ไมโครเอนแคปซูเลชันของยาอะมอกซีซิลลินไตรไฮเดรต โดยวิธีโคอะเซอเวชันเชิงซ้อนและวิธีพ่นแห้ง

นางสาวอัจฉรา หมายมั่นสมสุข

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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MICROENCAPSULATION OF AMOXYCILLIN TRIHYDRATE BY COMPLEX COACERVATION AND SPRAY-DRYING TECHNIQUES

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การศึกษาอะมอกซีซิลลินไมโครแคปซูลเตรียมโดย 2 วิธี คือ วิธีการเกิดโคอะเซอเวชันเชิงซ้อน และวิธีการพ่นแห้ง โดยในวิธีของการเกิดโคอะเซอเวชันเชิงซ้อนนั้น ใช้สารก่อผนัง 2 ชนิดคือ เจลาตินกับอะคาเซีย และเจลาตินกับโซเดียมคาร์บอกซีเมทิลเซลลูโลส ส่วนในวิธีการพ่นแห้ง ใช้สารก่อผนังคือ โพลีไวนิลอะซีเตท (คอลลีโคท เอส อาร์ 30 ดี®) ปัจจัยในการเตรียมอะมอกซีซิลลินไมโครแคปซูลโดยวิธีโคอะเซอเวชันเชิงซ้อนที่ทำการศึกษาคือ อัตราส่วนของสารแกนต่อสารก่อผนัง พีเอชในการเกิดโคอะเซอเวชัน ความเข้มข้นของสารก่อผนังและอัตราเร็วในการปั่น ซึ่งปัจจัยต่างๆ มีผลต่อการเตรียม ปริมาณที่เตรียมได้ ปริมาณยา ปริมาณยาที่ถูกห่อหุ้ม ขนาด การกระจายขนาดอนุภาค ลักษณะรูปร่างและพื้นผิว และรวมถึงลักษณะการปลดปล่อยตัวยาออกจากไมโครแคปซูล ส่วนวิธีการพ่นแห้งมีปัจจัยที่ทำการศึกษาคือ อัตราส่วนของสารแกนต่อสารก่อผนัง อุณหภูมิของลมเข้า อัตราเร็วในการป้อนสารระหว่างการพ่นแห้ง และความเข้มข้นของสารละลายที่ใช้ระหว่างการผลิต ซึ่งวัดผลเช่นเดียวกัน

ผลการศึกษาพบว่าการเตรียมอะมอกซีซิลลินไมโครแคปซูลโดยวิธีโคอะเซอเวชันเชิงซ้อนโดยใช้เจลาตินและอะคาเซียอัตราส่วนของสารแกนต่อสารก่อผนัง 1:2 ความเข้มข้นของสารก่อผนัง 2% พีเอช 3.5 และอัตราเร็วในการปั่น 700 รอบต่อนาที สามารถเตรียมไมโครแคปซูลได้ในปริมาณที่สูงถึง 88% ปริมาณยาและปริมาณยาที่ถูกห่อหุ้มมีปริมาณสูงและมีการปลดปล่อยตัวยาจากไมโครแคปซูลที่ช้ากว่าเมื่อเตรียมโดยใช้เจลาตินและโซเดียมคาร์บอกซีเมทิลเซลลูโลสเป็นสารก่อผนัง อะมอกซีซิลลินไมโครแคปซูลเตรียมโดยเจลาตินและอะคาเซียเป็นสารก่อผนัง มีการปลดปล่อยตัวยา 57.82% ในเวลา 2 ชั่วโมงที่พีเอช 1.2 และปลดปล่อยยา 100% ในเวลา 12 ชั่วโมงที่พีเอช 6.8 ส่วนอะมอกซีซิลลินเตรียมโดยวิธีการพ่นแห้งโดยใช้ อัตราส่วนของสารแกนต่อสารก่อผนัง 1:2 อุณหภูมิลมเข้า 120 องศาเซลเซียส อัตราเร็วในการป้อนสาร 24 มิลลิลิตรต่อนาที และความเข้มข้นของสารละลายที่ใช้ระหว่างการผลิต 10% จะให้ปริมาณไมโครแคปซูลที่ต่ำเพียง 60% ที่มีการไหลอิสระ แต่การปลดปล่อยตัวยาอะมอกซีซิลลิน ในพีเอช 6.8 ต่ำที่สุดคือ ปลดปล่อยตัวยา 93.09% ใน 12 ชั่วโมง

ภาควิชา	เภสัชกรรม	ลายมือชื่อนิสิต.....
สาขาวิชา	เภสัชกรรม	ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา	2544	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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KEY WORD: MICROENCAPSULATION / AMOXYCILLIN TRIHYDRATE / COMPLEX COACERVATION / SPRAY-DRYING

ATCHARA MAIMANSOMSOOK: MICROENCAPSULATION OF AMOXYCILLIN TRIHYDRATE BY COMPLEX COACERVATION AND SPRAY-DRYING TECHNIQUES. THESIS ADVISOR: ASSOC. PROF. UBONTHIP NIMMANNIT, Ph.D., THESIS CO-ADVISOR: DUSADEE CHARNVANICH, M.D. 261 pp. ISBN 974-03-0609-8.

In this study, amoxycillin microcapsules were prepared by 2 methods, complex coacervation and spray-drying techniques. The complex coacervation used two types of polymer to form wall i.e., gelatin-acacia and gelatin-SCMC. In the spray-drying technique polyvinyl acetate (Kollicoat SR30D®) was used as a polymer to form wall. In addition, the factors of core to wall ratio, pH, concentration of wall and stirring rate on the preparation of amoxycillin microcapsules by complex coacervation were investigated from the percent yield, drug content, core entrapment, size, size distribution, shape, surface area and drug release profile characteristics. In spray-drying technique the factors of core to wall ratio, inlet air temperature, feed rate and solid content were also investigated in the same way.

It was found that gelatin-acacia complex coacervation with 1:2 core to wall ratio of 2% concentration of wall prepared at pH 3.5 with 700 rpm of stirring rate provided high percent yield of 88%, higher drug content, higher core entrapment and lower release profile than gelatin-SCMC as a wall. The release of amoxycillin from gelatin-acacia walled microcapsules was 57.82% in 2 hours at pH 1.2 and 100% in 12 hours at pH 6.8. Whereas in spray-drying technique, microcapsules prepared with 1:2 core to wall ratio, inlet air temperature of 120°C, feed rate of 24 mL/min and solid content of 10% provided percent yield of 60% with free-flowing properties but the release of amoxycillin in pH 6.8 was the lowest. It demonstrated that 93.09% of amoxycillin was released within 12 hours.

Department	Pharmacy	Student's signature. Atchara Maimansom sook
Field of study	Pharmacy	Advisor's signature. Ubonthip Nimmannit
Academic year	2001	Co-advisor's signature. Dusadee Charnvanich

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LIST OF ABBREVIATIONS

ANOVA	=	Analysis of variance
^{o}C	=	degree Celcius
cm	=	centimeter
conc.	=	concentration
C.V.	=	coefficient of variation
d.f.	=	degree of freedom
et al.	=	and others
gm	=	gram
G-A	=	gelatin-acacia
G-S	=	gelatin-sodium carboxymethylcellulose
GI	=	gastrointestinal tract
hr	=	hour
HPLC	=	High performance liquid chromatography
i.e.	=	that is
k	=	release rate constant
k_H	=	Higuchi release rate constant
L	=	liter
L.A.	=	labeled amount
mg	=	milligram
min	=	minute
mL	=	milliliter
MS	=	mean square
nm	=	nanometer
p	=	probability
PAR	=	peak area ratio
pp.	=	page

LIST OF ABBREVIATIONS (Cont.)

r	=	correlation coefficient
R^2	=	coefficient of determination
rpm	=	revolution per minute
SCMC	=	sodium carboxymethylcellulose
S.D.	=	standard deviation
SEM	=	scanning electron microscope
SS	=	sum of squares
t	=	time
T_{50}	=	time of 50% released
UV	=	ultraviolet
μg	=	microgram
μL	=	microliter
μm	=	micrometer
λ	=	wavelength
%w/v	=	percent weight by volume
%w/w	=	percent weight by weight

CHAPTER I

INTRODUCTION

In the pharmaceutical industry, the research for novel techniques using in the development of properties of drugs is necessary. Microencapsulation, one of those techniques, has been practiced in this field for several years and it is still of great interesting and useful today.

Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and the products from this process are called microcapsules. Microcapsules may be prepared by a number of methods which are coacervation, spray drying, pan coating, air suspension, interfacial polymerization and solvent evaporation method (Bakan, 1986, and Deasy, 1984).

Complex coacervation technique is the reduction in the solvation of colloid solutes in aqueous medium to form coacervate by charge neutralization between negative charge of acacia or SCMC and positive charge of gelatin polymer at pH below the isoelectric point of gelatin and in the appropriate concentration. Then the coacervate droplets deposit on surface of core particles which disperse in that medium and migrate to form the coating in order to reduce total free interfacial energy. The coating is shrank and crosslinked to rigidize. Finally, dried by the appropriate method, the desired microcapsules are collected (Deasy, 1984, and Madan, 1978). Additionally, there are many literatures reported that the changing the variables, e.g. ratio of gelatin and acacia (Newton, Mcmullen, and Becker, 1977), ratio of drug core and wall (Mohamed and Nazik, 1983), ratio of gelatin and SCMC (Koh and Tucker, 1988), stirring rate (Nazik and Mohamed, 1981), pH (Takenaka, Kawashima, and Linn, 1981) could affect the microencapsulation procedure and the properties of microcapsules.

Spray drying is a useful method for the processing of pharmaceuticals since a number of formulations can be accomplished in a single step in a spray dryer. This can both simplify the process and shorten the processing time. In addition, it offers means for obtaining powders with predetermined properties such as particle size and shape (Broadhead, Rouan, and Rhodes, 1992). Spray drying has a wide range of applications within pharmaceutical industries including drying of heat sensitive material (Labrude et al., 1989), improving solubility of poorly water soluble substances (Tsuda et al., 1988), preparing direct compression vehicles (Raff, Robinson, and Svedres, 1961), coating drugs with suitable polymers to produce dust-free powder and modifying the release characteristics of the pharmaceutical products (Bodmeier and Chen, 1988).

Amoxycillin trihydrate is semisynthetic penicillin which is acid resistant and can therefore be given orally (Alfonso, ed., 1985). Its biological half-life is about 1-2 hours (Lung, ed., 1979). Amoxyciilin was chosen as the candidate drug because it is currently the most widely prescribed oral semisynthetic penicillin worldwide. In the past, there were many reports about amoxycillin microcapsules. Ertan et al. (1997) investigated amoxycillin and nitrofurantoin microcapsules by complex coacervation technique at pH 3.5 using carboxymethylcellulose-gelatin at a weight ratio of 3:7. They found that nitrofurantoin microcapsules needed appropriate glidant but amoxycillin trihydrate microcapsules did not. Moreover, it was observed that the microencapsulation changed the micromeritic properties of the drugs significantly. Alan and Patrick (1993) investigated amoxycillin trihydrate using matrix formulation based on the enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS). They found that the polymer could suppress drug release in the presence of gastric pH but could enhance drug release in the presence of small intestinal pH, compared with compacts of pure drug.

The present study was designed to prepare amoxycillin microcapsules via the complex coacervation and spray-drying techniques. Additionally, effects of process and formulation factors on physicochemical properties of the microcapsules were also investigated.

The purposes of the study were as follows:

1. To study the complex coacervation and spray drying techniques in the preparation of amoxycillin microcapsules.
2. To characterize the physicochemical and pharmaceutical properties of amoxycillin microcapsules, e.g., %yield, morphology, size and size distribution, drug content and drug release.
3. To investigate the effects of stirring rate, core to wall ratio, pH and concentration of wall in complex coacervation technique, and the effects of inlet air temperature, flow rate, core to wall ratio and solid content in spray-drying technique on physicochemical properties of amoxycillin microcapsules.
4. To elucidate the release kinetics of amoxycillin from amoxycillin microcapsules.

CHAPTER II

REVIEW OF LITERATURES

Microencapsulation

Microencapsulation is a process of applying relatively thin coatings to small particles of solid or droplets of liquids and the products from this process are called microcapsules (Deasy, 1984, and Luzzi, 1970). The microcapsules developed for use in medicine consist of a solid or liquid core material containing one or more drugs enclosed in coating as shown in Figure 1. The core may also be referred to as the nucleus or fill and the coating as the wall or shell. Particle size of the microcapsules is defined in various ranges but can be varied from approximately 1 μm to 5000 μm.

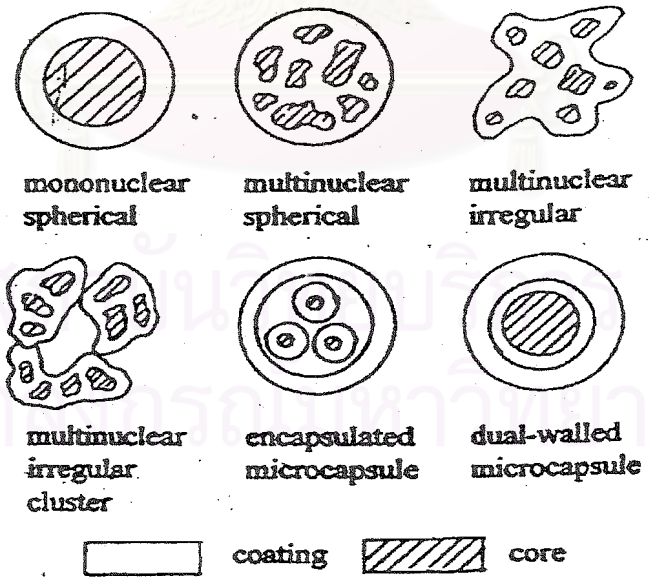


Figure 1. Some typical structures of microcapsules (Luzzi, 1970).

