and amylopectin. Amylose is a linear polymer in which the anhydroglucose units are linked by α-1,4 glucosidic bonds. The amylose chains tend to assume a helical rearrangement. The characteristic deep blue color when iodine-iodine solution added, is believed to be due to a complex between iodine and helical amylose. It may contain from about 200 to 2000 anhydroglucose units. A schematic diagram of amylose is shown in Figure 2.

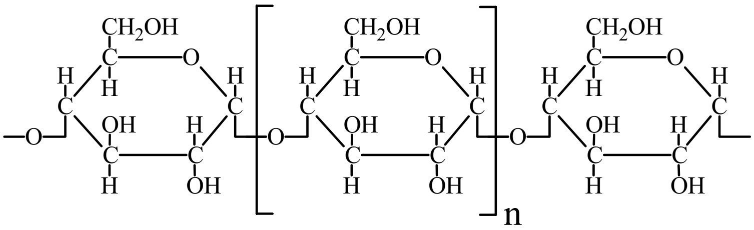


Figure 2 Schematic diagram of amylose.

Amylopectin is a branched polymer of glucose. In addition to α-1,4-glycosidic linkage as in amylose branching takes place between C_6 of one glucose unit and C_1 of another. This 1,6- glycosidic linkage occur at interval of 20 to 30 anhydroglucose units. A schematic diagram of amylopectin is shown in Figure 3.

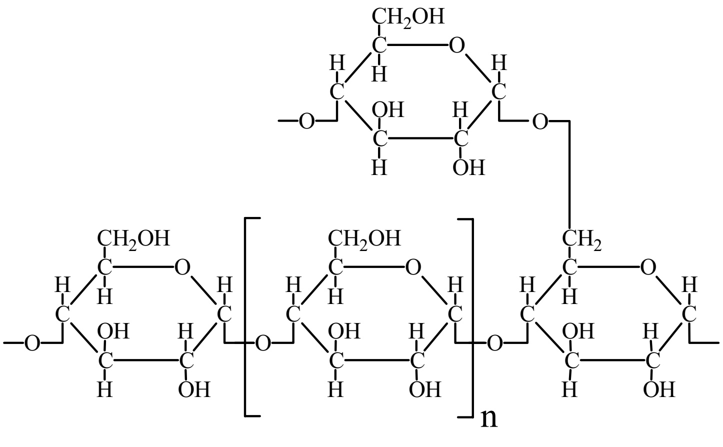


Figure 3 Schematic diagram of amylopectin.

Properties of each starch are varied depending upon the ratio of amylose to amylopectin. Native starches may be subjected to modification procedures to provide the desired properties for specific applications. Various types of modification have been developed including physical, chemical, and genetic modification.

1. Physical modifications

1.1 Pregelatinization Pregelatinized starches are obtained by gelatinizing and drying of starch suspension. During pregelatinization the granular structure of the starch is destroyed. Gelatinization is a process involving the transformation of an aqueous starch suspension in to a starch paste, in other words, the mixture of water, a swollen starch granule fragment and dissolved starch molecules leach from the granule. Pregelatinized starches have the property of marked swelling in contact with cold water. Anastasiades et al. (2002 : 57–66) characterized physical properties of pregelatinized maize starch. The modified starch presented excellent wettability and easily dispersed in cold water. With this special property in pharmaceutical applications, pregelatinized starch has been used as a tablet binder. This modified starch was also used to improve tablet disintegration (Erawan Pharmaceutical Research and Laboratory Co.,Ltd. : 1-17).

1.2 Spray drying Spray dried starches are obtained from a process that starch granules are agglomerated into spherical shape by spray drying technique. Spray dried starch exhibits excellent flowability and good compactibility (Shangraw 1991 : 85-106). Bos et al. (1992 : 93-106) evaluated spray dry rice starch (Primotab®ET) as an excipient for the preparation of tablets by direct compression. They found that spray dried rice starch was a filler that exhibited excellent flow and binding properties. This modified starch was used to improve the flowability of microcrystalline cellulose by co-spray drying technique (Limwong, Sutanthavibul and

Kulvanich 2004 : 1-10). The tablets made from this co-processing exhibited high bonding strength with good self disintegration.

2. Chemical modifications

2.1 Acid modification Acid modified starches are prepared by mild treatment of starch slurry with dilute acid below the gelatinized temperature of starch, When the desired viscosity is reached, the acid is neutralized and the starch granules are recovered by filtering, washing, and drying (Wurzburg 1986). When starch is treated with dilute acid, depolymerization occurred. The viscosity of the modified starch paste was reduced. The paste had a strong tendency to gel after cooled (Swinkels 1992). Moreover, the crystallinity of the acid hydrolyzed starch was increased, resulting in higher bonding strength tablets (Varavinit and Atichokudomchai 2003 : 263-270).

2.2 Crosslinked modification Cross-linking reaction is employed in the most starch modification processes. Crosslinked starches are modified starch in which starch chains are bridged by mean of bifunctional or polyfunctional chemicals such as phosphorus oxychloride, sodium trimetaphosphate, adipic acid and epichlorohydrin (Swinkels 1992). The cross-linking treatment is used to reinforce the strength of the starch granule or grain, higher gelatinization temperature resulted. When the cross-linked starch is heated in water, the hydrogen bonds is weaken or destroyed. The degree of cross-linking controls the rate and extent of which starch swelling (Wurzburg 1986). Increasing the degree of crosslinking lead to more resistance to swelling and gelatinization. (Visvarungroj and Remon 1990 : 1091-1108).

2.3 Etherification and Esterification Starch ethers and starch esters are modified starch in which some or all of the available hydroxyl group in starch molecules were etherified and esterified, respectively.

Starch acetate is an example of esterified starch. The presence of acetyl group improves filming properties and reduces gelling tendencies of the starch paste (Swinkels 1992). Applications of starch acetate were widely investigated by many researchers. Korhonen et al. (2000 : 1138-1143) reported that starch acetate is potential useful as direct compression excipient. Tuovinen, Peltonen and Jarvinen (2003 : 345-354) used starch acetate to controlled drug release. The results showed that acetylation of potato starch substantially retarded the drug release. The drug release profiles were controlled by the degree of substitution. The drug release from the lower degree of substitution was faster than the corresponding release from the higher degree of substitution.

Carboxymethyl starch (CMS) is an example of etherified starch. The hydroxyl groups of starch molecules were etherified by carboxymethyl groups. In carboxymethylation, starch was reacted with sodium monochloroacetate in the presence of sodium hydroxide. The first step is the formation of starch alkoxide (StO^-Na^+).

$$\text{St-OH} + \text{NaOH} \rightarrow \text{St-O}^-\text{Na}^+ \qquad (1)$$

In the second step, glucose unit is etherified by carboxymethyl groups:

$$\text{St-O}^-\text{Na}^+ + \text{ClCH}_2\text{COO}^-\text{Na}^+ \rightarrow \text{St-O-CH}_2\text{COO}^-\text{Na}^+ + \text{NaCl} \qquad (2)$$

Additionally, an undesired side reaction of SMCA with NaOH can also occur

$$\text{NaOH} + \text{ClCH}_2\text{COO}^-\text{Na}^+ \rightarrow \text{H-O-CH}_2\text{COO}^-\text{Na}^+ + \text{NaCl} \qquad (3)$$

The efficiency of reaction was determined by degree of substitution. The carboxymethylation of starch progressively increases water solubility. As the degree of substitution increase, the modified starch is more soluble in the cold-water yielding a clear solution (Wurzburg 1986). Carboxymethyl starch acts as an anionic polyelectrolyte in an aqueous slurry or paste. The rate of swelling to reach peak viscosity and cooked out viscosity of modified starch is higher than natural starch. CMS paste is more cohesive and tendency to gel. The retrogradation is greatly diminished. Carboxymethyl starch is an official ingredient in pharmacopoeias in the name of sodium starch glycolate (The United States Pharmacopeial Convention 2007 : 1213-1214 ; The British pharmacopeia commission 2007 : 1943-1946). CMS is named to be a supper disintegrant (Bandelin 1989 : 131-190). Te Wierik et al. (1992 : 239-244) found that the dissolution from tablets of poorly soluble and hydrophobic drugs was strongly improved by addition of sodium starch glycolate. Calinescu et al. (2005 : 53–60) proposed that carboxymethyl high amylose starch (CM-HAS) was a novel excipient for oral tablet formulation of bioactive agents ensuring their protection in the stomach and delivery in the intestine. The bacteria in this formulation displayed higher survival rates in acidic gastric conditions than the bacteria formulated with the non-derivertized starch.

3. Genetic modification (Wurzburg 1986)

3.1 High amylose starch High amylose starch is a genetically selected from varieties of corn starch which contain more than 50% apparent amylose. Several varieties have been selected and are found to contain approximately 55 to 80% amylose. The high content of linear amylose gives stronger films based on a comparison with cellophane. In pharmaceutical application, high amylose film is used for delivery drug to the target organs (Nabais et al. 2007 : 371–378).

3.2 High amylopectin starch High amylopectin starch, in the other word, waxy starch is obtained from varieties of certain cereal starch. This starch provides the user with highly branched molecules in with only 0 to 4% of the linear component is present. Waxy starch provides naturally non gelling pastes which are usually stringy and cohesive paste. Waxy starch is used in textile finishing because of its clear film.

Optimization of Modification

Optimization may be interpreted as the way to find those values of controllable independent variable that give the most desired value of the dependent variable. This, however, is a product-or system-centered definition, the system consisting of composition and process variables and the properties of the product.

Before starting with optimization studies, one should have clear picture of the possible approaches. From the non systemic method of "trial and error" to the univariate and multivariate systemic ones, the sequential "hill climbing", and the simultaneous "response surface" methods, and several possible combinations. It must be emphasized that there is no "best" strategy. The strategy to be chosen depends not only on the character of the problem and the required quality of the answer, but importance is also the justification of the experiment effort in view of the gained information.

Under the heading "optimization", it is often suggested that a choice should be made between a sequential method and simultaneous method or eventually a combination of both. The concept “strategy” is however more complex. A strategy consists of a number of successive steps to approach problems in order to get optimization. These steps have been visualized and numbered in the flow diagram (Amores et al. 1995 : 77-159).

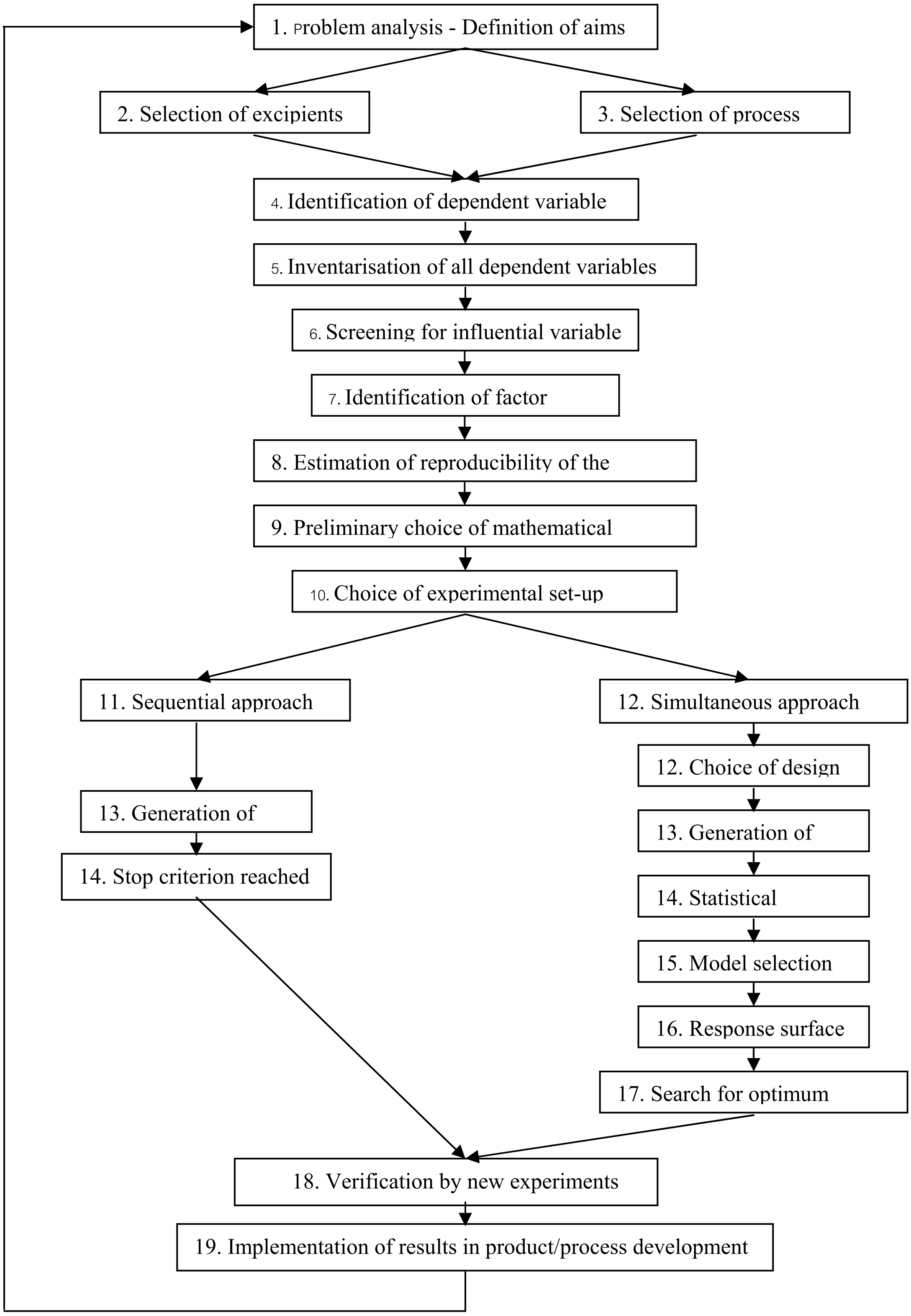


Figure 4 Diagram of an optimization strategy.

Experimental design

1. Sequential Methods It may be advantageous not to plan all the experiments at once but to adopt an interactive strategy. The response surface is a surface that exists, but is unknown to experimenter as long as experiments have not yet been performed. It should be possible to plan a small number of experiments, starting in an arbitrary part of the experimental regions evaluate a gradient on that part of the response surface, climb hill, plan some more experiments, and so on, until the response does not improve anymore. Several such of sequential or interactive methods, called "hill-climbing" methods, have been developed. The methods include of steepest ascent, the simplex method, the modified simplex, and the super modified simplex. They work efficiency, provided there are no multiple optima. However, they climb only one specific response surface and cannot be used on multiple-objective problems.

2. Simultaneous methods The tuning of variables that affects a property of interest in such a way that an optimum value for this property in attained, is an often occurring problem in many branches of technology. Because of the economical importance, a number of experimental optimization techniques have been developed. Response surface methodology, base on statistical experimental design and data modeling, is the most widely used technique. A theoretical model relating to independent variables does not exist or has not yet been found, as is most often the case in formulation research.

Statistical designs prescribe or advise a set of variable combinations. The number and layout of these design points within the experimental region depend on the number of regression coefficients that must be estimated, and thus depend on the postulated model. This, in turn, depends on number of factors, their levels and possible interactions, and the order of model (or models) that the experimenter postulates. The whole set of experiments is thus planned and subsequently performed and evaluated; this is the reason for the disintegration simultaneous. The pertaining response surface spans part of or the entire experimental domain.

Statistical designs require careful planning and adherence to statistical rule, for example, randomizing the experiments and /or blocking. When the design has property of orthogonality, it is possible to evaluate the significance of all model terms independently (main effect of all factors, interaction effects), except when fractional design have been used. (Although these designs are also orthogonal, some effects will be confounded, but still the aliased duplets, triplets, etc. can be estimated independently from the other aliased duplets, etc.)

With sound statistical designs, the design points are distributed within the experimental region in such a way that the regression coefficients can be estimated with equal accuracy. When the model is used for the prediction of response within that experimental region in points where no experiments were laid out, the predictions have also a reasonably homogenous distributed accuracy. (Outside the experimental region, extrapolation gives unreliable results.)

2.1 Factorial designs Each experiment can be represented as a point within the experimental domain, the point being defined by its coordinates, that is, the values given to the variables. A set of such points, the design points, constitutes the experimental design. Its basic problem is how to distribute the design points over the design space. If the surface response would be known, it could be decided which design points would be the most informative, but since the response surface is mostly unknown, there is a problem of circularity, as follows: "The relation related to the paradox that the best time to design an experiment is after it is finished, the converse of which is that the worst time is at the beginning, when least in known," and this "… points to the durability of a sequence of moderately size designs and reassessment of the results as each group of experiments become available."

The simplest factorial design is for two factors, each at two levels; without replication, four (2^2) experiments, situated in 2D factor space at the corners of a rectangle, are performed. If there are three factors, each at two levels, eight (2^3) experiments are necessary, situated at the corner of an orthogonal prism in 3D factor space (Figure 5). For k factors, the notation is a 2^k factorial design; experiment must be performed with all possible combinations of two different levels of the k factors. The number of experiments is simply obtained by evaluating the expression n^k arithmetically, where n = number of levels, and k = number of factors.

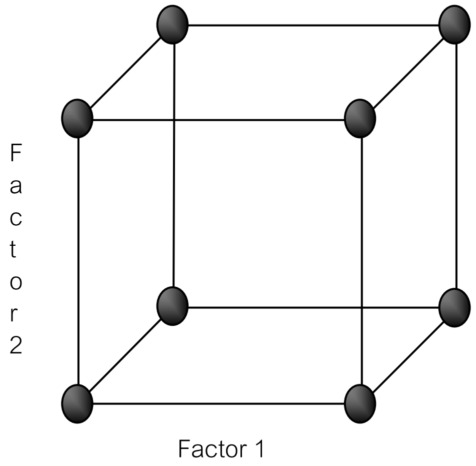


Figure 5 Two-level factorial for process variables.

2.2 Fractional factorial designs The literature of formulation research gives a number of examples of fractional designs. Unfortunately, in most papers experimental details are lacking, and therefore they are not suitable to explain the technique. If in a full factorial design become larger, the number of experiments increases rapidly. However, with a large number of factors it is plausible that the highest-order interactions have no significant effect. In such a case factorial design have a poor experimental efficiency and the number of experiments could be reduced in a systemic way. This has been explored for designs on two levels and resulting designs are called fractional factorial designs (FFD).

A FFD is a fraction (1/2, 1/4, etc., in general $1/(2^p)$) of a complete or “full” FD. The notation for FFDs (all factors at two levels) is $2^{(k-p)}$, where 2 = number of levels, k = number of factors in the FFD, and p = degree of fractionation. An example demonstrates this: A complete 2^5 FD requires 32 experiments; 32 main effects and the interactions of five factors are estimated. A $2^{(5-1)}$ FFD consists of 16 experiments; 16 effect are estimated but they are combined effects of factors and interactions. A $2^{(5-2)}$ FFD has eight experiments; eight (combined) main effects and interactions of five factors are estimated.

2.3 Special design for process variables As described above, by the use of (fractional) fractional designs main effects and interactions can be evaluated, but it is not possible to detect a curvature of the response surface as long as no more than two levels for a factor are chosen. A simple solution seems to be to augment the design with experiments at the center point of the factorial design (Figure 6). Then not only the average, linear and interaction effects, but also a combined quadratic effect can be estimated simply by comparing the prediction at center point (based on contrasts or regression using only the experimental points of 2^n FD) with the mean of the center point measurement(s). If there is any curvature in either one of the independent variables or in both, this effect can be found with the help of this design. The source of the effect in terms of a specific variable, however, can not be detected.

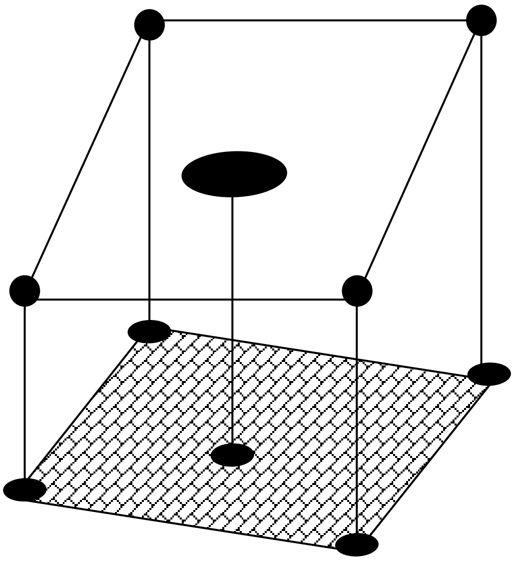


Figure 6 A 2^2 factorial design with replicate center point.

2.4 Star Design For two factors the star design is simply a 2^2 FD, rotated over 45° (Figure 7). A center point is usually added, which may be replicated, to estimated experiment error. Then each factor has three levels, and for each factor a quadratic effect can be estimated, but interaction cannot be measured.

In the star designs, 2^k FDs are rotated 45° in (k-1) directions is k-dimensional space with a replicated center points. They consist of ($2k$+ r_c) experiments, r_c being the number of replicates at the center. The design is rotatable; orthogonality depends on the number of replicates r_c.

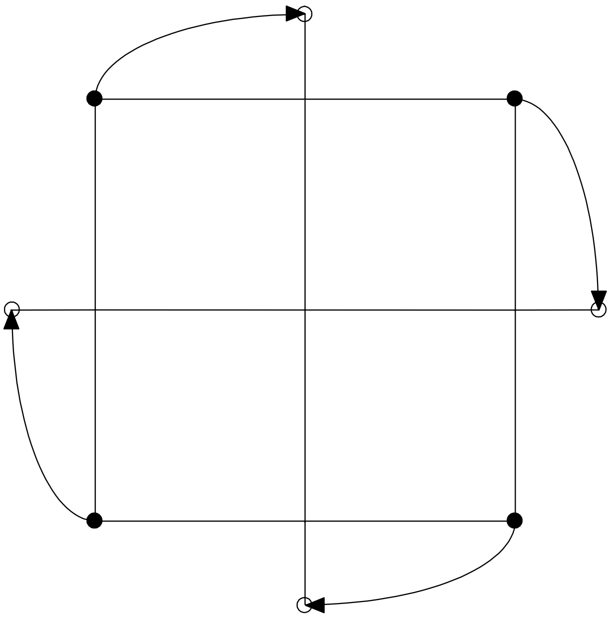


Figure 7 A star design, derived from the factorial design by rotation over 45^o, ● = factorial design, ○ = axial points, star design.

2.5 Central Composite Design A better solution that combines the advantages of the FD (or FFD) and the star design, is the central composite design (CCD), developed by Box and Wilson (Amores et al. 1995 : 77-159). It is composed of

- a 2^k FD ($n_c = 2^k r_c$ experiments or $2^{(k-p)}$) FFD ($n_c = 2^{(k-p)} r_c$ experiments), where r_c is the number of replicates of the FD part of the design,

- a $2*k$ star design ($2k$ axial points, $n_s = 2kr_s$ experiments), where r_s is the number of replicates of the star part of the design, and

- n_o center points.

This design allows the estimation of a full second order model. The case of two factors is giving by

$$E(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta 22 x_2^2 \quad (4)$$

If the coordinates of the FD part of the design are the type (± 1, ± 1, ... ± 1), the axial point of the star design are chosen with coordinates ($\pm\ \alpha$, 0,….,0), (0, $\pm\ \alpha$, 0,…0),…, (0, 0, …$\pm\ \alpha$). To a certain extend, one has the freedom to choose a value for α. For α =1, the result is a standard 3k FD with a replicated center point (Figure 8). There is one value, $\alpha = (n_c / r_c)^{1/4}$ that give the design the highly desirable property of rotatability.

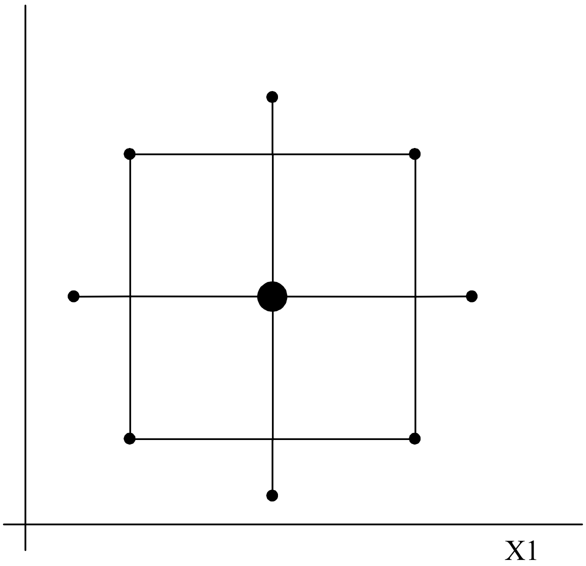


Figure 8 The central composite design, a 2^2 factorial design, augmented with a star design and replicated center point.

2.6 Box-Behnken Design In central composite design each factor has five levels. If the number of factors increases, the number of experiments may become too high. The Box-Behnken design for three or more factors are an economical alternative with each factor is given three levels. The design is called an orthogonal balanced incomplete block design. It can be split into a set of incomplete blocks, which means that every effect is not estimated in every block but every effect is measure an equal number of time with a balanced partition over the different blocks.

The design for three factors case is shown in Figure 9, where it is completed to the face-centered CCD. The design points in BB design are at the midst of the edge of the cube instead of at the corners and the center of the sides. No design points are placed on the extreme points of the (hyper) cube which spans the complete design space. This can be advantageous when physical-chemical problems arise under these extreme conditions.

Optimization techniques have become more widely used in the pharmaceutical study. Experimental design, involving mostly some type or modification of factorial design, has been used to study many different types of formulation and processing problems (Soyeux et al. 1998 : 95–103 ; Tijsen et al. 1999 : 2765-2772 ; Tijsen, Voncken and Beenackers 2001 : 411-418 ; Kooijmana et al. 2003 : 495–503 ; Kuentz, Egloff and Röthlisberger 2006 : 37–43 ; Gutiérrez et al. 2008 : 245-251).

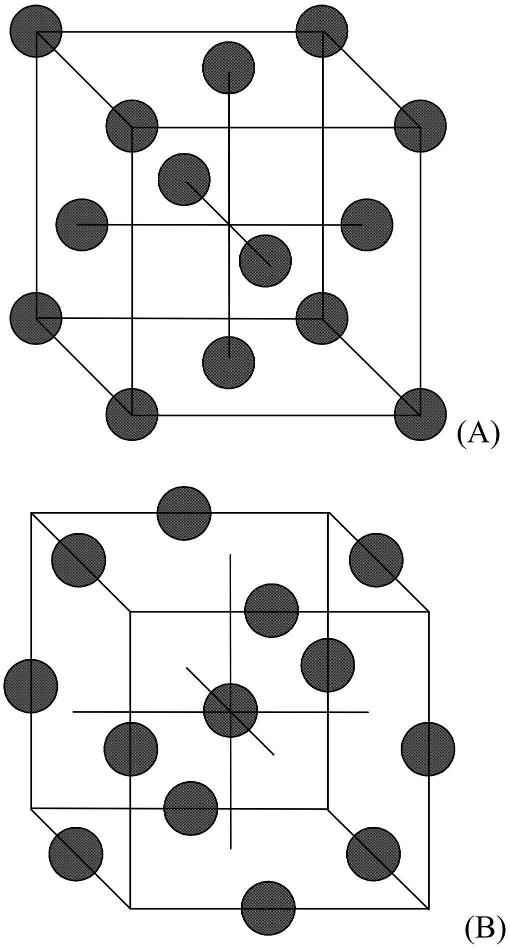


Figure 9 The central composite design (A) Face-centered CCD and (B) a Box-Behnken design; three factors.

Nowadays, starch has been widely used in pharmaceutical industry. Because of its inexpensive and multifunctional properties, starch is an excipient exhibiting important roles in tablet formulation. For example:

Tablet Disintegrant

Disintegration of a compressed tablet is the process by which a whole tablet breaks up into small pieces when it contacts with fluid. The disintegration of compressed tablet into granules or individual particles is a rate limiting step for the dissolution of drug. Disintegration is usually the presupposition for effective absorption and high bioavailability of the drug in a compressed tablet.

Mechanism of action of tablet disintegrants In the present days, it still has no proper theory to explain the mechanism of disintegration action. But it is rather obvious that no single mechanism occurred in disintegration action but must be depend on several factors involved such as wetting ability which depend in contact angle, hydrophillicity and appropriate porosity according to capillary action that rapidly absorb the water and then swell to promote the forces. However the mechanisms were classified into 6 groups as follow:

1. Swelling Swelling is the most accepted mechanism in disintegration action. Because most disintegrant can swell and there are several works demonstrating that an efficiency in swelling promote more rapid water uptake into the tablet (Van Kamp et al. 1986 : 22-29). The conventional disintegrants such as starch granule has small degree in swelling but enough to cause the tablet disintegrate when starch is incorporated enough to form hydrophilic networks (Guyot-Hermann 1992 : 445-462).

Swelling mechanism is more important in most new disintegrants for example modified starches, modified celluloses, both have the swelling efficiency much more than native material up to 200-300 times (Rudnic and Rhodes 1982 : 87-109). Certainly that swelling is not the first or direct mechanism in disintegration action. Swelling occurs following the water penetration into the tablet (Paronen, Juslin and Kasnanen 1986 : 621-630 ; Wan and Prasad 1989 : 115-121). Since starch granules have a high hydrophilic property in nature, do not dissolve and do not increase the viscosity hence they do not form a mucilaginous layer which accordingly blocks water penetration. Swelling ability of some modified starches are depend on various factors for examples: degree of substitution. Sodium starch glycolate can be prepared by both crosslinking and substitution by carboxymethylation of potato starch. The swelling capacity strongly depends on both reactions which the particle is inversely proportional to the degree of crosslinking on the other hand swelling volume increases with degree of carboxymethylation.

Edge et al. (2002 : 67-78) study physicochemical properties of different sources of sodium starch glycolate. They found that even though commercial products meet the requirement of National Formula Specification but the effect of functionality is general different. The workers reasoned that the difference in chemical composition probably reflect the different manufacturing processes used.

2. **Deformation** Deformation is considered to be disintegration mechanism by some authors such as Lowentahl (1972 : 455-459), Kanig and Rudnic (1984 : 50,52,54,56,58,61).

Lowentahl (1972 : 455-459) illustrated maize starch grain deformation using the light microscope, the result obviously show that the particle return to original shape when exposed to moisture to moisture. Paronen et al. (1986 : 621-630) study the deformed agglomerated cellulose powder to their original shape occurred, it come to contact with water, at least may create stress and strain inside the tablet and result some extent of force this action also occur un Ac-Di-Sol$^{®}$ and Avicel$^{®}$.

3. **Particle-particle Repulsion Theory** Another theory of disintegration mechanism proposed by Guyot-Hermann and Ringard (1981 : 155-177) to explain the action of non-swellable material, but can promote the same

performance and sometime superior to highly swell materials (Lowentahl 1972 : 303-304 ; Guyot-Hermann et al. 1981 : 155-177). It is proved that force do not necessarily depend upon the increase of volume or swelling extent. A number of high swelling capacity disintegrant can not explain the whole mechanism of the tablet disintegration. Since the destruction of cohesion forces of the compressed tablet under the action of water may be ascribed to creation of repulsion force when contact with water. This hypothesis first described by Bendin in the observation of the ejection of starch grain out of tablet immersed in water. The observation under microscope by Guyot-Hermann et al. (1981 : 155-177) found that when a drop of starch suspension in nonaqueous medium contacted with a drop of water, the aggregates immediately dispersed into individual grains. This seemed to present a real force when it contacted with water. The same report also showed that the exiting of water or dielectric constant of immersed medium affected the disintegration of DCP tablet containing maize starch or carboxymethyl starch. This hypothesis also described the mechanism of carmellose sodium, microcrystalline cellulose and crospovidone (List and Muazzam 1979 : 161-162,167-170) with such mechanism of action, the porosity of the tablet is important that disintegrant particle should be closer to another to provide the best repulsion energy (Caramella et al. 1984 : 701-705 ; Hill 1976 : 1964).

4. Heat of immersion Heat of immersion sometimes called heat of wetting. Matsumaru and Yakugaku (1959 : 198) was the first who proposed this mechanism. He observed that starch granule exhibit exothermic property when immersed in water and caused the localized stress from the entrapped air in the tablet to expand and break the tablet apart. List et al. (1979 : 161-162,167-170) examined this hypothesis with calorimeter to measure the swelling heat of various disintegrants and found that the disintegrant showed different behavior and they noted that

- Swelling is a part of mixing processes. The changes in enthalpy by mixing two components may show positive, negative or no sign of heat.
- The process is often overlapped by adsorption with strongly positive sigh of heat. So far it has not been possible to separate the adsorption heat from the swelling heat.

In the later, phenomenon study of heat of wetting. They found that the exothermic reaction was not always corresponding to the disintegration time (Kanig et al. 1984 : 50,52,54,56,58,61).

5. **Capillary Action** Capillary action or wicking likely depends upon porosity and also on hydrophilic pore wall, contact angle between pore wall and liquid, liquid viscosity and liquid surface tension. Capillary action mechanism is considered to be the mechanism of action of starch, since starch is incorporate to from hydrophilic chains. Starch which very hydrophilic has contact angle of 0°. However an optimum porosity of the tablet is a prerequisite for the entry of water in to the tablet and consequently for implementing the swelling (List et al. 1979 : 161-162,167-170). Lowentahl (1972 : 303-304) reported the correlation of tablet mean pore diameter and porosity if the tablets obtained from four types of drug with and without corn starch. He found that corn starch had an effect on the relationship of mean pore diameter and porosity. Several experiments proved that capillary action alone is not enough to break tablet apart. List et al. (1979 : 161-162,167-170) proved that DCP tablet with crosslinked polyvinylpyrolidone (PVP XL) disintegrated only in water, or alcohol were PVP XL can swell but did not disintegrate in acetone or glycerol. This

mean swelling mechanism must have actually involved. Capillary action is obviously important since hydrophobic acetylsalicylic acid tablets without any disintegrant show neither disintegration nor water penetration even at high porosity of the tablets (Caramella et al. 1986 : 1749-1766). It is because acetylsalicylic acid has contact angle of about 59° which is poorly wettable. Such case can be easily improved by adding starch to form hydrophilic pore wall.

6. Water uptake Water uptake mechanism become important since non has succeeded in explanation about disintegration. This mechanism seem to be more applicable to most modern disintegration. It is no doubt that water uptake must be the first step in any process of disintegration and force must develop inside the tablet before disintegration (Paronen, et al. 1986 : 621-630 ; Van Kamp et al. 1986 : 22-29 ; Pasonen, Paronen and Ketotainen 1989 : 139-147). There are series of the outcomes described by Caramella et al. (1987 : 2111-2145):

a. The hydrodynamic process from the pressure exerted by the air entrapped in pore structure when tablet was immersed into water.

b. The particles swell and setup localized stress that breakup the tablet.

c. The repulsion among particles when solid contact liquid.

Colombo et al. (1981 : 135-153) evaluated the force development in relation to the characteristic of the tablet disintegration. Since the disintegration process depend on a properly wetting of the tablet, a force developed inside according to a saturated kinetics can be expressed by a hyperbolic equation as follows:

$$\frac{x}{y} = \frac{x}{y_0} + \frac{b}{y_0} \tag{5}$$

When X is the time, y is the force, y_0 and b are constants, y is the maximum force from the curve and b is the half maximum force from calculation. The workers found that y_0 relate to the amount of water absorbed by the tablet, which depend on the quality of the disintegrant, and b is relate to water penetration rate which depend on porosity (or compression force). Thus disintegration time seem to be dependent on b more than y_0. It can be seen that for certain formulations of tablet containing starch, the reduction of porosity induce greater capillary pressure, bur for non swellable disintegrant such as Avicel® the b value increase as porosity is reduced. The authors suggested that the measurement of y_0 and b parameters could be very useful to understand the disintegration mechanism.