History of microencapsulation technique

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenberg de Jong and Kass (1931) and dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. In the late 1930s and 1940s, Green and co-workers developed the gelatin coacervation process to prepare carbonless carbon paper. The microcapsules, containing a colorless dye precursor (3,3-bis-(p-dimethylaminophenyl)-6-dimethylamino phthalide), were fixed to the under surface of the top page and released the dye precursor upon rupture by pressure from the tip of writing instrument. The liberated dye precursor then reacted with and acidic clay (attapulgite) on the top surfce of the underlying page to form the copy image, dark blue color (Deasy, 1984).

Microencapsulation procedures

Many microencapsulation procedures have been developed for the coating of pharmaceuticals. There are difficulties to classify simply under any one heading; however, they may be classified in to 3 major categories which are coacervation or phase separation, interfacial reactions, and miscellaneous mechanical methods (Madan, 1978). These major microencapsulation procedures were summarized briefly in Table 1 (Deasy, 1984). The coacervation or phase separation using aqueous vehicles, the microencapsulation technique used in this research, will be presented in more details in the next topic.

Table 1. Summary of major microencapsulation procedures.

Process	Principle	Type of core	Type of coating
1. Coacervation/ Phase separation	Reduction in the solvation of polymeric solute(s) in a medium to form coacervate droplets to deposit and coat the dispersed phase.	Vehicle-insoluble drug.	Vehicle-soluble polymer(s).
2.Interfacial reactions	Reaction of various monomers at the interface between two immiscible liquid-phase to form a film of polymer that encapsulated the dispersed phase.	High-molecular weight materials such as enzymes and hemolysis.	Water-soluble and water-insoluble monomers.

Table 1. Summary of major microencapsulation procedures (continued).

Process	Principle	Type of core	Type of coating
3. Miscellaneous mechanical methods			
3.1 Air suspension	Polymer solution is Spray-applied to the suspending and moving particles in the coating zone portion of the coating chamber of air suspension apparatus.	Non-volatile and solid drug.	Water-soluble or organic solvent-soluble polymer(s).
3.2 Pan coating	Polymer solution is spray-applied to the desired solid core material, which is adhered on spherical substrate, e.g., sucrose pellets, in the coating pan while rotating.	Non-volatile and solid drug.	Water-soluble or organic solvent-soluble polymer(s).

Table 1. Summary of major microencapsulation procedures (continued).

Process	Principle	Type of core	Type of coating
4. Miscellaneous mechanical methods (continued)			
4.1 Spray drying	Dispersing the core material in coating solution and then atomizing the mixture into a hot air stream to remove the solvent from the coating material.	Solvent-insoluble drug.	Solvent-soluble polymer(s).

Various microencapsulation procedures will give the different characteristic size ranges of microcapsules (Deasy, 1984).

Table 2. Microcapsule size range produced by various production procedures.

Production process	size range (μm)
Coacervation/Phase separation	1-2000
Interfacial polycondensation	2-2000
Air suspension	50-1500
Pan coating	200-5000
Spray drying	5-800

Coacervation Technique

Microencapsulation by coacervation-phase separation was developed in 1950's. The technique was quickly developed because it can be used to microencapsulate a large number of liquids, solids and gases. The polymers used to coat the core materials can be both water soluble and water insoluble. Water-soluble core materials are microencapsulated with water insoluble polymer in organic solvent, on the other hand water-insoluble core materials are microencapsulated with water soluble polymer.

There are two types of coacervation : simple and complex. Simple coacervation involves the use of only one colloid, e.g., gelatin in water, and involves removal of the associated water around the dispersed colloid by agents with a greater affinity for water,

such as various alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form the coacervate.

Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are most frequently used. The coacervation is accomplished mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration.

General process of coacervation-phase separation consists of three steps (Figure 2) carried out under continuous agitation. The first step is formulation of three immiscible phases, the liquid-vehicle phase, the core material, and the liquid polymer coating. The second step is deposition of liquid-polymeric coating material on the core materials and the last step is solidification of coating material.

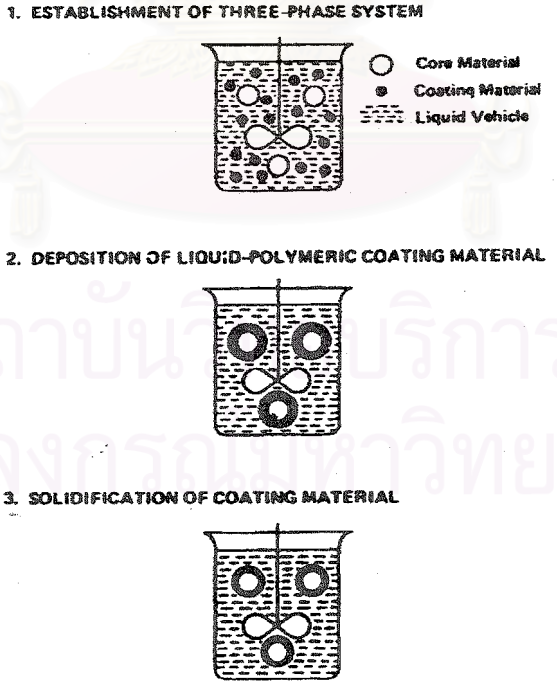


Figure 2. General process of coacervation technique (Bakan, 1994).

In step one the three immiscible chemical phases are formed, where the core material is dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle. The core material and immiscible polymer in a liquid state is formed by utilizing one of the methods of phase separation or coacervation, that is, by simple or complex coacervation, temperature change, addition of a nonsolvent, or polymer-polymer incompatibility.

In step two the liquids polymer coating is deposited around the core material by controlled physical mixing of the coating and the core material in the liquid manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid manufacturing vehicle phase. This sorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating is promoted by a reduction of the total free interfacial energy of the system, brought about by decrease of the coating material surface area during coalescence of the liquid polymer droplet. Step three of the process involves solidifying the coating, usually by thermal, cross linking, or desolvation methods, to form a rigid microcapsule (Bakan, 1994).

Spray drying technique

Spray drying converts a liquid into a powder in a one step process (Nielson, 1982). It is capable of producing fine, dustless or agglomerated powders to precise specifications. The spray drying process encompassed the following four stages (Masters, 1979).

(i) Atomization of the feed into a spray.

(ii) Spray-air contact.

(iii) Drying of the spray.

(iv) Separation of the dried product from the drying gas.

There are a variety of atomization systems available, which may be classified according to the nozzle design as rotary atomization, pressure atomization or two-fluid (pneumatic) atomization. In rotary atomization the feed fluid is introduced into the drying chamber by means of a spinning disc or wheel which creates a spray of droplets. Pressure atomization, as the name suggests, occurs when the feed is fed to the nozzle under pressure which caused the fluid to be dispersed into droplets as it leaves the nozzle. Finally, in two-fluid nozzles, the feed fluid and atomizing air are passed separately to the nozzle where they mix and the air causes the feed to break up into a spray. Two-fluid nozzles are generally confined to laboratory scale spray dryers (such as the Buchi 190 which is commonly used in pharmaceutical research).

Spray dryers may be designed to operate in a co-current manner, where spray and drying air pass through the dryer in the same direction or in a counter-current manner where the spray and drying air enter the drying chamber at opposite ends. Other spray dryer designs are available where the spray-air contact is intermediate between co- and counter-current. Co-current operation is preferable for the drying of heat sensitive materials since the dry product is in contact with only the coolest air. Also, the high rates of moisture evaporation enable the temperature of the dry product to be considerably lower than that of the air leaving the drying chamber. Counter-current drying, on the other hand, is a superior process in terms of heat utilization and economics, but subjects the driest powders to the hottest air stream (Masters, 1979).

The final step in the spray drying process involves the separation of the product from the air steam. This is usually accomplished by means of a cyclone separator through which the air and product pass after exiting the drying chamber. Many dryers also allow for product collection at the base of the drying chamber.

There are numerous different spray dryer designs. Spray dryer systems are usually open cycle whereby the drying gas is discharged after use. For dryers operating in this manner, the drying gas would usually be air. In addition, however, closed cycle spray dryers are available which enable organic solvents to be used as the feed medium. In this type of dryer, the drying air is replaced by an inert gas, usually nitrogen, which is continuously recirculated. The organic solvent is also recovered. Other dryers are available which operate using air with a reduce oxygen content. This may be required if the material being dried is extremely susceptible to oxidation or has explosive tendencies (Nielson, 1982). Various dryer layouts suitable for toxic materials which operate so as to avoid air pollution have also been developed. From a pharmaceutical point of view, it is important to note that aseptic systems are available which operate to produce a sterile powder. This is achieved by filtration of the liquid feed material and the atomizing air, contamination free atomization and product collection, and careful dryer design. These systems are currently used for the production of antibiotics. Also, dryers which incorporate fluid beds into the base of the drying chamber have been designed. These are capable of producing large agglomerated powders more economically than other types of spray dryer.

The main disadvantage of spray drying for many applications is its cost, in terms of both equipment and operation. Spray dryers have poor thermal efficiency unless extremely high drying temperatures are used. This is impossible for the majority of

products, including pharmaceuticals because of the heat degradation which would result. For many pharmaceuticals, however, the cost of the end product may be sufficiently high that the use of spray drying is both feasible and desirable. Thus the expense of the process must be balanced against the advantages to be gained by using spray drying instead of an alternative processing strategy, and the value of the end product.

The applications of spray drying in pharmaceuticals

A microcapsule can be either an individually coated solid particle on liquid droplet, or a matrix of wall material containing many small, fine core particles. The former type of microcapsule can be prepared by numerous methods including coacervation, coating and interfacial reaction technique. Matrix microcapsules are usually prepared by spray drying or spray congealing. Spray drying can be used simply to separate previously prepared microcapsules from the vehicle, or for the preparation on microcapsules in a single operation. In the spray congealing process, no solvent is used. The feed, which consists of the coating and core materials, is fed to the atomizer in the molten state. Microcapsule form when the droplets meet the cool air in the drying chamber and congeal (Deasy, 1984).

Luzzi et al. (1970) used spray drying in order to produce a free flowing powder from a slurry containing nylon microcapsules. In this case, the spray dryer was used simply to separate the microcapsules from the vehicle. The diameter of the particles produced was approximately 10 μm. By comparison, vacuum dried microcapsules had a larger particle size and the powder was not free flowing.

Biodegradable microcapsules have been prepared by spray drying. Polylactic acid (PLA) microcapsules were prepared from solutions, suspensions of a number of drugs dissolved or dispersed in methylene chloride (Bodmeier and Chen, 1988). Microcapsules of progesterone-PLA were formed with diameters of less than 5 μm. The microcapsules became more spherical as the progesterone content was increased. Crystallization occurred in the aqueous phase when the microspheres were prepared by a solvent evaporation method, but spray drying avoided this problem. The major difficulty encountered in preparing the spray dried microcapsules was the formation of polymer fibres as a result of inadequate forces to disperse the filaments into droplets; the successful atomization into droplets was dependent on both the type of polymer used and, to a lesser extent, the viscosity of the spray solution.

Takenaka et al. (1980) prepared enteric coated microcapsules of sulphamethoxazole by spray drying an aqueous solution of drug and cellulose acetate phthalate (5%), with or without various additives, such as monmorillonite clay and colloidal silica. Particles with diameters ranging from 3.6 to 22.0 μm were obtained. Formulations containing additives yielded smaller particles than those without additives. The addition of additives also improved the surface texture of the spray dried products, as compared to articles prepared from non-additive formulations also exhibited poor flow properties and thus were not easily tableted, whereas formulations which included additives were tableted easily. All sulphamethoxazole formulations containing cellulose acetate phthalate (CAP) exhibited some conversion of the drug from crystalline form I to form II and an amorphous form during spray drying (Takenaka et al., 1981). Form II was also obtained by freeze drying or vacuum drying sulphamethoxazole. When microcapsules were prepared by a coacervation technique the drug remained in form I. CAP was presumed to interact with the sulphamethoxazole since the degree of

amorphism increased with an increase in the concentration of CAP in the formulation.

Further studies examined the effect of spray drying sulphamethoxazole with xanthan gum or guar gum, with and without colloidal silica or cellulose acetate phthalate (Kawashima, Lin, and Takenaka, 1983). It was found that the film forming capacity of xanthan gum alone was superior to that of guar gum, but inclusion of colloidal silica or cellulose acetate phthalate made the resultant product smoother. X-ray diffraction data showed that the presence of cellulose acetate phthalate actually caused a polymorphic change resulting in a mixture of forms I, II and III (form III had been indistinguishable in the previous study using IR analysis). When the formulation contained colloidal silica, however, the sulphamethoxazole was always present in form I, irrespective of the gum type. When neither CAP or colloidal silica was included in the formulation, the product was usually a mixture of all three forms.

Broadhead et al. (1992) prepared phenobarbital microcapsules from aqueous polyacrylate dispersions by means of spray drying. They observed increase in microcapsule size with an increasing viscosity of the feed dispersion, which is presumably related to the increased proportion of polymer present in the feed.

Microencapsulation by spray drying can be used to stabilize volatile compounds. Several binders were investigated in a study to evaluate the agglomeration of volatile pharmaceuticals (Kawashima et al., 1972). The binders evaluated were gelatin, gum arabic, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), carboxymethylcellulose (CMC), methylcellulose and tragacanth. Formulations containing binder, salicylic acid (which sublimes at 75 °C) and sodium salicylate were spray dried at an air inlet temperature of 150°C. Salicylic acid was only retained in the gum arabic and PVP

products; it was presumed that these binders must have encapsulated the medicaments. As the gum arabic concentration in the slurry increased, the amount of retained salicylic acid increased.

Takenaka et al. (1982) used spray polycondensation to produce smooth, spherical microcapsules of L-ascorbyl monostearate of size 1-10 μm. The average size of the microcapsules increased and the drug content decreased with increasing amounts of reactive monomer; this was attributed to enhanced polymerization leading to the formation of microcapsules with thicker walls. These authors also evaluated the rheology of ointments incorporating the microcapsules, and observed an increase in the mechanical strength with an increase in the amount of reactive monomer present in the formulation. In addition, increasing amounts of reactive monomer enhanced the stability of the drug to oxidation.

Release of Drug from Microcapsules

The pattern of delivery achieves by a controlled release system can vary over a wide range, but most release profiles categorized into three types : (Baker, 1987)

1. Zero – order release pattern
2. Square – root – time release pattern
3. First – order release pattern

1. Zero – order release pattern

An ideal controlled release device is one which can deliver the drug at a constant rate until the device is exhausted of active agent.

Mathemetically, the release rate from this device is given as

$$\frac{dM_t}{dt} = k \qquad \text{.....(1)}$$

Where k is constant, t is time, and the mass of active agent released is Mt. This pattern of release is called zero-order release model.

2. Square-root-time model (Higuchi's model)

The second common release pattern, frequently referred to as square root of time release, provided compound release that was linear with the reciprocal of the square root of time the release rate then given as

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad \text{.....(2)}$$

In contrast to first-order release, the release rate here remained finite as the device approached exhaustion.

The release pattern of this type can be described by Higuchi's equation (Higuchi, 1963).

$$Q = \frac{[D\varepsilon((2A - \varepsilon C_s)C_s t]^{1/2}}{\tau} \qquad \text{.....(3)}$$

where Q is weight in grams of drug released per unit surface area, D is diffusion coefficent of drug in the release medium, ε is porosity of the matrix, τ is tortuosity of matrix, Cs is solubility of drug in release medium, A is concentration of drug in the microcapsules, expressed as gm/mL, and t is time.

The assumption made for deriving equation 3 are as follows:

1. A pseudo-steady state is maintained during release.
2. A >> Cs, ie. excess solute is present.
3. The system is in perfectly sink condition in which C is approximately zero at all time.
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction between the drug and the matrix occurs.

For purpose of data treatment, the equation (3) is usually reduced to

$$Q = k_H t^{1/2} \quad \text{.....(4)}$$

Where k_H is Higuchi constant. Therefore, the plot of amount of drug released from matrix versus the square root of time should increase linearly if the drug released from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may be used to describe diffusion-controlled released from all surface matrix.

3. First-order model

The first order pattern is the third common type of the release model. The release rate in this case is proportional to the mass of active agent contained within the device. The rate is then given as

$$\frac{dM_t}{dt} = k(M_0 - M_t) \quad \text{.....(5)}$$

where M_0 is the mass of agent in the device at t = 0. On rearrangement, this gives

$$\frac{dM_t}{dt} = kM_0 exp^{-kt} \quad \text{.....(6)}$$

In first order model, therefore, the rate declines exponentially with time, approaching a release rate of zero as the device approaches exhaustion.

On the assumption that the exposed surface area of matrix decreased exponentialy with time, Wagner (1996) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics.

$$A_t = A_0 e^{-k1t} \quad \text{.....(7)}$$

Where k_1 = first order release constant

A_0 = initial amount of drug

A_t = amount of drug remaining in the matrix at time t

Simplifying and taking the logarithm of equation (7) yields

$$\ln A_t = \ln A_0 - k_1 t \quad \text{.....(8)}$$

First order pattern can be predicted by plotting the logarithm of percentage of drug remaining against time. The release of drug is said to be first order model if the linear relationship is obtained. Gupta (1990) reported that the initial curvature of the plot may be obtained because of the presence of surface drugs and they suggested to ignore it.

The release pattern for each class of device is illustrated in figure 3. The release patterns of zero-order, square-root of time, and first-order are depictated .

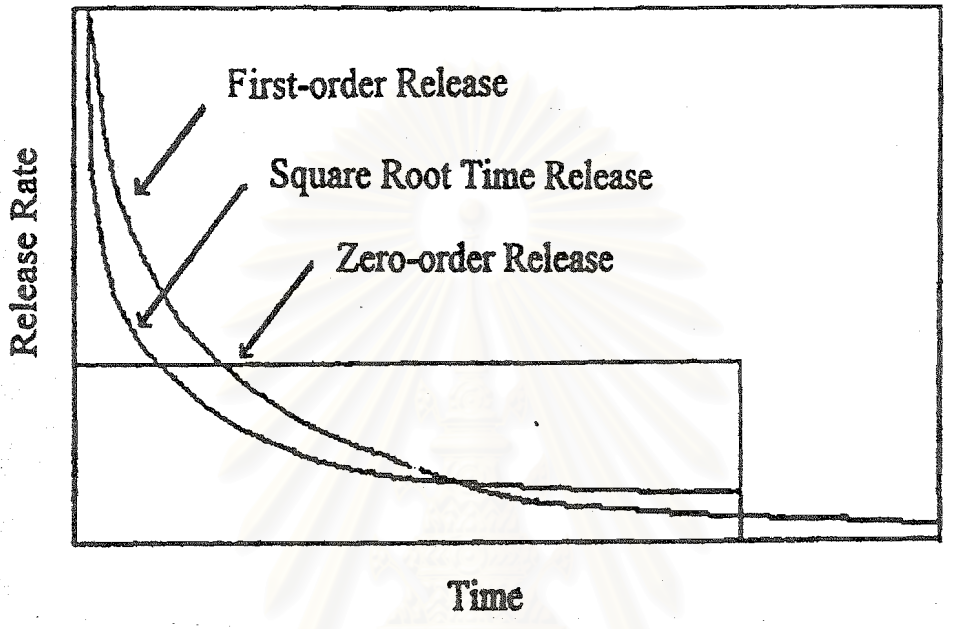


Figure 3. Zero-order, First-order, and Square root of time release patterns form devices containing the same initial active agent content (Baker, 1987).

CHAPTER III

MATERIALS AND METHODS

I. Materials

- Amoxycillin trihydrate (Ferinsa,Maxico), Lot no. F401744.
- Gelatin type A (Biochemika, Switzerland), Lot & Filling code: 375858/1 34399.
- Polyvinyl acetate 27%w/v solution (Kollicoat SR 30 D, BASF Co.Ltd., Germany), Lot no. 69-0855.
- Acacia (Blue Diamond, England)
- SCMC (Wendt Cheme, Germany)
- Formaldehyde solution 37% (Merck, Germany), Lot no. UN-NO.2209.
- Isopropanol (Merck, Germany), Lot no. k27290134 002.
- Acetic acid (J.T. Baker, USA), Lot no. 9515-03.
- Potassium dihydrogen phosphate GR (Merck, Germany), Lot no. A217988 023.
- Sodium hydroxide GR (Mallinckrodt Baker, Mexico), Lot no. 7708MVKK.
- Sodium chloride (Srichard United Dispensing Co.,Ltd., Thailand), Lot no. SHE 49/928.
- Hydrochloric acid (Merck, Germany), Lot no. K25741517.
- Deionized water.

II. Instruments

- Variable-speed stirring motor fitted with a four-blade stirring shaft (Model R30, GmgH & Co., France).
- Vacuum Pump (DOA-V130-BN, Waters, USA).
- High performance liquid chromatography (HPLC) (Shimadzu, Japan) equipped with
  - LC workstation (Class-LC10 Version 1) (Shimadzu, Japan).
  - Automatic sample injector SIL-10A I (Shimadzu, Japan).
  - Solvent delivery module (LC-10AD; bigradient) (Shimadzu, Japan).
  - Detector (SPD-10A UV-visible detector) (Shimadzu, Japan).
  - Communicator bus module (CBM-10A) (Shimadzu, Japan).
  - Column oven (CTO-10A) (Shimadzu, Japan).
  - μ-Bondapak C_{18} stainless steel column (30 cm x 3.9 mm I.D., 10 μm packing) .
- pH meter (Orion Model 420A, Orion Research Inc., USA).
- UV-visible spectrophotometer (Sotax AT7, Art no. 4100-1, Allschwil, Switzerland).
- Suction circulator (Miniplus 3, model M312, Gilson, France).
- Optical microscope (BH-2, Olympus, Japan).
- Ultra sonicator (Model 3210E-MTH, Branson, USA).
- Scanning Electron Microscope (Model JSM-6400, Jeol Co.,Ltd., Japan).
- Spray dryer (Mobile Minor Unit, Niro Atomizer, Denmark).

III. Method

1. HPLC analysis

The analysis of amoxycillin contents in microcapsules were determined using the modified reverse phase HPLC assayed with UV detector. Chromatographic conditions for determination of amoxycillin were as follows:

Column	: Bondapak C_{18} with particle size of 10 μm, 300x3.9 mm.
Mobile phase	: 0.05M Potassium dihydrogen phosphate: Acetonitrile = 70:30.
Flow rate	: 1.5 mL/min.
Injection volume:	10 μL.
Detector	: UV, 230 nm.
Temperature	: ambient.

1.1 Preparation of internal standard solution

A 20 mg of cloxacillin was accurately weighed into a 50 mL volumetric flask. The mobile phase was added and the mixture was swirled until cloxacillin was completely dissolved and then adjusted to volume. The final concentration of the stock solution of internal standard was 0.4 μg/mL.

One millilite of the 0.4 μg/mL internal standard was pipetted into a 10 mL volumetric flask of each concentration of amoxycillin standard solution.

1.2 Preparation of standard solution

A 50 mg of amoxycillin was accurately weighed into a 50 mL volumetric flask. Mobile phase was added and the mixture was swirled until amoxycillin was completely dissolved and then adjusted to volume. The stock solution had a final concentration of 1000 μg/mL. Standard solution with known concentrations of 100, 200, 300, 400, 500, 600 and 700 μg/mL were then prepared by dilution of the stock solution with mobile phase. The final solution was assayed by HPLC method.

1.3 Preparation of sample solution

Samples were diluted with an appropriate amount of mobile phase, if necessary, to obtain peak area ratio in the range of standard curve. The appropriate amount of internal standard was added to the sample solution prior to the HPLC analysis.

1.4 Assay validation

1.4.1 Accuracy in terms of percent recovery was determined by analyzing three sets of calibration curves of amoxycillin. Percent recovery of each concentration was calculated from the ratio of inversely estimated concentration to known concentration of amoxycillin multipled by 100.

1.4.2 Within run precision was determined by analyzing three sets of calibration curves in the same day. The percent coefficient of variation (%C.V.) of the peak area ratios of amoxycillin to the internal standard of each concentration was determined.

1.4.3 Between run precision was determined by comparing the peak area ratios of amoxycilline to the internal standard of three sets of calibration curves for three different days. The percent coefficient of variation (%C.V.) of each concentration was determined.

II. UV Analysis

2.1 Calibration curve of amoxycillin in simulated gastric fluid without pepsin pH 1.2

Six appropriate dilutions of amoxycillin made with the same vehicle were prepared to contain 10, 15, 20, 25, 30 and 40 μg/mL, respectively, in simulated gastric fluid without pepsin pH 1.2±0.1. The calibration curve was plotted between amoxycillin concentration in μg/mL and absorbance at 229 nm and the linear regression was applied.

2.2 Calibration curve of amoxycillin in simulated intestinal fluid without pancreatin pH 6.8.

Six appropriate dilutions of amoxycillin made with the same vehicle were prepared to contain 10, 15, 20, 25, 30 and 40 μg/mL, respectively, in simulated intestinal fluid without pancreatin pH 6.8±0.1. The calibration curve was plotted between amoxycillin concentration in μg/mL and absorbance at 229 nm and the linear regression was applied.

2.3 Assay validation.

2.3.1 Accuracy in terms of percent recovery was determined by analyzing three sets of calibration curves of amoxycillin. Percent recovery of each concentration

was calculated from the ratio of inversely estimated concentration to known concentration of amoxycillin multipled by 100.

2.3.2 Within run precision was determined by analyzing three sets of calibration curves in the same day. The percent coefficient of variation (%C.V.) of the absorbance of amoxycillin of each concentration was determined.

2.3.3. Between run precision was determined by comparing the absorbance of amoxycillin of three sets of calibration curves for three different days. The percent coefficient of variation (%C.V.) of each concentration was determined.

3 Preparation of Amoxycillin Microcapsules

3.1. Complex coacervation process

3.1.1. Gelatin-acacia complex coacervation (Palmieri et. al., 1996)

Amoxycillin powder was seived through a sieve no.100 before being used in every formulation. Five grams of amoxycillin was accurately weighed and put in a gelatin solution at 40°C. The suspension was stirred for 5 minutes, then, an equal volume of acacia solution at 40°C was added to the suspension, and the system was stirred at the rate of 700 rpm under the same condition. Finally, a 10%v/v acetic acid solution was added to reduce the pH to the predetermined value. The stirring was continued until the coacervation was formed. After the system was cooled to 3-5°C the stirring was continued for 30 minutes further. Then, a 2 mL of formaldehyde was added as a hardening agent and allow to stand for 60 minutes. Three successive equal volumes of cold isopropanol (5°C) were added to the system for dehydration of microcapsules. Then the microcapsules were separated from the solution by vacuum filtration. The filtered

microcapsules were washed three times with isopropanol and dried at room temperature for 12 hours and stored in a desiccator for further studies. The diagram of gelatin-acacia complex coacervation is shown in figure 4.

3.1.1.1 Effect of core to wall ratio

The amoxycillin microcapsules were prepared using the procedure described in 3.1.1. The core to wall ratios of 1:1, 1:2 and 1:3, were prepared with 1.5% total concentration of wall (gelatin:acacia ratio 1:1). The pH are adjusted to 3.5, the system was stirred at a constant rate of 700 rpm. The parameters were shown in Table 3.

The proposed formula of 1:1 core to wall ratio was amoxycillin 5 gm, gelatin 2.5 gm in concentration of 1.5% and acacia 2.5 gm in concentration of 1.5%.

The proposed formula of 1:2 core to wall ratio was amoxycillin 5 gm, gelatin 5 gm in concentration of 1.5%and acacia 5 gm in concentration of 1.5%.

The proposed formula of 1:3 core to wall ratio was amoxycillin 5 gm, gelatin 7.5 gm in concentration of 1.5% and acacia 7.5 gm in concentration of 1.5%.

Table 3. The parameters used in the preparation of amoxycillin microcapsules by gelatin-acacia coacervation with varying the core to wall ratios.