Van Kamp et al. (1986 : 22-29) emphasized the role of water uptake, he found that disintegration time depend upon the rate and extent of liquid absorption. The authors expressed the equation derived from Washburn's relationship as follows:

$$V2 = \frac{2m\,\gamma\,\cos\theta\ t}{K_0\eta} \qquad (6)$$

When m is the hydraulic pore radius, γ is the surface tension of liquid, θ is the contact angle between liquid and solid in the pores, η is the liquid viscosity and K_0 is a constant depend on pore shape. This equation indicates the water penetration (v) relate to time (t). The water uptake into the tablet depend upon the controlling factor like the following: only some material fit with this equation. The equation is not appropriate the tablet structure that change during the penetration process or if the excipient can dissolved in liquid causing the high viscosity and surface tension of the liquid change by the time. That is the reason why Washburn's equation does not appropriately to apply to most tablets. Increase the water uptake can be discussed regarding the rules as follows:

1. Pore diameter directly depends on compression force and particle sizes. The influence of porosity factor is more pronounced in the hydrophilic materials than 8 in hydrophobic material. Guyot-Hermann et al., found that pure aspirin tablets did not disintegrate when compressed at low compression force. But for the tablet containing starch, if continuous chains of starch are established in the whole tablet, the water can penetrate even at high compression force (Caramella et al. 1987 : 2111-2145 , 1988 : 2167-2177). The reduced porosity, unless less than critical pore diameter, promote greater capillary pressure. But in case of cellulose the observation is altered.

2. Contact angle (θ) of drug or excipient plays the important role in wetting. Most insoluble drugs have high contact angle with poor wettability in water. To promote the fast uptake of water, the whole tablet must possesses continuous hydrophilic network with low viscosity inside, and other hydrophobic substance such as lubricant should be added as low as possible (Van Kamp et al. 1986 : 22-29 ; Guyot-Hermann 1992 : 445-462).

3. Continuous hydrophilic network must be created, which the reason why the term "critical concentration" of disintegrant become considerable. Critical concentration is a least amount of disintegrant that promotes best disintegration time. Since much more disintegrant in excess inserted always caused the tablet weaken or gain high friability.

Ringard and Guyot-Hermann (1988 : 2321-2339 ; 1992 : 445-462) expressed a method in calculation the critical concentration of a binary-mixture of two sizes spheres by term “contact coordination” that is the number of small spherical particles which close to a large one. By this way the weight of disintegrant is referred to number of particle. The equation is:

$$\text{Gm disintegrant needed} \quad = \quad 0.32\frac{d_1}{d_2}[(\frac{D_1}{D_2}+1)^3-1]\frac{D_1}{D_{1s}} \qquad (7)$$

By 1 gm of drug/diluent

Where d1 and d2 are the real density of disintegrant and the drug diluent respectively, determined by air comparison pycnometer. D1 and D2 are the average diameters determined by microscopy, D1s is the disintegrant diameter in the disintegration medium.

This calculated concentration is occasionally unsuitable for the mechanical properties of tablets. It may not be the best concentration according to the limitation in application. The limitation such as particle shape must not differ from spherical too much, and the authors give the ratio of width/length limit equal to 0.3. The diameter ratio of two particles must be at most 0.3 for a correct coating of big particle by smaller ones, when drug or diluent particle and the concentration may not suitable in practically.

4. Increase hydrophillicity and decrease hydrophobicity of the tablet system to promote the pore wall wettability. It is worth to say that more hydrophilic the water can penetrate better. Several authors study hydrophillicity of the disintegrants in attention to understanding the disintegration mechanism. They found that water affinity of disintegrant provide different efficiency. The term “super disintegrant” is applied to mostly use disintegrant which are sodium starch glycolate, croscarmellose sodium and cross povidone. These are the ideal materials that have

been modified from plain material of native starch or cellulose to improve the hydrophillicity and swelling properties without increasing their solubility. The hydrophillicity of disintegrant may be investigated directly from contact angle value (Stamm, Gissinger and Boymond 1984 : 381-408 ; Guyot-Hermann 1992 : 445-462), quantity of water uptake (Guyot-Hermann 1992 : 445-462) and vapor adsorption (Khan and Rhodes 1975 : 451-477 ; Faroongsang and Peck 1994 : 779-798). These always relate to the disintegration efficiency. Where hydrophilicity concomitantly relate to swelling force produced in the tablet when contact angle with water (List et al. 1979 : 161-162,167-170). However it is very often evidence that very high water absorption disintegrant eliminate the disintegration efficiency, such disintegrant as sodium carboxymethyl cellulose high substitution, carboxymethyl starch, hydroxyl propylcellulose which from a viscous colloidal barrier that block the water penetration (List et al. 1979 : 161-162,167-170 ; Guyot-Hermann, Guyot and Ringard 1983 : 159-177 ; Kanig et al. 1984 : 50,52,54,56,58,61 ; Wan et al. 1989 : 115-121 ; Acquier et al. 1992 : 469-474). To overcome this problem all the modified substances should be optimized in term of cross-linked degree and substitution degree since the crosslinking reaction will decrease swelling ability. Sodium starch glycolate (Explotab®), croscarmellose sodium (Ac-Di-Sol®), crospovidone (Kollidon XL®) are example of excellent products from this aspects. Kanig et al. (1984 : 50,52,54,56,58,61) demonstrated that high level of cross-linking and carboxymethylation of sodium starch glycolate are detrimental to the function of disintegrant.

Wan et al. (1989 : 115-121), determined the various degree substitution of carboxymethyl cellulose and found that the disintegration time of tablets containing Nymcel® ZSD 16 was much longer than that of tablet containing Nymcel® ZSB 10 it could be due to higher content that of water soluble substances of the former. However it can be seen that hydrophilic substances offer most advantages as tablet disintegrant if they possess optimum degree of cross-linking and substitution. Hydrophobicity of tablet component has been found to affect disintegration of the tablet. Bolhuis, Smallenbroek and Lerk (1981 : 1328-1330), explained the effect of lubricant on the prolongation of the tablet disintegration time by formation of lubricant film on substrate particles during mixing thus affecting wettability of tablet ingredient and retarding water penetration. This effect also depends on mixing time and mixing intensity. However different disintegrants have different ability to overcome this lubricant film for e.g. sodium starch glycolate is less affected than potato starch. Thus suitable compromise between the right technological properties and biopharmaceutical properties must be found by the choice of the best lubricant concentration to be used (Bolhuis et al. 1981 : 1328-1330 ; Guyot-Hermann 1992 : 445-462). The effect of lubricant also have been widely studied by a number of authors (Bossert and Stamm 1980 : 573-589 ; Kikuta and Kitamori 1994 : 343-355) Van Kamp et al. (1986 : 22-29) expressed the obviously different results of lubricated and unlubricated tablet system of the same disintegrant system. They found that magnesium stearate strongly reduced the efficiency of disintegrant both extent and rate of water uptake in low swelling substance such as potato starch, but only rate of water uptake is reduce in high swelling such as sodium starch glycolate.

Direct compressible fillers

Direct compression excipients, particularly filler-binders, are desired excipients. In most case they are common materials that have been modified in the chemical manufacturing process to impart to them greater fluidity and compressibility. The physical and chemical properties of these desired products are extremely important if they are to perform optimally. It is more important for the direct compression than is in the wet granulation process.

Many factors influence the choice of the optimum direct compression filler to be use in a tablet formulation. These factors vary from primary properties of powder (particle size, shape, bulk density, solubility) to characteristics needed for making compact (flowability and compressibility) to factor affecting stability (moisture), to cost, availability, and governmental acceptability. It is extremely important that raw material specifications be set up the reflect many of these properties if batch to batch manufacturing uniformity is to be assured. This is particularly true in the case of filler-binder because they often make up the majority of the tablet weight and volume. However, this fact is still not fully appreciated by pharmaceutical formulators and production personnel.

Ideal requirements of directly compressible filler (Gohel and Jogani 2005 : 76-93). The directly compressible filler should be free flowing. Flowability is required in the case of high speed rotary tablet machine in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (millisecond), the required amount of powder blend should be transferred into the die cavities with reproducibility of ± 5%. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and in accurate filling.

Compressibility is required for satisfactory tableting, i.e., the mass must remain in the compact from once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible diluents should have good compressibility, i.e. relation between compaction pressure and volume.

Dilution potential can be defined as amount of an active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipient. The compressible excipient should have high dilution potential so that the final dosage form has a minimum possible weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient. A directly compressible excipient should be capable of being reworked without loss of flow or compressibility. On recompression, the adjuvant should exhibit satisfactory tableting characteristics. The adjuvant should remain unchanged chemically and physically. The directly compressible adjuvant should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat.

Habib et al. (1996 : 205-212) developed a method to assess the dilution capacity of direct compression excipients based on a technique previously proposed by Minchom and Amstrong (1987 : 69). The technique involved the addition of increasing quantities of a poorly compactible material to the excipient and measuring the resultant decrease in the area under the curve (AUC) if the tensile strength versus compaction force profiles. It reflected only the ability of the excipient to handle internal stress induced by the drug which did not take into account the intrinsic of the drug free excipient to form strong compacts. A new index was thus proposed, called the Dilution Capacity Index (DCI). The dilution capacity value obtained by linear regression and back extrapolation to zero area ratio (MA index) by natural tendency of the virgin excipient to form strong compacts.

A directly compressible adjuvant should have a particle size equivalent to the active ingredient present in the formulation. The particle size distribution should be consistent from batch to batch. Reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient in order avoid segregation.

Most drugs can not be compressed directly into tablets because they lack the bonding properties necessary to form tablet. The powder drugs, therefore, require additives and treatment to confer bonding and free flowing properties on them to facilitate compression by a tablet press. Starches from various natural origins and their common derivative are well-known, safe, and have been extensively investigated in tablet formulations. However, their poor flow and high lubricant sensitivity make them less flavored in direct compression. Spray dried rice starches (Era-Tab®, Primotab®) were introduced as direct compression filler. It has excellent flow and binding properties (Bos et al. 1992 : 93-106). Limwong et al. (2004 : 1-10) introduced spherical composite particles of rice starch and microcrystalline cellulose (RS-MCJ-73) as new co-process excipients for direct compression. The tablet made from RS-MCJ-73 exhibited low friability and good self-disintegrating property. Puchongkavarin et al. (2003 : 464-475) studied acid modified, agglomerated rice starch for use as a filler for tablet preparation. Korhonen et al. (2000 : 1138-1143) evaluated starch acetate as a novel direct compression excipient. Starch acetate was a potentially useful as direct compression excipient. The powder properties depended on degree of substitution.

Starch in pharmaceutical pharmacopoeia

1. Official Native Starches

USP30/NF 25 described starch in individual monograph; corn starch consists of the granules separated from the mature grain of corn, *Zea mays* Linne (Fam. Gramoneae), potato starch is obtained from the tuber of *Solanum tuberosum* L., Tapioca starch consists of the granules separated from the tubers of tapioca (cassava) *Manihot utilissima* Pohl (Fam. Euphobiaceae), Wheat starch is obtained from the caryopsis of *Triticum aestivum* L., (*T. vulgare* Vill.).

The BP 2007 described starch in individual monograph; potato starch is obtained from the tuber of *Solanum tuberosum* L. Maize starch is obtained from the caryopsis of *Zea mays* L. Rice starch is obtained from the caryopsis of *Oryza sativa* L. Tapioca Starch is obtained from the rhizomes of *Manihot utilissima* Pohl. Wheat starch is obtained from the caryopsis of *Triticum aestivum* L. (*T. vulgare* Vill.). BP 2007 also mention about tapioca starch in all individual monograph that “When starch is specified and the type is not indicated, maize starch, potato starch, rice starch, wheat starch or, in tropical countries where these are not available, tapioca starch may be supplied or used”.

2. Official Modified Starches

USP30/NF 25 described modified starch in individual monograph;

Modified starch is starch (corn, tapioca, potato, wheat) modified by chemical means. Food starch may be acid- modified, bleached, oxidized, or treated enzymatically to change its functional properties.

Pregelatinized Starch is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Some type of pregelatinized starch may be modified to render them compressible and flowable in character.

Pregelatinized Modified Starch is modified starch that has been chemically or mechanically processed, or both, to rupture all or part of the granules to produce a product that swells in cold water.

Sodium starch glycolate is the sodium salt of a carboxymethyl starch and of a cross-linked carboxymethyl starch. It may contain not more than 7.0 percent of sodium chloride.

The BP 2007 described modified starch in individual monograph;

Pregelatinised starch is prepared from maize starch, potato starch or rice starch by mechanical processing in the presence of water, with or without heat, to rupture all or part of the starch granules and subsequent drying. It contains no added substances but it may be modified to render it compressible and to improve its flow characteristics.

Sodium starch glycolate Type A is the starch which composed of 2.8-4.2% of sodium salt of a cross-linked partly *O*-carboxymethylated potato starch.

Sodium starch glycolate Type B is the sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains 2.0 - 3.4% of sodium.

Sodium starch glycolate Type C is the sodium salt of a cross-linked partly *O*-carboxymethylated potato starch. It contains not less than 2.8 - 5.0% of sodium.

Yam Starch (Dioscorea sp.)

Yams (Dioscorea species) are annual or perennial tuber-bearing and climbing plants. The genus Dioscorea has over 600 species but only a few are cultivated for food or medicine. The major edible species of African origin are white Guinea yam (*D. rotundata* Poir.), yellow Guinea yam (*D. cayenensis* Lam.), and trifoliate or bitter yam (*D. dumetorum* Kunth). Edible species from Asia include water or greater yam (*D. alata* L.), and lesser yam (*D. esculenta* [Lour.] Burkill), Cush-cush yam (*D. trifida* L.) originated from the Americas. White Guinea yam and water yam are the most important food yams in terms of cultivation and utilization. Yam tubers may be eaten with sauce direct after boiling, roasting, or frying in oil. The tubers may also be mashed or pounded into dough after boiling, processed into flour, or cooked into pottage with added protein sauce and oils. In addition to their food and market values, yams play a major role in social cultural life for a wide range of smallholder households especially in the dominant production zone of West Africa (IITA 2006). Yam *(D. alata*) is a food crop of economic value in southern Brazil. The yam flour has been used in bread products and snacks (Alves et al. 2002 : 476-481). Additional to use as food, it is believed that the mixture of yam flour, rice flour and some nutrients is beneficial to infant health (Yu et al. 1999 : 5-10). In traditional Chinese medicine, yam (*D. opposita*) tuber has been used as an important invigorant. It can invigorate the spleen, stomach, and kidney. Promotion of the body fluids has also been reported (Shujun et al. 2006 : 30-37). Yam starch is being studied as an alternative source for the food industry. Freitas et al. (2004 : 3-8) investigated the composition, rheological properties, and kinetic analysis of gelatization of yam (*D. alata*) in compared with cassava (*Manihot utilissima*) starches. The results showed that yam starch had more energetic gelatinization process than the cassava starch. Yam gel was a more stable than a cassava gel after storage in refrigeration for 24 hours. Alves et al. (2002 : 476-481) reported the chemical, structural, morphological, rheological and thermal properties of yam (*D. alata*) starch. The onset of gelatinization temperature was 74.4°C. When submitted to heat and shear, the absence of break down in the amylograph indicated the stable structure of starch gel. The results demonstrated that yam starch have promising application in the food industry. Brunnschweiler et al. (2005 : 107-117) studied the application of yam (*D. alata* and *D. cayenensis-rotundata*) starch as thickening agent and gelling agent. Mali (Mali et al. 2002 : 379–386) prepared and characterized the microstructure of yam (*D. alata*) starch films. Yam starch films can be described as biofilms with a homogenous matrix. Apart from the biodegrability, this starch film shows interesting water barrier properties which increase the possibilities of its application.

Dioscorea esculenta

English name: Lesser yam, Lesser Asiatic yam, Chinese yam, Potato yam

Thai name: Mun mue sua, Mun aun, Mun mung, Mun juag

Classification (United States Department of Agriculture and Natural Resources Conservation Service 2006)

Kingdom:	*Plantae* – Plants

Subkingdom: *Tracheobionta* – Vascular plants
Superdivision: *Spermatophyta* – Seed plants
Division: *Magnoliophyta* – Flowering plants
Class: *Liliopsida* – Monocotyledons
Subclass: *Liliidae*
Order: *Liliales*
Family: *Dioscoreaceae* – Yam family
Genus: *Dioscorea* L. – yam
Species: *Dioscorea esculenta* (Lour.) Burkill – lesser yam

Dioscorea esculenta, the “lesser yam”, was one of the first yam species cultivated since about 300 CE. It is native to Southeast Asia and is the third most commonly cultivated species there, although it is cultivated very little in other parts of the world. It is called “lesser” because it does not keep well and generally eaten as a cooked vegetable. The tubers are eaten baked, boiled, or fried much like potatoes. Because of the small size of the tubers, mechanical cultivation is possible; which, along with its easy preparation and good flavor, could help the lesser yam to become more popular in the future (Wikipedia 2008 ; International Starch Institute 2006). Its vines exhibit left twining, sparingly spiny. Leaves alternate, yellowish green, blades round or broadly ovate, base cordate or auriculate, apex acute (Herbarium National Taiwan University 2006).

The proximate composition of the starch on dry weight basis was found to be 23.9% carbohydrate, 0.5%protein, 1.0% fat, 0.6% fiber, 0.1% ash, 0.012% calcium, 0.035% phosphorus, 0.0008% ferrous, 0.0008% niacin, 0.0001% vitamin B1, 0.00001% vitamin B2, 0.015% vitamin C. (Vorasuntharosoj 2001 : 124-127 ;

Vegetable in Thailand 2006). Yams are high in vitamin C, dietary fiber, vitamin B6, potassium, and manganese; while being low in saturated fat and sodium. Vitamin C, dietary fiber and vitamin B6 may all promote good health. Furthermore, a product that is high in potassium and low in sodium is likely to produce a good potassium-sodium balance in the human body, and so protect against osteoporosis and heart disease. Having a low level of saturated fat is also helpful for protection against heart disease (Wikipedia 2008). Olayemi and. Ajaiyeob (2007 : 1913-1915) studied anti-inflammatory activity of the extract of the tuber of *D. esculenta* on wistar rats. The result indicated that the yam has anti-inflammatory activity. In Thailand, there is no yam processing and yam flour application in the food industry or a pharmaceutical industry was observed.

Figure 10 Leaves and tubers of *Dioscorea esculenta*.

CHAPTER III

MATERIALS AND METHODS

Materials

1. Yam (*Dioscorea esculenta*) tuber
2. Chloroacetic acid (Lot No. 1056856, Fluka, Germany)
3. Ethyl alcohol (Lot No. 08 06 0377, Lab-Scan, Thailand)
4. Methyl alcohol (Lot No. 08 07 1023, Lab-Scan, Thailand)
5. Isopropyl alcohol (Lot No. 94708, Shell Chemical, Thailand)
6. Soduim hydroxide (Lot No. B0183198749, Merck, Germany)
7. Glacial acetic acid (Lot No. 0603278, Lab-Scan, Thailand)
8. Hydrochloric acid (Lot No. 08 03 0362, Lab-Scan, Thailand)
9. Hydrochlorothiazide (Lot No. 060412, Huzhou Koreh Pharmaceutical Co., Ltd., China)
10. Dimenhydrinate (Lot No. 0607005, Shanghai Pharmaceutical Co.,Ltd., China)
11. Ascorbic acid (Lot No. DY205005, Northeast General Pharmaceutical Factory, China)
12. Dicalcium phosphate dihydrate granular (Lot No. 071113, SD BNI, China)
13. Sodium starch glycolate (Exposol®) (Lot No. 19404/07, Blanver, Brazil)

14. Spray dried rice starch (Era-Tab®) (Lot No. T501103 Erawan Pharmaceutical Research and Laboratory, Thailand)
15. Magnesium stearate (Lot No. MGSF0215, Faci Asia Pacific Pte Ltd, China)
16. Monobasic sodium phosphate (Lot No. 6H024086I, Carlo Erba, Italy) Acetonitrile (Lot No. 08 02 0176, Lab-Scan, Thailand)
17. Phosphoric acid (Lot No. 5B022015D, Carlo Erba, Italy)
18. Ammonium bicarbonate (Lot No. 6D088286F, Carlo Erba, Italy)

Equipments

1. Analytical balance
    1.1 AR3130, S/N 1203360337, Ohaus, USA
    1.2 BP110S, S/N 029438, Sartorius, Germany
    1.3 CP225D, S/N SWB: 18907594, Sartorius, Germany
2. Hydraulic Press (P-16B-027, S/N 37876, Riken power, China)
3. Diameteral Crushing Strength, Diameter and Thickness Tester (TBH 210TD, S/N 112367.0f3f, Erweka, Germany)
4. Friability Apparatus (TA 200, S/N 112127.0c1f, Erweka, Germany)
5. Disintegration Apparatus (VK100, S/N 36-431-0403, Vankel, USA)
6. Dissolution Apparatus(VK7000, S/N 1-6633-0403, Vankel, USA)
7. UV/Visible Spectrophotometer(U-2000, S/N 0512-018, Hitachi, Japan)
8. High Performance Liquid Chromatography (HPLC) instrument consisted with the following
    8.1 HPLC pumps (P680, Dionex, Germany)
    8.2 Quaternary pump degas (Dionex, Germany)

8.3 UV-VIS detector (UVD340U, PDA type, Dionex, Germany)

8.4 Autosampler (ASI-100, , Dionex, Germany)

8.5 Thermostatted column (TCC-100, Dionex, Germany)

8.6 Software Chromeleon (Version 6.8, Dionex, Germany)

9. Column HPLC (Apollo C8 5 μm, 4.6x250 mm, S/N 606020382.1, Alltech, USA)

10. Column HPLC (Apollo C18 5 μm, 4.6x250 mm, S/N 04111840.1, Alltech, USA)

11. pH meter (pH900, S/N L04245, Precisa, Switzerland)

12. Scanning Electron Microscope (Maxim 2000s, Camscan, England).

13. Differential Scanning Calorimeter (Pyris Sapphire DSC, Perkin Elmer, JAPAN)

14. FT-IR Spectrometer (Spectrum one, S/N 74150, Perkin Elmer, England)

15. Viscometer (RVDV-II+PRO, S/N RTP81370, Brookfield, USA)

16. Spray dryer (Mobile minor, S/N 2697, Niro, Denmark)

17. Laser scattering particle size distribution analyzer (Partica LA-950 (organic type), S/N EYHC00000, Horiba, Japan)

18. Magnetic stirrer (CB162, S/N R000113882, Stuart, UK)

19. Centrifuge (Digicen 20, S/N 070084/4, Ortoalresa, Spain)

Methods

1. Preparation of yam starch Yam tubers were washed, peeled, trimmed to remove defective parts. The tubers were then sliced, diced and blended with distilled water in a food blender. The mixture was sieved through a 80-mesh sieve and the retained solids were exhaustively rinsed on the sieve with distilled water. The filtrate was allowed to stand overnight at 15°C, the precipitate was collected and the supernatant was discarded. The re-suspension and sedimentation operations were repeated until white starch was obtained. The starch was dried at 50°C for 6 hours. Finally, the dried yam flour was ground and sieved through a 100-mesh sieve. Yam starch was kept in a tight-light resistance container.

2. Physico-chemical characterization of yam starch Native yam starch was characterized according to the starch monograph in The United State Pharmacopoeia (2004 : 2939).

2.1 Identification

2.1.1 Identification A. Yam starch was prepared at 50% w/v in cold water. The slurry was stirred into 15 mL of boiling water and gently boiled for 2 minutes and cooled.

2.1.2 Identification B. Starch suspension was prepared in concentration of 0.2% w/v. Iodine test solution was dropped to the starch suspension and the suspension change color from white to deep blue was observed.

2.2 pH determination Yam starch was prepared at 20% w/v in purified water at room temperature. The suspension was agitated continuously at a moderate rate for 5 minutes, and then pH of the dispersion was immediately measured with pH-meter.

2.3 Microbial limits Starch was cultured in medium agar and incubated at room temperature for 3 days.

2.4 Loss on drying The starch powder (2.000 g) was dried at 120°C for 4 hours.

2.5 Residue on ignition Two grams of starch were ignited at 600°C for 4 hours. The weight of residue was calculated to the percentage of residue.

2.6 Iron The residue on ignition (0.005 g) was dissolved in 8 mL of hydrochloric acid with warming. The volume was adjusted to 100.00 mL with water. After that 25.00 mL of the mixture was added water 22.00 mL. Ammonium peroxydisulfate crystals (50 mg) and 30% w/v ammonium thiocyanate solution (3 mL) were added. The color of the solution is not darker than that of standard solution.

2.7 Oxidizing substances Four grams of starch were suspended in 50 mL water, and then swirled for 5 minutes. The mixture was centrifuged at 3000 rpm for 10 minutes. The clear supernatant 30 mL was transferred to a glass-stoppered, 125-mL erlenmeyer flask. Glacial acetic acid 1 mL and potassium iodide (0.500 g) were added. The mixture was swirled and allowed to stand in the dark for 30 minutes in the dark. After that starch solution (1 mL) was added. The mixture was titrated with 0.002 N sodium thiosulfate to the disappearance of the starch-iodine color. Blank sample was performed for determination, and made any necessary correction. Each mL of 0.002 N sodium thiosulfate was equivalent to 34 µg of oxidant.

2.8 Sulfur dioxide Starch (2.0 grams) was dispersed in 20 mL of water. And then centrifuged at 3000 rpm for 10 minutes. The filtrate (10 mL) were added 0.3 mL of starch TS. The mixture was titrated with 0.01 N iodine. The end point was the color of the mixture change to permanent blue solution.

Moreover, the amount of fat, protein, and amylose were determined according to the Association of Official Analytical Chemistry (AOAC) procedures (AOAC. : 1990).

2.9 Protein Protein content was determined using Kjeldahl method. Percentage of nitrogen in the sample was obtained which was then converted to protein content.

2.10 Fat The dried sample was exhaustively extracted with petroleum ether using soxhlet apparatus for 2 hours. The solvent was evaporated. The percentage of fat content was calculated.

2.11 Amylose Amylose content of the sample was determined using UV/Visible spectrophotometric method. The analysis was based on quantitative determination of the complex from reaction between amylose and iodine. Potato amylose was employed as the standard.

Physicochemical properties were also analyzed.

2.12 Morphology Surface structure of starch granules was examined with a scanning electron microscope. Sample powders were sprinkle on stub which double adhesive tape and had been attached. Excess samples were removed by gently tapping the holder. The samples were sputter coated with gold to increase their conductance. The samples were then viewed and photographed.

2.13 Particle size distribution The particle size distribution was studied using 10% w/v starch absolute ethanol suspension. Particle size and size distribution of starch were measured by using a particle size analyzer (Horiba, Japan).

2.14 Swelling power Swelling powers of yam starch, in terms of weight and volume, were determined.

2.14.1 The swelling power by weight Half a gram of starch was dispersed in 10 mL water. The suspension was heated at 85°C in a water bath for 30 minutes with vigorous shaking (vortex mixer) every 5 minutes. The starch gel was then centrifuged at 2,200 rpm for 15 minutes. The weight of sediment was used for calculation of the swelling power. The determination was run in triplicate.

2.14.2 The swelling power by volume Two grams of yam starch were transferred into a 100 mL measuring cylinder. The initial volume was determined and 90 mL of distilled water was then added and shaken for 2 minutes or until all particles were well dispersed. The dispersion was adjusted to the volume and shaken for 1 minute. The cylinder was let stand for 24 hours and the swollen volume was determined. The swelling volume was the ratio of swollen volume to the initial volume.

2.15 Gelatinization temperature Thermograms of starch were measured using a differential scanning calorimetry (Perkin Elmer, JAPAN). A 10% w/w aqueous suspension of starch was prepared and filled in aluminum pans with hermetical sealing. Scans were performed from 10 to 100°C at a controlled constant increasing rate of 10°C per minute.

3. Preparation of carboxymethyl yam starch (CMS) The effect of sodium hydroxide concentration, ratio between content of starch and sodium monochloroacetate and carboxymethylation time on the properties of CMS were studied**.** The experimental design using Box-Behnken design was shown in Table 1, and the standard preparation was prepared by mixing ten grams of starch with 200 mL of isoproprуl alcohol, a reaction medium. Twenty milliliters of aqueous sodium hydroxide solution were added. The mixture was stirred for 10 minutes. Eighty milliliters of aqueous sodium monochloroacetate solution were added and the mixture was stirred at 30°C for the predetermined reaction time. The reaction mixture was then added 50% v/v glacial acetic acid until the pH of about 5.0 was obtained. The product was filtered and washed with 80% aqueous ethanol until the pH of the washed liquid was neutral (7.0). The product was finally washed with absolute ethanol. The CMS was dried at 50°C for 6 hours. The dried CMS was powdered and sieved through a 100 mesh sieve and kept in a tight-light resistance container.

Table 1 Levels for the main factors in the Box-Behnken design.

Run no.	Coded values			Real values		
	A	B	C	nNaOH:nAGU (mol/mol)	nSMCA:nAGU (mol/mol)	Time (hrs)
1	0	0	0	1.5	2.150	4
2	0	-1	1	1.5	1.433	6
3	1	1	0	2.0	2.867	4
4	-1	1	0	1.0	2.867	4
5	1	0	1	2.0	2.150	6
6	1	0	-1	2.0	2.150	2
7	1	-1	0	2.0	1.433	4
8	0	0	0	1.5	2.150	4
9	0	1	1	1.5	2.867	6
10	-1	0	1	1.0	2.150	6
11	0	1	-1	1.5	2.867	2
12	0	-1	-1	1.5	1.433	2
13	-1	-1	0	1.0	1.433	4
14	-1	0	-1	1.0	2.150	2
15	0	0	0	1.5	2.150	4

4. Physico-chemical characterization of CMS

4.1 Physico-chemical characterizations of CMS The procedures were carried out in the same manner with that of 2.12 to 2.15.

4.2 Degree of substitution (DS) The degree of carboxymethyl group substituted in starch was determined by using back titration method (Stojanovic et al., 2005 : 79-83). About 0.500 g of CMS was dissolved in 20 mL of 0.2 M NaOH and 50 mL of purified water was added. The solution was transferred to a 100 mL volumetric flask, which was then filled up to the volume with purified water. A 25.00 mL of the solution was transferred to an erlenmeyer flask and diluted by addition of 50-100 mL of purified water. The excess of NaOH was back-titrate with standard 0.05 M HCl using phenolphthalene as an indicator. The titration was repeated in triplicate and the average value of HCl volume was used for the calculations. A blank was also titrated. The amount of COOH being equal to

$$n_{COOH} = (V_b - V).C_{HCl}.4 \tag{8}$$

where V_b was the volume of HCl used for the titration of the blank; V was volume of HCl used for titration of the sample; C_{HCl} was the HCl concentration and 4 was the ratio of the total solution volume (100 mL) and the volume taken for titration (25 mL).

The D.S. was calculated using the following equation

$$\text{D.S.} = \frac{162 \times \text{nCOOH}}{\text{mds} - 58 \times \text{nCOOH}} \tag{9}$$

where mds was the mass of the dried sample, 162 was the molar mass of anhydro glucose unit (AGU) in g/mol and 58 was the molar mass of CH_2COOH.

4.3 IR determination IR spectra of native yam starch and CMS were determined using KBr technique on a FTIR spectrophotometer (Spectrum One, Perkin Elmer, England). The substitution was confirmed by the presence of carbonyl group in the IR spectrum.

4.4 Viscosity The viscosity of a 2% w/v starch suspensions was determined by using a viscometer (Brookfield, RVDV-II$^+$PRO, USA) with a spindle no.RV-02, speed 200 rpm at 25°C. The readings of viscosity were taken after 30 second rotation. All measurements were performed in triplicate.

5. Applications of CMS as pharmaceutical excipients.

5.1 Tablet disintegrant

5.1.1 Efficacy of native yam starch as tablet disintegrant

5.1.1.1 Tablet preparation The efficiency of native yam starch as a tablet disintegrant was evaluated and compared with tapioca starch, corn starch and rice starch. Dibasic calcium phosphate and magnesium stearate were used as filler and lubricant, respectively. HCTZ was used as a model drug in drug release evaluation. The formulations are shown in Table 2. Tablets were prepared using the direct compression method. All ingredients except magnesium stearate were mixed for 15 minutes. After that magnesium stearate was added and further mixed for 5 minutes. The powder blend was compressed into tablets using a hydraulic compressor (Riken Power, P-16B-027, China) equipped with a 8-mm flat face punch. The tablet was compressed at a controlled compression pressure of 150 MPa. The tablet weight was 250 mg.

Table 2 Formulations of DCP tablets.

Ingredient	Blank tablet (%w/w)	HCTZ tablet (%w/w)
Starch, as disintegrant	0, 3, 6, 9, 12 or 15	9
HCTZ	-	20
Magnesium stearate	0.25	0.25
DCP q.s. to	100	100

5.1.1.2 Tablet evaluation

5.1.1.2.1 Weight variation Weight variation test were determined by weighing 20 tablets individually. The average weight and standard deviation were determined.

5.1.1.2.2 Tablet thickness, diameter and crushing strength Tablet thickness, diameter and crushing strength were monitored by using multipurpose measuring device (Erweka, Germany). Ten tablets were measured individually. The average thickness, diameter or crushing strength and their standard deviations were determined.

5.1.1.2.3 Tablet friability The friability was conducted on 6.5 g of DCP tablets using friabilator (Erweka, Germany). The drum was rotated at 25 rpm for 4 min. Loss of tablet weight with respect to the initial value was then calculated as percent friability.

5.1.1.2.4 Disintegration time The disintegration time was determined based on the USP 30 disintegration test for uncoated tablets. Six tablets were testes. Place 1 tablet in each of the six tubes of the basket and then operated the apparatus. The medium was maintained at 37+ 2°C. The average disintegration time and standard deviation of six tablets were determined.

5.1.1.2.5 Dissolution study

5.1.1.2.5.1 The tablet properties The properties of tablets including weight variation, thickness, diameter, crushing strength, friability, and disintegration time were evaluated as the same manner of 5.1.1.2.1 to 5.1.1.2.4.

5.1.1.2.5.2 Assay and uniformity of weight The procedures employed for assay and uniformity of weight followed the monographs of HCTZ tablets in the USP30. (The detailed could be seen in Appendix B)

5.1.1.2.5.3 Dissolution of HCTZ tablet The procedures employed for the dissolution tests followed the USP30 dissolution test method for HCTZ tablets. The dissolution apparatus setup consisted of a dissolution station using rotation basket at a speed of 100 rpm and an UV/visible spectrophotometer. For HCTZ, the absorbance at the wavelength of 272 nm was determined every 10 minutes for 1 hour. The concentration of drug in the dissolution medium was calculated from the calibration curve and the percent dissolved of the drug was subsequently determined. The dissolution profile was obtained by plotting the average percent dissolved of HCTZ against time.

5.1.2 Evaluation of CMS as tablet disintegrant

5.1.2.1 DCP tablet preparation DCP tablets containing various concentrations of CMS or Exposol® (0.5, 1.0, 2.0, 3.0 and 4.0% w/w) were prepared. The tablets were compressed using the hydraulic press at compression pressures of 50, 100, 150 and 200 MPa. The tablet properties were evaluated after storage for 24 hours.

5.1.2.2 Evaluation of DCP tablets The properties of tablets including weight variation, thickness, diameter, crushing strength, friability, and disintegration time were evaluated as the same manner of 5.1.1.2.1 to 5.1.1.2.4.