Parameters	Value
Core to wall ratio	**1:1, 1:2, 1:3**
pH	3.50
Concentration of wall	1.5%
Stirring rate	700

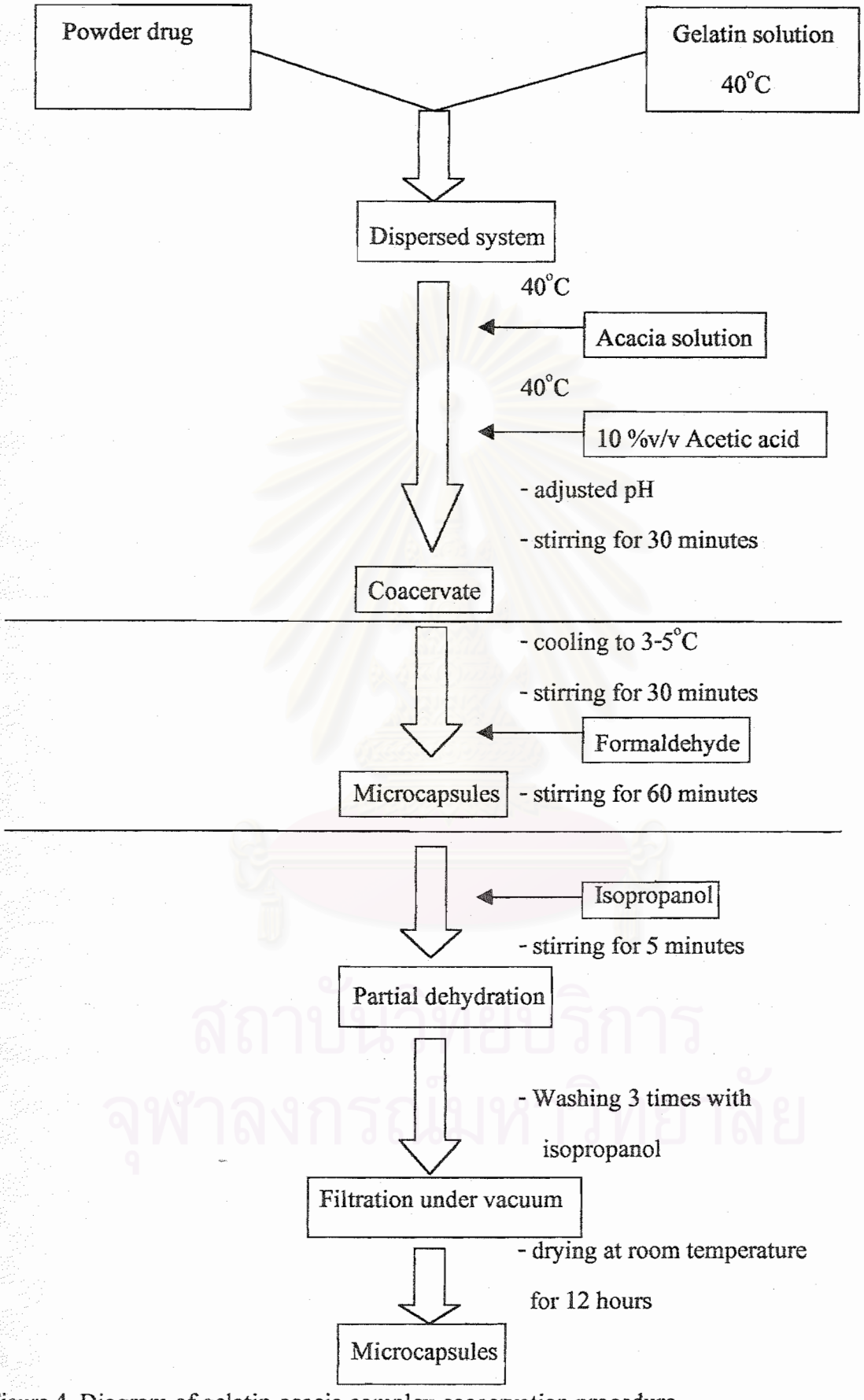


Figure 4. Diagram of gelatin-acacia complex coacervation procedure.

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of core to wall ratio was chosen to apply in further studies.

3.1.1.2 Effect of pH

The amoxycillin microcapsules were prepared using the procedure described in 3.1.1. The core to wall ratio of 1:2 was selected. The pH of medium was adjusted to 3.5, 3.75 and 4.0. The parameters are shown in Table 4.

Table 4. The parameters used in the preparation of amoxycillin microcapsules by gelatin-acacia coacervation with varying pH of medium.

Parameters	Value
Core to wall ratio	1:2
pH	**3.50, 3.75, 4.00**
Concentration of wall	1.5%
Stirring rate	700

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of pH was chosen to apply in further studies.

3.1.1.3 Effect of concentration of wall

The amoxycillin microcapsules were prepared by using the core to wall ratio of 1:2. The total concentration of wall was varied at 1, 1.5 and 2%. The pH of medium was adjusted to 3.5. The parameters are shown in table 5.

Table 5. The parameters used in the preparation of amoxycillin microcapsules by gelatin-acacia coacervation with varying the concentration of wall.

Parameters	Value
Core to wall ratio	1:2
pH	3.5
Concentration of wall	**1%, 1.5%, 2%**
Stirring rate	700

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of concentration of wall was chosen to apply in further studies.

3.1.1.4 Effect of stirring rate

The amoxycillin microcapsules were prepared by using the core to wall ratio of 1:2 . The total concentration of wall was 2%, and the pH of medium was adjusted to 3.5. The stirring rates were varied at 500, 700 and 900 rpm. The parameters are shown in Table 6.

Table 6. The parameters used in the preparation of amoxycillin microcapsules by gelatin-acacia coacervation with varying the stirring rates.

Parameters	Value
Core to wall ratio	1:2
pH	3.5
Concentration of wall	2%
Stirring rate	**500, 700, 900**

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated.

3.1.2 Gelatin-sodium carboxymethycellulose (SCMC) complex coacervation (Palmieri et al., 1996).

Amoxycillin powder was seived through a sieve no. 100 before being used in every formulation. Five grams of amoxycillin powder was accurately weighed and put in a gelatin type A solution at 40°C. The suspension was stirred for 5 minutes, then, an equal volume of SCMC solution at 40°C was added to the suspension, and the system was stirred at the rate of 700 rpm under the same condition. Finally, a 10%v/v acetic acid solution was added to reduce the pH to the predetermined value. The stirring was continued until the coacervation was formed. After that the system was cooled to 3-5°C the stirring was continued for 30 minutes further. Then, a 2 mL of formaldehyde was added as a hardening agent and allow to stand for 60 minutes. Three successive equal volumes of cold isopropanol (5°C) were added to the system for dehydration of microcapsules. Then the microcapsules were separated from the solution by vacuum filtration. The filtered microcapsules were then washed with isopropanol and dried at room temperature for 12 hours and stored in a desiccator for further studies. The diagram of gelatin-SCMC complex coacervation is shown in figure 5.

3.1.2.1 Effect of core to wall ratio

The amoxycillin microcapsules were prepared by using the procedure described in 3.1.2. The core to wall ratios of 1:1, 1:2 and 1:3, were prepared with 1.5% total concentration of wall (gelatin:SCMC ratio 8:2). The pH of medium was adjusted to 3.5. The system was stirred at a constant rate of 700 rpm. The parameters are shown in Table 7.

The proposed formula of 1:1 core to wall ratio was amoxycillin 5 gm, gelatin 4 gm in concentration of 1.5% and SCMC 1 gm in concentration of 1.5%.

The proposed formula of 1:2 core to wall ratio was amoxycillin 5 gm, gelatin 8 gm in concentration of 1.5% and SCMC 2 gm in concentration of 1.5%.

The proposed formula of 1:3 core to wall ratio was amoxycillin 5 gm, gelatin 12 gm in concentration of 1.5% and SCMC 3 gm in concentration of 1.5%.

Table 7. The parameters used in the preparation of amoxycillin microcapsules by gelatin-SCMC coacervation with varying the core to wall ratios.

Parameters	Value
Core to wall ratio	**1:1, 1:2, 1:3**
pH	3.50
Concentration of wall	1.5%
Stirring rate	700

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of core to wall ratio was chosen to apply in the further studies.

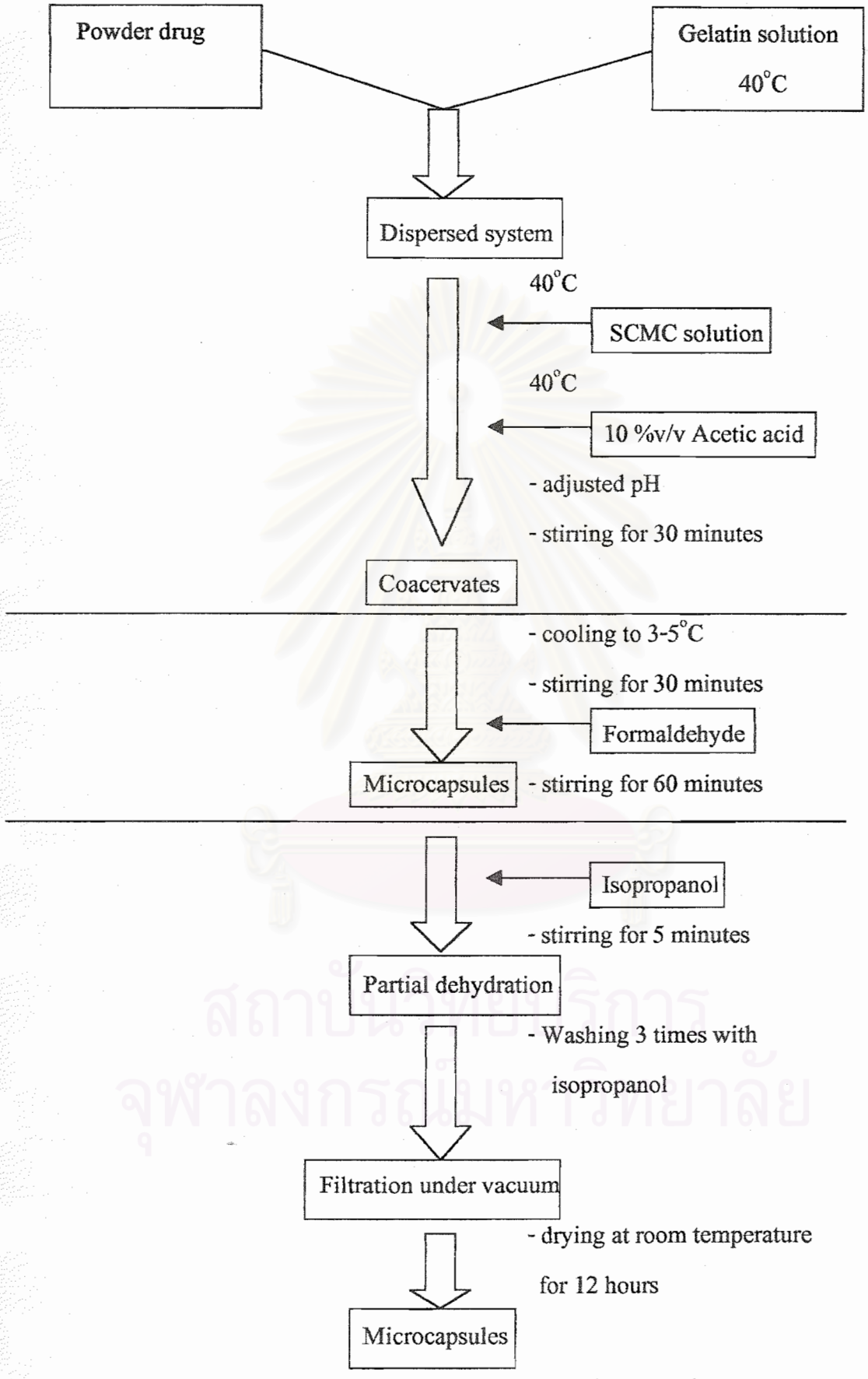


Figure 5. Diagram of gelatin-SCMC-complex coacervation procedure.

3.1.2.2 Effect of pH

The amoxycillin microcapsules were prepared by using the procedure described in 3.1.2. The core to wall ratio of 1:2 was selected. The pH of medium was adjusted to 3.5, 3.75 and 4.0, respectively. The parameters are shown in Table 8.

Table 8. The parameters used in the preparation of amoxycillin microcapsules by gelatin-SCMC coacervation with varying pH of medium.

Parameters	Value
Core to wall ratio	1:2
pH	**3.50, 3.75, 4.00**
Concentration of wall	1.5%
Stirring rate	700

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of pH was chosen to apply in further studies.

3.1.2.3 Effect of concentration of wall

The amoxycillin microcapsules were prepared by using the core to wall ratio of 1:2. The total concentration of wall was varied at 1, 1.5 and 2%. The pH of medium was adjusted to 3.75. The parameters are shown in Table 9.

Table 9. The parameters used in the preparation of amoxycillin microcapsules by gelatin-SCMC coacervation with varying the concentration of wall.

Parameters	Value
Core to wall ratio	1:2
pH	3.75
Concentration of wall	**1%, 1.5%, 2%**
Stirring rate	700

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of concentration of wall was chosen to apply in the further studies.

3.1.2.4 Effect of stirring rate

The amoxycillin microcapsules were prepared by using the core to wall ratio of 1:2. The total concentration of wall was 1.5% and the pH of medium was adjusted to 3.75. The stirring rates were varied at 500, 700 and 900 rpm. The parameters are shown in Table 10.

Table 10. The parameters used in the preparation of amoxycillin microcapsules by gelatin-SCMC coacervation with varying the stirring rates.

Parameters	Value
Core to wall ratio	1:2
pH	3.75
Concentration of wall	1.5%
Stirring rate	**500, 700, 900**

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated.

3.2 Spray drying process

3.2.1 Spray drying process

The spray drying apparatus used is a laboratory type, with drying chamber of 80 cm in diameter, 60 cm in cylindrical height and conical base. The cone angle is 60°. The suspension was atomized into a drying chamber by rotating centrifugal wheel atomizer.