5.1.2.3 HCTZ tablet preparation The 250 mg DCP tablets containing 50 mg of HCTZ and various concentrations of CMS or sodium starch glycolate, Exposol®, (0.5, 1.0, 2.0, 3.0 and 4.0% w/w) were prepared. The tablet properties were evaluated after storage for 24 hours.

5.1.2.4 Evaluation of HCTZ tablets The physical properties of tablets including weight variation, thickness, diameter, crushing strength, friability, disintegration time, HCTZ content and dissolution were evaluated as the same manner of 5.1.1.2.1 to 5.1.1.2.4 and 5.1.1.2.5.2 to 5.1.1.2.5.3.

5.2 Direct compressible filler

5.2.1 Preparation of spray dried yam starches (SDYS) Yam starches were co-sprayed with 0%, 0.5%, 1.0%, 1.5% w/w CMS. Suspension of 30 % w/w of starch in purified water were prepared. The starch slurry was fed into the drying chamber via a two-fluid fountain nozzle. The dried spherical agglomerated particles were collected from the bottom product receiver. The types and descriptions of spray dried products are shown in Table 3.

Table 3 Types and descriptions of various products.

Products	Descriptions
SDYS + CMS 0%	Plain spray dried yam starch
SDYS + CMS 0.5%	Spray dried yam starch co-sprayed with CMS 0.5% w/w
SDYS + CMS1.0%	Spray dried yam starch co-sprayed with CMS 1.0% w/w
SDYS + CMS1.5%	Spray dried yam starch co-sprayed with CMS 1.5% w/w

5.2.2 Evaluation of spray dried yam starch

5.2.2.1 Physical characterizations of SDYS The procedures were carried out in the same manner of 2.4, 2.12 and 2.13.

5.2.2.2 Flowability

5.2.2.2.1 Percent compressibility The measurement of powder compressibility followed the USP 30 test procedures for bulk and tapped density method I (The United States Pharmacopeial Convention 2007 : 242-243). About 25 g of starch were gently poured into a 100-mL cylinder. The initial volume was determined and the bulk density was calculated. To determine the packed density, the cylinder was tapped 500 times. The tapped volume was measured. The tapped density was calculated in g per mL. The percent compressibility was calculated from the bulk and tapped densities according to the equation 10.

$$\%\ \text{Compressibility} \quad = \quad \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \qquad (10)$$

Each reported value was an average of three determinations.

5.2.2.2.2 Angle of repose The powder flow property was measured by the angle of repose. The powder was poured into a cylindrical tube standing on a circular plate. Upon lifting the tube, the powder fell freely and formed a cone on a petridish. The angle of repose was calculated from the height of the cone and the radius of the petridish. The average of three determinations was reported.

5.2.2.2.3 Flow rate About 50 g of yam starch were poured into the funnel having a 15.20 mm aperture. The time used when all starch passed through the funnel was measured. The flow rate measurements were done in triplicate.

5.2.2.3 Compactability study

Compression hardness profile SDYSs were compressed to tablets by varying compression pressures ranging from 30 to 120 MPa. The tablet weight was adjusted to 200 mg. The tablet hardness was measured after storage for 24 hours.

5.2.2.4 Disintegration study

5.2.2.4.1 Preparation of tablet The SDYSs tablets, obtained from 5.2.2.3, were used to studied their disintegration properties.

5.2.2.4.2 Tablet evaluation The physical properties of tablets including weight variation, thickness, diameter, crushing strength, friability, disintegration time, HCTZ content and dissolution were evaluated as the same manner of 5.1.1.2.1 to 5.1.1.2.4.

5.2.2.5 Dissolution study

5.2.2.5.1 Preparation of tablet Fifty milligrams of hydrochlorothiazide (HCTZ) or dimenhydrinate in 200 mg tablets were prepared. Each SDYS was used as a direct compressible filler.

5.2.2.5.2 Tablet evaluation

5.2.2.5.2.1 The tablet properties The properties of tablets including weight variation, thickness, diameter, crushing strength, friability, and disintegration time were evaluated as the same manner of 5.1.1.2.1 to 5.1.1.2.4.

5.2.2.5.2.2 Assay and uniformity of weight The procedures employed for assay and uniformity of weight followed the monographs of HCTZ tablets and dimenhydrinate tablets in the USP30. (The detailed could be seen in Appendix B)

5.2.2.5.2.3 Dissolution of HCTZ tablet The procedures employed for the dissolution tests followed the USP30 dissolution test method for HCTZ tablets. The dissolution apparatus setup consisted of a dissolution station using rotation basket at a speed of 100 rpm and an UV/visible spectrophotometer. For HCTZ, the absorbance at the wavelength of 272 nm was determined every 10 minutes for 1 hour. The concentration of drug in the dissolution medium was calculated from the calibration curve and the percent dissolved of the drug was subsequently determined. The dissolution profile was obtained by plotting the average percent dissolved of HCTZ against time.

5.2.2.5.2.4 Dissolution of dimenhydrinate tablet The procedures employed for the dissolution tests followed the USP30 dissolution test method for dimenhydrinate tablets. The dissolution apparatus setup consisted of a dissolution station using rotation paddle at a speed of 50 rpm and a UV/visible spectrophotometer. For dimenhydrinate, the absorbance at the wavelength of 276 nm was determined every 10 minutes for 40 minutes and the last point at 45 minutes. The concentration of dissolved drug in the dissolution medium was calculated from the calibration curve and the percent dissolved of the drug was subsequently determined. The dissolution profile was obtained by plotting the average percent dissolved of dimenhydrinate against time.

5.2.2.5.3 Dilution capacity Ascorbic acid was added to each SDYS at various concentrations, 0%, 10%, 20%, 30% and 40% w/w. The mixture was mixed for 10 min. The tablets were compressed using hydraulic press at compression pressures ranging from 30 to 120 MPa. Dilution potential of yam starch was determined by using dilution capacity index (DCI) which was introduced by Habib et al. (1996 : 205-212).

The tensile strength was calculated from the hardness the thickness according to Fell and Newton's (1968 : 657-659) method in which tensile strength (σx) was given by:

$$\sigma x = \frac{2X}{\pi D t} \qquad (11)$$

where σx was tensile strength in N/cm^2, X was force required to caused failure in tension in N, D was diameter of the tablet in cm, and t is thickness of the tablet in cm.

Numerical analysis (MATLAB®) was used to fit the tensile strength/ compression force profile to be a quadratic equation of the form:

$$\sigma x = aP^2+bP+c \qquad (12)$$

where P is the compression force in kN and a, b and c are constants.

Integrating Equation 12 in the limits of compression force, P1 to P2, the area under the tensile strength-compression force curve (AUC) was as follow:

$$\mathrm{AUC} = \int_{P_1}^{P_2} \sigma x dP = \int_{P_1}^{P_2} (aP^2 + bP + c) \qquad (13)$$

where P_1 and P_2 are the lowest and highest compression forces

Solving equation 13 results in an expression for the area under the curve (AUC) as a function of compression force.

$$\mathrm{AUC} = \left[\frac{aP_2{}^3}{3} + \frac{bP_2{}^2}{2} + cP_2 + d\right] - \left[\frac{aP_1{}^3}{3} + \frac{bP_1{}^2}{2} + cP_1 + d\right] \qquad (14)$$

The AUC of each mixture was divided by the AUC of the 0% w/w mixture of the corresponding SDYS to give a ratio known as work potential or “area ratio” defined by Minchom and Arnstrong (1987 : 69). This area ratio was plotted against the %w/w ascorbic acid for each SDYS. Linear regression and back extrapolate to 0 area ratio gave the value reflecting the dilution capacity or MA index. The dilution capacity index (DCI) was determined from multiplying MA index by AUC of the ascorbic acid tablet subtract AUC of free blend.

5.2.2.5.4 Effect of lubricant concentration SDYSs were lubricated with magnesium stearate at 0%, 0.25%, 0.5%, 0.75% and 1.0% w/w levels. The tablets were compressed using the hydraulic press at compression pressures of 30, 60, 90 and 120 MPa. The tablet weight was 200 mg. The tablet hardness, friability and disintegration time were evaluated after storage for 24 hours.

6. Data analysis

6.1 The surface response plots and correlation between sodium hydroxide concentration, starch and sodium monochloroacetate ratio or reaction time and degree of substitution was determined by linear relationship of the plots of degree of substitution against each carboxymethylation condition. Coefficient of determination, r^2, was calculated using STATGRAPHICS® program.

6.2 The correlation between tablet hardness and compression pressure was determined by quadratic equation. Coefficient of determination, r^2, was calculated using MATLAB® program. Area under the curve obtained from the quadratic plot was used to determine the dilution capacity index of the SDYS.

6.3 The different in means of tablet properties among formulations were statistical analyzed using one-way analysis of variance (ANOVA) with least significant difference (LSD). The p-value of 0.05 was used to judge the significant difference.

CHAPTER IV

RESULTS AND DISCUSSION

1. Preparation of yam starch

Yam tuber contains starch, water and mucilage. The yam starch was obtained in 10% of wet weight of yam tuber, as an odorless and tasteless, fine and white powder.

2. Physico-chemical characterization of native yam starch

2.1 General physico-chemical properties of yam starch Native yam starch was tested for their general characteristics. Preparation of native yam starch met the requirements of USP27/NF22, the results showed in Table 4. Chemical compositions of yam starch are shown in Table 5. It was found that yam starch contained 12.24% amylose with traces of protein and fat. Therefore, it could be assumed that yam starch contained about 87.76% amylopectin.

Table 4 Physico-chemical characterization of yam starch according to USP27/NF22.

Test	Specification	Results
1. Identification		
A.	The product is a translucent, whitish jelly.	Conform
B.	A slurry of starch is colored deep blue by	Conform
2. pH determination	iodine.	7.2
3. Microbial limit	5.0-8.0	Conform
4. Loss on drying	Absence of *Salmonella* and *E.coli*	12.08%
5. Residue on ignition	Not more than 14%	Conform
6. Iron	Not more than 0.5%	Conform
7. Oxidizing substance	Not more than 0.002%	Conform
8. Sulfur dioxide	Not more than 0.002%	Conform
	Not more than 0.008%	

Table 5 Amount of protein, fat and amylose found in yam starch.

Test	Results
1. Protein	0.01%
2. Fat	0.01%
3. Amylose	12.24%

2.2 Morphology and Size distribution The shape and surface structure of yam starch granule were studied using scanning electron microscope (Camscan, England). The particle size of yam starch was found in a range of 2 to 20 µm which was nearly the same as that of rice starch (2-20 µm) but smaller than those of potato starch (10-100 μm), corn starch (2-32 μm), and tapioca starch (5-45 μm). The scanning electron microscopic photograph Figure 11, showed that the yam starch granule was polygonal similar to rice starch granule, while those of corn and tapioca starch were round shape (Arthur and Kibbe 2000).

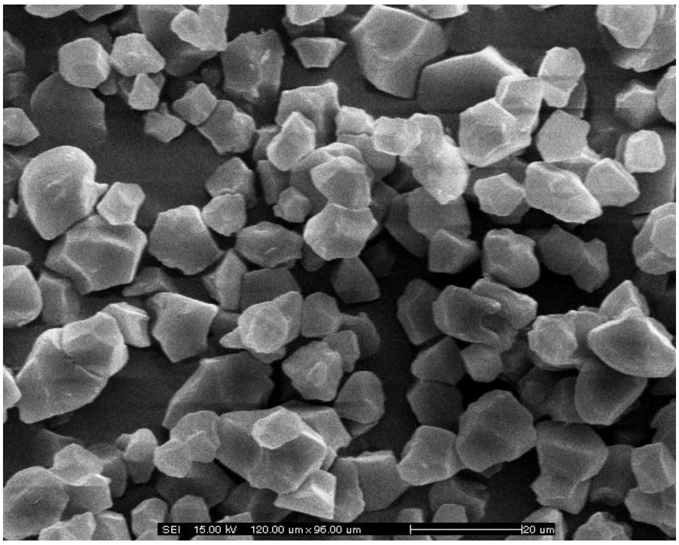


Figure 11 Scanning electron micrograph of yam starch (scale bar = 20 μm).

2.3 Swelling power The swelling powers by weigh and by volume of yam starch were found to be 17.04 and 1.00 times of the initial starch, respectively. The native yam starch was not swell in cold water. To compare the swelling power with other starches, swelling property by the weight of 4 starches i.e. yam starch, tapioca starch, corn starch and rice starch were determined. The decreasing order of the swelling power was yam starch > tapioca starch > corn starch > rice starch. The result was correspondent to the suggestion of Tester and Marison (1990 : 551-557) that swelling power of starch was attributed to amylopectin, the swelling power has a negative correlation with amylose. Rice and corn starch (cereal seed starch) have higher amylose than yam and tapioca starch (tuberous starch). The amylose contents of yam, tapioca, rice and corn starch were 12.24, 19.71, 27.22 and 22.61, respectively (Nattapulwat, Purkkao, and Suwithayapanth 2006 : 1-6).

2.4 Gelatinization temperature The DSC thermogram of yam starch was shown in Figure 12. The endothermic peak indicating the formation of gel was found at 76°C. The gelatinization temperatures of corn starch, potato starch, wheat starch, cassava starch, and yam (*Dioscorea alata*) starch were 73, 72, 63, 63.5 and 73°C respectively (Arthur and Kibbe 2000 ; Freitas 2004 : 4 ; Waliszewski 2003 : 241).

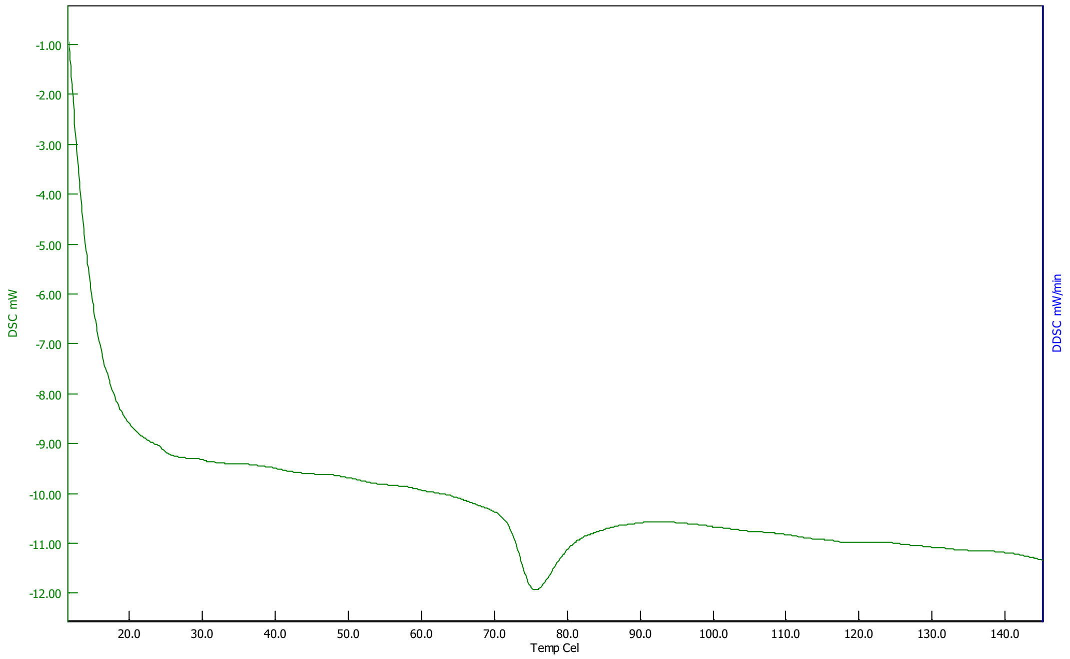


Figure 12 DSC thermogram of native yam starch.

3 Preparation and optimization of carboxymethyl yam starch

CMS with various degrees of substitution were prepared according to Box-Benkhen experimental design. The DS of CMS are shown in Table 6.

Table 6 Levels for the main factors in the Box-Behnken design.

Run no.	Coded values			Real values			DS (SD)
	A	B	C	nNaOH:nAGU (mol/mol)	nSMCA:nAGU (mol/mol)	Time (hrs)	
1	0	0	0	1.5	2.150	4	0.1844 (0.0056)
2	0	-1	1	1.5	1.433	6	0.1676 (0.0059)
3	1	1	0	2.0	2.867	4	0.1833 (0.0000)
4	-1	1	0	1.0	2.867	4	0.1377 (0.0066)
5	1	0	1	2.0	2.150	6	0.1810 (0.0034)
6	1	0	-1	2.0	2.150	2	0.1591 (0.0036)
7	1	-1	0	2.0	1.433	4	0.1784 (0.0037)
8	0	0	0	1.5	2.150	4	0.1852 (0.0039)
9	0	1	1	1.5	2.867	6	0.1934 (0.0030)
10	-1	0	1	1.0	2.150	6	0.1304 (0.0086)
11	0	1	-1	1.5	2.867	2	0.1506 (0.0090)
12	0	-1	-1	1.5	1.433	2	0.0833 (0.0030)
13	-1	-1	0	1.0	1.433	4	0.0970 (0.0034)
14	-1	0	-1	1.0	2.150	2	0.0954 (0.0032)
15	0	0	0	1.5	2.150	4	0.1889 (0.0040)

Effect of reaction parameters on carboxymethylation

The regression analysis of DS and experimental variables from the Table 6 as a quadratic model are given in Table 7. The model from the analysis of variance was significant and adequate to represent the relationship between the DS and the variables, with the p-value less than 0.05 and a satisfied correlation coefficient of 0.95. Results from regression analysis showed that the DS was mainly affected by the amount of NaOH and SMCA followed by the reaction time. The positive values of regression coefficient indicated that DS increased with increasing the amount of NaOH, SMCA content and reaction time. The negative coefficients for the interaction terms suggested that, the DS was decreased at certain levels of NaOH and SMCA contents and the time. The results indicated that there was an optimum value for the DS (Figure 13).

From the equation (1), the presence of NaOH in the reaction yield more reactive of starch alkoxide, thus increasing the amount of NaOH caused an increase in the DS. However, at high level of NaOH, the side reaction of NaOH with SMCA (eq.3) becomes more significant resulting in a decrease of DS. Similar results on the effect of NaOH were also observed in other studies (Khalil 1990 ; Tijsen et al. 2001 ; Sangseethong K. et al. 2005).

SMCA had a positive effect on the DS, especially at the high NaOH content. At low level of NaOH, the amount of activated alkoxide of starch molecules was limited. The presence of small amount of SMCA was already saturated, thus increasing amount of SMCA slightly increase the DS value. As the concentration of NaOH increased, the effect of SMCA became prominent, the DS increased with an increasing of SMCA content (Figure 13a). The results shown in the Figures 13b and

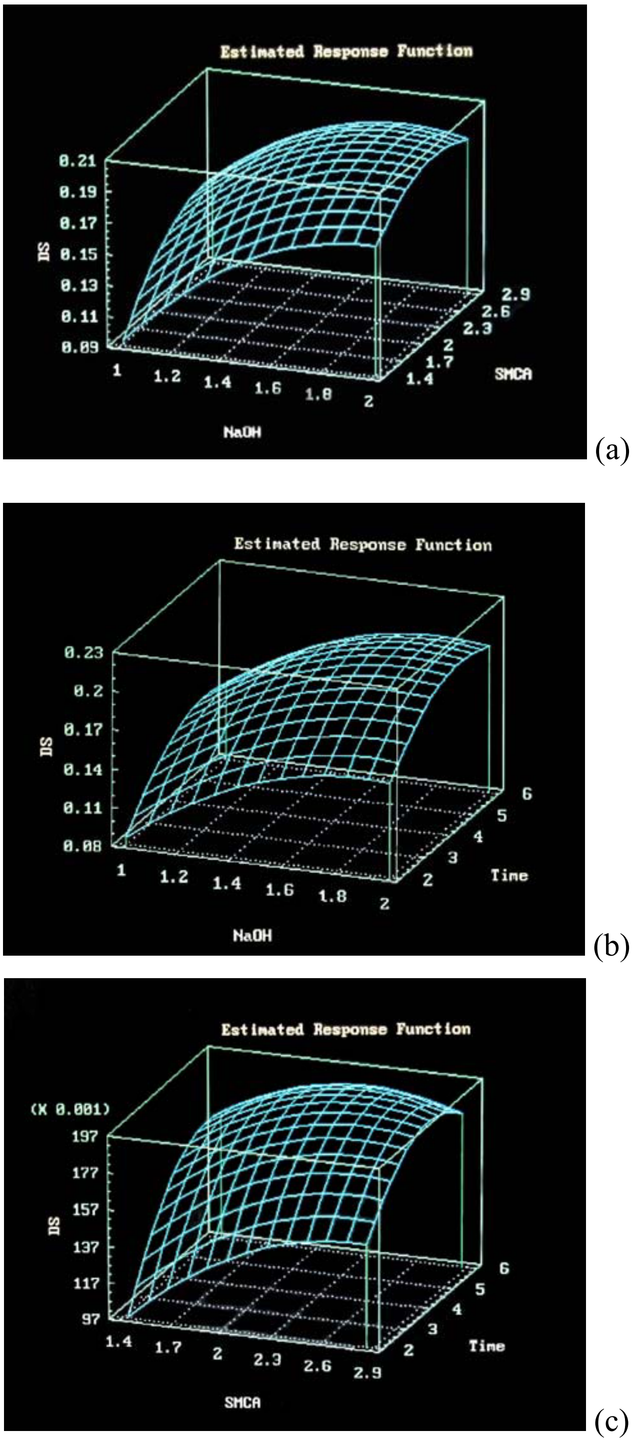
13c indicated that reaction time had a little effect on the DS. However, the DS was slightly increased with increasing the reaction time until it reached the optimum value. The optimum conditions were shown in Table 8. The experimental values of DS were found to be very close to the predicted values. The roles of reaction parameters in carboxymethylation of other study were reported. Comparison of the result in this study with those starches was shown in Table 9.

Table 7 Regression coefficients for degree of substitution (DS).

Factor	Coefficient	p-value	R^2
Constant	-0.588301		0.9525
A: NaOH	0.3930	0.0015	
B: SMCA	0.2153	0.0156	
C: Time	0.0770	0.0050	
AB	-0.0250	0.2463	
AC	-0.0033	0.6561	
BC	-0.0072	0.1886	
AA	-0.0886	0.0262	
BB	-0.0290	0.0897	
CC	-0.0056	0.0247	

Table 8 Optimum conditions and properties of optimized CMS.

nNaOH:nAGU (mol/mol)	nSMCA:nAGU (mol/mol)	Time (hrs)	DS	
			Predicted	Experimental (SD)
1.80	2.35	4.8	0.2019	0.1966 (0.0056)



(a)

(b)

(c)

Figure 13 Response surface plots of (a) effects of molar ratio of NaOH:AGU and of molar ratio of SMCA: AGU on DS of CMS, (b) effects of time and molar ratio of NaOH:AGU on DS of CMS, (c) effects of time and molar ratio of SMCA:AGU on DS of CMS.

Table 9 Literature results for carboxymethylation of starch.

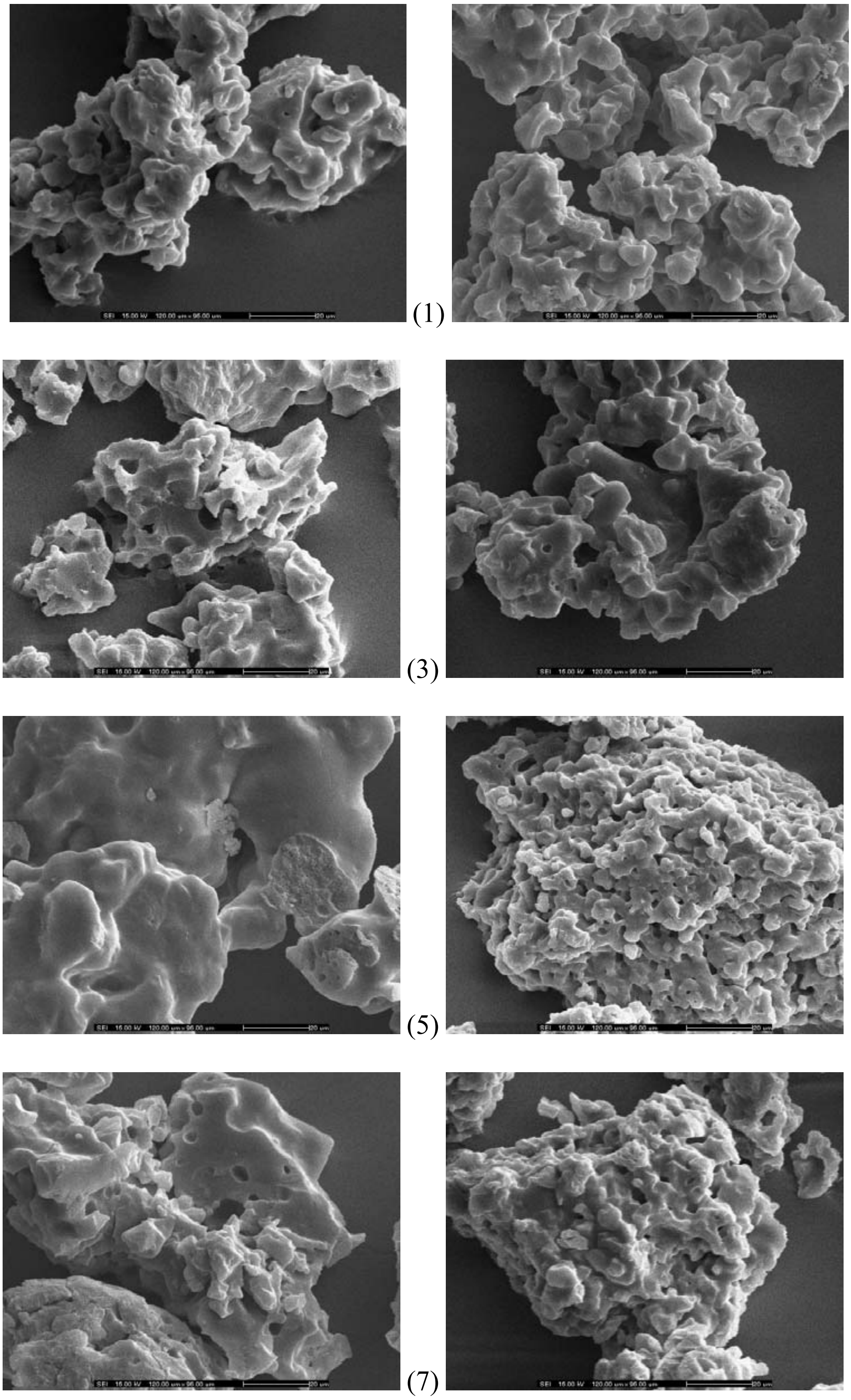
	Bhattacharyya et al. (1995)	Tijsen et al. (2001)	Kooijman et al. (2003)	Sangseethong et al. (2005)	This study
Starch	Corn	Potato	Arrowroot	Cassava	Yam
Temperature (°C)	65	40	30	40	30
Water (%)	16	10	7	28.5	30
NaOH/SCMA (mol/mol)	2.6	1.0	0.5	1.5	0.8
Time (min)	90	150	300	180	290
DS	0.2	0.5	0.07	0.53	0.19

4. Physico-chemical characterization of CMS

4.1 Morphology Morphology of CMS was shown in Figure 14. Investigation of granule surface by scanning electron microscopy (SEM) showed partial eruption and coalescence of starch granules. The degree of granule eruption and coalescence were effected by the amounts of NaOH and/or SMCA. Increasing amount of NaOH and/or SMCA increased the granule eruption and coalescence.

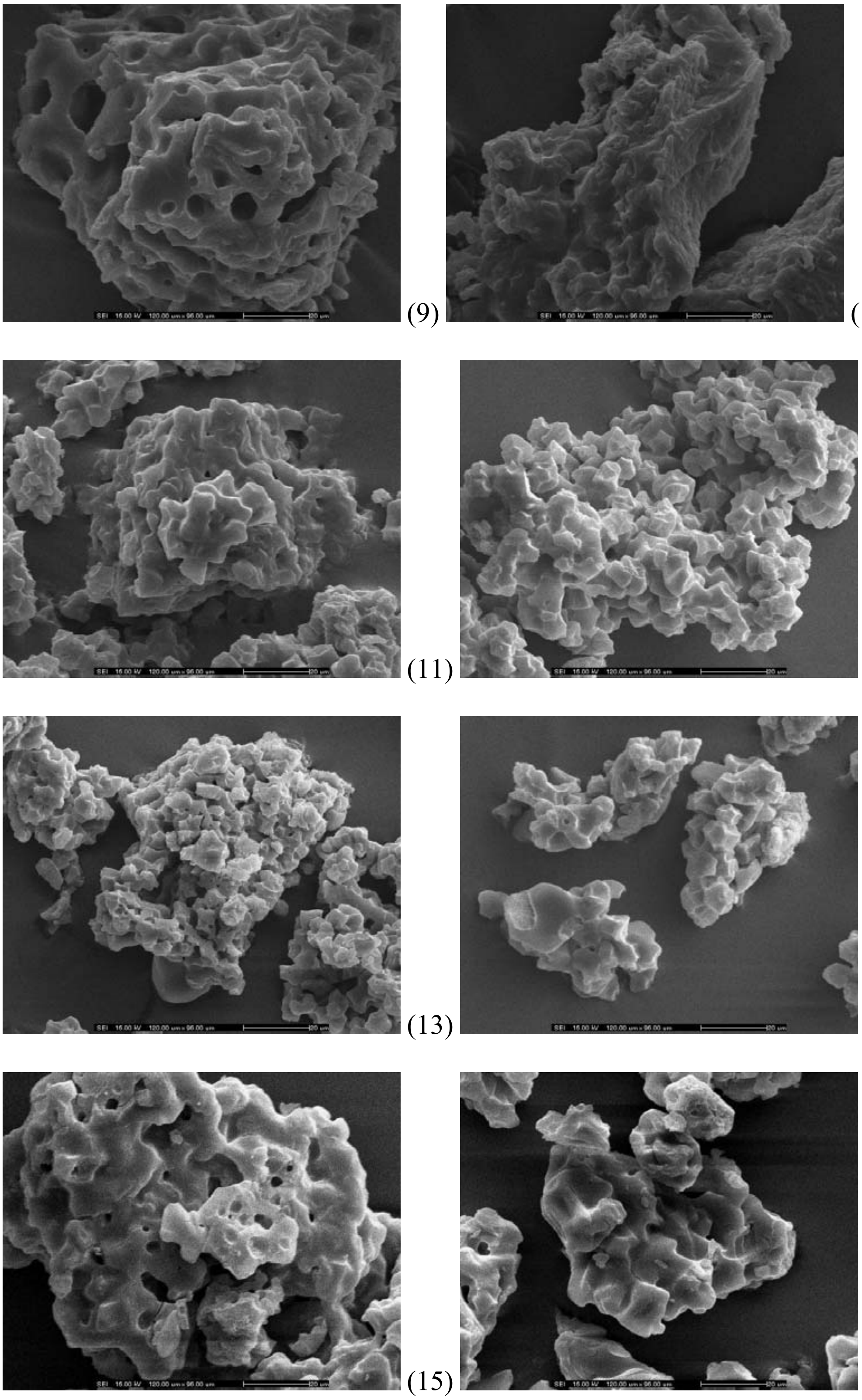
4.2 Swelling power Swelling property, gelatinization temperature and viscosity of carboxymethyl yam starches were shown in Table 10. Swelling power and viscosity of CMS were higher than the native yam starch. For CMS, the swelling power and viscosity increased with an increase in the degree of modification. This is due to the higher hydrophilicity of the carboxyl group which takes up more of water, resulting in more swelling power.

4.3 Gelatinization temperature Gel formation was observed when water was added to CMS powder at room temperature (30°C). Thus the gelatinization temperature of CMS was less or equal to the room temperature. The results were confirmed by DSC, there was no endothermic peak found in the DSC thermograms (Figure 15).



(1) (2) (3) (4) (5) (6) (7) (8)

Figure 14 Morphology of carboxymethyl yam starch various preparation conditions (run no. 1-16) magnification 1000 x.



(9) (10) (11) (12) (13) (14) (15) (16)

Figure 14 (continued) Morphology of carboxymethyl yam starch various preparation conditions (run no. 1-16) magnification 1000 x.

Table 10 Physicochemical properties of carboxymethyl yam starch.

Run no.	Swelling power by weight, times (SD)	Swelling power by volume, times (SD)	Viscosity, Cps (SD)	Gelatinization temperature, ^{o}C
1	95.39 (0.94)	125.27 (1.84)	148.07 (0.12)	≤30
2	65.03 (5.38)	60.72 (3.20)	127.60 (0.53)	≤30
3	96.27 (1.24)	78.81 (1.87)	143.50 (0.50)	≤30
4	38.73 (0.80)	52.40 (3.63)	122.00 (0.00)	≤30
5	93.69 (3.43)	98.70 (1.88)	142.50 (0.50)	≤30
6	65.87 (2.29)	62.26 (1.83)	123.00 (0.00)	≤30
7	78.61 (3.64)	67.04 (3.19)	134.23 (0.25)	≤30
8	96.44 (4.37)	130.33 (3.18)	149.17 (0.29)	≤30
9	109.31 (3.39)	206.35 (3.68)	228.33 (0.29)	≤30
10	35.29 (0.46)	57.21 (1.87)	114.13 (0.23)	≤30
11	61.91 (4.18)	60.33 (3.18)	122.83 (0.76)	≤30
12	21.19 (1.19)	43.44 (1.84)	59.17 (0.29)	≤30
13	23.46 (3.51)	51.15 (1.81)	106.60 (0.17)	≤30
14	22.95 (0.81)	51.10 (3.19)	97.13 (0.12)	≤30
15	98.38 (0.79)	128.21 (4.86)	158.50 (0.00)	≤30
Optimization	131.38 (1.82)	315.89 (3.67)	373.33 (0.29)	≤30

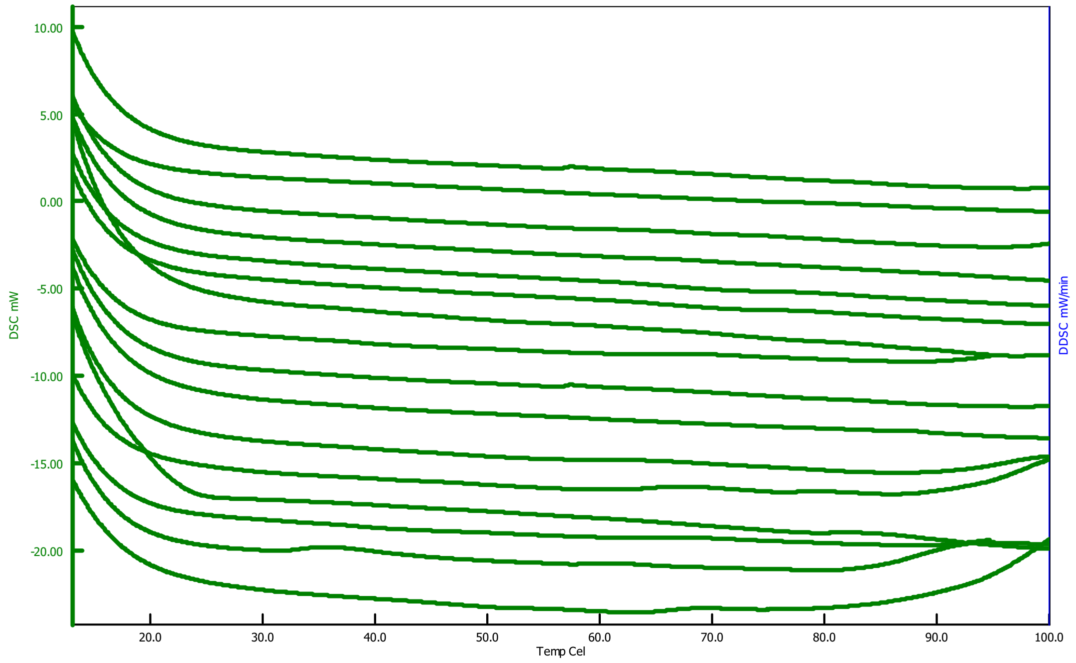


Figure 15 DSC thermogram of carboxymethyl yam starch (Run no. 1-15 and optimized CMS from top to bottom).

4.4 IR determination The substitution was confirmed by the presence of carbonyl group in the IR spectrum of the CMS as shown in Figure 16. An adsorption band at 1591.25 cm^{-1} indicated the presence of a carbonyl group as a result of carboxymethylation.

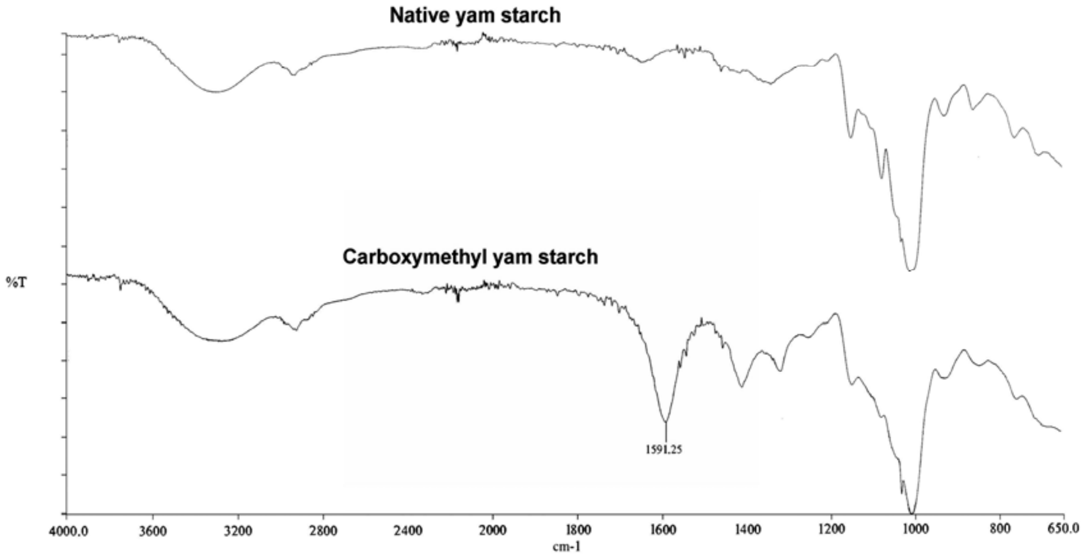


Figure 16 IR spectrum of native yam starch and carboxymethyl yam starch.

5. Application of Carboxymethyl yam starch as pharmaceutical excipients.

5.1 Tablet disintegrant

5.1.1 Evaluation of native yam starch as tablet disintegrant

5.1.1.1 Hardness The effect of concentration of the yam starch compared with tapioca starch, corn starch and rice starch on tablet hardness was shown in Figure 17. The hardness increased with the increase of starch concentration in all formulations. Yam starch and rice starch gave higher tablet hardness than corn and tapioca starch. This could be due to their polygonal shape granule that bonding with mechanical interlocking.

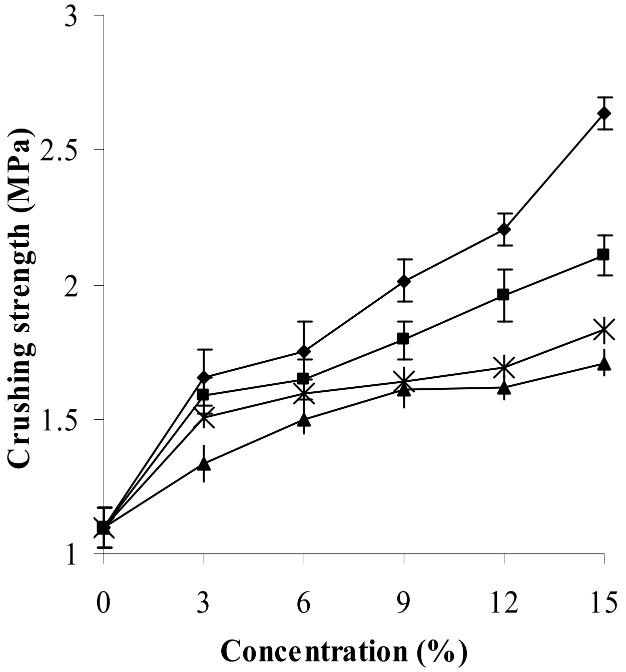


Figure 17 Effect of starch concentrations on the hardness of tablets ((■) Rice starch, (▲) Corn starch, (×) Tapioca starch, (◆) Yam starch).

5.1.1.2 Friability The tablet friability decreased with increasing amount of starch in the tablets (as shown in Figure 18). The higher the tablet hardness, the lower the tablet friability was observed, because the interparticulate cohesiveness was increased with increasing of starch concentration. The increasing order of tablet friability was yam starch < rice starch < corn starch < tapioca starch, respectively.

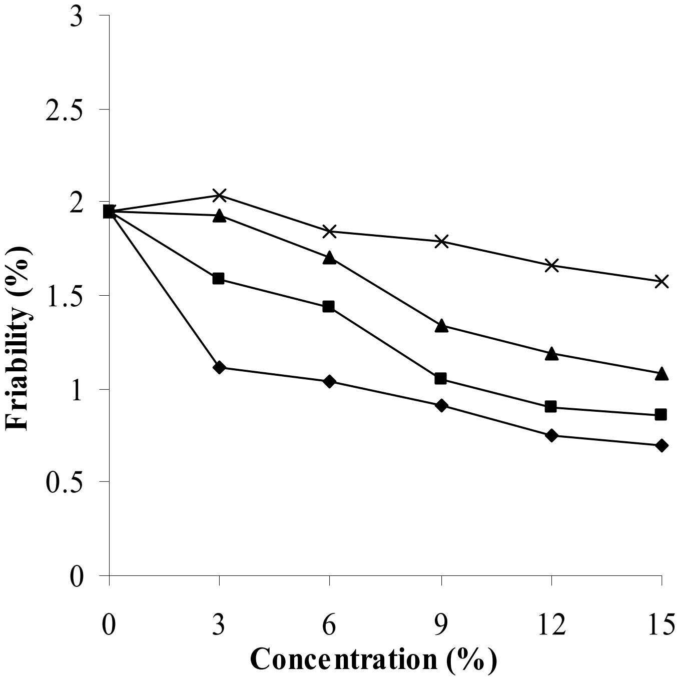


Figure 18 Effect of starch concentrations on the friability of tablets ((■) Rice starch, (▲) Corn starch, (×) Tapioca starch, (◆) Yam starch).

5.1.1.3 Disintegration time The effect of starch concentration on the disintegration time of the tablets is showed in Figure 19. The HCTZ tablets without starch and the tablets with 3% of rice starch, corn starch, or tapioca starch were not disintegrated in the tested time of 30 minutes. However, HCTZ tablet containing 3% of yam starch disintegrated in 4 minutes. With increasing amount of all starches, a decreasing in the disintegration time was observed, due to the swelling of starch granules.

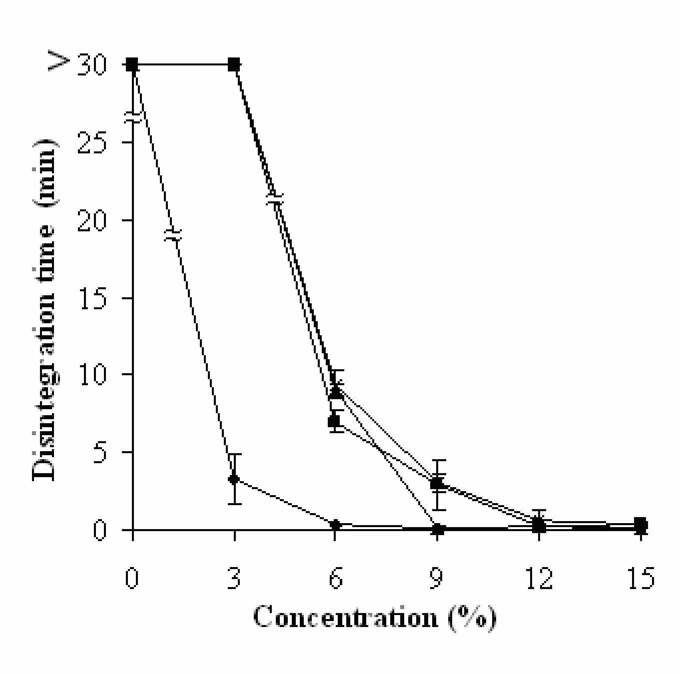


Figure 19 Effect of starch concentrations on disintegration time of tablets ((■) Rice starch, (▲) Corn starch, (×) Tapioca starch, (◆) Yam starch).

5.1.1.4 Dissolution The dissolution profiles of HCTZ tablets are shown in Figure 20. It can be concluded that the dissolution corresponded to the disintegration property of the tablets. The faster tablet disintegration time, the faster drug released. However, all formulations were released more than 80% in 40 minutes, and a complete dissolution was obtained in 60 minutes.

Yam starch can be used as a tablet disintegrant, The DCP tablet containing 3% yam starch was disintegrated within 4 minutes and dissolution of HCTZ from the tablets was completed within 60 minutes.

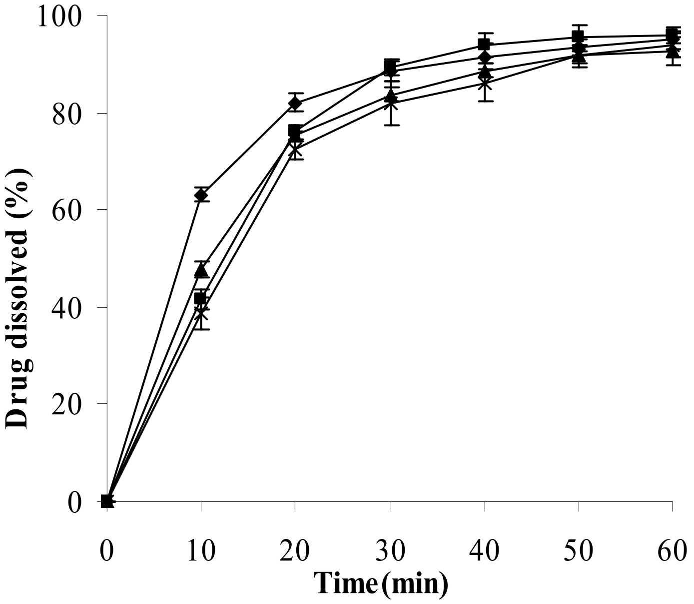


Figure 20 Effect of starch concentrations on dissolution of tablets ((■) Rice starch, (▲) Corn starch, (×) Tapioca starch, (◆) Yam starch).

5.1.2 Evaluation CMS as tablet disintegrant

5.1.2.1 Preparation of Dibasic calcium phosphate (DCP) tablets DCP was used as direct compression filler because DCP is practically insoluble in water and disintegrate only when a disintegrant is incorporated. The insoluble filler was ideal for the study of the disintegrant because it had no intrinsic disintegration property.

5.1.2.2 Physical properties of DCP tablet

5.1.2.2.1 Weight variation Weight variation data are shown in Table 18. All formulations met the USP30 requirement in weight variation test. Since DCP exhibited good flowability, weight variations of DCP tablets are not anticipated. The incorporation with small amount of disintegrants has no effect on flowability of the blend, hence good uniformity of tablet weight was obtained.

5.1.2.2.2 Tablet thickness and diameter The results on tablet thickness and diameter are shown in Table 18. Although, the evaluations of tablet thickness and diameter are not official in pharmacopoeia, in general, tablet thickness and diameter were monitored for controlling the appearance uniformity of the tablets. It could be seen in Table 18 that the variation of the thickness and the diameter at any compression pressures was negligible. Incorporation of small amount of CMS or Exposol®, the DCP tablets were found to have minute increase in thickness.

5.1.2.2.3 Tablet hardness The hardness of DCP tablet using CMS as tablet disintegrant compared with Exposol® were shown in Figure 21 and 22. The tablet hardness was increased with the increment of compression pressure. It was found that effect of disintegrant concentrations on the hardness was less conspicuous. The tablet contained CMS gave slightly higher tablet hardness than the tablet contained Exposol®.

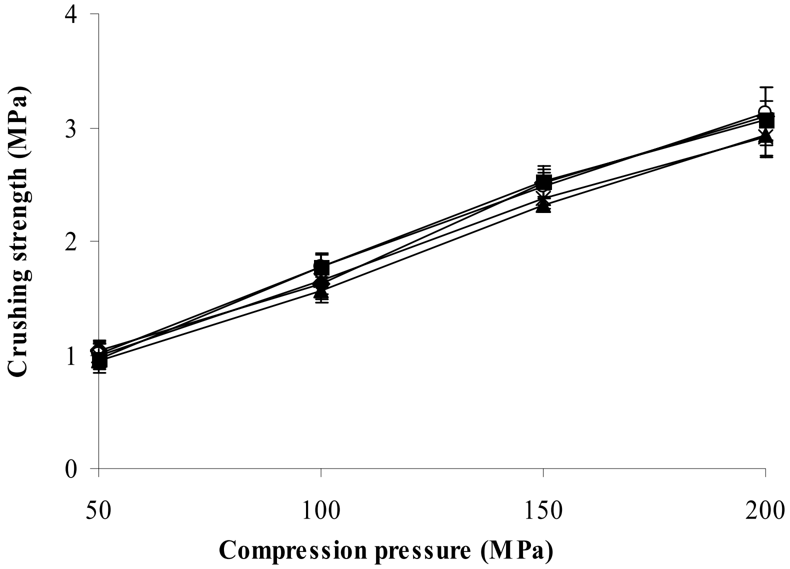


Figure 21 Effect of various CMS concentrations on tablet hardness of DCP tablets, ◆, CMS 0.5% w/w; ○, CMS 1.0%w/w; ■, CMS 2.0%w/w; ∗, CMS 3.0%w/w; ▲, CMS 4.0%w/w

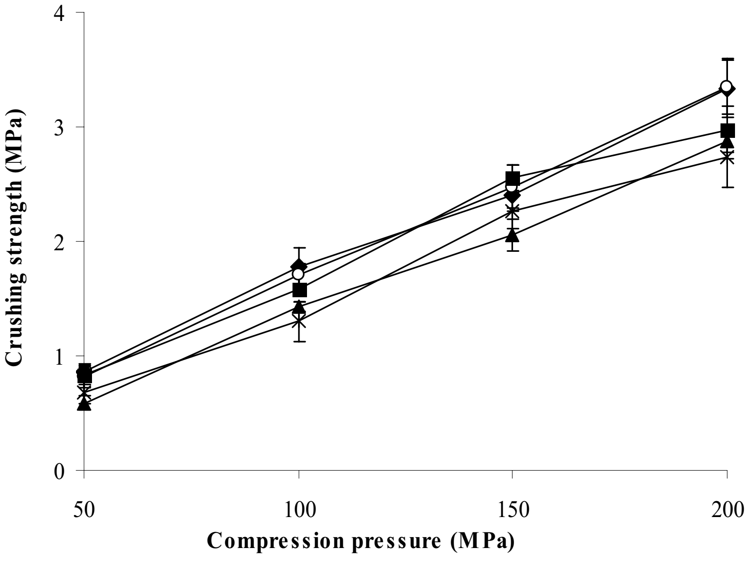


Figure 22 Effect of various Exposol® concentrations on tablet hardness of DCP tablets, ◆, Exposol® 0.5% w/w; ○, Exposol® 1.0%w/w; ■, Exposol® 2.0%w/w; ∗, Exposol® 3.0%w/w; ▲, Exposol® 4.0%w/w.

5.1.2.2.4 Tablet friability The friability of DCP tablets containing CMS as tablet disintegrant compared with Exposol® are shown in Figure 23 and 24. The increasing in compression pressure resulted in decreasing tablet friability. The friability of tablet decreased with an increasing amount of disintegrant. The friability of tablets with CMS was slightly lower than that of Exposol®.

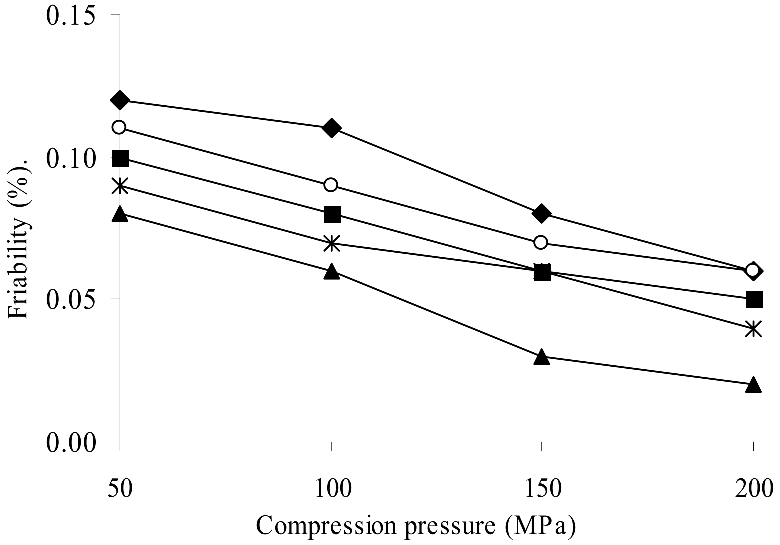


Figure 23 Effect of various CMS concentrations on tablet friability of DCP tablets, ◆, CMS 0.5%w/w; ○, CMS 1.0%w/w; ■, CMS 2.0%w/w; ✳, CMS 3.0%w/w; ▲, CMS 4.0%w/w.

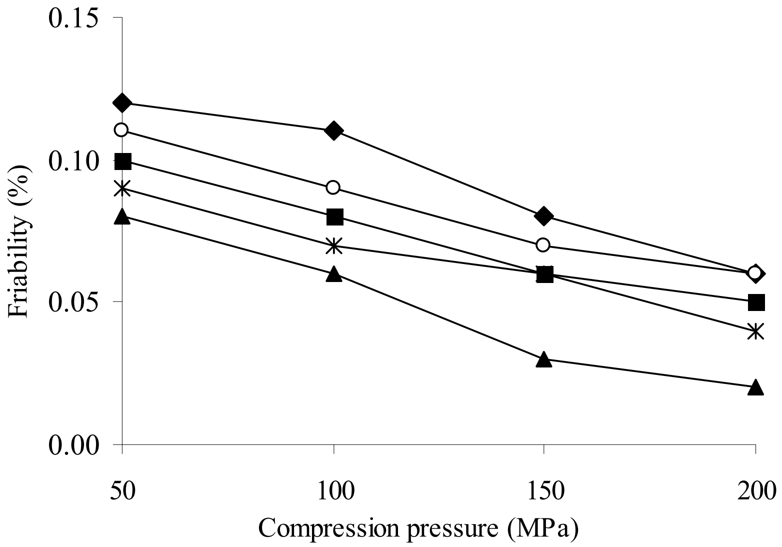


Figure 24 Effect of various Exposol® concentrations on tablet friability of DCP tablets, ◆, Exposol® 0.5% w/w; ○, Exposol® 1.0%w/w; ■, Exposol® 2.0%w/w; ✳, Exposol® 3.0%w/w; ▲, Exposol® 4.0%w/w.

5.1.2.2.5 Disintegration time The disintegration times of DCP tablets containing various CMS concentrations are shown in Figure 25. The disintegration times of DCP tablets were corresponded with compression pressure. Disintegration time increased with increasing in compression pressure. The tablets containing 0.5% w/w CMS were not disintegrated, excepted that was compressed at a low compression pressure of 50 MPa. The tablets containing 2.0% w/w CMS showed fastest disintegration time ($p\text{-value} < 0.05$). The disintegration times of tablets containing 3.0 and 4.0 %w/w CMS were slightly slower. This could be attributed to the viscous gel mass formation of CMS when contacted with water. Consequently, penetration of water into the tablet was impediment, resulting in retarding tablet disintegration. The disintegration times of DCP tablets containing various Exposol®

concentrations are shown in Figure 26. The effect of compression pressure on disintegration time of tablet containing Exposol® was similar to the tablet containing CMS. However the effects of concentrations of Exposol® on disintegration time were different. Increasing in concentration of Exposol®, disintegration time was decreased (p-value < 0.05). Comparison of disintegration time of DCP tablet containing CMS (2 %w/w) with that of the tablet containing 2% Exposol® showed that CMS is comparable with Exposol® at this concentration.

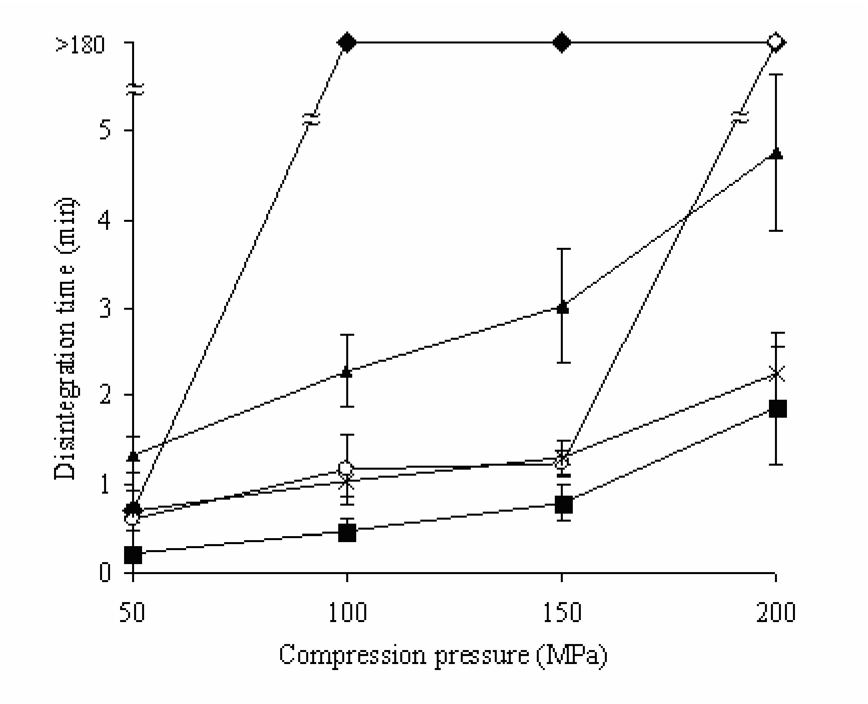


Figure 25 Effect of various CMS concentrations on disintegration time of DCP tablets, ◆, CMS 0.5% w/w; ○, CMS 1.0%w/w; ■, CMS 2.0%w/w; ✳, CMS 3.0%w/w; ▲, CMS 4.0%w/w.

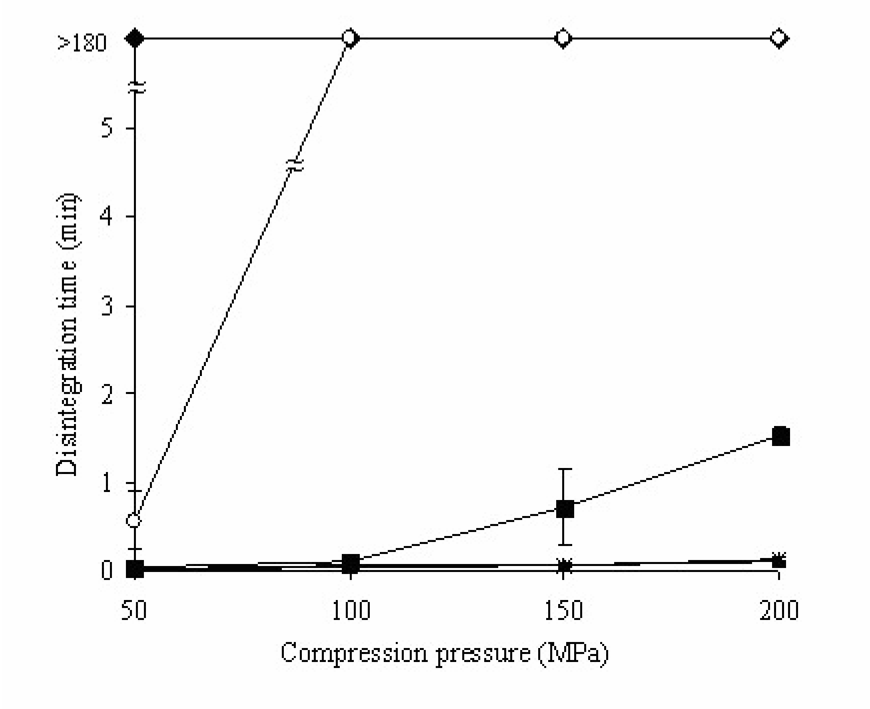


Figure 26 Effect of various Exposol® concentrations on disintegration time of DCP tablets, ◆, Exposol® 0.5%w/w; ○, Exposol® 1.0%w/w; ■, Exposol® 2.0%w/w; ✳, Exposol® 3.0%w/w; ▲, Exposol® 4.0%w/w.

5.1.2.3 Evaluation of HCTZ tablets containing CMS as disintegrant.

5.1.2.3.1 Preparation of HCTZ tablets Throughout this studies, HCTZ was employed as a model drug representing poorly water-soluble. Dibasic calcium phosphate granular (DCP) was used as a direct compressible filler. The effect of CMS in comparison with Exposol® on the HCTZ release was determined.

5.1.2.3.2 Tablet properties of HCTZ tablets The HCTZ tablets were determined the effect of CMS and Exposol® on the drug dissolution. The tablet weight, thickness, diameter and hardness were in predetermined range. The percent label amount, uniformity of weight, disintegration time and friability were met the requirement of USP 30. The results are shown in Tables 22, 23 and 35.

5.1.2.3.3 Disintegration time of HCTZ tablets The disintegration times of HCTZ tablets containing CMS and Exposol® were shown in Figure 27. The effect of concentrations of CMS on the disintegration time of HCTZ tablets was similar to that of DCP tablets. Addition of either CMS or Exposol® caused tablet to disintegrate. The result in Figure 27 indicated that an optimum concentration of CMS, which gave the fastest disintegration, was 2% w/w (p-value < 0.05). At higher concentration, the disintegration was slightly retarded as the result of viscous barrier formation. This evidence was not found in the tablet containing Exposol®. The faster disintegration observed with increasing amount of Exposol®.

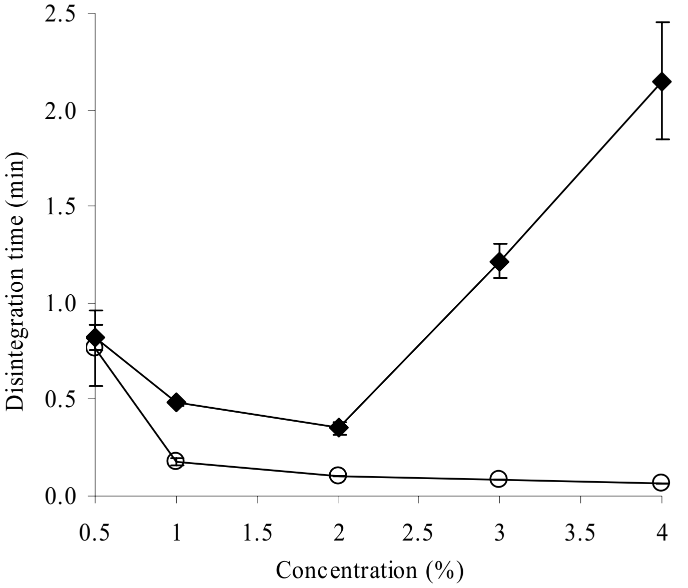


Figure 27 Effect of tablet disintegrant on disintegration time of HCTZ tablets, ◆, CMS; ○, Exposol®.

5.1.2.3.4 Dissolution of HCTZ tablets In this study HCTZ, a poor water soluble drug, was employed as a model drug for evaluation of the effect of CMS on the drug dissolution. Dissolution profiles of the HCTZ are shown in Figure 28. The dissolution profiles corresponded with the disintegration property of tablets. The faster tablet disintegration resulted in a faster drug release. The monograph of HCTZ tablets in the USP 30 specified that the dissolution of HCTZ tablets at 60 min must not less than 65% (Q+5%). All formulations were fulfilled the requirement, except the HCTZ tablet containing 4.0% CMS, the dissolution was retarded. The drug release pattern was fitted to the zero order drug release kinetic. As mention before, high amount of CMS could form the viscous gel which impeded water permeation into the tablets. In this case, the viscous layer acted as a drug release controlling agent. Figure 29 showed dissolution profiles of drug released from HCTZ tablets containing Exposol®. All tablets disintegrated within 1 minute, hence concentration of Exposol® had no effect on a drug release.

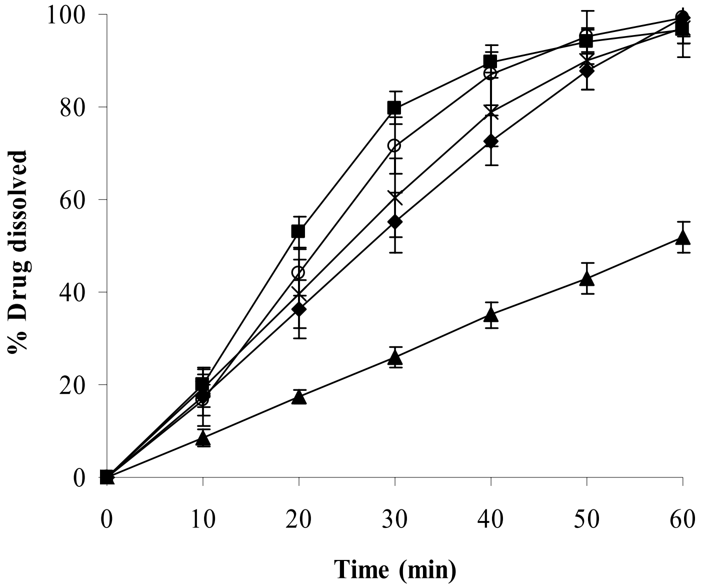


Figure 28 Dissolution profile of HCTZ tablets with various concentrations of CMS, ◆, 0.5%w/w; ○, 1%w/w; ■, 2%w/w; ✳, 3%w/w; ▲, 4%w/w.

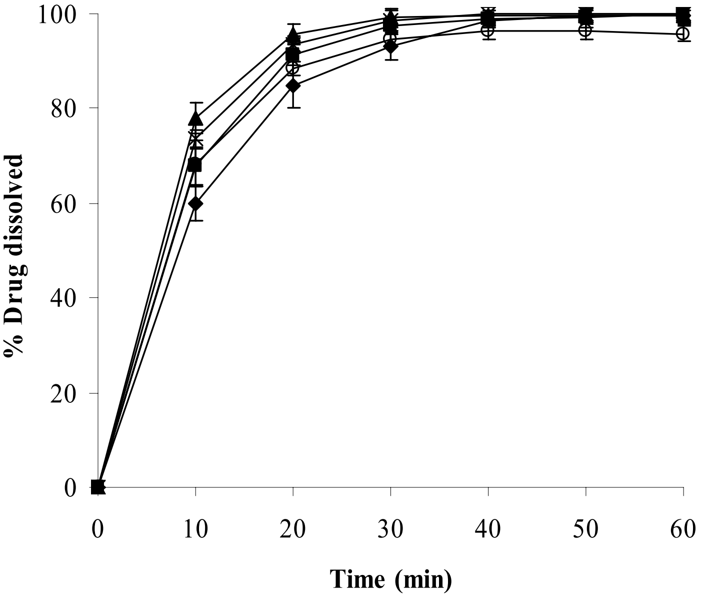


Figure 29 Dissolution profile of HCTZ tablets with various concentrations of Exposol®, ◆, 0.5%w/w; ○, 1%w/w; ■, 2%w/w; ✳, 3%w/w; ▲, 4%w/w.

5.2 Direct compressible filler

Direct compression technique has been one of the well-accepted methods of tablet manufacture. A wide range of materials from various sources has been developed and marketed as directly compressible vehicles. Spray drying is a well known technique in the development of directly compressible excipients. Their poor flowability and binding properties are improved. The examples of commercial spray dried directly compressible excipient are Tabbletose® (spray dried lactose) and Era-Tab® (spray dried rice starch). In present, directly compressible excipients prepared by co-processing with two or more established excipients are interesting. The co-processing method could lead to the formation of excipients having superior properties compare to the simple physical mixture of their components. The composite particles or co-processed multicomponent-based excipients are introduced to achieve better powder characteristics and tableting properties than a single substance or the physical mixture. The excipient is physically modified in a special way without altering the chemical structure. The product is fixed and homogeneous distribution for the components is achieved by embedding them within minigranules. Several of these excipients are commercially available e.g., Cellactose® (Microcrystallline cellulose/ Lactose), Celocal® (Microcrystallline cellulose/ Calcium phosphate), Di-pac® (Sucrose/ Dextrin) and Carbofarma® GM11 (Calcium carbonate/ Maltodextrin). In the light of CMS preparation, co-sprayed of yam starch and CMS could give a novel direct compressible excipient.

5.2.1 Preparation of various spray dried yam starch (SDYS) In this study, yam starch was co-sprayed with various concentrations of carboxymethyl yam starch (CMS), i.e., 0%, 0.5%, 1.0%, 1.5% w/w. The starch slurry contained 30% w/w solid content. The mixture was recovered by using spray drying technique. The obtained products were white, spherical agglomerated particles having free flow property. The spray drying process yielded about 50% w/w of products in the bottom collector and about 20% w/w of fine particles in the cyclone chamber.

5.2.2 Morphology of spray dried yam starches Figure 30 showed the scanning electron micrographs (SEM) of spray dried yam starches. SEM indicated that the products from the bottle collector entirely composed of aggregates of yam starch grains with spherical particle form. The aggregated particles were similar to structure of spray dried rice starch (Era-Tab®).

5.2.3 Particle size and size distribution of spray dried yam starches The particle sizes of all formulations of spray dried yam starches are shown in Table 11. The particle sizes of all formulations of spray dried yam starch were larger than that of Era-Tab®. The decreasing order of particle size of spray dried yam starch was SDYS+CMS 0.5% > SDYS+CMS 1.0% > SDYS+CMS 1.5% > SDYS+CMS 0% > Era-Tab®.