The processing variables of spray drying technique were varied according to Table 11. The outlet temperature could not be directly controlled, but was a function of the dryer inlet air temperature and the solution feed rate, in this study a range of 80-95 °C was used.

Table 11. Parameters of spray drying process variables.

Parameters	Value
Core to wall ratio	1:1, 1:2, 1:3
Inlet air temperature (°C)	110, 120, 130
Feed rate (mL/min)	18, 24, 30
Solid content (%)	5, 7, 10

A constant atomizing air pressure was used at 2 bar. In order to study the effect of each variable in spray drying process, it was necessary to keep the other variable constant and only the desired variable was varied.

3.2.2 Preparation of spray dried solution

Amoxycillin powder was sieved through a sieve no. 100 before being used in every formulation. Amoxycillin powder was homogenized in an aqueous dispersion of polyvinyl acetate (Kollicoat® SR30D). The total concentration of amoxycillin and polyvinyl acetate was the solid content of formula that varied in the range of 5-10%. The volume was adjusted to 1000 mL with deionized water. The suspension was subsequently spray dried under variable conditions.

3.2.2.1 Effects of core to wall ratio

The amoxycillin microcapsules were prepared by spray drying process with varying core to wall ratios of 1:1, 1:2, and 1:3. The parameters are shown in Table 12.

The proposed formula of 1:1 core to wall ratio was amoxycillin 35 gm and polyvinyl acetate equivalent to 35 gm.

The proposed formula of 1:2 core to wall ratio was amoxycillin 23.3 gm and polyvinyl acetate equivalent to 46.7 gm.

The proposed formula of 1:3 core to wall ratio was amoxycillin 17.5 gm and polyvinyl acetate equivalent to 52.5 gm.

Table 12. The parameters of spray drying process with varying the core to wall ratios.

Parameters	Value
Core to wall ratio	1:1, 1:2, 1 :3
Inlet air temperature (°C)	120
Feed rate (mL/min)	24
Solid content (%)	7

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate results of core to wall ratio was chosen to apply in further studies.

3.2.2.2 Effects of inlet air temperature

The amoxycillin microcapsules were prepared by spray drying process using the parameters as shown in table 13.

Table 13. The parameters of spray drying process with varying the inlet air temperature.

Parameters	Value
Core to wall ratio	1:2
Inlet air temperature (°C)	110, 120, 130
Feed rate (mL/min)	24
Solid content (%)	7

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of inlet air temperature was chosen to apply in the further studies.

3.2.2.3 Effects of feed rate

The amoxycillin microcapsules were prepared by spray drying process using the parameters as shown in table 14.

Table 14. The parameters of spray drying process with varying feed rates.

Parameters	Value
Core to wall ratio	1:2
Inlet air temperature (°C)	120
Feed rate (mL/min)	18, 24, 30
Solid content (%)	7

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated. The appropriate result of feed rate was chosen to apply in further studies.

3.2.2.4 Effects of solid content

The amoxycillin microcapsules were prepared by spray drying process using the parameters as shown in table 15.

Table 15. The parameters of spray drying process with varying the solid content.

Parameters	Value
Core to wall ratio	1:2
Inlet air temperature (°C)	120
Feed rate (mL/min)	24
Solid content (%)	5, 7, 10

The percent yield, percent content, core entrapment, morphology, particle size distribution and the release characteristics of microcapsules were investigated.

4. Evaluation of amoxycillin microcapsules

4.1 Yield of microcapsules

The prepared microcapsules were accurately weighed. The net weight was divided with the theoretical weight of microcapsules. The percentage of microcapsule yield was calculated.

$$\%Yield = \frac{Wt.\ of\ dried\ microcapsules\ (g) \times 100}{Theoretical\ wt.\ of\ microcapsules\ (g)} \quad \ldots\ldots\ldots\ldots\ldots\ldots (9)$$

Where,

- Theoretical wt. of microcapsules (g) = wt. of drug (g) + wt. of polymer (g)

4.2 Percent content and percent entrapment of core

The percent content and entrapment of amoxycillin were determined using the HPLC method. Triplicate samples of microcapsules of approximately 100 mg were accurately weighed, then dissolved with 0.1 N HCl in 100 mL volumetric flask and diluted to the appropriate concentration. This solution was assayed by HPLC. The amounts of amoxycillin were determined from the standard curves. The percent content and entrapment of amoxycillin were calculated from equation (10) and (11), respectively.

$$\%Observed\ amoxycillin\ content = \frac{Assayed\ amount\ of\ amoxycillin(g) \times 100}{Amount\ of\ weighed\ microcapsules(g)} \quad \ldots\ldots\ldots (10)$$

$$\%Amoxycillin\ entrapment = \frac{\%Observed\ amoxycillin\ content}{\%Theoretical\ amoxycillin\ content} x\ 100 \quad \text{.....(11)}$$

where,

- $$\%Theoretical\ amoxycillin\ content = \frac{wt.\ of\ amoxycillin\ (g)}{wt.\ of\ amoxycillin\ (g) + wt.\ of\ polymer(g)} x100 \quad \text{...(12)}$$

4.3 Morphology and particle size analysis

The morphology of the microcapsules was observed by scanning electron microscopy (SEM). The sample was coated with gold by ion sputtering under a high vacuum and high voltage. The coated samples were then examined under SEM. The particle size of the microcapsules was measured three times by Laser particle size analyzer. The median size was obtained, and the mean and standard deviation were calculated.

4.4 Dissolution studies

4.4.1 Drug release in simulated gastric fluid without pepsin pH 1.2.

The release studies of pure amoxycillin and microencapsulated amoxycillin were performed in gastric fluid without pepsin pH 1.2± 0.1 using the USP 24 dissolution apparatus 2 (paddle method) for 2 hours. Tripicate samples of microcapsules equivalent to about 250 mg of amoxycillin was accurately weighed and transferred into 900 mL of the dissolution medium which was maintained at 37±0.1 ^{o}C and stirred at a constant stirring rate of 75 rpm. Five milliliters samples were withdrawn at definite time intervals and replaced with fresh dissolution medium. The sample was then filtered through a 0.22 μm filter unit and diluted with dissolution medium to an

appropriate concentration. The sample was assayed by UV spectrophotometer at a wavelength of 229 nm. The concentrations of amoxycillin were quantified using calibration curve. The percent released was calculated from the concentration of amoxycillin at each interval divided by total amount of amoxycillin in sample of microcapsules multiply by 100. The mean value and standard deviation were computed. Finally the mean and ln mean of percent released was plotted versus time, the mean of percent released was plotted versus square root of time to obtain the release profile. The release rate constant of zero-order, first order and Higuchi were calculated as shown in appendix F. From Higuchi's model, the time of 50% released was calculated from Higuchi equation.

4.4.2 Drug release in simulated intestinal fluid without pancreatin pH 6.8.

The release studies of amoxycillin microcapsules were performed in intestinal fluid without pancreatin pH 6.8±0.1 using the USP 24 dissolution apparatus 2 (paddle method) for 12 hours. Triplicate samples of microcapsules equivalent to about 250 mg of amoxycillin was accurately weighed and transferred into 900 mL of the dissolution medium which maintained at 37±0.1 °C and stirred at a constant stirring rate of 75 rpm. Five milliliters samples were withdrawn at definite time intervals and replaced with fresh dissolution medium. The samples were then filtered through a 0.22 μm filter unit and diluted with dissolution medium to an appropriated concentration. The samples were assayed by UV spectrophotometer at a wavelength of 229 nm. The concentrations of amoxycillin were quantified using calibration curve. The percent released was calculated from the concentration of amoxycillin at each interval divided by total amount of amoxycillin in sample of microcapsules multiply by 100. The mean value and standard deviation were computed. Finally the mean and ln mean of percent released was plotted versus time and the mean of percent released was plotted versus

square root of time to obtain the release profile. The release rate constant of zero-order, first order and Higuchi were calculated as shown in appendix F. From Higuchi's model, the time of 50% released was calculated from Higuchi equation.

4.5. Micromeretic properties

The formulation selected suitably was determined for bulk density, tap density and angle of repose compared with amoxycillin powder.

4.5.1. Bulk density

The bulk density was determined from the weight of microcapsules about 10 gm. (an accurate weight was recorded), carefully charged into a 100 mL graduated cylinder and the bulk volume was recorded. Division of weight by bulk volume showed bulk density. Results were obtained from the average of three determinations.

4.5.2 Tap density

Tap density was performed by dropping graduated cylinder on a hard wood surface from a height of 5 cm until a constant volume was obtained. Division of weight by this volume showed tap density. Results were obtained from the average of three determinations.

4.5.3 Angle of repose

Angle of repose was determined by the cylinder method. An appropriate amount of powder was carefully filled into a cylinder (height = 5.2 cm and

radius = 2.4 cm) placed on the graph paper. When the powder was filled to the top of the cylinder, the cylinder was slowly lifted in a vertical direction, thus producing around heap of powder. The results were averaged from three determinations and reported. Angle of repose was calculated from the following equation.

$$\alpha = \tan^{-1}(H/R) \quad \text{.....(13)}$$

where

α is the angle of repose

H is the height of heap

R is the radius of heap

4.6 Statistical determination

For the data of release studies, time at 50% amoxycillin released (T_{50}) was used for determination of statistical values. Two-way ANOVA was selected for data analysis of amoxycillin microcapsules prepared by complex coacervation and one-way ANOVA for data analysis of amoxycillin microcapsules prepared by spray-drying technique at $\alpha = 0.05$. If the results showed statistically significant difference, the rank order of those values would be examined by Duncan's New Multiple Range test. The statistic values were examined by SPSS version 7.5.

CHAPTER IV

RESULTS AND DISCUSSION

1. Validation of analytical method of amoxycillin by HPLC method.

The analysis of amoxycillin in microcapsules was determined using the reverse phase HPLC with UV detection. The UV detection wavelength was at 230 nm which was the optimal wavelength given the complete resolution of peak for HPLC analysis.

1.1. Specificity

The specificity of amoxycillin chromatograms are illustrated in Figure 79, Appendix B, the retention time of amoxycillin was at 2.4 minutes and cloxacillin as a internal standard at 6.9 minutes. In addition, there was no interference to the peak of both constituents in the chromatogram.

1.2. Linearity

The calibration curves of amoxycillin standard solution are shown in Figure 6. Calibration curves were plotted between the peak area ratio of amoxycillin to cloxacillin and the concentration of amoxycillin in μg/mL. The linear regression was used to test the fitting of data with a straight line. The coefficient of determination (R^2) of amoxycillin standard curve was 0.9999.

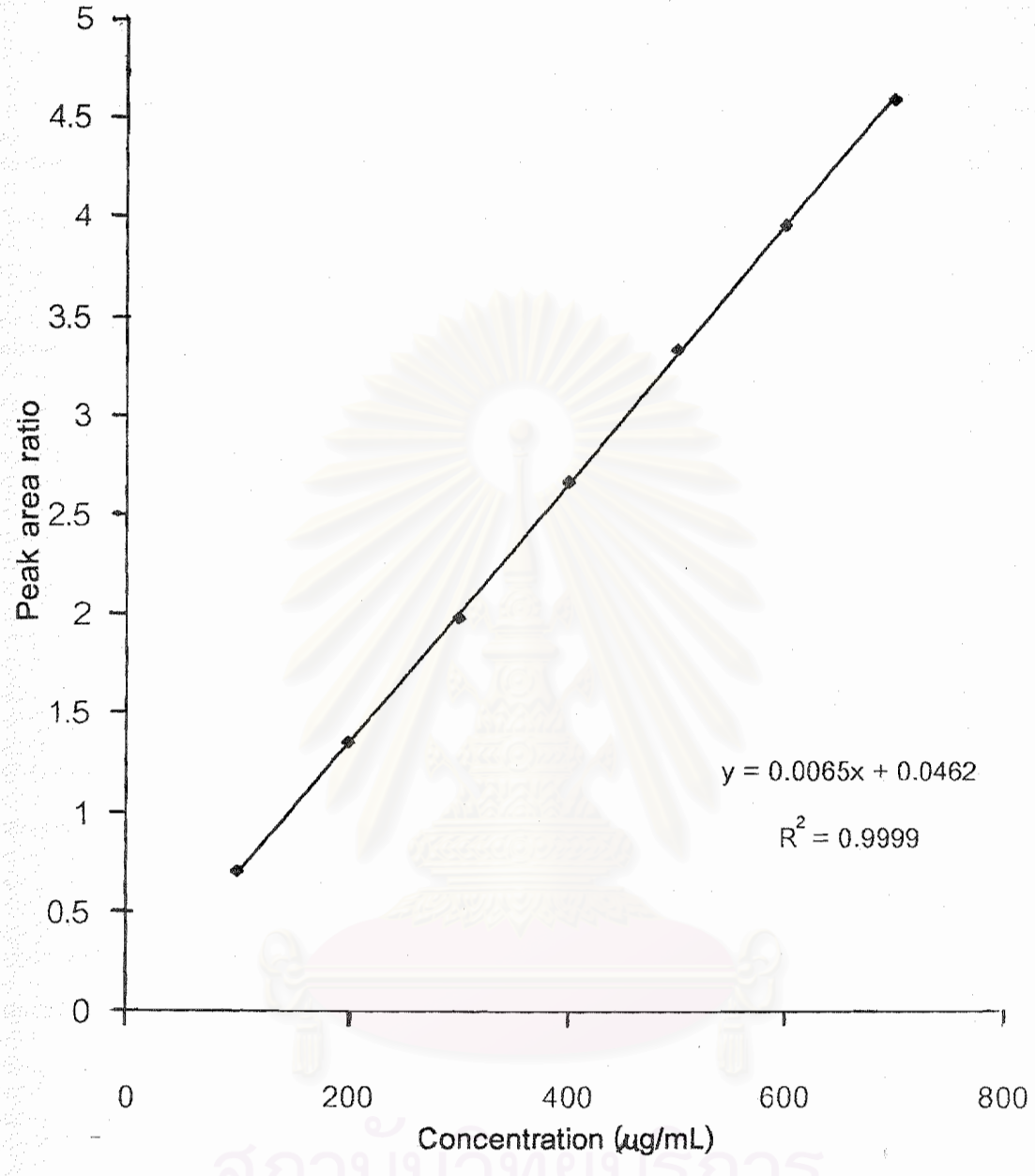


Figure 6. Calibration curve of amoxycillin by HPLC method.

1.3. Accuracy

The determination of accuracy of the analysis of amoxycillin by HPLC method was performed by analyzing the percent analytical recovery of 7 injections of standard solution (Table 64, Appendix B). The obtained percent recoveries ranged from 98.42-101.23 (acceptance criteria, the percent recovery should not less than 90-110%). It indicated that the HPLC method could be used to determine the drug content with high accuracy.

1.4. Precision

The precision of the analysis of amoxycillin by HPLC method was determined within run and between run as illustrated in Table 65 and 66, Appendix B. The percent coefficients of variation (%C.V.) of all precision determinations were 0.293-3.337 (accepted criteria of the percent coefficients of variation are not greater than 2-3%). In conclusion, the analysis of amoxycillin by HPLC in this study showed good specificity, linearity, accuracy and precision. Thus this method could be used for the determination of the content in the study.

2. Validation of analytical method of amoxycillin by UV method.

The analysis of amount of amoxycillin released from microcapsules was determined using the UV/visible spectrophotometer. The UV detection wavelength was at 230 nm which was the optimal wavelength for UV analysis of amoxycillin.

2.1. Accuracy

The determination of accuracy of the analysis of amoxycillin by UV method was performed by analyzing the percent analytical recovery of standard solution (Table 67 and 68, Appendix C). The obtained percent recoveries ranged from 98.75-100.99 in pH 1.2 and 98.75-100.69 in pH 6.8 (accepted criteria of the percent recovery should not less than 90-110%). It indicated that the UV method could be used to determine the concentration of amoxycillin in dissolution study.

2.2. Precision

The precision of the analysis of amoxycillin by UV method was determined within run and between run as illustrated in Table 69-72, Appendix C. The percent coefficients of variation (%C.V.) of all precision determinations were 0.23-1.87 (acceptance criteria of the percent coefficents of variation are not greater than 2-3%). In conclusion, the analysis of amoxycillin by UV method in this study showed good accuracy and precision.

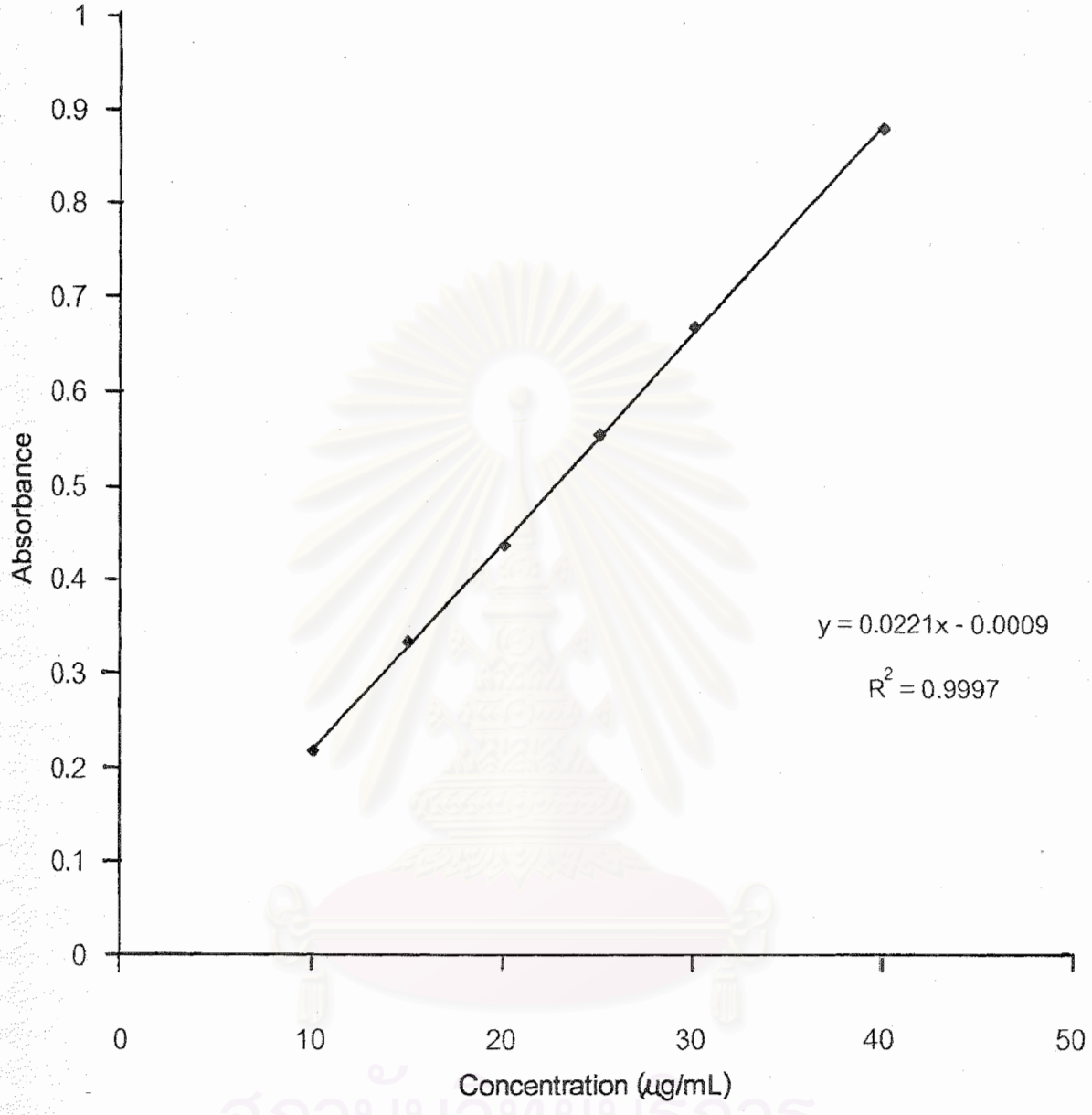


Figure 7. Calibration curve of amoxycillin by UV method in gastric fluid without pepsin pH 1.2.

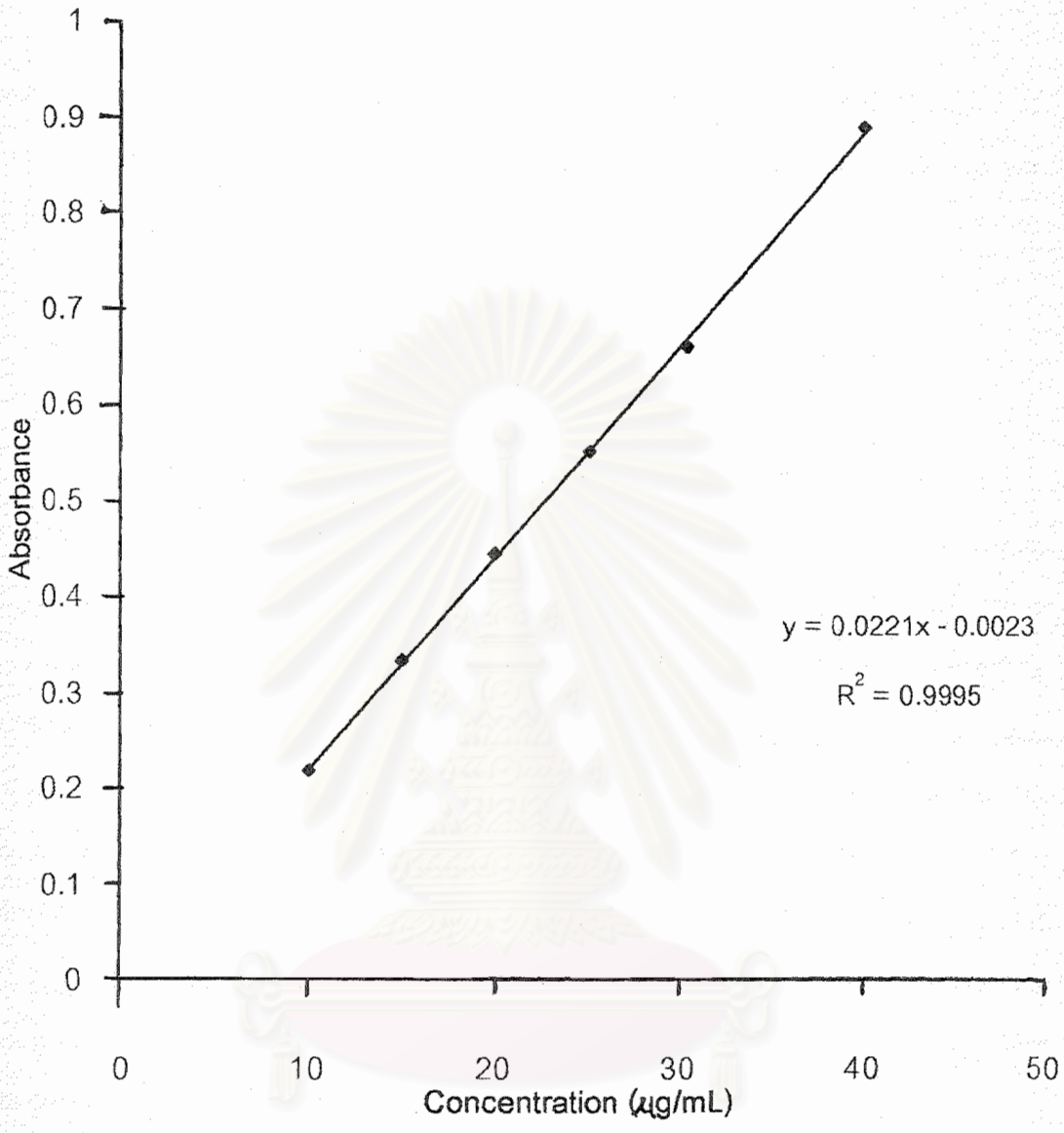


Figure 8. Calibration curve of amoxycillin by UV method in intestinal fluid without pancratin pH 6.8.

3. Preparation of amoxycillin microcapsules by coacervation technique

Amoxycillin microcapsules prepared using gelatin-acacia as the wall material had spherical-like shape while microcapsules prepared using gelatin-SCMC as the wall material were aggregated.

3.1 Effect of core to wall ratio

Amoxycillin microcapsules prepared by using gelatin-acacia with various core to wall ratios of 1:1, 1:2 and 1:3, respectively, exhibited high percent yield between 87-88% while amoxycillin microcapsules prepared by using gelatin-SCMC with various core to wall ratios of 1:1 and 1:2, respectively, exhibited lower percent yield between 82-83% as shown in Table 16. The core to wall ratio of 1:3 tended to form a lumpy mass and difficult to filter. It cannot form a complete coacervation, possibly because of the excess of ionized polymer and the viscosity and adhesive effect of polymers. From Table 17, the gelatin acacia walled microcapsules prepared with 1:3 core to wall ratio have the highest percent entrapment of amoxycillin. The increase in amount of wall resulted in the increase of percent entrapment due to the increase in particle size of microcapsules (Mohamed and Nazik, 1983) as shown in Table 18.

Table 16. The percent yield of amoxycillin microcapsules prepared by coacervation technique with various core to wall ratios.

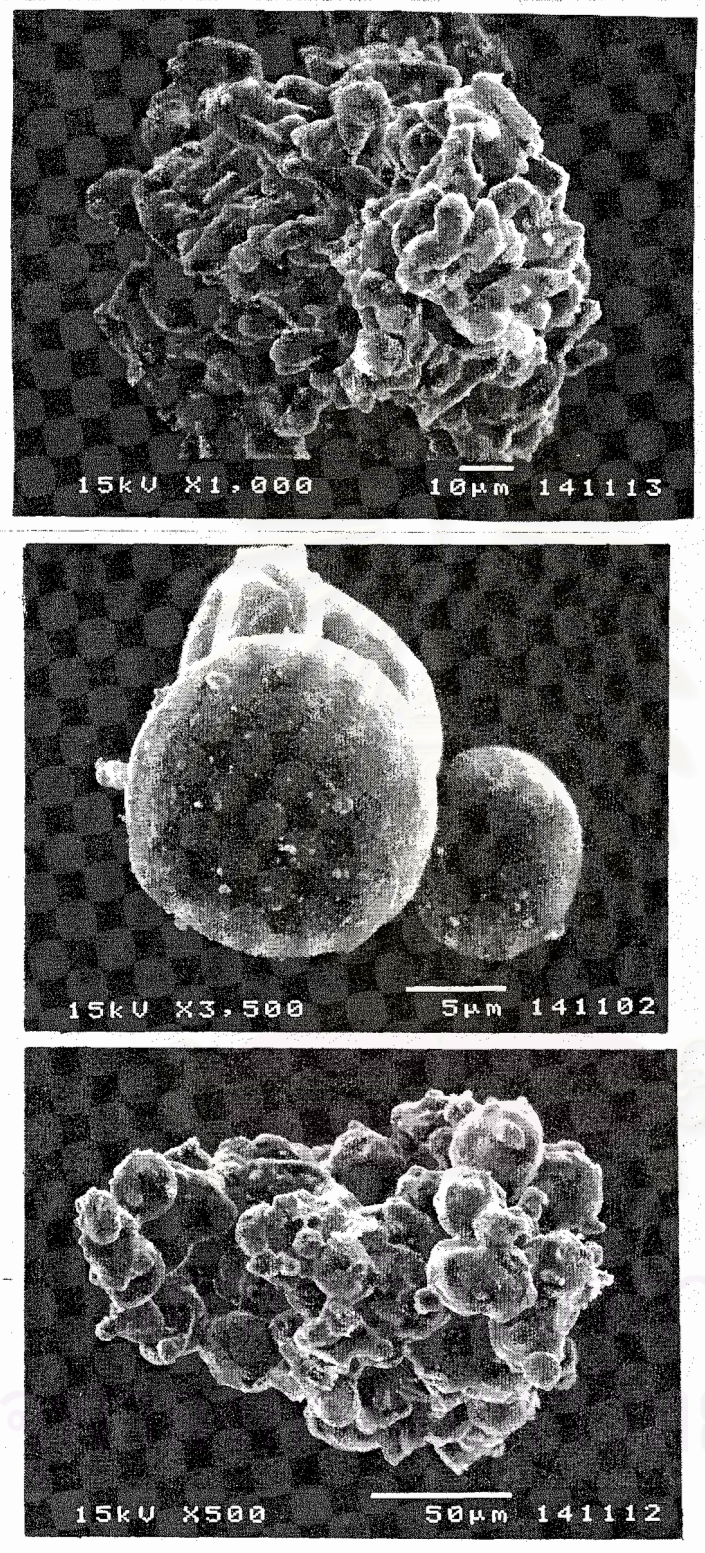
Polymer	%Yield		
	1:1	1:2	1:3
G-A	88.25	87.86	87.59
G-S	82.27	83.61	-

Table 17. The percent content and entrapment of amoxycillin microcapsules prepared by coacervation technique with various core to wall ratios.