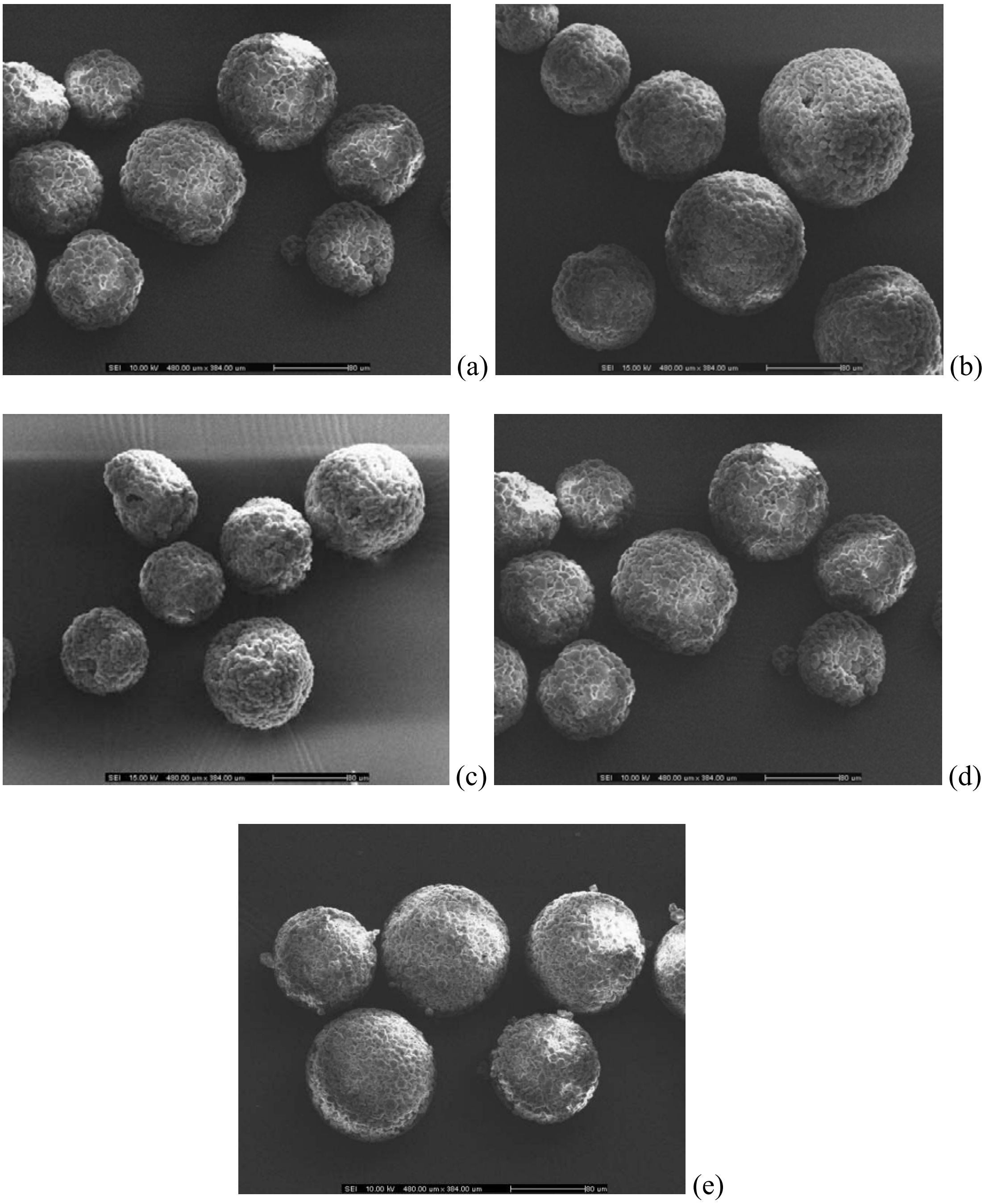


Figure 30 Morphology of spray dried yam starches (a) SDYS, (b) SDYS+CMS 0.5%, (c) SDYS+CMS 1.0%, (d) SDYS+CMS 1.5%, (e) Era-tab® (magnification 250X).

Table 11 Particle size distribution of spray dried yam starches.

Products	Particle size (μm), (Geometric mean size), (SD)	(Geometric standard deviation), (SD)
SDYS+CMS 0%	84.43 (0.28)	1.58 (0.01)
SDYS + CMS 0.5%	121.79 (1.71)	1.84 (0.02)
SDYS + CMS 1.0%	104.35 (0.31)	1.70 (0.00)
SDYS + CMS 1.5%	98.61 (0.45)	1.57 (0.01)
Era-Tab®	60.14 (0.13)	1.73 (0.00)

5.2.4 Loss on drying The loss of volatile substances in SDYS and Era-Tab® upon drying was found to be in a range of 8 to 10% as shown in Table 12. The percentage loss on drying of spray dried yam starches were lower than Era-Tab® (11.03%) but all products met the requirement of USP30/NF25. The loss on drying of starches not more than 14%.

Table 12 Loss on drying of spray dried yam starches.

Products	Loss on drying % (SD)
SDYS+CMS 0%	9.38 (0.03)
SDYS+CMS 0.5%	8.80 (0.10)
SDYS+CMS 1.0%	8.73 (0.06)
SDYS+CMS 1.5%	8.86 (0.04)
Era-Tab®	11.03 (0.03)

5.2.5 Flowability study

5.2.5.1 Compressibility index The bulk and tapped densities as well as Carr's compressibility index or % compressibility of spray dried yam starches were listed in Table 13. The term "compressibility" refers to the packing characteristics of the materials, and it has been suggested that the lower the value, the better is the flow (Neumann 1967 : 181). In this study, the order of decreasing flowability judged by the compressibility index was Era-Tab® > SDYS + CMS 1.5% = SDYS + CMS 1.0% > SDYS + CMS 0.5% > SDYS + CMS 0%. However, it could be seen that all products had very good flow property.

5.2.5.2 Angle of repose The angles of repose of all products were reported in Table 13. The low value of angle of repose indicated the low interparticulate friction, thus resulting in good flowability. The angles of repose of the samples ranged from 8 to18 degrees. The results on the flowability by angle of repose study agreed with those found in the compressibility index study.

5.2.5.3 Flow rate Although the compressibility index and the angle of repose are parameters that can determine powder flowability, but they are indirect methods for the evaluation of flowability. To direct measure the flow characteristic, flow rate measurement should be considered. In this study, flow rate of each product in gram per second was evaluated. The results are shown in Table 13. Spherical particles were free flowing.

Table 13 Flowability of spray dried yam starch.

Products	Compressibility, %, (SD)	Angle of repose, degree, (SD)	Flow rate g/sec (SD)
SDYS + CMS 0%	11.50 (1.32)	17.29 (0.81)	17.41 (0.76)
SDYS + CMS 0.5%	9.67 (1.04)	11.53 (0.57)	30.20 (1.43)
SDYS + CMS 1.0%	9.50 (0.87)	12.88 (0.61)	26.81 (0.91)
SDYS + CMS 1.5%	9.50 (1.80)	14.36 (1.45)	23.20 (1.94)
Era-Tab®	6.17 (0.29)	8.58 (0.00)	24.59 (0.17)

5.2.6 Compression hardness profile

5.2.6.1 Preparation of SDYS and Era-Tab® tablets SDYS and Era-Tab® were compressed by using a hydraulic compressor (Riken Power, China) equipped with a 8-mm flat face punch. The tablet weight was 200 mg. The compression pressures were 30, 60, 120, 150 MPa.

5.2.6.2 Tablet Weight, thickness and diameter Weight variation of all formulations of SDYS and Era-Tab® tablets were met the USP 30 requirement. The diameter of the tablet was kept constant by using only one set of tooling. Tablet thickness was a function of compression pressure, the increase in compression pressure resulted in decreased thickness. The variations of thickness at any compression pressure were negligible. The data are shown in Table 24 (Appendix A).

5.2.6.3 Tablet hardness The tablet hardness of SDYS and Era-Tab® tablets were expressed as a crushing strength of tablet. The crushing strength is a compressive stress required to cause a tablet to break apart, in essence, it is the resistance of the tablet to vertical pressure placed upon it. The tablet hardness of

SDYS and Era-Tab® tablets were illustrated in Figure 31 and Table 25. The hardness increased with compression pressure. The presence of CMS increased tablet strength. As during SDYS preparation, CMS was swelled and mixed with starch slurry resulting in the increasing viscosity of the starch slurry. Upon spraying and drying, the added CMS increasing the binding efficiencies between grains of yam starch which enhanced the granule consolidation under compression. Higher tablet strength was observed in tablets containing higher levels of CMS. SDYS+CMS 1.5% showed the highest tablet hardness followed by SDYS+CMS 1.0%, SDYS+CMS 0.5% and SDYS+CMS 0%, respectively. Moreover, tablet hardness of all SDYS was higher than Era-Tab®. The statistical treatment applied was found that there were statistically significant differences ($p < 0.05$).

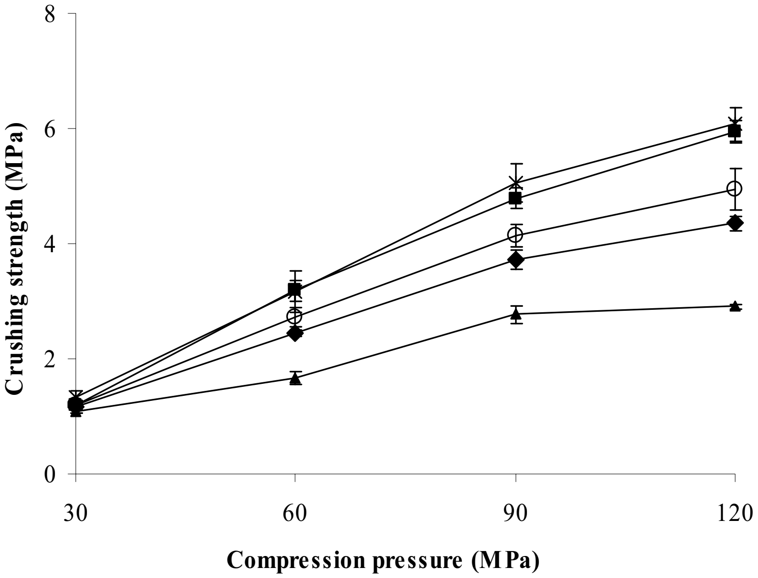


Figure 31 Hardness compression profile of SDYS and SDYS co-sprayed with CMS, ◆, SDYS; ○, SDYS+CMS 0.5%w/w; ■, SDYS+CMS 1.0%w/w; ∗, SDYS+CMS 1.5%w/w; ▲, Era-Tab®.

5.2.6.4 Tablet disintegration The most widely accepted mechanism of action for tablet disintegration is swelling. Disintegration times of SDYS and Era-Tab® tablets are shown in Figure 32 and Table 25. The SDYS+CMS 0% tablets disintegrated slower than the SDYS+CMS 0.5% tablets. This could be attributed to swelling power. SDYS lacked of adequate swelling force. The CMS swelled and became gel-like when wetted. For the tablet containing 0.5% w/w CMS, the amount of CMS was sufficient to give adequate swelling force and caused tablet a fast disintegrating. With higher amount of CMS, gel packing was higher, fluid was unable to penetrate into the tablet resulting in a slowdown disintegration. The tablet made form Era-Tab® disintegrated faster than the SDYS. This could be due to the lesser tablet bonding strength.

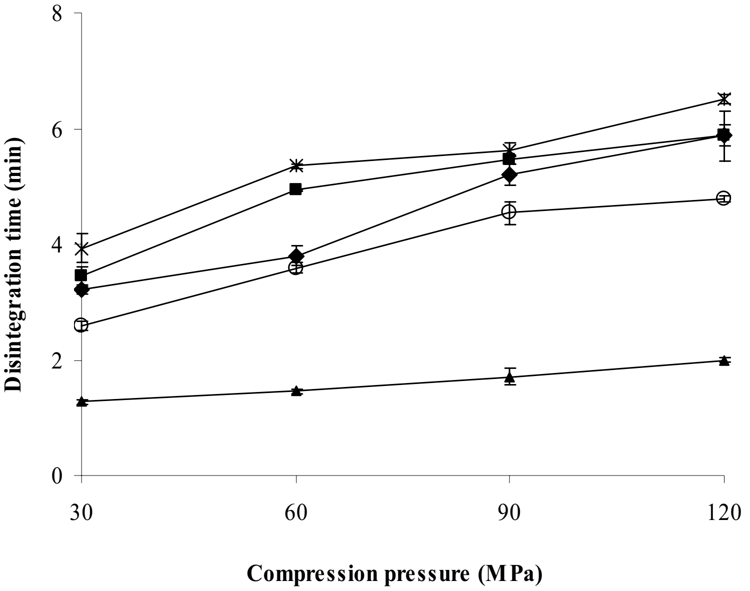


Figure 32 Disintegration time of SDYS and SDYS co-sprayed with CMS, ◆, SDYS+0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-Tab®.

5.2.6.5 Dissolution of HCTZ and dimenhydrinate tablet

HCTZ, a poorly water-soluble drug, and dimenhydrinate, a water readily soluble drug, were employed as model drugs for evaluation the effect of SDYS on the dissolution of the drugs. To determine the effect of SDYS on drug dissolution. The tablets with average strength of about 1.2-1.5 MPa were selected. Properties of HCTZ tablets and dimenhydrinate tablets, i.e., dosage uniformity, drug content, tablet weight, thickness, diameter, hardness and disintegration time, were determined. The results are shown in Table 26 and Table 36.

Without the disintegrating agent, the filler play the major role on disintegrating activity of the tablets. The drug will dissolve and release into the dissolution medium after tablet disintegration. Therefore, the dissolution of poorly soluble drugs is more dependent on disintegration time than the water soluble drugs. Since the tablets made from SDYS or Era-Tab® disintegrated very fast, the dissolution of drugs, either HCTZ or dimenhydrinate was not affected by the disintegration, but depend only on their solubility. However, the dissolution of HCTZ and dimenhydrinate were not difference. They released more than 80% in 20 minutes, and complete dissolutions were obtained in 40 minutes. The dissolution profiles of HCTZ tablets and dimenhydrinate tablets are shown in Figures 33 and 34, respectively.

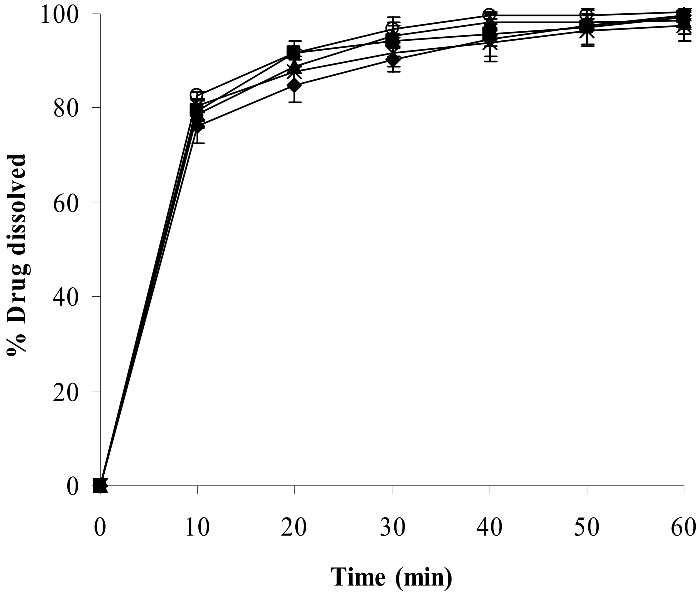


Figure 33 Dissolution profile of HCTZ tablets which various tablet bases, ◆, SDYS+CMS 0% w/w; ○, SDYS+CMS 0.5% w/w; ■, SDYS+CMS 1.0% w/w; ✳, SDYS+CMS 1.5% w/w; ▲, Era-Tab®.

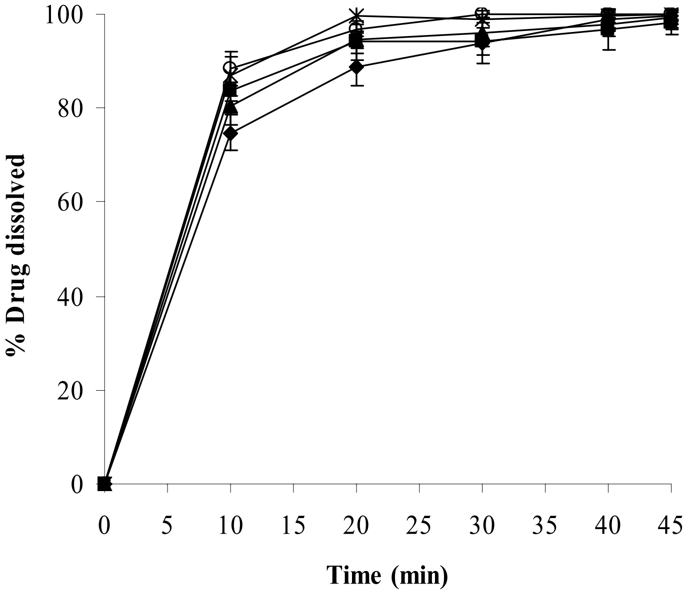


Figure 34 Dissolution profile of dimenhydrinate tablets which various tablet bases, ◆, SDYS+CMS 0% w/w; ○, SDYS+CMS 0.5% w/w; ■, SDYS+CMS 1.0% w/w; ✳, SDYS+CMS 1.5% w/w; ▲, Era-Tab®.

5.2.7 Dilution potential Dilution capacity is a measurement of the proportion of poorly compactable drug which can be incorporated into a vehicle to produce satisfying tablets. The term "dilution potential" or "carrying capacity" is defined as the amount of active ingredients which the diluent can successfully carry in the direct compression technique (Lachman, Liberman, and Kanig 1970 : 1531). The ability of SDYS and Era-Tab® to carry ascorbic acid was studied. Since ascorbic acid itself is not compactable, it was an ideal excipient for evaluation of dilution potential of these products. Kanig (1970) and Lamberson and Raynor (1976 : 55-61) suggested that the dilution potential was expressed in terms of the highest percentage of non-compressible material in the acceptable tablets or as optimum drug to carrier or filler ratio. Most commonly, dilution potential is assessed by comparing the hardness (or tensile strength) versus compaction pressure curves for various binary mixtures of the filler and some poorly compactable substances, such as ascorbic acid. The tensile strength of tablet is the resistance of a tablet to a force tending to tear it apart.

Figure 35-39 showed the compaction profiles of SDYS and Era-Tab®. Their pattern was observed with increasing concentrations of ascorbic acid. The result indicated that increasing the %w/w of ascorbic acid, the hardness of the tablets at the compression pressure range studied decreased. Thus the area under the curve (AUC) obtained by integrating the fitted quadratic equation between the compression pressure ranging of 30 MPa-120 MPa. The general form of quadratic equation is shown below

$$Y = p_1X^2 + p_2X + p_3 \qquad (15)$$

where p_1, p_2 and p_3 are constant

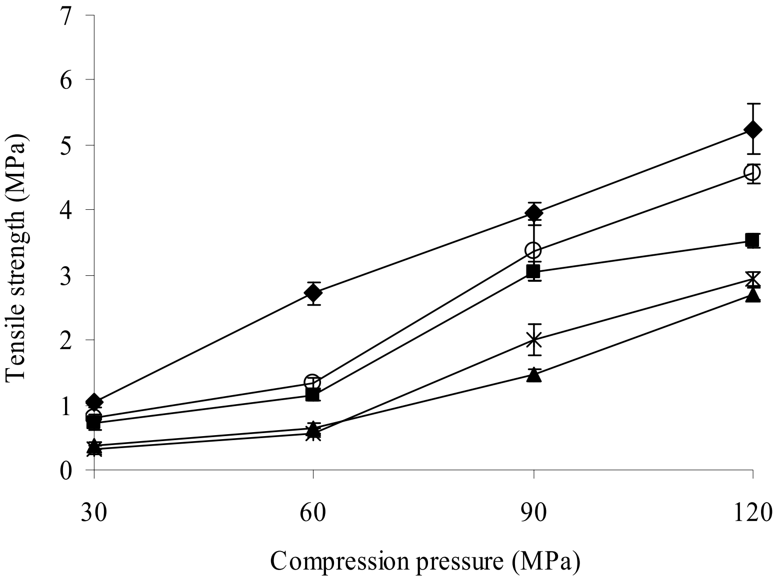


Figure 35 Compaction profile of mixture of SDYS+CMS 0%w/w and ascorbic acid, ◆, 0%w/w ascorbic acid; ○, 10%w/w ascorbic acid; ■, 20%w/w ascorbic acid; ✳, 30%w/w ascorbic acid; ▲, 40%w/w ascorbic acid.

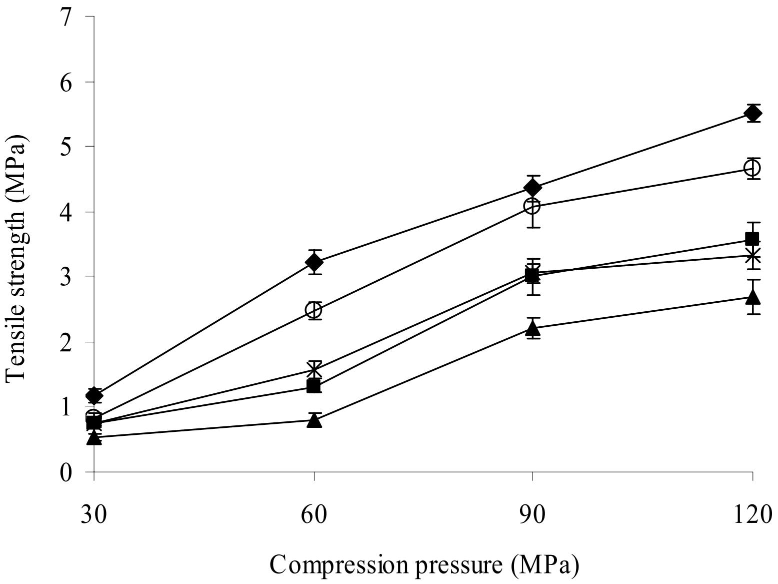


Figure 36 Compaction profile of mixture of SDYS+CMS 0.5%w/w and ascorbic acid, ◆, 0%w/w ascorbic acid; ○, 10%w/w ascorbic acid; ■, 20%w/w ascorbic acid; ✳, 30%w/w ascorbic acid; ▲, 40%w/w ascorbic acid.

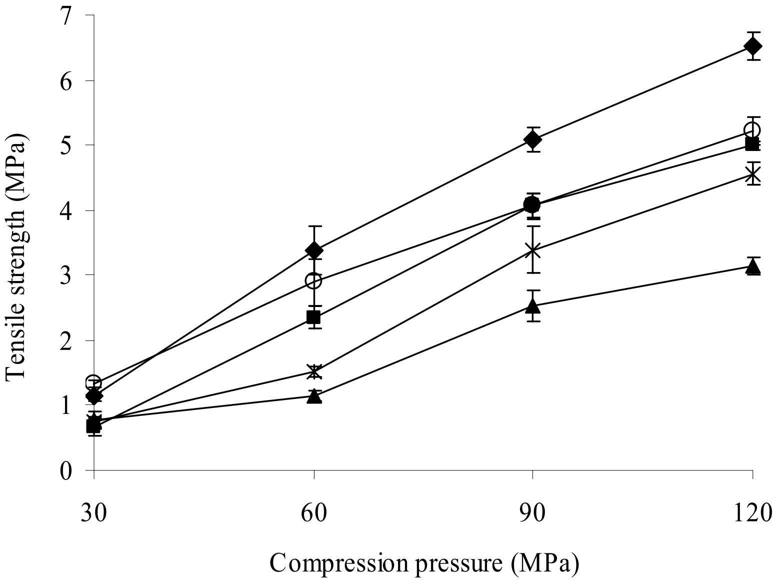


Figure 37 Compaction profile of mixture of SDYS+CMS 1.0%w/w and ascorbic acid, ◆, 0%w/w ascorbic acid; ○, 10%w/w ascorbic acid; ■, 20%w/w ascorbic acid; ✳, 30%w/w ascorbic acid; ▲, 40%w/w ascorbic acid.

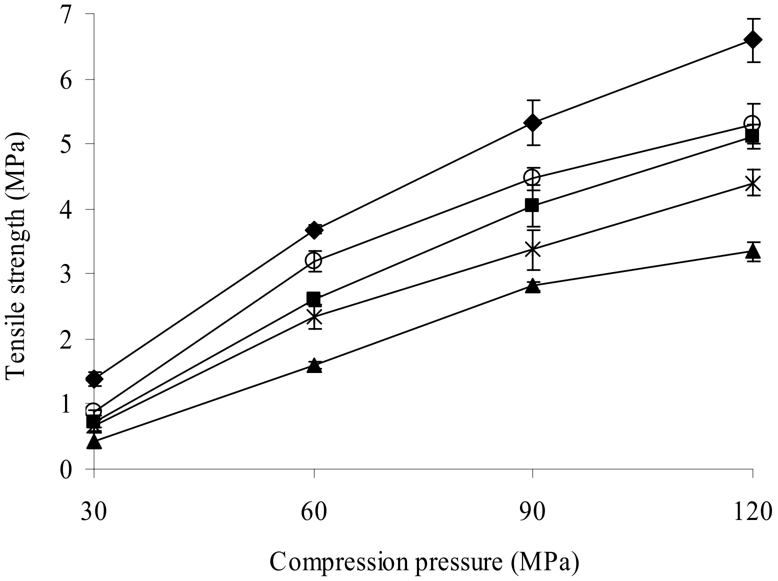


Figure 38 Compaction profile of mixture of SDYS+CMS 1.5%w/w and ascorbic acid, ◆, 0%w/w ascorbic acid; ○, 10%w/w ascorbic acid; ■, 20%w/w ascorbic acid; ✳, 30%w/w ascorbic acid; ▲, 40%w/w ascorbic acid.

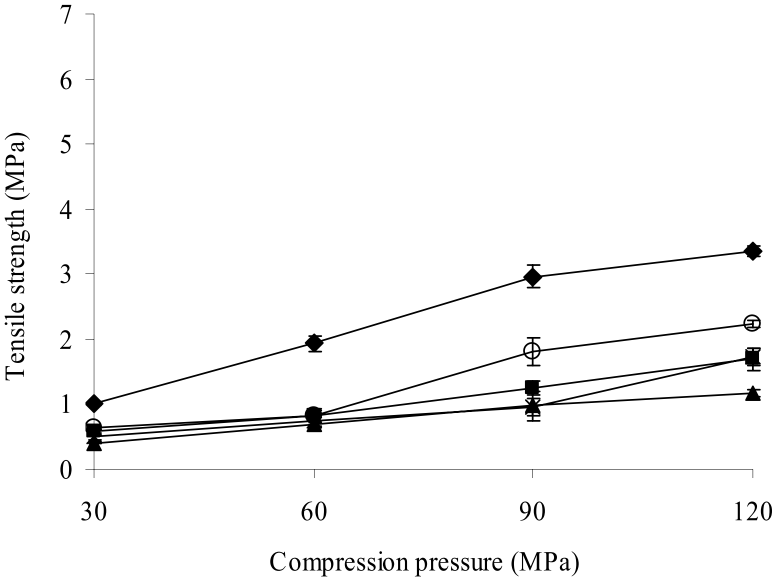


Figure 39 Compaction profile of mixture of Era-Tab® and ascorbic acid, ◆, 0%w/w ascorbic acid; ○, 10%w/w ascorbic acid; ■, 20%w/w ascorbic acid; ✳, 30%w/w ascorbic acid; ▲, 40%w/w ascorbic acid.

It was found that AUC decreased with the increase of ascorbic acid content. The decreased AUC was simply due to the increase in the proportion of poorly compactable component. The AUC of each mixture of ascorbic acid and SDYS or Era-Tab® divided by the AUC of plain SDYS or Era-Tab® would give area ratio known as work potential (area ratio) which is presented in Table 14.

Table 14 AUC of each mixture of SDYS and ascorbic acid.

Products	%AA	AUC	$AUC = \int_{x=30}^{x=120} p_1x^2 + p_2x + p_3$			
		(MPa^2)	p_1	p_2	p_3	R^2
SDYS +CMS0%	0	323.18	-0.0001	0.0621	-0.7110	0.9986
	10	226.35	0.0002	0.0162	0.0383	0.9561
	20	203.73	0.0000	0.0326	-0.4245	0.9267
	30	125.07	0.0002	0.0029	-0.0260	0.9443
	40	99.13	0.0003	-0.0143	0.5485	0.9287
SDYS +CMS0.5%	0	368.76	-0.0002	0.0843	-1.0813	0.9766
	10	321.26	-0.0003	0.0869	-1.5645	0.9644
	20	207.87	0.0000	0.0325	-0.3430	0.9506
	30	226.30	-0.0002	0.0536	-0.8105	0.9445
	40	145.10	0.0001	0.0175	-0.1588	0.9305
SDYS +CMS1.0%	0	414.03	-0.0002	0.0932	-1.4393	0.9896
	10	335.53	-0.0001	0.0601	-0.3530	0.9941
	20	316.52	-0.0002	0.0804	-1.5993	0.9843
	30	238.24	0.0001	0.0285	-0.2993	0.9782
	40	176.73	0.0001	0.0185	0.0713	0.9552
SDYS +CMS1.5%	0	439.49	-0.0003	0.1006	-1.3558	0.9821
	10	377.73	-0.0004	0.1104	-2.0453	0.9495
	20	327.50	-0.0002	0.0827	-1.5460	0.9845
	30	279.58	-0.0002	0.0667	-1.1398	0.9849
	40	218.11	-0.0002	0.0591	-1.2150	0.9755
Era-Tab®	0	236.15	-0.0001	0.0489	-0.3600	0.9704
	10	126.26	0.0001	0.0102	0.2068	0.9430
	20	96.96	0.0001	0.0033	0.4263	0.9801
	30	80.14	0.0000	0.0128	0.0438	0.9020
	40	79.47	0.0001	-0.0080	0.6383	0.9918

The plot of these ratios against ascorbic acid concentration is shown in Figure 40. A linear relation was observed similar to that reported by MA index (%w/w ascorbic acid). Linear regression and back extrapolate to 0 area ratio yielded MA index values. MA index value of SDYS and Era-Tab® can be found in Table 16. The order of decreasing MA index was SDYS+CMS 1.5% > SDYS+CMS 1.0% > SDYS+CMS 0.5% > SDYS+CMS 0% > Era-Tab®. The MA index was a theoretical measure of the maximum ability of the excipient to hold ascorbic acid in a tablet mass, while its integrity upon release of pressure was maintained.

Habib et al. (1996 : 205-212) presented that the MA index reflected the decrease in the AUC of microcrystalline/ ascorbic acid mixtures relative to that of the ascorbic acid-free blend as a function of the %w/w of ascorbic acid. Thus, the higher value was the higher capacity of that excipient to compensate for poorly compactable ascorbic acid. In order to account for the higher AUC of the drug excipient, a new index was proposed. This index, the dilution capacity index (DCI) was determined from multiplying MA index by AUC % of drug-free blend. The DCI values from this study are shown in Table 17. The largest DCI was assigned to SDYS+CMS 1.5%. The DCI is multiplicative index combining the AUC of drug free excipient and the dilution capacity. Therefore, having high DCI values reflects a higher AUC of drug free excipient, and/ or less sensitivity of the excipient to loss of compactability due to the presence of poorly compactable component. The results showed SDYS+CMS 1.5% could be the highest compactible excipient. The results indicated that the order of decreasing the dilution capacity index was SDYS+CMS 1.5% > SDYS+CMS 1.0% > SDYS+CMS 0.5% > SDYS+CMS 0% > Era-Tab®.

Table 15 Area ratio of each mixture of SDYS and various concentrations of ascorbic acid.

Products	%AA	AUC	Area ratio
SDYS+CMS0%	0	323.18	1.0000
	10	226.35	0.7004
	20	203.73	0.6304
	30	125.07	0.3870
	40	99.13	0.3067
SDYS+CMS0.5%	0	368.76	1.0000
	10	321.26	0.8712
	20	207.87	0.5637
	30	226.30	0.6137
	40	145.10	0.3935
SDYS+CMS1.0%	0	414.03	1.0000
	10	335.53	0.8104
	20	316.52	0.7645
	30	238.24	0.5754
	40	176.73	0.4269
SDYS+CMS1.5%	0	439.49	1.0000
	10	377.73	0.8595
	20	327.50	0.7452
	30	279.58	0.6362
	40	218.11	0.4963
Era-Tab®	0	236.15	1.0000
	10	126.26	0.5346
	20	96.96	0.4106
	30	80.14	0.3394
	40	79.47	0.3365

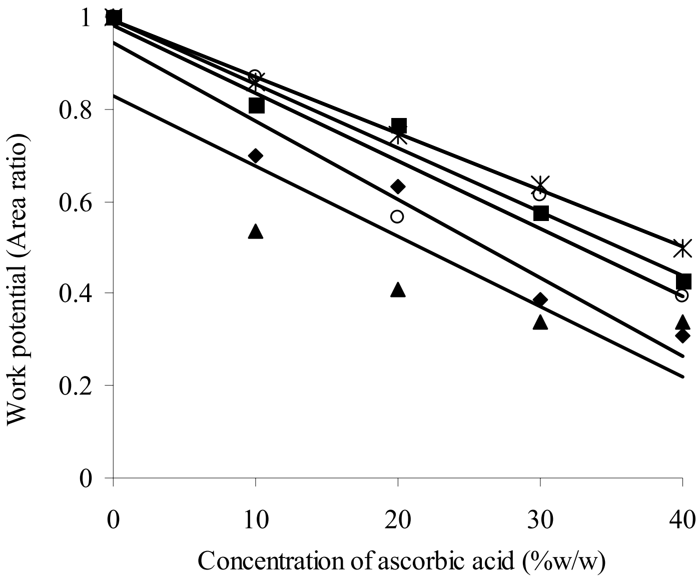


Figure 40 Plot between area ratio of SDYS and concentration of ascorbic acid (%w/w), ◆, SDYS; ○, SDYS+ CMS 0.5%w/w; ■, SDYS+ CMS 1.0%w/w; ✳, SDYS+ CMS 1.5%w/w; ▲, Era-tab®.

Table 16 MA index (%w/w ascorbic acid) values.

Products	MA index (%w/w AA)	Y = aX+b		
		a	b	R^2
SDYS+CMS 0%	55.58	-0.017	0.9449	0.9561
SDYS+CMS0.5%	66.84	-0.0147	0.9825	0.9063
SDYS+CMS1.0%	71.86	-0.0138	0.9917	0.977
SDYS+CMS1.5%	80.78	-0.0123	0.9936	0.9978
Era-Tab®	54.52	-0.0152	0.8287	0.7504

Table 17 Dilution capacity and dilution capacity index of SDYS and SDYS co-sprayed with CMS.

Products	AUC* (MPa^2)	Dilution capacity (MA index) (%w/w AA)	DCI** (%w/w AA, MPa^2)
SDYS + CMS 0%	323.18	55.12	17963.05
SDYS+CMS0.5%	368.76	66.45	24646.65
SDYS+CMS1.0%	414.03	71.40	29753.09
SDYS+CMS1.5%	439.49	80.84	35501.96
Era-Tab®	236.15	54.01	12874.82

*AUC of ascorbic acid free blend between compression pressure of 30 and 120 MPa.
** DCI = Dilution capacity index

5.2.8 Lubricant sensitivity The effects of lubricant concentrations on properties of SDYS and Era-Tab® tablets were as the following

5.2.8.1 Tablet weight, thickness and diameter Weight variation data at various compression pressures are shown in Table 27-30. All formulations met the USP 30 requirement on weight variation test. Tablet thickness was a function of tablet weight, the increase in comparison force resulted in the decrease of thickness. It could be seen that the variation of thickness at any compression force was negligible. Since only one set of tooling was employed in this study, the diameter of the tablet should remain constant regardless of the material being compressed. The data are shown in Tables 27-30.

5.2.8.2 Tablet hardness The effect of magnesium stearate concentration on the tablet hardness at various compression pressures is illustrated in Table 31 and Figures 41-49. As expected, the hardness increased with increasing compression pressure. The hardness decreased with increasing lubricant level. (Figures 41-45) It was reported that the increase in alkali stearate lubricant markedly reduced the hardness of plastic and elastic material (Bolhuis, Holzer 1996 : 517-559). The sensitivity of excipient to magnesium stearate depended on the deformation behavior and on the bonding mechanism of the materials (Lerk et al. 1975 : 317-325 ; 1977 : 33-39). Mitrevej, Faroongsarng, and Sinchaipanid (1996 : 66) reported that starch undergoes elastic deformation upon compaction. The hardness of Era-Tab® tablets, showed in the Figures 46 to 49, was the most sensitive to the increasing of lubricant concentration. The overall order of decreasing compactibility was SDYS+CMS 1.5% > SDYS+CMS 1.0% > SDYS+CMS 0.5% > SDYS+CMS 0% > Era-Tab®. ($p < 0.05$).