Value	Core : wall 1:1		Core : wall 1:2		Core : wall 1:3	
	G-A	G-S	G-A	G-S	G-A	G-S
Theoretical content	50	50	33.33	33.33	25	-
Observed content	38.53±0.98	39.63±0.25	29.72±1.78	28.55±1.12	22.52±0.02	-
% entrapment	77.06±3.46	79.26±2.54	89.17±5.48	85.66±4.96	90.08±1.37	-

The effects of core to wall ratios on the surface morphology are shown in Figures 9 and 10, and sizes of microcapsules are shown in Table 18. The frequency distribution curve is shown in Figure 11. When the amount of wall increased, the particle sizes also increased. Since the amount of amoxycillin was kept constant, thus, the increased amount of wall material resulted in an increase of the particle size of microcapsules. As the amount of wall increased, it is resonable to expect a thicker wall and consequently larger average size diameter. This finding is in agreement with that reported by Mohamed and Nazik (1983). The particle sizes of microcapsules prepared by using gelatin-SCMC as a wall had diameters between 484.92-904.18 μm which were larger than those using gelatin-acacia (39.79-87.57 μm) because SCMC has higher molecular weight than acacia and this resulted in higher viscosity at the same concentration. Thus it is more difficult to disperse amoxycillin in medium phase of SCMC. Therefore microcapsules prepared by gelatin-SCMC were aggregated in irregular shape as shown in Figures 9 and 10. From Figure 9, the microcapsules prepared with 1:2 core to wall ratio of gelatin-acacia were spherical-like shape. The effect of core to wall ratios on the in vitro drug release are shown in Figures 12-19. From the drug release profile, the data were analyzed according to different models to obtain the release rate constant (k) and the regression coefficient or coefficient of determination (R^2) was determined to present the linearity. Among all of the models tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 149-152,

(Appendix F). The overall release mechanism of drug encapsulated in the polymer is thought to involve by the permeation of solvent into the microcapsules, dissolution of drug and diffusion through the wall of microcapsules to surrounding fluid. The time used for penetration of the solvent into microcapsules is called lag time. In this study the lag time could not be determined. It was observed that the initial drug release profile showed burst effect in every core to wall ratio of both walls. From the scanning electron micrograph (Figures 9 and 10), the presence of drug crystals adhered on the surface of microcapsules is resonable to expect a burst effect in the initial drug release. At the pH 1.2 and pH 6.8, the 1:1 core to wall ratio of both walls showed the fastest release profile. The solvent was permeated into the microcapsules with the fastest rate and dissolved amoxycillin inside before diffusion through the wall of microcapsules and because of the smallest particle size, which resulted in the highest surface area available for drug release. Thus the k_H of 1:1 core to wall ratio was higher than 1:2 and 1:3, respectively (Tables 19 and 20). The 1:3 core to wall ratio of gelatin-acacia and 1:2 core to wall ratio of gelatin-SCMC showed the slowest release profile due to the largest particle size and the highest polymer content in the microcapsules. The microcapsules prepared by gelatin and SCMC showed faster release profile than the microcapsules prepared by gelatin and acacia because it had pores with rough surface areas (Figures 9 and 10), then the medium could easily diffuse into microcapsules. The time of 50% released of the microcapsules with various core to wall ratios and various types of wall which obtained from the release profiles of Higuchi's model are shown in Tables 19-22. From the time of 50% released, the amoxycillin microcapsules prepared by gelatin-acacia and gelatin-SCMC were significantly different in both media of pH 1.2 and pH 6.8 ($p<0.05$). The time of 50% released of amoxycillin microcapsules prepared by 1:1 core to wall ratio was the lowest than those of other core to wall ratios in both media of pH 1.2 and 6.8 ($p<0.05$). But in the medium pH 6.8, the time of 50% released of amoxycillin microcapsules prepared by 1:3 core to wall ratio was the highest ($p<0.05$).

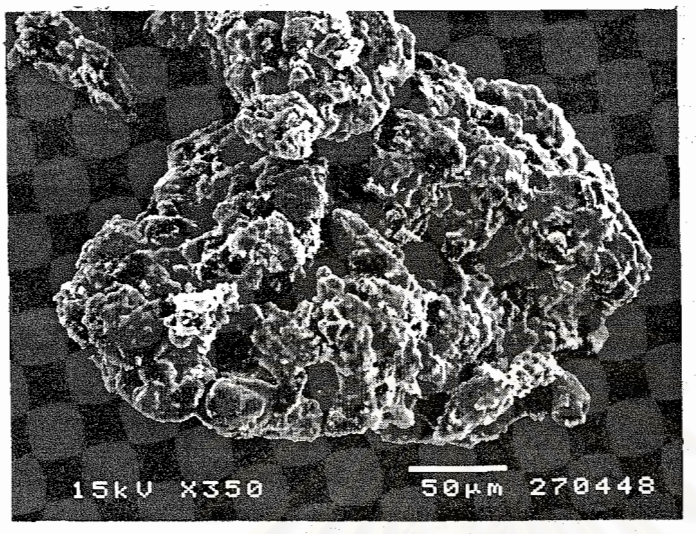


A

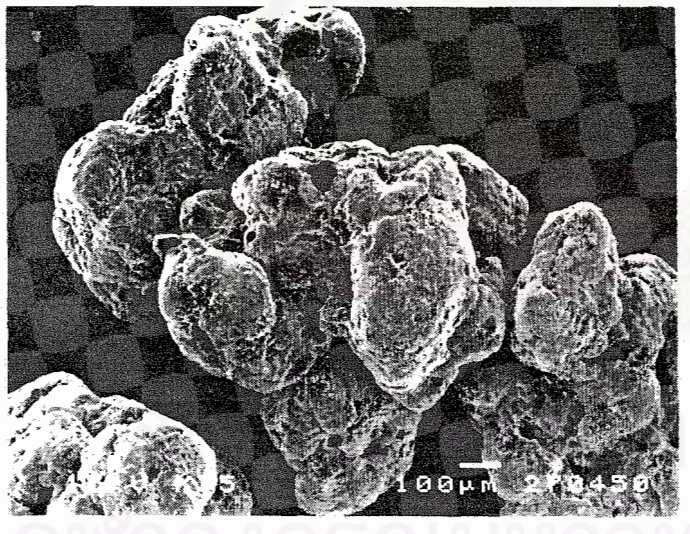
B

C

Figure 9. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-acacia coacervation technique with various core to wall ratios (A) 1:1 (B) 1:2 (C) 1:3. Magnification 1000x, 3500x and 500x, respectively.



A



B

Figure 10. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-SCMC coacervation technique with various core to wall ratios (A) 1:1 (B) 1:2. Magnification 350x and 75x respectively.

Table 18. The particle sizes of amoxycillin microcapsules prepared by complex coacervation technique with various core to wall ratios.

Polymer	No.	Particle size (μm)		
		1:1	1:2	1:3
Gelatin-Acacia	1	40.16	50.98	89.68
	2	39.92	50.24	87.95
	3	39.28	49.77	85.09
	Mean	39.79	50.33	87.57
	S.D.	0.45	0.61	2.32
Gelatin-SCMC	1	476.74	866.04	-
	2	498.37	897.44	-
	3	479.65	949.05	-
	Mean	484.92	904.18	-
	S.D.	11.74	41.91	-

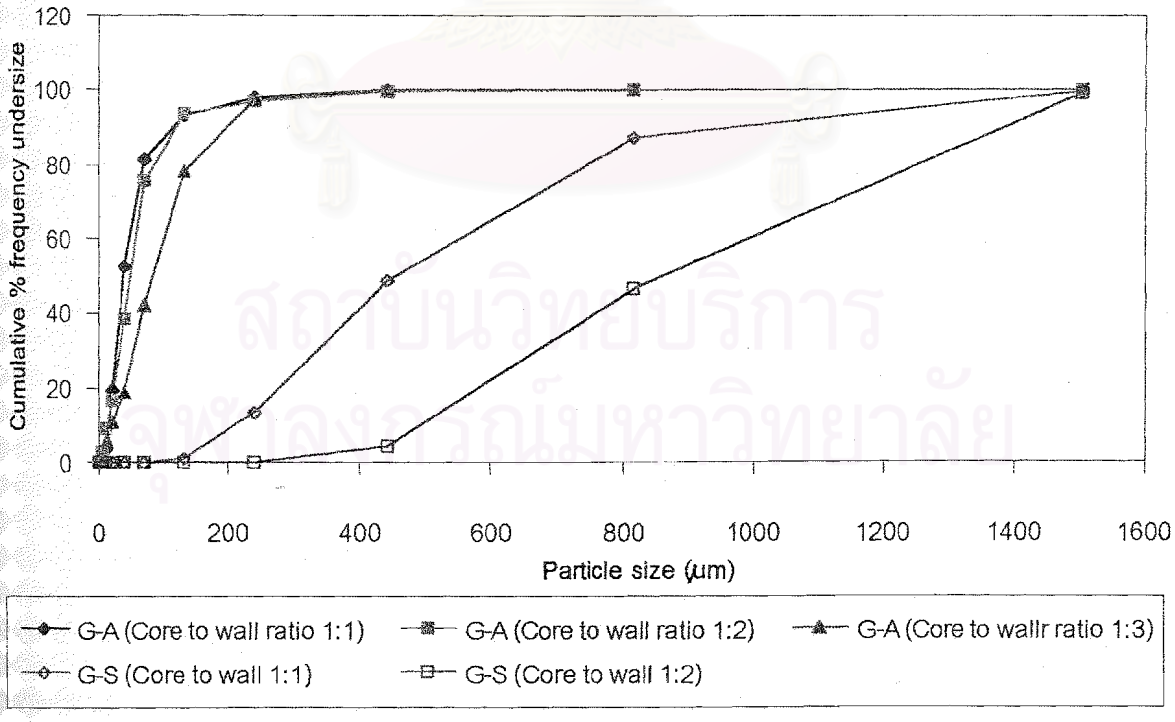


Figure 11. Cumulative %frequency undersize of amoxycillin microcapsules prepared by complex coacervation technique with various core to wall ratios.