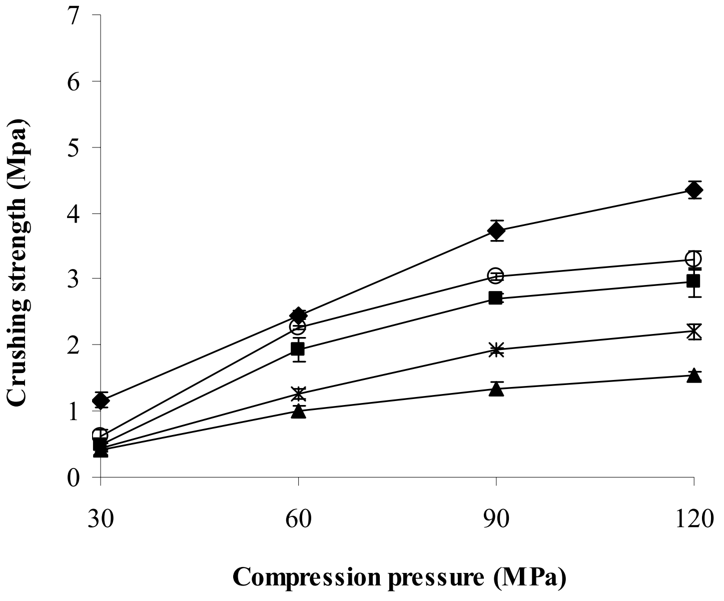


Figure 41 Effect of various concentrations of magnesium stearate on hardness of SDYS+CMS 0% tablets; ◆, 0% w/w; ○, 0.25% w/w; ■, 0.50% w/w; ∗, 0.75% w/w; ▲, 1.0% w/w

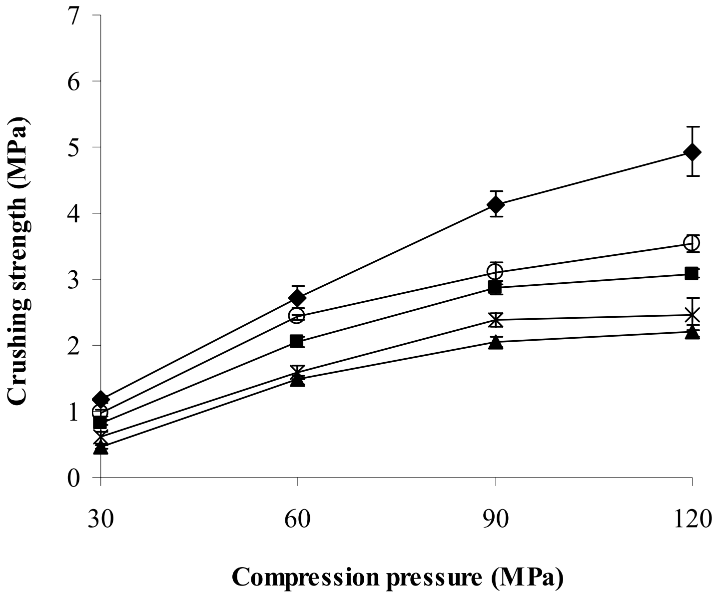


Figure 42 Effect of various concentrations of magnesium stearate on hardness of SDYS+CMS 0.5% tablets; ◆, 0% w/w; ○, 0.25% w/w; ■, 0.50% w/w; ✳, 0.75% w/w; ▲, 1.0% w/w

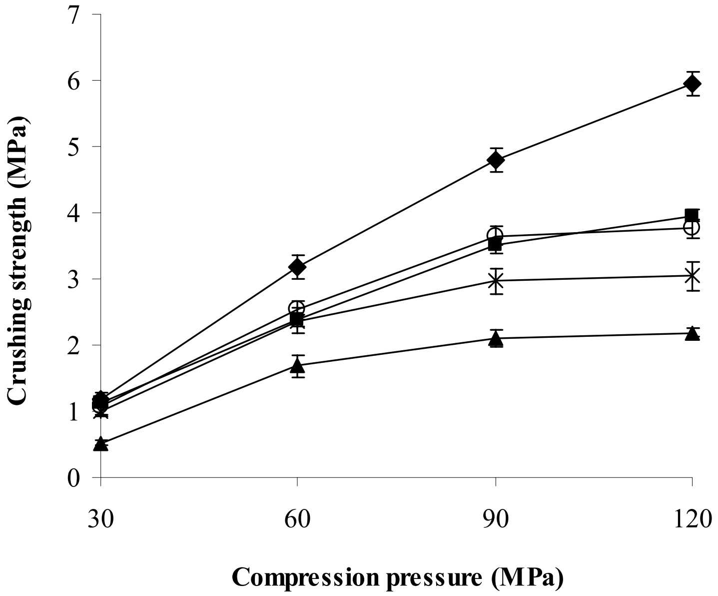


Figure 43 Effect of various concentrations of magnesium stearate on hardness of SDYS+CMS 1.0% tablets; ◆, 0% w/w; ○, 0.25% w/w; ■, 0.50% w/w; ✳, 0.75% w/w; ▲, 1.0% w/w

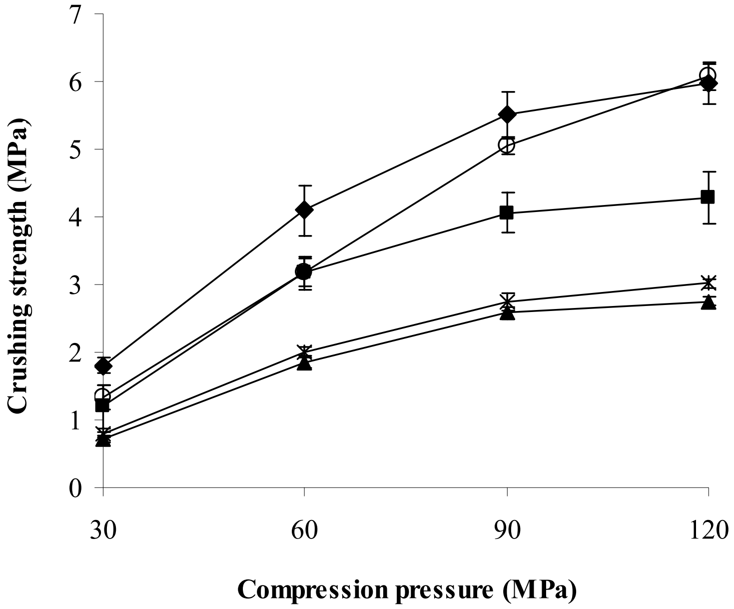


Figure 44 Effect of various concentrations of magnesium stearate on hardness of SDYS+CMS 1.5% tablets; ◆, 0% w/w; ○, 0.25% w/w; ■, 0.50% w/w; ∗, 0.75% w/w; ▲, 1.0% w/w

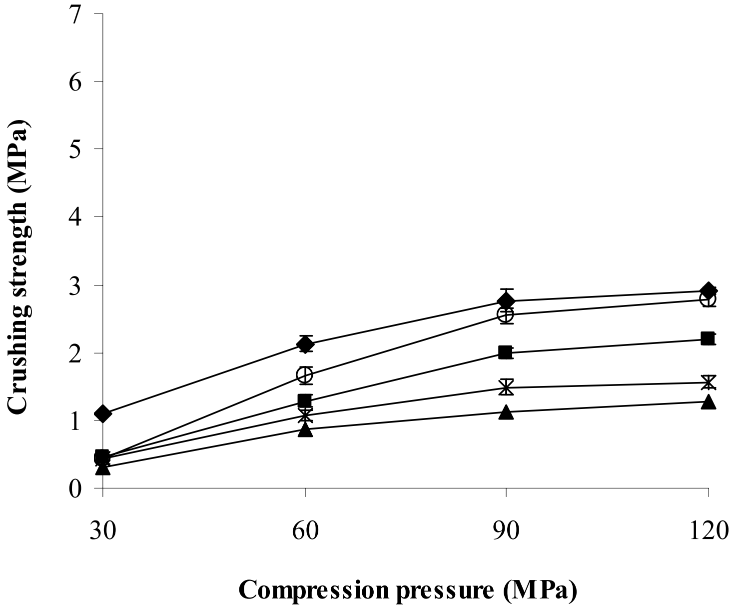


Figure 45 Effect of various concentrations of magnesium stearate on hardness of Era-Tab® tablets; ◆, 0% w/w; ○, 0.25% w/w; ■, 0.50% w/w; ∗, 0.75% w/w; ▲, 1.0% w/w

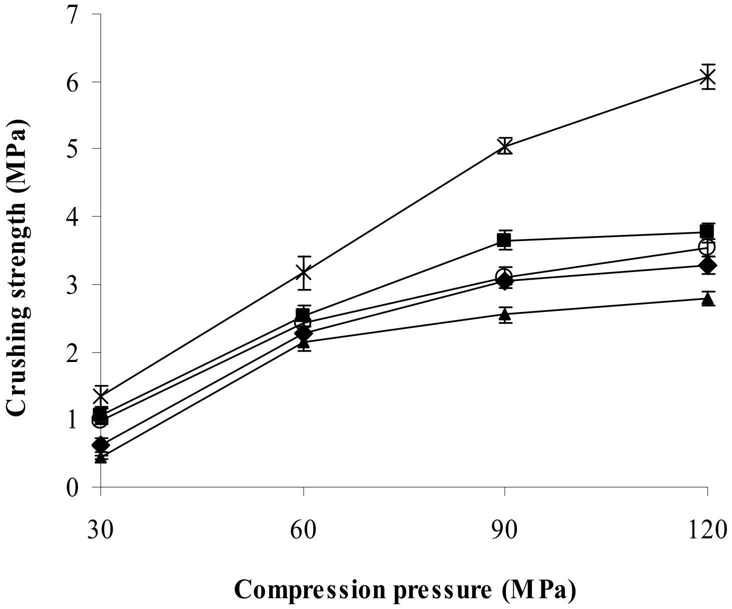


Figure 46 Effect of 0.25% w/w magnesium stearate on hardness of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

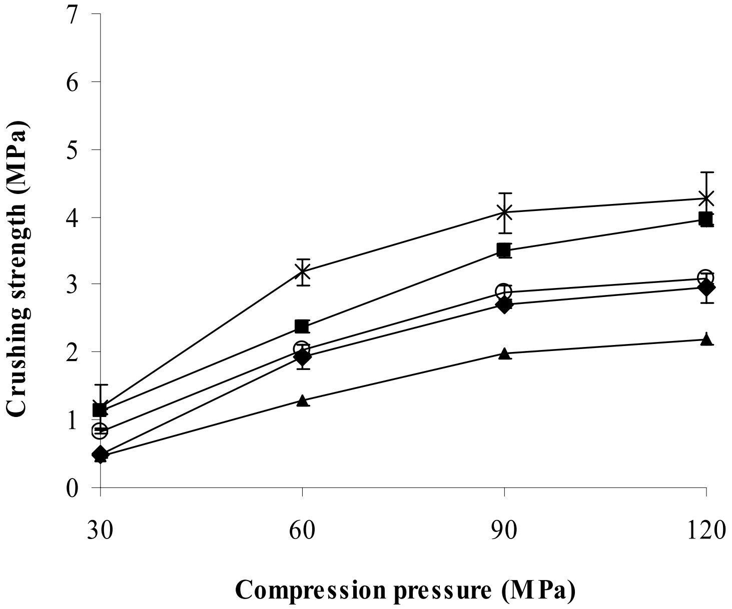


Figure 47 Effect of 0.5% w/w magnesium stearate on hardness of SDYS tablets, ◆, SDYS + CMS 0%; ○, SDYS+ CMS 0.5%; ■, SDYS+ CMS 1.0%; ✳, SDYS+ CMS 1.5%; ▲, Era-tab®.

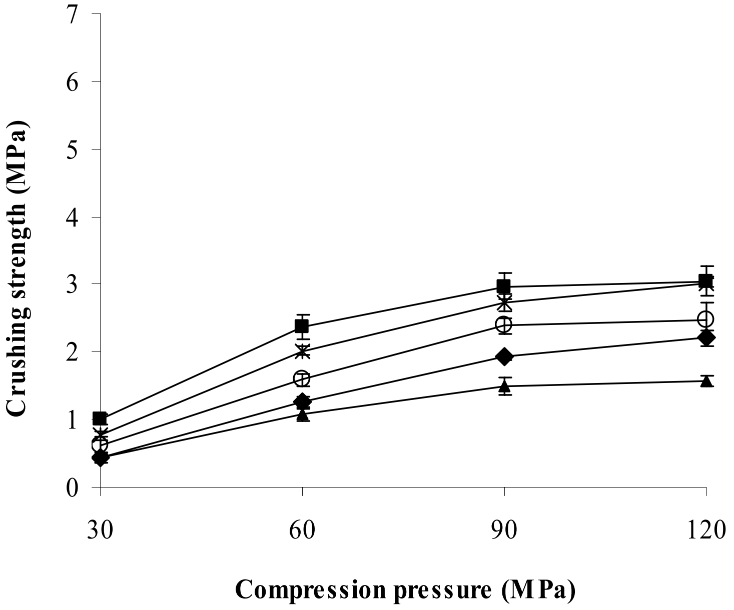


Figure 48 Effect of 0.75% w/w magnesium stearate on hardness of SDYS tablets, ◆, SDYS + CMS 0%; ○, SDYS+ CMS 0.5%; ■, SDYS+ CMS 1.0%; ✳, SDYS+ CMS 1.5%; ▲, Era-tab®.

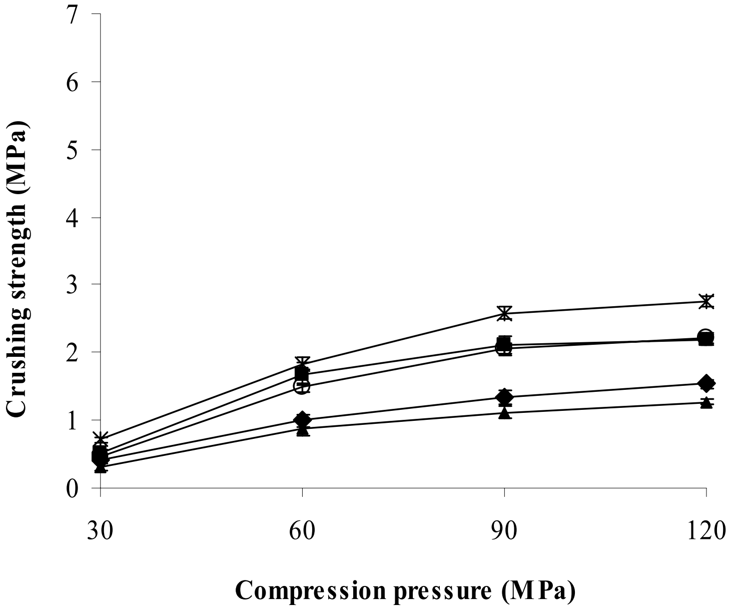


Figure 49 Effect of 1.0% w/w magnesium stearate on hardness of SDYS tablets, ◆, SDYS + CMS 0%; ○, SDYS+ CMS 0.5%; ■, SDYS+ CMS 1.0%; ✳, SDYS+ CMS 1.5%; ▲, Era-tab®

5.2.8.3 Tablet friability The tablet friability data and friability profiles are shown in Table 32 and graphically illustrated in Figure 50-53. In general, the friability decreased with increasing in compression pressure and increased with lubricant concentration. Similar to the hardness, magnesium stearate interfered the bonding of powder, causing weakening of interparticular cohesive force. As a result, the tablets were more friable. The effect was more pronounced at lower compression force. Era-Tab® tablet exhibited the highest friability while SDYS+CMS 1.5% exhibited the lowest friability. The difference in friability was of course due to the difference in amount of CMS that enhanced interparticular bonding strength.

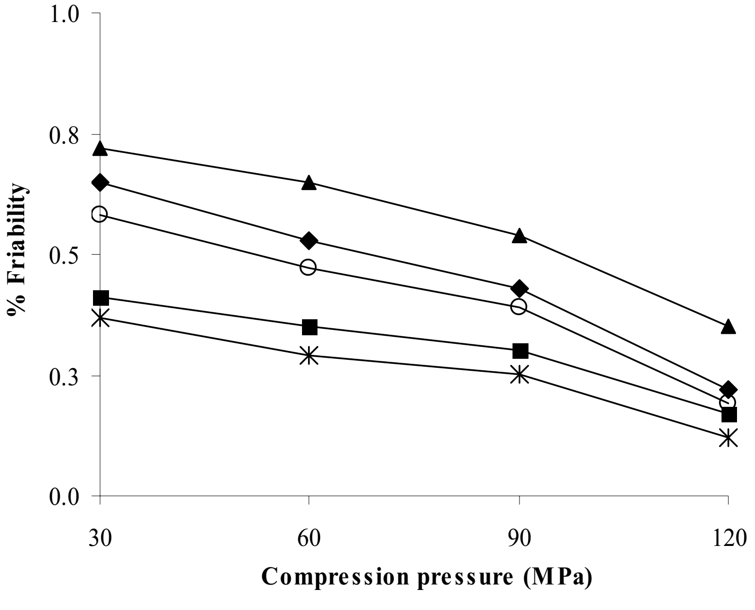


Figure 50 Effect of 0.25% w/w magnesium stearate on %friability of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

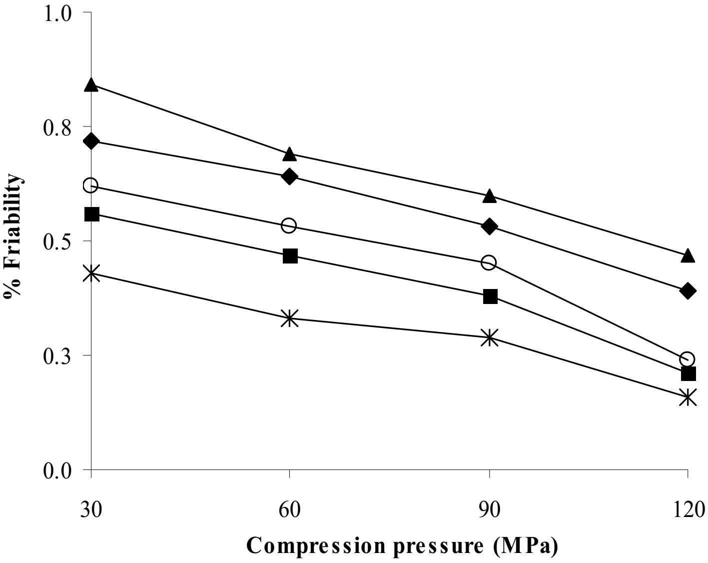


Figure 51 Effect of 0.5% w/w magnesium stearate on %friability of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

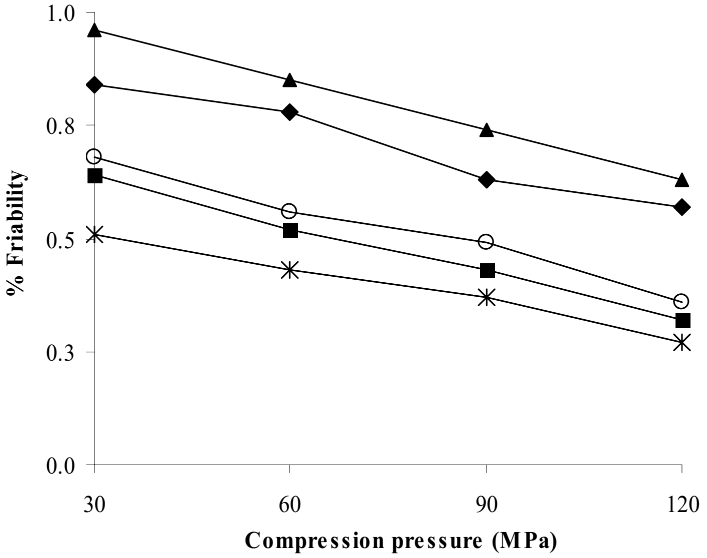


Figure 52 Effect of 0.75% w/w magnesium stearate on %friability of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

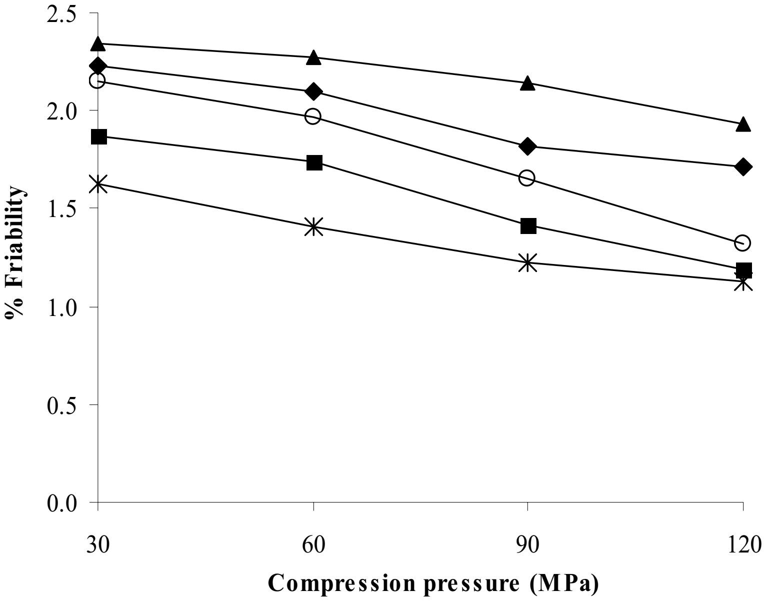


Figure 53 Effect of 1.0% w/w magnesium stearate on %friability of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

5.2.8.4 Disintegration time The disintegration of tablets depended on the filler types, the lubricant, the concentration and mixing time of lubricant, and tablet strength. Generally disintegration time is inversely proportional to the tablet strength. The increase in compression pressure prolonged the disintegration time by reducing the porosity of the compacts, and thus decreased the penetration of water into the tablet (Bolhuis et al. 1996 : 517-559). Disintegration times of SDYS tablets lubricated with various concentrations of magnesium stearate were shown in Table 33 and Figures 54-57. The disintegration time was increased with increasing the compression pressure. The tablet disintegration depended at least on tablet hardness and hydrophobicity of the lubricant. The addition of lubricant caused the reduction of tablet hardness, in consequence reduced disintegration time.

Moreover, the addition of lubricant increased the hydrophobicity of the tablets, thus resulted in the decreasing in wettability of the tablets, in consequence increasing disintegration time. Therefore, the disintegration time observed would be a result of these two opposing effects. This study, indicated that the reduction in tablet hardness had more pronounced effect on the disintegration time than did the increased hydrophobicity. The results revealed that Era-tab® tablets was found to disintegrate much faster than the others while SDYS+CMS 1.5%w/w tablets showed the longest disintegration time. However, all tablets made from SDYS were disintegrated within 8 minutes.

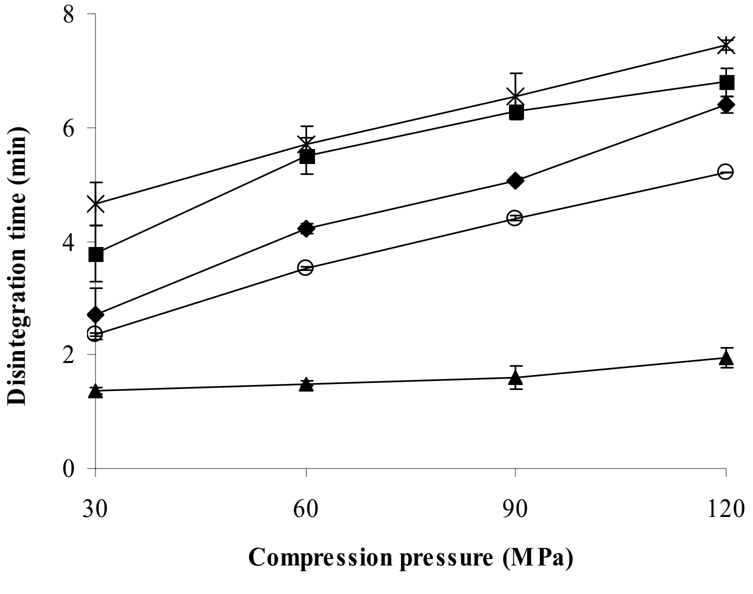


Figure 54 Effect of 0.25% w/w magnesium stearate on disintegration times of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

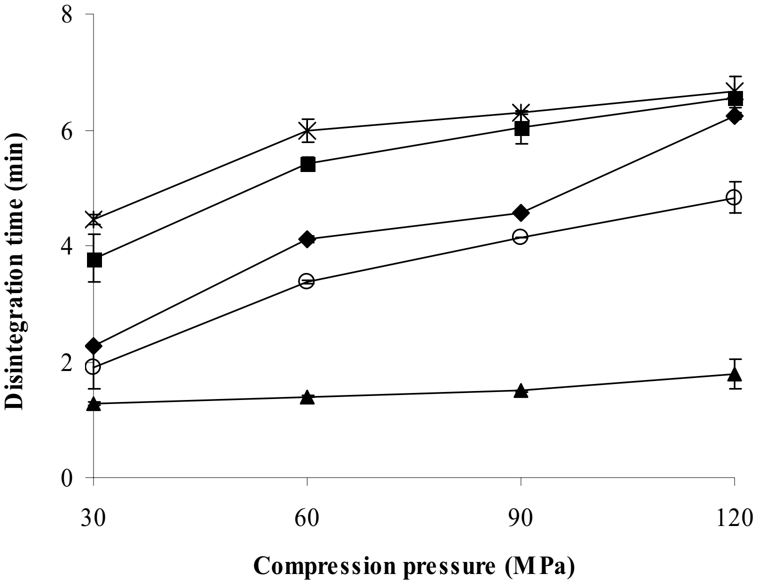


Figure 55 Effect of 0.5% w/w magnesium stearate on disintegration times of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ∗, SDYS+CMS 1.5%; ▲, Era-tab®.

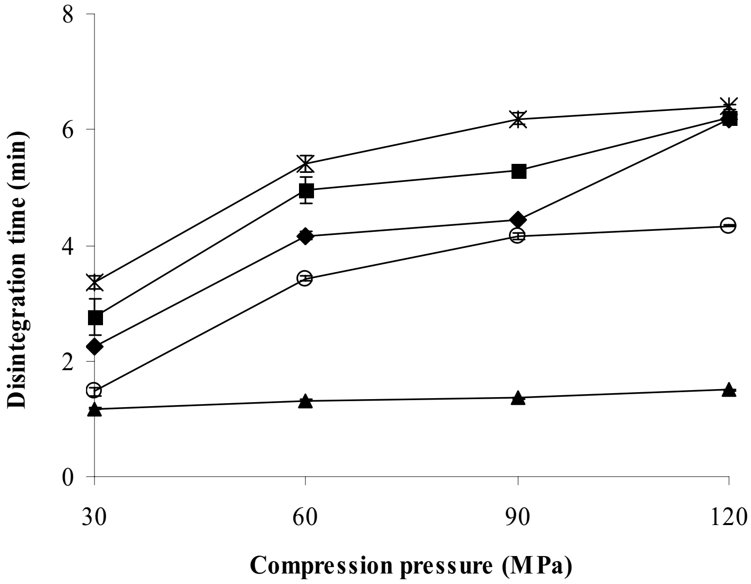


Figure 56 Effect of 0.75% w/w magnesium stearate on disintegration times of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ∗, SDYS+CMS 1.5%; ▲, Era-tab®.

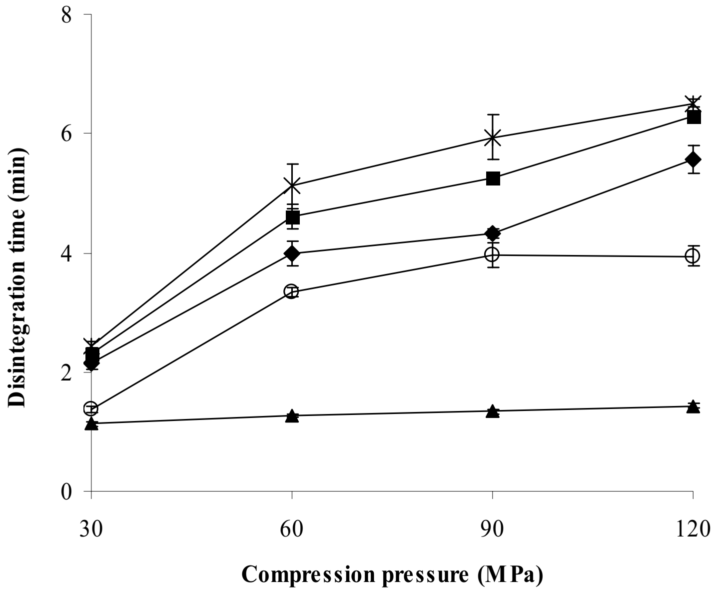


Figure 57 Effect of 1.0% w/w magnesium stearate on disintegration times of SDYS tablets, ◆, SDYS+CMS 0%; ○, SDYS+CMS 0.5%; ■, SDYS+CMS 1.0%; ✳, SDYS+CMS 1.5%; ▲, Era-tab®.

CHAPTER V

CONCLUSIONS

The results from this study could be summarized as follows:

1. Yam tuber contains about 10% w/w of yam starch. The extracted native yam starch met the requirements for starches in the USP27/NF22.

2. Preparation and properties of CMS.

   2.1 Optimum conditions for CMS preparation at 30°C in order to obtain the highest DS of about 0.2 were found to be molar ratio of NaOH and SMCA to AGU of 1.80 and 2.35, respectively, with reaction time of 4.8 hours. Carboxymethylation was confirmed by FT-IR determining. CMS granules were partially erupted under this reaction conditions.

   2.2 CMS formed gel at room temperature, gelatinization temperature of CMS was found to be equal or less than 30°C.

   2.3 The swelling powers by the weight and by the volume of optimized CMS were 131.38 and 315.89 times, respectively.

   2.4 The swelling power and viscosity of CMS increased with increasing the DS.

3. Evaluation of native yam starch and CMS as tablet disintegrant.

   3.1. The tablet containing native yam starch showed superior tablet properties i.e., tablet hardness, friability, disintegration and drug dissolution, when compared with those containing corn, tapioca and rice starch as tablet disintegrants.

3.2. The increasing of compression pressures resulted in increasing tablet hardness and decreasing friability. The effect of disintegrant concentrations on the hardness was less conspicuous. The tablet containing CMS showed slightly higher tablet hardness and lower friability than the tablet containing Exposol®.

3.3. The disintegration time increased with compression pressures. DCP tablets disintegrated when 1.0% w/w or more of CMS or Exposol® were added. CMS 2.0 % was the optimum concentration to be a tablet disintegrant in DCP tablet. With higher amount of CMS, disintegration time was slightly prolonged.

3.4. The drug dissolution was corresponded to the tablet disintegration time. The HCTZ dissolution from the tablets containing Exposol® and up to 3.0% CMS was met the USP30 requirements. The drug dissolution of HCTZ tablet was prolonged, when 4% CMS was added. CMS was comparable disintegrant with Exposol® when 2% w/w added. CMS, at the concentration of 2% w/w, was good disintegrant as Exposol® in HCTZ tablet.

4. Preparation and evaluation of SDYS as direct compressible fillers.

4.1. The SEM photographs revealed that SDYS were spherical agglomeration of yam starch grain. The particle sizes were in the range of 84.43 - 104.35 μm. SDYS exhibited satisfactory flowability and compactibity.

4.2. Dilution capacity indices (DCI) of SDYS were higher than that of the Era-Tab®. SDYS+CMS 1.5% was possed the highest carrying capacity.

4.3. The increase of magnesium stearate content reduced the hardness of SDYS and Era-Tab®. Era-tab® was the most sensitive to magnesium stearate. The disintegration of SDYS tablets seem to be more dependent on tablet hardness than the lubricant concentration.

4.4. The SDYS tablets were stronger than the Era-Tab® tablet. Consequently, they disintegrated slower than the Era-Tab® tablet. SDYS+CMS 0.5% exhibited a powerful tablet disintegrating agent. Incorporation with higher amount of CMS in SDYS retarded the tablet disintegration.

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APPENDIX

APPENDIX A

TABLET PROPERTIES

Table 18 Weight, thickness and diameter of DCP tablets with various concentrations CMS as tablet disintegrant.

Concentrations of CMS	CP (MPa)	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
CMS 0%	50	250.83 (0.62)	2.81 (0.01)	7.99 (0.01)
	100	250.61 (0.70)	2.69 (0.01)	8.00 (0.01)
	150	250.86 (0.83)	2.59 (0.01)	8.01 (0.01)
	200	251.41 (0.64)	2.48 (0.03)	8.02 (0.01)
CMS 0.5%	50	250.81 (0.69)	2.82 (0.02)	7.99 (0.00)
	100	251.28 (0.91)	2.66 (0.04)	8.00 (0.00)
	150	251.11 (0.67)	2.61 (0.01)	8.01 (0.00)
	200	250.60 (0.90)	2.58 (0.03)	8.01 (0.00)
CMS 1.0%	50	250.36 (0.80)	2.77 (0.01)	7.99 (0.00)
	100	250.85 (0.74)	2.68 (0.02)	8.00 (0.00)
	150	250.92 (1.23)	2.63 (0.03)	8.00 (0.00)
	200	251.44 (0.70)	2.56 (0.02)	8.01 (0.00)
CMS 2.0%	50	250.32 (0.81)	2.81 (0.04)	7.99 (0.01)
	100	251.06 (1.16)	2.68 (0.03)	7.98 (0.01)
	150	250.74 (1.11)	2.60 (0.03)	8.00 (0.00)
	200	261.13 (5.84)	2.58 (0.01)	8.00 (0.00)
CMS 3.0%	50	251.09 (0.91)	2.81 (0.02)	7.99 (0.00)
	100	250.96 (0.92)	2.70 (0.03)	8.00 (0.00)
	150	251.43 (0.77)	2.63 (0.02)	8.00 (0.00)
	200	251.17 (0.88)	2.57 (0.02)	8.01 (0.00)
CMS 4.0%	50	251.20 (0.70)	2.87 (0.02)	7.99 (0.01)
	100	250.65 (0.84)	2.75 (0.03)	8.00 (0.01)
	150	250.89 (0.97)	2.65 (0.02)	8.01 (0.00)
	200	251.45 (0.61)	2.60 (0.02)	8.01 (0.01)

Table 19 Hardness, friability and disintegration time of DCP tablets with various concentrations of CMS as tablet disintegrant.

Concentrations of CMS	CP (MPa)	Hardness MPa (SD)	%Friability	DT min (SD)
CMS 0%	50	1.63 (0.12)	0.08	N/A*
	100	2.28 (0.09)	0.06	N/A*
	150	3.32 (0.22)	0.05	N/A*
	200	4.39 (0.20)	0.03	N/A*
CMS 0.5%	50	1.03 (0.09)	0.12	0.42 (0.13)
	100	1.63 (0.17)	0.11	180.00 (0.00)
	150	2.51 (0.09)	0.08	180.00 (0.00)
	200	3.10 (0.34)	0.06	180.00 (0.00)
CMS 1.0%	50	1.01 (0.05)	0.11	0.37 (0.03)
	100	1.78 (0.10)	0.09	0.90 (0.43)
	150	2.47 (0.25)	0.07	1.14(0.05)
	200	3.12 (0.16)	0.06	180.00 (0.00)
CMS 2.0%	50	0.97 (0.13)	0.10	0.14 (0.05)
	100	1.77 (0.12)	0.08	0.29 (0.07)
	150	2.53 (0.07)	0.06	0.54 (0.25)
	200	3.06 (0.17)	0.05	1.73 (0.73)
CMS 3.0%	50	1.00 (006)	0.09	0.42 (0.05)
	100	1.65 (0.09)	0.07	0.82 (0.32)
	150	2.38 (0.07)	0.06	1.12 (0.28)
	200	2.92 (0.20)	0.04	2.08 (0.44)
CMS 4.0%	50	0.95 (0.06)	0.08	1.20 (0.12)
	100	1.57 (0.22)	0.06	2.04 (0.42)
	150	2.32 (0.19)	0.03	2.82 (0.61)
	200	2.94 (0.22)	0.02	4.52 (1.75)

* The tablets did not disintegrate.

Table 20 Weight, thickness and diameter of DCP tablets with various concentrations of Exposol® as tablet disintegrant.

Concentrations of Exposol®	CP (MPa)	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
Exposol® 0%	50	250.83 (0.62)	2.81 (0.01)	7.99 (0.01)
	100	250.61 (0.70)	2.69 (0.01)	8.00 (0.01)
	150	250.86 (0.83)	2.59 (0.01)	8.01 (0.01)
	200	251.41 (0.64)	2.48 (0.03)	8.02 (0.01)
Exposol® 0.5%	50	251.62 (0.86)	2.85 (0.04)	7.99 (0.00)
	100	251.71 (0.76)	2.71 (0.03)	8.00 (0.00)
	150	251.62 (0.61)	2.65 (0.02)	8.01 (0.00)
	200	251.39 (0.86)	2.59 (0.02)	8.01 (0.00)
Exposol® 1.0%	50	251.25 (0.97)	2.84 (0.02)	7.99 (0.00)
	100	250.93 (0.87)	2.72 (0.02)	8.00 (0.00)
	150	251.20 (0.91)	2.66 (0.02)	8.01 (0.00)
	200	251.49 (0.87)	2.60 (0.02)	8.01 (0.00)
Exposol® 2.0%	50	250.62 (0.68)	2.85 (0.04)	7.99 (0.00)
	100	250.50 (1.00)	2.68 (0.01)	8.00 (0.01)
	150	251.67 (0.78)	2.62 (0.01)	8.01 (0.00)
	200	251.19 (1.67)	2.60 (0.02)	8.01 (0.00)
Exposol® 3.0%	50	250.19 (0.45)	2.85 (0.03)	7.99 (0.00)
	100	251.32 (0.94)	2.72 (0.02)	8.01 (0.01)
	150	251.49 (0.71)	2.62 (0.03)	8.01 (0.00)
	200	251.54 (0.83)	2.57 (0.05)	8.02 (0.00)
Exposol® 4.0%	50	251.67 (0.81)	2.86 (0.02)	8.01 (0.01)
	100	251.00 (0.54)	2.71 (0.03)	8.01 (0.00)
	150	251.05 (0.64)	2.63 (0.03)	8.01 (0.00)
	200	251.61 (0.58)	2.60 (0.03)	8.02 (0.00)

Table 21 Hardness, friability and disintegration time of DCP tablets with various concentrations of Exposol® as tablet disintegrant.

Concentrations of Exposol®	CP (MPa)	Hardness MPa (SD)	%Friability	DT min (SD)
Exposol® 0%	50	1.63 (0.12)	0.08	N/A*
	100	2.28 (0.09)	0.06	N/A*
	150	3.32 (0.22)	0.05	N/A*
	200	4.39 (0.20)	0.03	N/A*
Exposol® 0.5%	50	0.86 (0.07)	0.08	180.00 (0.00)
	100	1.77 (0.16)	0.06	180.00 (0.00)
	150	2.40 (0.13)	0.03	180.00 (0.00)
	200	3.34 (0.26)	0.02	180.00 (0.00)
Exposol® 1.0%	50	0.82 (0.09)	0.09	0.34 (0.20)
	100	1.70 (0.10)	0.08	1.47 (0.55)
	150	2.48 (0.19)	0.05	180.00 (0.00)
	200	3.34 (0.24)	0.04	180.00 (0.00)
Exposol® 2.0%	50	0.83 (0.09)	0.11	0.03 (0.01)
	100	1.58 (0.04)	0.09	0.07 (0.03)
	150	2.56 (0.12)	0.06	0.50 (0.38)
	200	2.98 (0.20)	0.05	1.32 (0.06)
Exposol® 3.0%	50	0.68 (0.10)	0.13	0.02 (0.00)
	100	1.30 (0.18)	0.11	0.04 (0.01)
	150	2.27 (0.15)	0.06	0.05 (0.01)
	200	2.73 (0.26)	0.04	0.08 (0.01)
Exposol® 4.0%	50	0.59 (0.06)	0.15	0.02 (0.00)
	100	1.43 (0.04)	0.12	0.03 (0.01)
	150	2.05 (0.14)	0.07	0.04 (0.01)
	200	2.87 (0.14)	0.05	0.06 (0.00)

Table 22 Weight, thickness, diameter of physical properties of HCTZ tablets.

Concentrations of CMS	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
CMS 0%	251.74 (0.35)	2.77(0.03)	8.01(0.00)
CMS0.5%	250.90(1.10)	2.78(0.03)	8.01(0.01)
CMS1.0%	250.49(0.88)	2.76(0.03)	8.01(0.00)
CMS2.0%	250.66(0.82)	2.75(0.02)	8.01(0.00)
CMS3.0%	251.11(0.90)	2.74(0.01)	8.02(0.00)
CMS4.0%	250.94(1.28)	2.77(0.02)	8.01(0.00)
Exposol 0.5%	250.34(0.70)	2.76(0.04)	8.02(0.01)
Exposol 1.0%	250.72(0.92)	2.77(0.02)	8.02(0.00)
Exposol 2.0%	250.47(0.82)	2.79(0.03)	8.02(0.00)
Exposol 3.0%	250.59(0.85)	2.74(0.01)	8.01(0.00)
Exposol 4.0%	251.22(0.83)	2.78(0.01)	8.02(0.00)

Table 23 Hardness, friability and disintegration time physical properties of HCTZ tablets.

Concentrations of CMS	Hardness MPa (SD)	%Friability	DT min (SD)
CMS 0%	1.65 (0.13)	0.18	N/A*
CMS0.5%	1.66 (0.13)	0.17	0.49 (0.04)
CMS1.0%	1.70 (0.04)	0.17	0.29 (0.01)
CMS2.0%	1.67 (0.15)	0.15	0.21 (0.02)
CMS3.0%	1.63 (0.21)	0.14	1.13 (0.05)
CMS4.0%	1.84 (0.05)	0.11	1.96 (0.36)
Exposol 0.5%	1.63 (0.23)	0.15	0.46 (0.12)
Exposol 1.0%	1.59 (0.17)	0.18	0.11 (0.01)
Exposol 2.0%	1.34 (0.22)	0.20	0.06 (0.00)
Exposol 3.0%	1.58 (0.07)	0.21	0.05 (0.00)
Exposol 4.0%	1.50 (0.11)	0.24	0.04 (0.00)

* N/A = The tablets did not disintegrate.

Table 24 Weight variation, thickness and diameter of SDYS tablets.

Products	CP MPa	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
SDYS	30	205.19 (0.83)	4.07 (0.04)	8.02 (0.01)
	60	205.21 (1.56)	3.54 (0.03)	8.00 (0.01)
	90	204.44 (1.11)	3.33 (0.02)	7.98 (0.00)
	120	201.39 (0.49)	3.31 (0.01)	7.97 (0.01)
SDYS+CMS0.5%	30	204.88 (0.55)	3.98 (0.03)	8.03 (0.01)
	60	204.46 (0.76)	3.49 (0.02)	7.99 (0.00)
	90	204.96 (1.49)	3.34 (0.02)	7.98 (0.01)
	120	204.68 (0.79)	3.28 (0.02)	7.97 (0.01)
SDYS+CMS1.0%	30	205.62 (0.94)	4.09 (0.01)	8.03 (0.00)
	60	204.80 (0.62)	3.56 (0.03)	8.01 (0.02)
	90	204.32 (1.19)	3.31 (0.02)	7.97 (0.01)
	120	202.89 (1.80)	3.22 (0.03)	7.95 (0.01)
SDYS+CMS1.5%	30	203.68 (0.88)	4.05 (0.05)	8.03 (0.01)
	60	202.90 (2.15)	3.53 (0.03)	8.01 (0.01)
	90	204.52 (0.85)	3.33 (0.02)	7.97 (0.02)
	120	202.48 (2.05)	3.24 (0.05)	7.94 (0.01)
Era-Tab®	30	205.00 (1.64)	3.80 (0.02)	8.02 (0.01)
	60	205.75 (0.72)	3.43 (0.02)	8.01 (0.01)
	90	204.84 (0.90)	3.30 (0.02)	7.99 (0.00)
	120	203.94 (1.58)	3.27 (0.02)	7.98 (0.00)

Table 25 Hardness, friability and disintegration time of SDYS tablets.

Products	CP	Hardness MPa(SD)	Friability (%)	DT min (SD)
SDYS	30	1.16 (0.12)	0.63	3.12 (0.04)
	60	2.45 (0.06)	0.40	3.48 (0.10)
	90	3.72 (0.16)	0.25	5.06 (0.25)
	120	4.35 (0.12)	0.15	5.66 (0.31)
SDYS+CMS0.5%	30	1.18 (0.06)	0.55	2.36 (0.05)
	60	2.73 (0.16)	0.36	3.36 (0.05)
	90	4.14 (0.19)	0.17	4.32 (0.11)
	120	4.93 (0.36)	0.12	4.47 (0.03)
SDYS+CMS1.0%	30	1.19 (0.08)	0.43	3.27 (0.09)
	60	3.19 (0.18)	0.28	4.56 (0.01)
	90	4.79 (0.18)	0.13	5.28 (0.05)
	120	5.95 (0.19)	0.09	5.72 (0.43)
SDYS+CMS1.5%	30	1.33 (0.11)	0.34	3.83 (0.35)
	60	3.17 (0.37)	0.26	5.21 (0.02)
	90	5.05 (0.33)	0.12	5.38 (0.07)
	120	6.07 (0.30)	0.08	6.31 (0.05)
Era-Tab®	30	1.09 (0.03)	1.95	1.16 (0.02)
	60	1.66 (0.11)	1.71	1.27 (0.03)
	90	2.77 (0.16)	1.54	1.43 (0.08)
	120	2.91 (0.04)	1.18	1.87 (0.22)

Table 26 Physical properties of HCTZ and dimenhydrinate tablets which various SDYSs as tablet base.

Drug	Filler	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)	Hardness MPa (SD)	DT min (SD)
HCTZ						
	SDYS	205.12(1.21)	3.20(0.02)	8.01(0.00)	1.32 (0.10)	2.39 (0.02)
	SDYS+CMS0.5%	205.70(1.22)	3.42(0.06)	8.01(0.01)	1.34 (0.05)	2.24 (0.03)
	SDYS+CMS1.0%	205.08(0.70)	3.35(0.07)	8.02(0.00)	1.30 (0.14)	2.47 (0.07)
	SDYS+CMS1.5%	203.89(1.07)	3.51(0.03)	8.05(0.00)	1.34 (0.14)	3.53 (0.02)
	Era-Tab®	201.16(0.56)	3.38(0.02)	8.03(0.00)	1.31 (0.05)	1.05 (0.02)
Dimenhydrinate						
	SDYS	205.06(0.72)	3.29(0.02)	8.05(0.01)	1.32 (0.02)	2.45 (0.03)
	SDYS+CMS0.5%	204.98(0.67)	3.23(0.03)	8.06(0.01)	1.28 (0.09)	2.24 (0.06)
	SDYS+CMS1.0%	204.25(0.86)	3.21(0.01)	8.09(0.01)	1.33 (0.07)	3.12 (0.07)
	SDYS+CMS1.5%	204.45(0.82)	3.23(0.01)	8.07(0.01)	1.26 (0.10)	3.77 (0.27)
	Era-Tab®	200.46(0.71)	3.18(0.02)	8.08 (0.01)	1.35 (0.08)	1.87 (0.25)

Table 27 Weight variation, thickness and diameter of SDYS tablet with 0.25%w/w magnesium stearate.

Products	CP MPa	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
SDYS	30	205.14 (0.96)	3.99 (0.02)	8.06 (0.01)
	60	205.36 (1.64)	3.44 (0.02)	7.98 (0.01)
	90	204.98 (0.79)	3.34 (0.03)	7.98 (0.01)
	120	203.60 (1.02)	3.29 (0.01)	7.98 (0.01)
SDYS+CMS0.5%	30	205.14 (0.97)	3.82 (0.05)	8.02 (0.01)
	60	203.62 (1.02)	3.42 (0.03)	7.97 (0.02)
	90	205.26 (0.71)	3.36 (0.02)	7.98 (0.01)
	120	204.91 (0.76)	3.32 (0.02)	7.96 (0.01)
SDYS+CMS1.0%	30	205.24 (1.64)	3.94 (0.14)	8.04 (0.02)
	60	203.52 (1.03)	3.43 (0.03)	7.98 (0.01)
	90	205.17 (0.74)	3.32 (0.04)	7.95 (0.01)
	120	204.81 (0.76)	3.35 (0.03)	7.96 (0.01)
SDYS+CMS1.5%	30	204.60 (1.13)	3.96 (0.03)	8.06 (0.00)
	60	205.00 (1.58)	3.50 (0.02)	8.02 (0.01)
	90	204.51 (0.83)	3.37 (0.02)	8.01 (0.01)
	120	203.02 (1.17)	3.29 (0.03)	7.99 (0.01)
Era-Tab®	30	201.57 (0.54)	3.86 (0.03)	8.05 (0.00)
	60	204.91 (0.80)	3.45 (0.02)	8.02 (0.00)
	90	204.54 (0.66)	3.33 (0.03)	8.00 (0.00)
	120	203.75 (0.91)	3.25 (0.03)	8.00 (0.00)

Table 28 Weight variation, thickness and diameter of SDYS tablet with 0.50%w/w magnesium stearate.

Products	CP MPa	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
SDYS	30	201.07 (0.66)	3.96 (0.05)	8.06 (0.01)
	60	205.24 (0.71)	3.47 (0.02)	8.04 (0.01)
	90	204.93 (0.61)	3.32 (0.02)	8.02 (0.01)
	120	204.14 (0.99)	3.27 (0.02)	8.02 (0.01)
SDYS+CMS0.5%	30	200.52 (0.64)	3.79 (0.02)	8.02 (0.01)
	60	204.06 (1.14)	3.45 (0.03)	7.99 (0.01)
	90	201.25 (0.50)	3.37 (0.05)	7.97 (0.01)
	120	205.35 (1.65)	3.31 (0.02)	7.96 (0.01)
SDYS+CMS1.0%	30	204.18 (0.70)	3.70 (0.04)	8.00 (0.01)
	60	205.00 (0.65)	3.40 (0.03)	7.99 (0.02)
	90	204.72 (0.66)	3.33 (0.02)	7.95 (0.01)
	120	205.06 (0.98)	3.32 (0.02)	7.95 (0.01)
SDYS+CMS1.5%	30	201.47 (0.60)	3.90 (0.03)	8.05 (0.02)
	60	204.73 (0.93)	3.44 (0.02)	8.00 (0.00)
	90	204.41 (0.65)	3.35 (0.01)	7.97 (0.01)
	120	203.66 (0.96)	3.31 (0.02)	7.96 (0.01)
Era-Tab®	30	204.71 (0.63)	3.76 (0.03)	8.04 (0.01)
	60	203.67 (1.22)	3.41 (0.01)	8.01 (0.01)
	90	201.65 (0.62)	3.34 (0.02)	8.00 (0.01)
	120	204.46 (0.69)	3.32 (0.01)	7.99 (0.00)

Table 29 Weight variation, thickness and diameter of SDYS tablet with 0.75%w/w magnesium stearate.

Products	CP MPa	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
SDYS	30	204.93 (0.76)	3.84 (0.02)	8.03 (0.00)
	60	204.29 (0.73)	3.43 (0.02)	8.00 (0.01)
	90	204.32 (1.00)	3.33 (0.04)	7.97 (0.01)
	120	200.53 (0.63)	3.32 (0.02)	7.95 (0.01)
SDYS+CMS0.5%	30	204.98 (0.80)	3.83 (0.08)	8.02 (0.01)
	60	201.08 (0.65)	3.45 (0.05)	7.99 (0.01)
	90	204.94 (0.61)	3.37 (0.02)	7.97 (0.01)
	120	204.13 (0.98)	3.31 (0.01)	7.95 (0.01)
SDYS+CMS1.0%	30	204.88 (0.81)	3.90 (0.02)	8.05 (0.01)
	60	200.98 (0.65)	3.47 (0.05)	8.01 (0.01)
	90	204.84 (0.63)	3.33 (0.02)	7.99 (0.01)
	120	204.01 (0.97)	3.32 (0.04)	7.99 (0.01)
SDYS+CMS1.5%	30	204.55 (0.92)	3.94 (0.05)	8.05 (0.01)
	60	203.74 (0.72)	3.50 (0.03)	8.02 (0.01)
	90	203.79 (1.08)	3.34 (0.03)	7.99 (0.01)
	120	201.05 (0.71)	3.29 (0.04)	7.98 (0.02)
Era-Tab®	30	204.80 (1.09)	3.79 (0.04)	8.05 (0.00)
	60	204.99 (1.52)	3.43 (0.02)	8.02 (0.00)
	90	204.60 (0.88)	3.33 (0.02)	8.01 (0.01)
	120	203.20 (0.98)	3.32 (0.03)	8.00 (0.01)

Table 30 Weight variation, thickness and diameter of SDYS tablet with 1.0%w/w magnesium stearate.

Products	CP MPa	Weight mg (SD)	Thickness mm (SD)	Diameter mm (SD)
SDYS	30	205.09 (0.63)	3.76 (0.05)	8.03 (0.01)
	60	204.08 (1.09)	3.46 (0.09)	8.00 (0.01)
	90	201.27 (0.49)	3.33 (0.03)	7.98 (0.01)
	120	204.80 (0.65)	3.30 (0.03)	7.97 (0.01)
SDYS+CMS0.5%	30	204.28 (0.73)	3.70 (0.05)	8.03 (0.01)
	60	204.32 (0.98)	3.42 (0.03)	8.00 (0.01)
	90	205.11 (0.65)	3.36 (0.01)	7.99 (0.01)
	120	204.80 (0.65)	3.30 (0.03)	7.98 (0.01)
SDYS+CMS1.0%	30	204.23 (0.99)	3.94 (0.04)	8.06 (0.01)
	60	200.42 (0.64)	3.44(0.03)	8.00 (0.01)
	90	203.96 (1.14)	3.35 (0.03)	7.99 (0.01)
	120	201.35 (0.50)	3.28 (0.02)	7.98 (0.01)
SDYS+CMS1.5%	30	204.73 (0.65)	3.97 (0.02)	8.06 (0.00)
	60	203.67 (1.20)	3.49 (0.03)	8.02 (0.00)
	90	201.74 (0.65)	3.35 (0.03)	8.00 (0.01)
	120	204.21 (0.77)	3.31 (0.02)	7.99 (0.01)
Era-Tab®	30	204.52 (0.92)	3.78 (0.02)	8.06 (0.00)
	60	203.93 (0.73)	3.46 (0.03)	8.02 (0.01)
	90	203.98 (1.03)	3.36 (0.01)	8.01 (0.00)
	120	201.08 (0.81)	3.33 (0.01)	8.00 (0.01)

Table 31 Effect of magnesium stearate on hardness of SDYS and SDYS co-sprayed with CMS tablets.

Products	CP (MPa)	Hardness, (MPa), (SD) Magnesium stearate (%w/w)			
		0.25	0.50	0.75	1.00
SDYS	30	3.12 (0.52)	2.49 (0.19)	2.18 (0.11)	2.03 (0.20)
	60	10.02 (0.14)	8.60 (0.74)	5.51 (0.36)	4.40 (0.42)
	90	13.03 (0.19)	11.53 (0.24)	8.20 (0.20)	5.71 (0.47)
	120	13.83 (0.58)	12.37 (0.92)	9.37 (0.49)	6.50 (0.28)
SDYS +CMS0.5%	30	4.78 (0.23)	4.04 (0.15)	3.00 (0.44)	2.20 (0.11)
	60	10.64 (0.20)	9.04 (0.33)	7.03 (0.42)	6.50 (0.26)
	90	13.30 (0.67)	12.40 (0.49)	10.31 (0.48)	8.82 (0.35)
	120	15.10 (0.55)	13.12 (0.28)	10.47 (1.07)	9.35 (0.38)
SDYS +CMS1.0%	30	5.40 (0.55)	5.33 (0.20)	5.00 (0.36)	2.64 (0.17)
	60	11.11 (0.67)	10.37 (0.37)	10.51 (0.84)	7.41 (0.71)
	90	15.51 (0.59)	14.96 (0.47)	12.68 (0.81)	9.05 (0.56)
	120	16.15 (0.59)	16.85 (0.38)	12.97 (0.94)	9.20 (0.27)
SDYS +CMS1.5%	30	9.15 (0.88)	5.97 (1.66)	3.97 (0.17)	3.61 (0.25)
	60	18.37 (1.06)	14.03 (0.88)	9.03 (0.27)	8.23 (0.35)
	90	23.84 (0.50)	17.46 (1.26)	11.70 (0.55)	11.07 (0.38)
	120	25.18 (0.79)	18.16 (1.63)	12.71 (0.27)	11.70 (0.28)
Era-Tab®	30	2.14 (0.15)	2.27 (0.11)	2.07 (0.33)	1.49 (0.28)
	60	9.44 (0.53)	5.62 (0.38)	4.72 (0.37)	3.89 (0.51)
	90	10.86 (0.46)	8.51 (0.34)	6.37 (0.53)	4.82 (0.41)
	120	11.62 (0.46)	9.36 (0.37)	6.68 (0.35)	5.44 (0.18)

Table 32 Effect of magnesium stearate on friability of SDYS and SDYS co-sprayed with CMS tablets.

Products	CP (MPa)	% Friability			
		Magnesium strarate (%w/w)			
		0.25	0.50	0.75	1.00
SDYS	30	0.65	0.72	0.84	2.23
	60	0.53	0.64	0.78	2.10
	90	0.43	0.53	0.63	1.82
	120	0.22	0.39	0.57	1.71
SDYS+CMS0.5%	30	0.58	0.62	0.68	2.15
	60	0.47	0.53	0.56	1.97
	90	0.39	0.45	0.49	1.65
	120	0.19	0.24	0.36	1.32
SDYS+CMS1.0%	30	0.41	0.56	0.64	1.87
	60	0.35	0.47	0.52	1.74
	90	0.30	0.38	0.43	1.42
	120	0.17	0.21	0.32	1.19
SDYS+CMS1.5%	30	0.37	0.43	0.51	1.63
	60	0.29	0.33	0.43	1.41
	90	0.25	0.29	0.37	1.22
	120	0.12	0.16	0.27	1.13
Era-Tab®	30	0.72	0.84	0.96	2.34
	60	0.65	0.69	0.85	2.27
	90	0.54	0.60	0.74	2.14
	120	0.35	0.47	0.63	1.93

Table 33 Effect of magnesium stearate on disintegration time of SDYS and SDYS co-sprayed with CMS tablets.

Products	CP (MPa)	Disintegration time, (min), (SD)			
		Magnesium strarate (%w/w)			
		0.25	0.50	0.75	1.00
SDYS	30	2.72 (0.46)	2.28 (0.04)	2.25 (0.03)	2.15 (0.11)
	60	4.21 (0.08)	4.11 (0.07)	4.17 (0.07)	3.99 (0.21)
	90	5.07 (0.05)	4.58 (0.01)	4.43 (0.02)	4.33 (0.07)
	120	6.40 (0.14)	6.24 (0.06)	6.17 (0.04)	5.57 (0.23)
SDYS +CMS0.5%	30	2.36 (0.04)	1.89 (0.35)	1.47 (0.08)	1.37 (0.05)
	60	3.52 (0.03)	3.37 (0.02)	3.43 (0.04)	3.33 (0.08)
	90	4.41 (0.05)	4.15 (0.01)	4.17 (0.06)	3.96 (0.21)
	120	5.20 (0.01)	4.83 (0.27)	4.33 (0.02)	3.94 (0.17)
SDYS +CMS1.0%	30	3.77 (0.49)	3.79 (0.41)	2.77 (0.30)	2.32 (0.09)
	60	5.50 (0.32)	5.41 (0.11)	4.96 (0.23)	4.61 (0.20)
	90	6.28 (0.02)	6.04 (0.28)	5.30 (0.08)	5.24 (0.07)
	120	6.79 (0.25)	6.66 (0.27)	6.21 (0.09)	6.29 (0.08)
SDYS +CMS1.5%	30	4.64 (0.38)	4.46 (0.08)	3.35 (0.11)	2.44 (0.09)
	60	5.70 (0.31)	5.98 (0.19)	5.42 (0.13)	5.12 (0.37)
	90	6.55 (0.41)	6.31 (0.03)	6.19 (0.09)	5.94 (0.36)
	120	7.45 (0.09)	6.56 (0.02)	6.40 (0.04)	6.51 (0.05)
Era-Tab®	30	1.38 (0.06)	1.27 (0.03)	1.17 (0.01)	1.13 (0.04)
	60	1.49 (0.04)	1.40 (0.02)	1.32 (0.01)	1.27 (0.03)
	90	1.60 (0.20)	1.49 (0.02)	1.36 (0.01)	1.34 (0.03)
	120	1.95 (0.18)	1.79 (0.26)	1.51 (0.02)	1.43 (0.03)

APPENDIX B

ASSAY AND DISSOLUTION

The procedures employed for assay and uniformity of weight followed the monographs of HCTZ tablets and dimenhydrinate tablets in the USP30.

Hydrochlorothiazide Tablets

1. Assay

Mobile phase : Prepare a degassed mixture of 0.1 M monobasic sodium phosphate (13.8 g of NaH_2PO_4 in 1000 mL of water) and acetonitrile (9:1), adjust with phosphoric acid to pH 3.0 ± 0.1, and filter.

System suitability solution: [Note – A volume of acetonitrile not exceeding 10% of the total volume of the solution may be used to dissolve Standard] Accurately weighed quantity 75.0 mg of chlorothiazide and hydrochlorothiazide Working Standard (WS) to a 100-mL volumetric flask. Add 70 mL of mixture solvent (water: acetonitrile; 1:1), sonicate until completely dissolved, adjust with same solvent to volume and mix. Transfer 10.0 mL of this solution 50-mL volumetric flask and dilute with mobile phase to volume and mix.

Standard preparation: [Note – A volume of acetonitrile not exceeding 10% of the total volume of the solution may be used to dissolve Standard] Accurately weighed quantity 75.0 mg of hydrochlorothiazide Working Standard (WS) to 50-mL volumetric flask. Dissolve with mobile phase to volume and mix. Transfer 5.0 mL of this solution to 50-mL volumetric flask and dilute to volume and mix.

Assay preparation: Weigh and finely powder not fewer than 20 tablets. Transfer and accurately weighed portion of powder, equivalent to 30 mg of hydrochlorothiazide, to 200-mL volumetric flask. Add about 20 mL of mobile phase, sonicate for 5 minutes, and add about 20 mL of acetonitrile. Sonicate for 5 minutes, add about 50 mL of mobile phase, and shake by mechanical means for 10 minutes. Dilute with mobile phase to volume and mix, and filter, discarding the first 10 mL of the filtrate.

Chromatographic system: The liquid chromatograph is equipped with 254-nm detector and 4.6 mm. x 25 cm. column that contains packing C18. The flow rate is about 2.0 mL per minutes. Chromatograph the system suitability solution, and record the peak responses as direct for procedure: the relative retention times are about 0.8 for chlorothiazide and 1.0 for hydrochlorothiazide; and the resolution, R, between chlorothiazide and hydrochlorothiazide is not less than 2.0. Chromatograph the standard solution, and record the peak responses as directed for procedure: the relative standard deviation is not more than 1.5%.

Procedure: Separately inject equal volume (20 μL) of the standard preparation, and the assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage labeled amount of hydrochlorothiazide by the formula:

$$\%\mathrm{LA} = \frac{\text{Peak area of Sample} \times \text{Wt. WS.} \times \text{\%Potency of WS} \times \text{Average Wt. per Tab} \times 0.4}{\text{Peak area of Standard} \times \text{Wt. Sample} \times \text{Dose per Tab}}$$

2. Uniformity of dosage units

2.1 Content Uniformity

Mobile phase, system suitability solution, chromatographic system, procedure prepare as direct in assay

Standard preparation: [Note – A volume of acetonitrile not exceeding 10% of the total volume of the solution may be used to dissolve Standard] Accurately weighed quantity 100.0 mg of hydrochlorothiazide Working Standard

(WS) to 50-mL volumetric flask. Dissolve with mobile phase to volume and mix. Transfer 5.0 mL of this solution to 50-mL volumetric flask and dilute to volume and mix. Filtrate through 0.45 micro membrane filters.

Assay preparation: Transfer 1 tablet to 250-mL volumetric flask. Add about 50 mL of mobile phase sonicate for 5 minutes, and add about 25 mL of acetonitrile. Sonicate for 5 minutes, add about 50 mL of mobile phase, and shake by mechanical means for 10 minutes. Dilute with mobile phase to volume and mix, and filter, discarding the first 10 mL of the filtrate.

$$\%\text{LA} = \frac{\text{Peak area of Sample} \times \text{Wt. WS.} \times \%\text{Potency of WS} \times \text{Wt. Sample} \times 0.5}{\text{Peak area of Standard} \times \text{Average Wt. per Tab} \times \text{Dose per Tab}}$$

2.2 Weight variation

X1, X2, …, Xn = individual estimated content of units tested, where

Xi = wi x A / W

w1, w2, …,wn = individual weights of the units tested,

A = content of drug substances (% of label claim) determined as described in the Assay, and

W = mean of individual weights (w1, w2, …, wn)

2.3 Calculation of Acceptance Value (AV)

$$\text{AV} = \left| \text{M} - \overline{\text{X}} \right| + \text{ks}$$

Criteria: The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1. If the acceptance value is greater than L1, test the next 20 dosage units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1 and no individual content of the dosage unit is less than (1 – (L2x0.01))M nor more than (1 + (L2x0.01))M in calculation of acceptance value under content uniformity or under weight variation. Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

Dimenhydrinate Tablets

1. Assay

Ammonium bicarbonate solution: Dissolve 4 g of ammonium bicarbonate in 250 mL of water.

Diluent: Dissolve 4 g of ammonium bicarbonate in 200 mL of water. Add 50 mL of methanol and mix.

Solution A: Dissolve 0.8 g of ammonium bicarbonate in 800 mL of water. Add 200 mL of methanol and mix.

Solution B: Dissolve 0.8 g of ammonium bicarbonate in 150 mL of water. Add 850 mL of methanol and mix.

Mobile phase: Use variable mixture of Solution A and Solution B as directed for chromatography system.

Internal standard: Prepare a solution in methanol by weigh 100 mg of 2-hydroxybenzyl alcohol in 50 mL of methanol (containing 2.0 mg of 2-hydroxybenzyl alcohol per mL.)

Standard preparation: Accurately weigh about 50 mg of dimenhydrinate Working Standard (WS), add about 5 mL of ammonium bicarbonate solution and 20.0 mL of internal standard solution, and mix. To 1 mL of this solution add about 9 mL of diluent, and mix.

Assay preparation: Transfer 5 tablets into 250-mL volumetric flask, add 25 mL of ammoniumbicarbonate solution, and shake gently to disperse, sonicating if necessary. Add about 100.0 mL of internal standard solution, shake vigorously for 30 minutes, and centrifuge. To 1 mL of the clear supernatant add about 9 mL of diluent, and mix.

Chromatographic system: The liquid chromatograph is equipped with 229-nm detector and a 4.6-mm x 25-cm column that contains packing C8. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Table 34 Dimenhydrinate chromatographic gradient.

Time (Minutes)	Solution A (%)	Solution B (%)	Elution
0	100	0	equilibration
0 – 7.0	100	0	isocratic
7.0 – 7.1	100 ---> 0	0 ---> 100	linear gradient
7.1 – 15.0	0	0	isocratic
15.0 – 15.1	0 ---> 100	100 ---> 0	linear gradient
15.1 – 22.0	100	0	isocratic

Chromatograph the standard preparation, and record the peak areas as directed for procedure: the relative retention times are about 0.3 for 8-chlorotheophylline, 0.5 for internal standard (2-Hydroxybenzyl alcohol), and 1.0 for diphenhydramine; the resolution, R, between 8-chlorotheophylline and the internal standard (2-Hydroxybenzyl alcohol) is not less than 4.5; the relative standard deviation for five replicate injections in not more than 2.0%.

Procedure: Separately inject equal volume (5 µL) of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of labeled amount of dimenhydrinate ($C_{17}H_{21}NO{\bullet}C_7H_7ClN_4O_2$).

$$\%LA = \frac{\text{Peak area of Sample} \times \text{Wt. WS.} \times \text{\%Potency of WS} \times \text{Average Wt. per Tab} \times 5}{\text{Peak area of Standard} \times \text{Wt. Sample} \times \text{Dose per Tab}}$$

2. Uniformity of dosage units

2.1 Content uniformity

Ammonium bicarbonate solution, diluent, solution A, solution B , mobile phase, internal standard solution, standard preparation, chromatographic system, procedure prepare as direct in assay.

Test solution: Transfer 1 tablets to 50-mL volumetric flask, add about 5 mL of ammonium bicarbonate solution, and shack gently to disperse, sonicating. Add 20.0 mL of internal standard solution, shack by mechanical means for 30 minutes, and centrifuge. To 1 mL of the clear supernatant add about 9 mL of diluent, and mix.

$$\%LA = \frac{\text{Peak area of Sample} \times \text{Wt. WS.} \times \text{\%Potency of WS} \times \text{Wt. Sample}}{\text{Peak area of Standard} \times \text{Average Wt. per Tab} \times \text{Dose per Tab}}$$

2.2 Calculation of Acceptance Value (AV)

$$AV = \left|M - \overline{X}\right| + ks$$

Criteria: The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1. If the acceptance value is greater than L1, test the next 20 dosage units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1 and no individual content of the dosage unit is less than (1 – (L2x0.01))M nor more than (1 + (L2x0.01))M in calculation of acceptance value under content uniformity or under weight variation. Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

Table 35 %Labeled amount and weight variation of HCTZ tablets.

Drug	Disintegrant	%Labeled amount (SD)	Weight variation Acceptance Value (AV)
HCTZ			
	CMS 0.5%	98.90 (0.27)	0.80
	CMS 1.0%	98.89 (0.25)	3.94
	CMS 2.0%	99.53 (0.12)	3.27
	CMS 3.0%	98.52 (0.40)	5.07
	CMS 4.0%	100.37 (0.36)	4.39
	Exposol® 0.5%	99.13 (0.23)	2.98
	Exposol® 1.0%	98.70 (0.56)	4.38
	Exposol® 2.0%	99.31 (0.34)	2.03
	Exposol® 3.0%	99.69 (0.16)	2.83
	Exposol® 4.0%	98.60 (0.37)	1.85

Table 36 %Labeled amount and content uniformity of HCTZ and dimenhydrinate tablets.

Drug	Filler	%Labeled amount (SD)	Content Uniformity Acceptance Value (AV)
HCTZ			
	SDYS + CMS 0%	98.84 (0.16)	1.13
	SDYS + CMS 0.5%	99.65 (0.12)	1.91
	SDYS + CMS 1.0%	99.73 (0.13)	0.95
	SDYS + CMS 1.5%	99.93 (0.14)	1.19
	Era-Tab®	100.18 (0.23)	0.77
Dimenhydrinate			
	SDYS + CMS 0%	100.92 (0.34)	0.94
	SDYS + CMS 0.5%	100.87 (0.04)	0.72
	SDYS + CMS 1.0%	101.02 (0.31)	1.19
	SDYS + CMS 1.5%	100.22 (0.26)	0.80
	Era-Tab®	99.66 (0.19)	0.96

Dissolution

1. Calibration curve of hydrochlorothiazide in 0.1N hydrochloric acid solution.

The absorbances at the wavelength of 272 nm of standard solutions of hydrochlorothiazide in 0.1N hydrochloric acid are tabulated in Table 37 and Figure 58. It was found to be a straight line with coefficient of determination (R^2) of 0.9997. Beer's law equation was calculated and presented as follows:

$$y = 59.082X-0.0151$$

Where y is the absorbance and X is concentration of hydrochlorothiazide (mg/mL)

Table 37 UV absorbance data of hydrochlorothiazide in 0.1N hydrochloric acid solution at 272 nm.

Concentration (mg/mL)	Absorbance
0.0000	0.000
0.0025	0.126
0.0050	0.273
0.0075	0.424
0.0100	0.567
0.0150	0.883

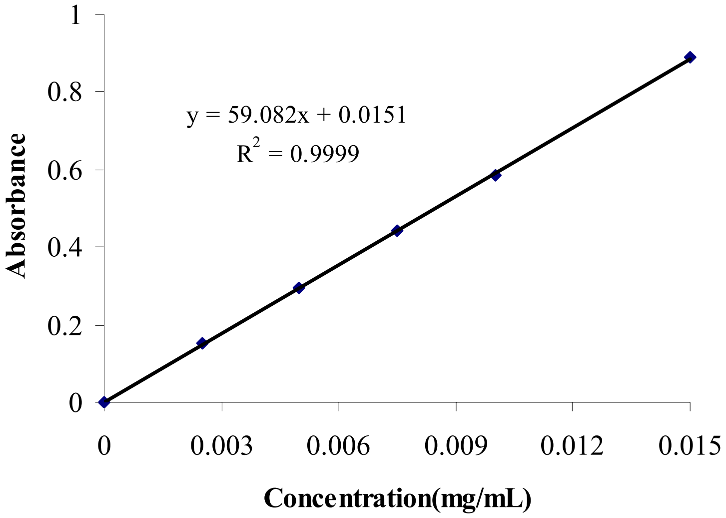

Figure 58 Standard curve of HCTZ in 0.1N hydrochloric acid at 272 nm.

2. Calibration curve of dimenhydrinate in purified water

The absorbances at the wavelength of 276 nm of standard solutions of dimenhydrinate in water are tabulated in Table 38 and Figure 59. It was found to be a straight line with coefficient of determination (R^2) of 0.9998. Beer's law equation was calculated and presented as follows:

$$y = 27.649X+0.0032$$

Where y is the absorbance and X is concentration of dimenhydrinate (mg/mL)

Table 38 UV absorbance data of dimenhydrinate in water at 276 nm.

Concentration (mg/mL)	Absorbance
0.0000	0.000
0.0025	0.071
0.0050	0.145
0.0075	0.209
0.0100	0.285
0.0150	0.416
0.02	0.558
0.025	0.692

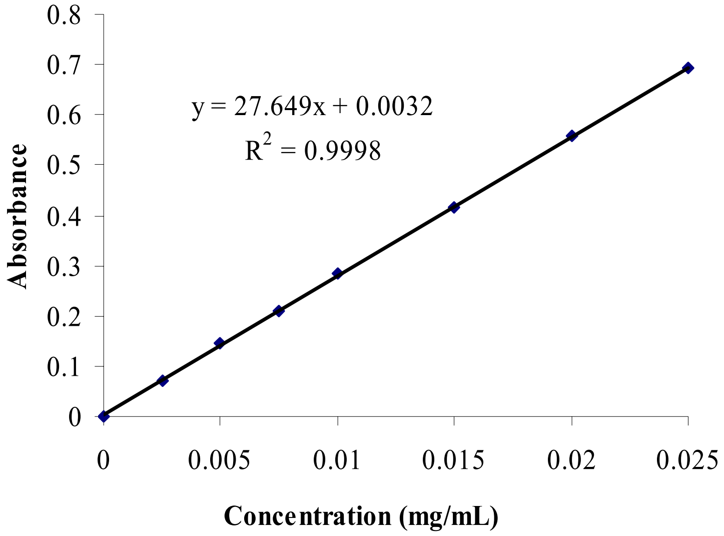

Figure 59 Standard curve of dimenhydrinate in water at 276 nm.

Table 39 Dissolution of HCTZ tablets which various SDYS co-sprayed with CMS as tablet filler.

Time (min)	% Drug dissolved (SD)				
	SDYS +CMS0%	SDYS +CMS0.5%	SDYS +CMS1.0%	SDYS +CMS1.5%	Era-Tab®
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
10	76.27 (3.70)	82.61 (0.64)	79.48 (2.00)	80.67 (2.90)	78.81 (3.04)
20	85.01 (3.72)	91.73 (0.70)	91.57 (2.83)	87.76 (2.48)	88.77 (3.51)
30	90.32 (2.52)	96.60 (1.04)	94.19 (3.85)	91.81 (3.06)	95.18 (4.10)
40	94.43 (1.41)	99.60 (0.75)	95.50 (4.39)	94.03 (3.96)	98.16 (1.83)
50	97.55 (1.21)	99.82 (0.80)	97.19 (3.73)	96.46 (3.22)	98.36 (1.78)
60	99.79 (0.78)	100.39 (0.53)	99.21 (1.06)	97.33 (2.16)	98.54 (2.01)

Table 40 Dissolution of dimenhydrinate tablets which various SDYS co-sprayed with CMS as tablet filler.

Time (min)	% Drug dissolved (SD)				
	SDYS	SDYS +CMS0.5%	SDYS +CMS1.0%	SDYS +CMS1.5%	Era-Tab®
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
10	74.81 (3.89)	88.32 (1.00)	83.65 (2.68)	86.88 (5.18)	80.50 (4.15)
20	88.88 (4.03)	96.83 (2.41)	94.13 (0.89)	99.70 (4.59)	94.44 (4.15)
30	93.74 (4.31)	99.88 (2.91)	94.34 (0.78)	98.80 (4.23)	96.12 (3.05)
40	99.08 (1.89)	100.09 (4.38)	96.86 (0.81)	99.64 (2.91)	97.90 (2.44)
45	99.66 (0.93)	100.04 (2.31)	98.11 (1.08)	99.91 (2.66)	99.36 (2.62)

Table 41 Dissolution of HCTZ tablets which various concentrations of CMS as tablet disintegrant.

Time (min)	% Drug dissolved (SD)				
	CMS0.5%	CMS1.0%	CMS2.0%	CMS3.0%	CMS4.0%
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
10	40.56 (6.60)	71.54 (2.65)	79.72 (3.48)	60.24 (8.53)	8.44 (1.81)
20	58.79 (5.50)	86.86 (1.99)	89.52 (2.26)	78.96 (7.36)	17.45 (1.42)
30	72.77 (4.07)	95.02 (6.46)	94.19 (2.75)	90.14 (6.43)	25.90 (2.08)
40	87.75 (2.56)	96.62 (5.63)	96.59 (3.52)	97.08 (4.23)	35.07 (2.68)
50	98.68 (1.71)	97.30 (0.39)	96.90 (4.45)	97.64 (4.20)	42.89 (3.31)
60	100.20 (0.83)	97.50 (1.59)	96.59 (3.52)	98.12 (3.55)	51.90 (3.82)

Table 42 Dissolution of HCTZ tablets which various concentrations of Exposol® as tablet disintegrant.

Time (min)	% Drug dissolved (SD)				
	Exposol® 0.5%	Exposol® 1.0%	Exposol® 2.0%	Exposol® 3.0%	Exposol® 4.0%
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
10	59.96 (3.63)	68.36 (4.97)	68.00 (3.96)	73.62 (1.99)	78.04 (3.20)
20	84.98 (4.97)	88.53 (1.53)	91.46 (2.45)	93.41 (1.77)	95.69 (2.17)
30	93.22 (3.02)	94.61 (1.48)	97.56 (1.80)	98.57 (2.34)	99.28 (1.66)
40	98.55 (1.13)	96.25 (1.70)	98.91 (1.86)	100.06 (2.35)	99.48 (1.83)
50	99.54 (1.09)	96.33 (1.72)	99.16 (1.94)	100.02 (1.95)	99.73 (1.68)
60	99.74 (1.34)	95.85 (1.70)	99.92 (1.45)	100.22 (2.28)	99.30 (1.63)

APPENDIX C

STATISTICAL ANALYSIS

Table 43 Analysis of variance of CMS concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

	Sum of Squares	df	Mean Square	F	Sig.
DT_DCP_CMS_50MPa					
Between Groups	160722.914	5	32144.583	1841334.340	.000
Within Groups	.524	30	.017		
Total	160723.437	35			
DT_DCP_CMS_100MPa					
Between Groups	255653.884	5	51130.777	839662.422	.000
Within Groups	1.827	30	.061		
Total	255655.710	35			
DT_DCP_CMS_150MPa					
Between Groups	254660.861	5	50932.172	573022.751	.000
Within Groups	2.667	30	.089		
Total	254663.527	35			
DT_DCP_CMS_200MPa					
Between Groups	282114.268	5	56422.854	93949.186	.000
Within Groups	18.017	30	.601		
Total	282132.285	35			

Table 44 Multiple comparison of CMS concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
DT_DCP_CMS_50MPa	0	0.5	179.30167*	.07628	.000
	0	1	179.38333*	.07628	.000
	0	2	179.77500*	.07628	.000
	0	3	179.30500*	.07628	.000
	0	4	178.67000*	.07628	.000
	0.5	1	.08167	.07628	.293
	0.5	2	.47333*	.07628	.000
	0.5	3	.00333	.07628	.965
	0.5	4	-.63167*	.07628	.000
	1	2	.39167*	.07628	.000
	1	3	-.07833	.07628	.313
	1	4	-.71333*	.07628	.000
	2	3	-.47000*	.07628	.000
	2	4	-1.10500*	.07628	.000
	3	4	-.63500*	.07628	.000
DT_DCP_CMS_100MPa	0	0.5	.00000	.14247	1.000
	0	1	178.83167*	.14247	.000
	0	2	179.52667*	.14247	.000
	0	3	178.97167*	.14247	.000
	0	4	177.71333*	.14247	.000
	0.5	1	178.83167*	.14247	.000
	0.5	2	179.52667*	.14247	.000
	0.5	3	178.97167*	.14247	.000
	0.5	4	177.71333*	.14247	.000
	1	2	.69500*	.14247	.000
	1	3	.14000	.14247	.334
	1	4	-1.11833*	.14247	.000
	2	3	-.55500*	.14247	.001
	2	4	-1.81333*	.14247	.000
	3	4	-1.25833*	.14247	.000
DT_DCP_CMS_150MPa	0	0.5	.00000	.17213	1.000
	0	1	178.76500*	.17213	.000
	0	2	179.20833*	.17213	.000
	0	3	178.69667*	.17213	.000
	0	4	176.97333*	.17213	.000
	0.5	1	178.76500*	.17213	.000
	0.5	2	179.20833*	.17213	.000
	0.5	3	178.69667*	.17213	.000
	0.5	4	176.97333*	.17213	.000
	1	2	.44333*	.17213	.015
	1	3	-.06833	.17213	.694
	1	4	-1.79167*	.17213	.000
	2	3	-.51167*	.17213	.006
	2	4	-2.23500*	.17213	.000
	3	4	-1.72333*	.17213	.000

Table 44 (continued) Multiple comparison of CMS concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
DT_DCP_CMS_200MPa	0	0.5	.00000	.44743	1.000
	0	1	.00000	.44743	1.000
	0	2	178.11667*	.44743	.000
	0	3	177.75500*	.44743	.000
	0	4	175.24500*	.44743	.000
	0.5	1	.00000	.44743	1.000
	0.5	2	178.11667*	.44743	.000
	0.5	3	177.75500*	.44743	.000
	0.5	4	175.24500*	.44743	.000
	1	2	178.11667*	.44743	.000
	1	3	177.75500*	.44743	.000
	1	4	175.24500*	.44743	.000
	2	3	-.36167	.44743	.425
	2	4	-2.87167*	.44743	.000
	3	4	-2.51000*	.44743	.000

*. The mean difference is significant at the 0.05 level.

Table 45 Analysis of variance of Exposol® concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

	Sum of Squares	df	Mean Square	F	Sig.
DT_DCP_Exposol_50MPa					
Between Groups	258719.121	5	51743.824	2842026.227	.000
Within Groups	.546	30	.018		
Total	258719.667	35			
DT_DCP_ Exposol _100MPa					
Between Groups	257924.194	5	51584.839	635886.001	.000
Within Groups	2.434	30	.081		
Total	257926.628	35			
DT_DCP_ Exposol _150MPa					
Between Groups	290675.458	5	58135.092	1924825.988	.000
Within Groups	.906	30	.030		
Total	290676.364	35			
DT_DCP_ Exposol _200MPa					
Between Groups	289710.224	5	57942.045	289710.224	.000
Within Groups	.054	30	.002		
Total	289710.278	35			

Table 46 Multiple comparison of CMS concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
DT_DCP_EXPOSOL_50MPa	0	0.5	.00000	.07790	1.000
	0	1	179.43000*	.07790	.000
	0	2	179.96000*	.07790	.000
	0	3	179.97000*	.07790	.000
	0	4	179.97000*	.07790	.000
	0.5	1	179.43000*	.07790	.000
	0.5	2	179.96000*	.07790	.000
	0.5	3	179.97000*	.07790	.000
	0.5	4	179.97000*	.07790	.000
	1	2	.53000*	.07790	.000
	1	3	.54000*	.07790	.000
	1	4	.54000*	.07790	.000
	2	3	.01000	.07790	.899
	2	4	.01000	.07790	.899
	3	4	.00000	.07790	1.000
DT_DCP_EXPOSOL_100MPa	0	0.5	.00000	.16444	1.000
	0	1	178.42500*	.16444	.000
	0	2	179.88667*	.16444	.000
	0	3	179.94000*	.16444	.000
	0	4	179.96000*	.16444	.000
		0	.00000	.16444	1.000
	0.5	1	178.42500*	.16444	.000
	0.5	2	179.88667*	.16444	.000
	0.5	3	179.94000*	.16444	.000
	0.5	4	179.96000*	.16444	.000
	1	2	1.46167*	.16444	.000
	1	3	1.51500*	.16444	.000
	1	4	1.53500*	.16444	.000
	2	3	.05333	.16444	.748
	2	4	.07333	.16444	.659
	3	4	.02000	.16444	.904
DT_DCP_EXPOSOL_150MPa	0	0.5	.00000	.10034	1.000
	0	1	.00000	.10034	1.000
	0	2	179.27667*	.10034	.000
	0	3	179.92500*	.10034	.000
	0	4	179.94000*	.10034	.000
	0.5	1	.00000	.10034	1.000
	0.5	2	179.27667*	.10034	.000
	0.5	3	179.92500*	.10034	.000
	0.5	4	179.94000*	.10034	.000
	1	2	179.27667*	.10034	.000
	1	3	179.92500*	.10034	.000
	1	4	179.94000*	.10034	.000
	2	3	.64833*	.10034	.000
	2	4	.66333*	.10034	.000
	3	4	.01500	.10034	.882

Table 46 (continued) Multiple comparison of CMS concentrations on tablet disintegration time data of DCP tablet compressed with compression pressure 50-200 MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
DT_DCP_EXPOSOL_200MPa	0	0.5	.00000	.02453	1.000
	0	1	.00000	.02453	1.000
	0	2	178.47500*	.02453	.000
	0	3	179.86833*	.02453	.000
	0	4	179.89667*	.02453	.000
	0.5	1	.00000	.02453	1.000
	0.5	2	178.47500*	.02453	.000
	0.5	3	179.86833*	.02453	.000
	0.5	4	179.89667*	.02453	.000
	1	2	178.47500*	.02453	.000
	1	3	179.86833*	.02453	.000
	1	4	179.89667*	.02453	.000
	2	3	1.39333*	.02453	.000
	2	4	1.42167*	.02453	.000
	3	4	.02833	.02453	.257

*. The mean difference is significant at the 0.05 level.

Table 47 Analysis of variance of concentration of CMS on tablet hardness data set of SDYSs with compression pressure 30-120MPa.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS _30MPa					
Between Groups	29.999	4	7.500	45.884	.000
Within Groups	7.355	45	.163		
Total	37.355	49			
	407.345	4	101.836	116.817	.000
SDCMS_60MPa	39.229	45	.872		
Between Groups	446.574	49			
Within Groups	667.989	4	166.997	182.224	.000
Total	41.240	45	.916		
	709.229	49			
SDCMS_90MPa	580.409	4	145.102	126.840	.000
Between Groups	51.479	45	1.144		
Within Groups	631.888	49			
Total	29.999	4	7.500	45.884	.000
	7.355	45	.163		
SDCMS_120MPa	37.355	49			
Between Groups	407.345	4	101.836	116.817	.000
Within Groups	39.229	45	.872		
Total	446.574	49			

Table 48 Multiple comparison of concentration of CMS on tablet hardness data set of SDYSs with compression pressure 30-120MPa.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_30MPa	0	0.5	-.62900*	.18081	.001
	0	1	-.60400*	.18081	.002
	0	1.5	-1.85700*	.18081	.000
	0	2	.44100*	.18081	.019
	0.5	1	.02500	.18081	.891
	0.5	1.5	-1.22800*	.18081	.000
	0.5	2	1.07000*	.18081	.000
	1	1.5	-1.25300*	.18081	.000
	1	2	1.04500*	.18081	.000
	1.5	2	2.29800*	.18081	.000
SDCMS_60MPa	0	0.5	-2.07200*	.41755	.000
	0	1	-3.10600*	.41755	.000
	0	1.5	-4.34900*	.41755	.000
	0	2	3.80000*	.41755	.000
	0.5	1	-1.03400*	.41755	.017
	0.5	1.5	-2.27700*	.41755	.000
	0.5	2	5.87200*	.41755	.000
	1	1.5	-1.24300*	.41755	.005
	1	2	6.90600*	.41755	.000
	1.5	2	8.14900*	.41755	.000
SDCMS_90MPa	0	0.5	-1.86400*	.42812	.000
	0	1	-4.79400*	.42812	.000
	0	1.5	-5.97400*	.42812	.000
	0	2	4.30400*	.42812	.000
	0.5	1	-2.93000*	.42812	.000
	0.5	1.5	-4.11000*	.42812	.000
	0.5	2	6.16800*	.42812	.000
	1	1.5	-1.18000*	.42812	.008
	1	2	9.09800*	.42812	.000
	1.5	2	10.27800*	.42812	.000
SDCMS_120MPa	0	0.5	-.87100	.47833	.075
	0	1	-4.58600*	.47833	.000
	0	1.5	-5.12600*	.47833	.000
	0	2	4.24400*	.47833	.000
	0.5	1	-3.71500*	.47833	.000
	0.5	1.5	-4.25500*	.47833	.000
	0.5	2	5.11500*	.47833	.000
	1	1.5	-.54000	.47833	.265
	1	2	8.83000*	.47833	.000
	1.5	2	9.37000*	.47833	.000

*. The mean difference is significant at the 0.05 level.

Table 49 Analysis of variance of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0%w/w magnesium stearate.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS_Mg0_30MPa					
Between Groups	29.999	4	7.500	45.884	.000
Within Groups	7.355	45	.163		
Total	37.355	49			
SDCMS_Mg0_60MPa					
Between Groups	407.345	4	101.836	116.817	.000
Within Groups	39.229	45	.872		
Total	446.574	49			
SDCMS_Mg0_90MPa					
Between Groups	667.989	4	166.997	182.224	.000
Within Groups	41.240	45	.916		
Total	709.229	49			
SDCMS_Mg0_120MPa					
Between Groups	580.409	4	145.102	126.840	.000
Within Groups	51.479	45	1.144		
Total	631.888	49			

Table 50 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0%w/w magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0_30MPa	.00	.50	-.6290(*)	.18081	.001
	.00	1.00	-.6040(*)	.18081	.002
	.00	1.50	-1.8570(*)	.18081	.000
	.00	2.00	.4410(*)	.18081	.019
	.50	1.00	.0250	.18081	.891
	.50	1.50	-1.2280(*)	.18081	.000
	.50	2.00	1.0700(*)	.18081	.000
	1.00	1.50	-1.2530(*)	.18081	.000
	1.00	2.00	1.0450(*)	.18081	.000
	1.50	2.00	2.2980(*)	.18081	.000
SDCMS_Mg0_60MPa	.00	.50	-2.0720(*)	.41755	.000
	.00	1.00	-3.1060(*)	.41755	.000
	.00	1.50	-4.3490(*)	.41755	.000
	.00	2.00	3.8000(*)	.41755	.000
	.50	1.00	-1.0340(*)	.41755	.017
	.50	1.50	-2.2770(*)	.41755	.000
	.50	2.00	5.8720(*)	.41755	.000
	1.00	1.50	-1.2430(*)	.41755	.005
	1.00	2.00	6.9060(*)	.41755	.000
	1.50	2.00	8.1490(*)	.41755	.000
SDCMS_Mg0_90MPa	.00	.50	-1.8640(*)	.42812	.000
	.00	1.00	-4.7940(*)	.42812	.000
	.00	1.50	-5.9740(*)	.42812	.000
	.00	2.00	4.3040(*)	.42812	.000
	.50	1.00	-2.9300(*)	.42812	.000
	.50	1.50	-4.1100(*)	.42812	.000
	.50	2.00	6.1680(*)	.42812	.000
	1.00	1.50	-1.1800(*)	.42812	.008
	1.00	2.00	9.0980(*)	.42812	.000
	1.50	2.00	10.2780(*)	.42812	.000
SDCMS_Mg0_120MPa	.00	.50	-.8710	.47833	.075
	.00	1.00	-4.5860(*)	.47833	.000
	.00	1.50	-5.1260(*)	.47833	.000
	.00	2.00	4.2440(*)	.47833	.000
	.50	1.00	-3.7150(*)	.47833	.000
	.50	1.50	-4.2550(*)	.47833	.000
	.50	2.00	5.1150(*)	.47833	.000
	1.00	1.50	-.5400	.47833	.265
	1.00	2.00	8.8300(*)	.47833	.000
	1.50	2.00	9.3700(*)	.47833	.000

*. The mean difference is significant at the 0.05 level.

Table 51 Analysis of variance of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.25%w/w magnesium stearate.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS_Mg0.25_30MPa					
Between Groups	290.906	4	72.726	255.750	.000
Within Groups	12.796	45	.284		
Total	303.702	49			
SDCMS_Mg0.25_60MPa					
Between Groups	536.737	4	134.184	352.562	.000
Within Groups	17.127	45	.381		
Total	553.864	49			
SDCMS_Mg0.25_90MPa					
Between Groups	1018.035	4	254.509	980.792	.000
Within Groups	11.677	45	.259		
Total	1029.713	49			
SDCMS_Mg0.25_120MPa					
Between Groups	1082.622	4	270.656	740.054	.000
Within Groups	16.458	45	.366		
Total	1099.080	49			

Table 52 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.25%w/w magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.25_30MPa	.00	.50	-1.6590(*)	.23848	.000
	.00	1.00	-2.2840(*)	.23848	.000
	.00	1.50	-6.0310(*)	.23848	.000
	.00	2.00	.9740(*)	.23848	.000
	.50	1.00	-.6250(*)	.23848	.012
	.50	1.50	-4.3720(*)	.23848	.000
	.50	2.00	2.6330(*)	.23848	.000
	1.00	1.50	-3.7470(*)	.23848	.000
	1.00	2.00	3.2580(*)	.23848	.000
	1.50	2.00	7.0050(*)	.23848	.000
SDCMS_Mg0.25_60MPa	.00	.50	-.6180(*)	.27590	.030
	.00	1.00	-1.0830(*)	.27590	.000
	.00	1.50	-8.3500(*)	.27590	.000
	.00	2.00	.5800(*)	.27590	.041
	.50	1.00	-.4650	.27590	.099
	.50	1.50	-7.7320(*)	.27590	.000
	.50	2.00	1.1980(*)	.27590	.000
	1.00	1.50	-7.2670(*)	.27590	.000
	1.00	2.00	1.6630(*)	.27590	.000
	1.50	2.00	8.9300(*)	.27590	.000
SDCMS_Mg0.25_90MPa	.00	.50	-.2710	.22781	.240
	.00	1.00	-2.4740(*)	.22781	.000
	.00	1.50	-10.8050(*)	.22781	.000
	.00	2.00	2.1760(*)	.22781	.000
	.50	1.00	-2.2030(*)	.22781	.000
	.50	1.50	-10.5340(*)	.22781	.000
	.50	2.00	2.4470(*)	.22781	.000
	1.00	1.50	-8.3310(*)	.22781	.000
	1.00	2.00	4.6500(*)	.22781	.000
	1.50	2.00	12.9810(*)	.22781	.000
SDCMS_Mg0.25_120MPa	.00	.50	-1.2650(*)	.27045	.000
	.00	1.00	-2.3200(*)	.27045	.000
	.00	1.50	-11.3460(*)	.27045	.000
	.00	2.00	2.2130(*)	.27045	.000
	.50	1.00	-1.0550(*)	.27045	.000
	.50	1.50	-10.0810(*)	.27045	.000
	.50	2.00	3.4780(*)	.27045	.000
	1.00	1.50	-9.0260(*)	.27045	.000
	1.00	2.00	4.5330(*)	.27045	.000
	1.50	2.00	13.5590(*)	.27045	.000

*. The mean difference is significant at the 0.05 level.

Table 53 Analysis of variance of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.5%w/w magnesium stearate.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS_Mg0.5_30MPa					
Between Groups	109.161	4	27.290	47.710	.000
Within Groups	25.740	45	.572		
Total	134.901	49			
SDCMS_Mg0.5_60MPa					
Between Groups	373.606	4	93.402	272.355	.000
Within Groups	15.432	45	.343		
Total	389.039	49			
SDCMS_Mg0.5_90MPa					
Between Groups	464.050	4	116.012	262.890	.000
Within Groups	19.858	45	.441		
Total	483.908	49			
SDCMS_Mg0.5_120MPa					
Between Groups	503.670	4	125.918	163.046	.000
Within Groups	34.753	45	.772		
Total	538.423	49			

Table 54 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.5%w/w magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.5_30MPa	.00	.50	-1.5450(*)	.33823	.000
	.00	1.00	-2.8390(*)	.33823	.000
	.00	1.50	-3.4710(*)	.33823	.000
	.00	2.00	.2290	.33823	.502
	.50	1.00	-1.2940(*)	.33823	.000
	.50	1.50	-1.9260(*)	.33823	.000
	.50	2.00	1.7740(*)	.33823	.000
	1.00	1.50	-.6320	.33823	.068
	1.00	2.00	3.0680(*)	.33823	.000
	1.50	2.00	3.7000(*)	.33823	.000
SDCMS_Mg0.5_60MPa	.00	.50	-.4450	.26189	.096
	.00	1.00	-1.7740(*)	.26189	.000
	.00	1.50	-5.4320(*)	.26189	.000
	.00	2.00	2.9790(*)	.26189	.000
	50	1.00	-1.3290(*)	.26189	.000
	.50	1.50	-4.9870(*)	.26189	.000
	.50	2.00	3.4240(*)	.26189	.000
	1.00	1.50	-3.6580(*)	.26189	.000
	1.00	2.00	4.7530(*)	.26189	.000
	1.50	2.00	8.4110(*)	.26189	.000
SDCMS_Mg0.5_90MPa	.00	.50	-.8680(*)	.29708	.005
	.00	1.00	-3.4280(*)	.29708	.000
	.00	1.50	-5.9360(*)	.29708	.000
	.00	2.00	3.0140(*)	.29708	.000
	.50	1.00	-2.5600(*)	.29708	.000
	.50	1.50	-5.0680(*)	.29708	.000
	.50	2.00	3.8820(*)	.29708	.000
	1.00	1.50	-2.5080(*)	.29708	.000
	1.00	2.00	6.4420(*)	.29708	.000
	1.50	2.00	8.9500(*)	.29708	.000
SDCMS_Mg0.5_120MPa	.00	.50	-.7450	.39301	.064
	.00	1.00	-4.4780(*)	.39301	.000
	.00	1.50	-5.7860(*)	.39301	.000
	.00	2.00	3.0120(*)	.39301	.000
		.00	.7450	.39301	.064
	.50	1.00	-3.7330(*)	.39301	.000
	.50	1.50	-5.0410(*)	.39301	.000
	.50	2.00	3.7570(*)	.39301	.000
	1.00	1.50	-1.3080(*)	.39301	.002
	1.00	2.00	7.4900(*)	.39301	.000
	1.50	2.00	8.7980(*)	.39301	.000

*. The mean difference is significant at the 0.05 level.

Table 55 Analysis of variance of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.75%w/w magnesium stearate.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS_Mg0.75_30MPa					
Between Groups	61.801	4	15.450	164.039	.000
Within Groups	4.238	45	.094		
Total	66.039	49			
SDCMS_Mg0.75_60MPa					
Between Groups	232.117	4	58.029	238.031	.000
Within Groups	10.970	45	.244		
Total	243.087	49			
SDCMS_Mg0.75_90MPa					
Between Groups	264.912	4	66.228	217.671	.000
Within Groups	13.692	45	.304		
Total	278.603	49			
SDCMS_Mg0.75_120MPa					
Between Groups	268.104	4	67.026	136.666	.000
Within Groups	22.070	45	.490		
Total	290.173	49			

Table 56 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 0.75%w/w magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SDCMS_Mg0.75_30MPa	.00	.50	-.8140(*)	.13725	.000
	.00	1.00	-2.8210(*)	.13725	.000
	.00	1.50	-1.7820(*)	.13725	.000
	.00	2.00	.1120	.13725	.419
	.50	1.00	-2.0070(*)	.13725	.000
	.50	1.50	-.9680(*)	.13725	.000
	.50	2.00	.9260(*)	.13725	.000
	1.00	1.50	1.0390(*)	.13725	.000
	1.00	2.00	2.9330(*)	.13725	.000
	1.50	2.00	1.8940(*)	.13725	.000
SDCMS_Mg0.75_60MPa	.00	.50	-1.5190(*)	.22081	.000
	.00	1.00	-5.0000(*)	.22081	.000
	.00	1.50	-3.5180(*)	.22081	.000
	.00	2.00	.7910(*)	.22081	.001
	.50	1.00	-3.4810(*)	.22081	.000
	.50	1.50	-1.9990(*)	.22081	.000
	.50	2.00	2.3100(*)	.22081	.000
	1.00	1.50	1.4820(*)	.22081	.000
	1.00	2.00	5.7910(*)	.22081	.000
	1.50	2.00	4.3090(*)	.22081	.000
SDCMS_Mg0.75_90MPa	.00	.50	-2.1160(*)	.24668	.000
	.00	1.00	-4.4860(*)	.24668	.000
	.00	1.50	-3.5010(*)	.24668	.000
	.00	2.00	1.8260(*)	.24668	.000
	.50	1.00	-2.3700(*)	.24668	.000
	.50	1.50	-1.3850(*)	.24668	.000
	.50	2.00	3.9420(*)	.24668	.000
	1.00	1.50	.9850(*)	.24668	.000
	1.00	2.00	6.3120(*)	.24668	.000
	1.50	2.00	5.3270(*)	.24668	.000
SDCMS_Mg0.75_120MPa	.00	.50	-1.1040(*)	.31319	.001
	.00	1.00	-3.6000(*)	.31319	.000
	.00	1.50	-3.3390(*)	.31319	.000
	.00	2.00	2.6870(*)	.31319	.000
	.50	1.00	-2.4960(*)	.31319	.000
	.50	1.50	-2.2350(*)	.31319	.000
	.50	2.00	3.7910(*)	.31319	.000
	1.00	1.50	.2610	.31319	.409
	1.00	2.00	6.2870(*)	.31319	.000
	1.50	2.00	6.0260(*)	.31319	.000

*. The mean difference is significant at the 0.05 level.

Table 57 Analysis of variance of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 1.0%w/w magnesium stearate.

	Sum of Squares	df	Mean Square	F	Sig.
SDCMS_Mg1_30MPa					
Between Groups	25.078	4	6.270	140.386	.000
Within Groups	2.010	45	.045		
Total	27.088	49			
SDCMS_Mg1_60MPa					
Between Groups	141.741	4	35.435	156.002	.000
Within Groups	10.222	45	.227		
Total	151.963	49			
SDCMS_Mg1_90MPa					
Between Groups	265.130	4	66.283	342.291	.000
Within Groups	8.714	45	.194		
Total	273.844	49			
SDCMS_Mg1_120MPa					
Between Groups	247.924	4	61.981	762.293	.000
Within Groups	3.659	45	.081		
Total	251.583	49			

Table 58 Multiple comparison of SDYS co-sprayed with various concentrations of CMS and Era-Tab® on tablet hardness data set that effected of 1.0%w/w magnesium stearate.

Dependent Variable	Conc (I)	Conc (J)	Mean Difference (I-J)	Std. Error	Sig.
SD SDCMS_Mg1_30MPa	.00	.50	-.1730	.09451	.074
	.00	1.00	-.6100(*)	.09451	.000
	.00	1.50	-1.5750(*)	.09451	.000
	.00	2.00	.5370(*)	.09451	.000
	.50	1.00	-.4370(*)	.09451	.000
	.50	1.50	-1.4020(*)	.09451	.000
	.50	2.00	.7100(*)	.09451	.000
	1.00	1.50	-.9650(*)	.09451	.000
	1.00	2.00	1.1470(*)	.09451	.000
	1.50	2.00	2.1120(*)	.09451	.000
SDCMS_Mg1_60MPa	.00	.50	-2.0960(*)	.21314	.000
	.00	1.00	-3.0100(*)	.21314	.000
	.00	1.50	-3.8290(*)	.21314	.000
	.00	2.00	.5090(*)	.21314	.021
	.50	1.00	-.9140(*)	.21314	.000
	.50	1.50	-1.7330(*)	.21314	.000
	.50	2.00	2.6050(*)	.21314	.000
	1.00	1.50	-.8190(*)	.21314	.000
	1.00	2.00	3.5190(*)	.21314	.000
	1.50	2.00	4.3380(*)	.21314	.000
SDCMS_Mg1_90MPa	.00	.50	-3.1100(*)	.19680	.000
	.00	1.00	-3.3400(*)	.19680	.000
	.00	1.50	-5.3630(*)	.19680	.000
	.00	2.00	.8890(*)	.19680	.000
	.50	1.00	-.2300	.19680	.249
	.50	1.50	-2.2530(*)	.19680	.000
	.50	2.00	3.9990(*)	.19680	.000
	1.00	1.50	-2.0230(*)	.19680	.000
	1.00	2.00	4.2290(*)	.19680	.000
	1.50	2.00	6.2520(*)	.19680	.000
SDCMS_Mg1_120MPa	.00	.50	-2.8440(*)	.12752	.000
	.00	1.00	-2.7020(*)	.12752	.000
	.00	1.50	-5.1950(*)	.12752	.000
	.00	2.00	1.0660(*)	.12752	.000
	.50	1.00	.1420	.12752	.271
	.50	1.50	-2.3510(*)	.12752	.000
	.50	2.00	3.9100(*)	.12752	.000
	1.00	1.50	-2.4930(*)	.12752	.000
	1.00	2.00	3.7680(*)	.12752	.000
	1.50	2.00	6.2610(*)	.12752	.000

*. The mean difference is significant at the 0.05 level.

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PRESENTATION Nattapulwat Nattawat, Narumol Purkkao and Ornamphai Suwithayapanth (2006) "Pharmaceutical application of yam (*Dioscorea esculenta*) starch as a tablet disintegrant." *Proceeding presented at The 6th National symposium on graduate research,* Chulalongkorn University, 14 October, 2006.