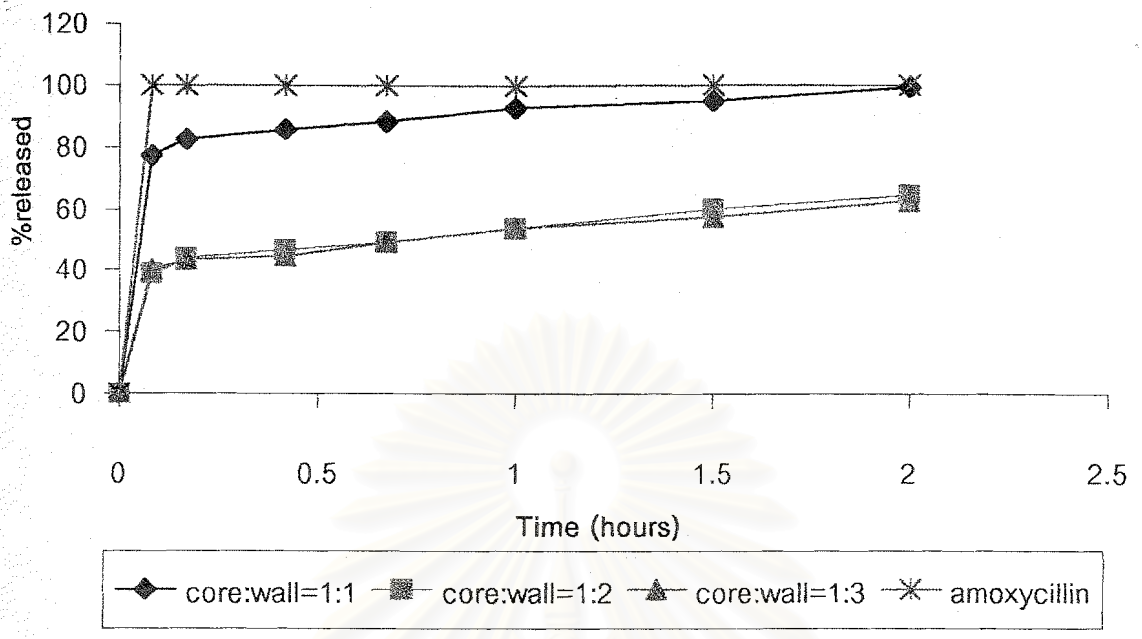


Figure 12. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

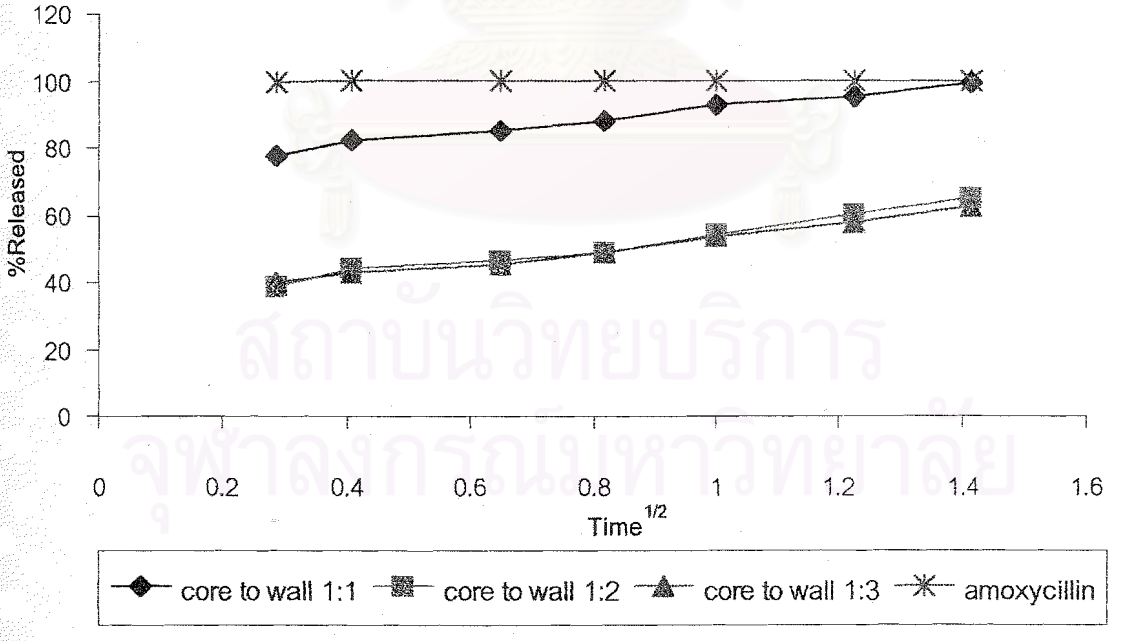


Figure 13. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

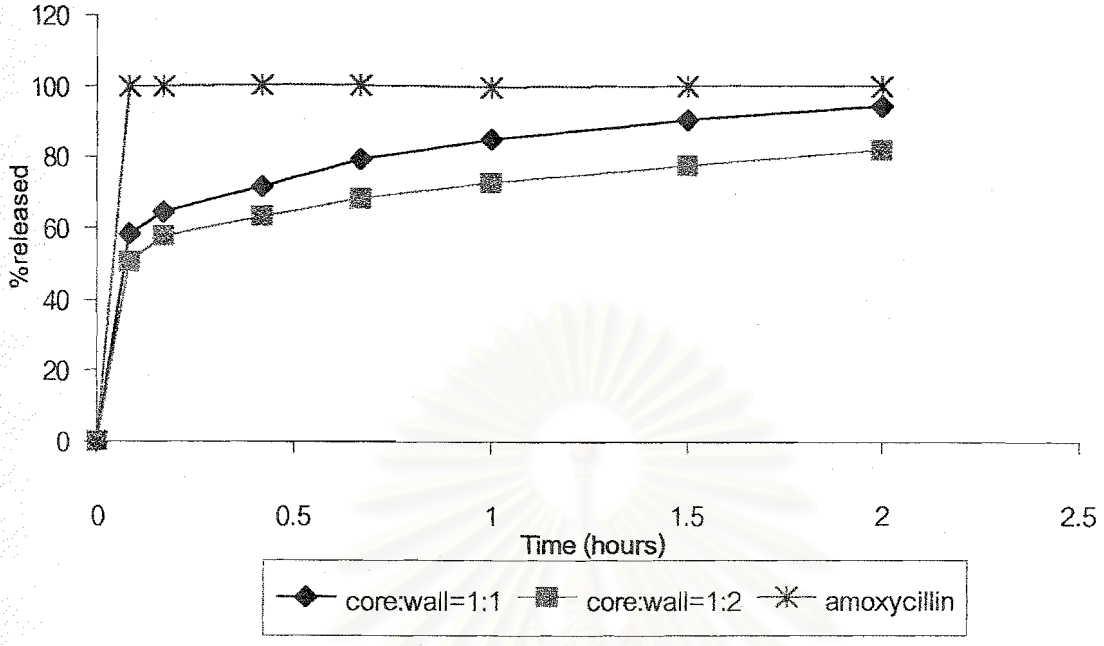


Figure 14. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

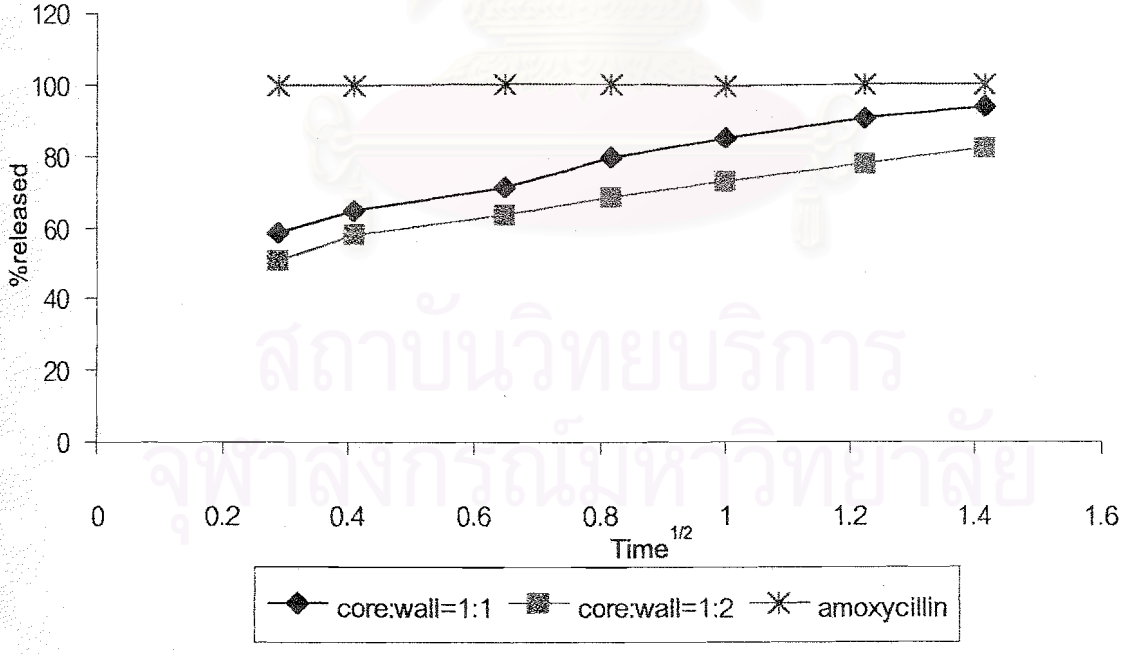


Figure 15. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2

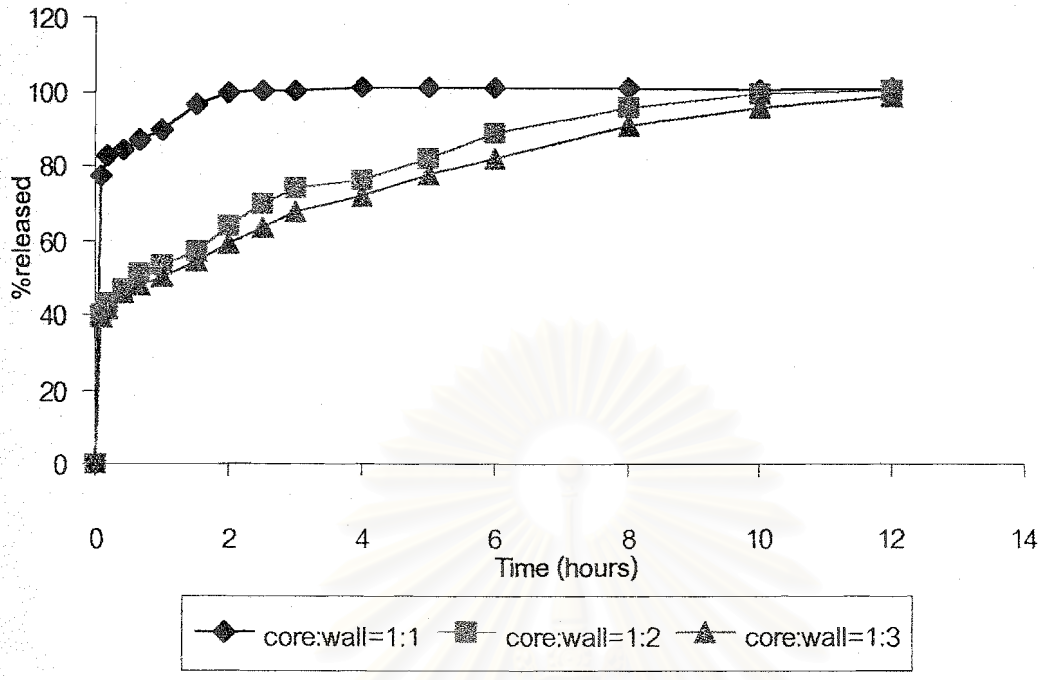


Figure 16. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

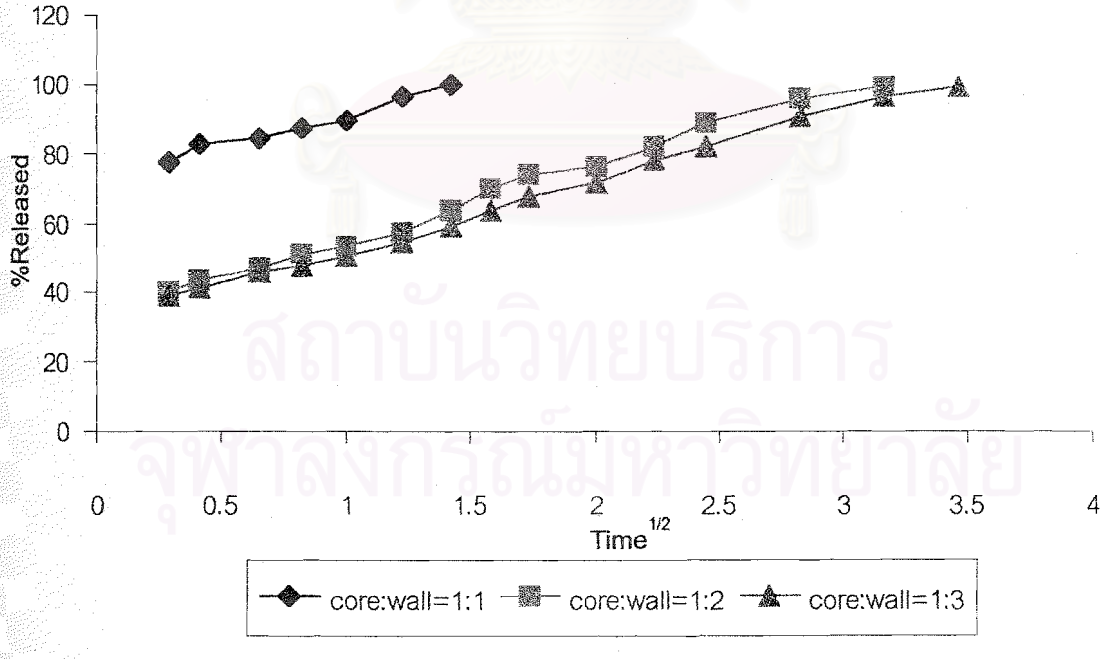


Figure 17. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratio in simulated intestinal fluid without pancreatin pH 6.8.

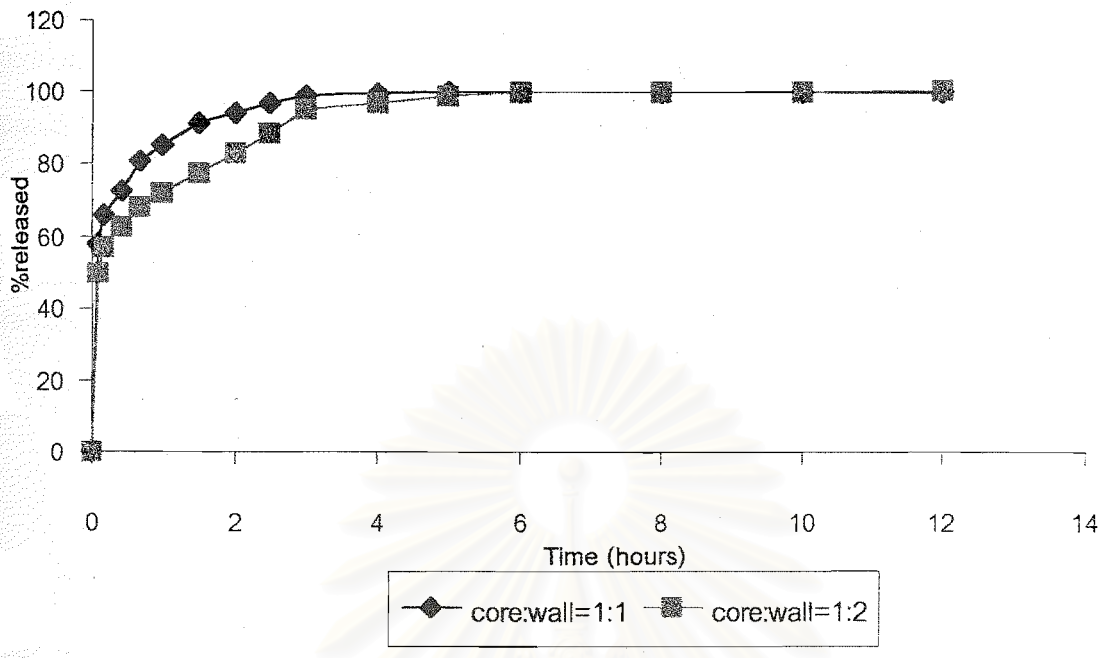


Figure 18. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

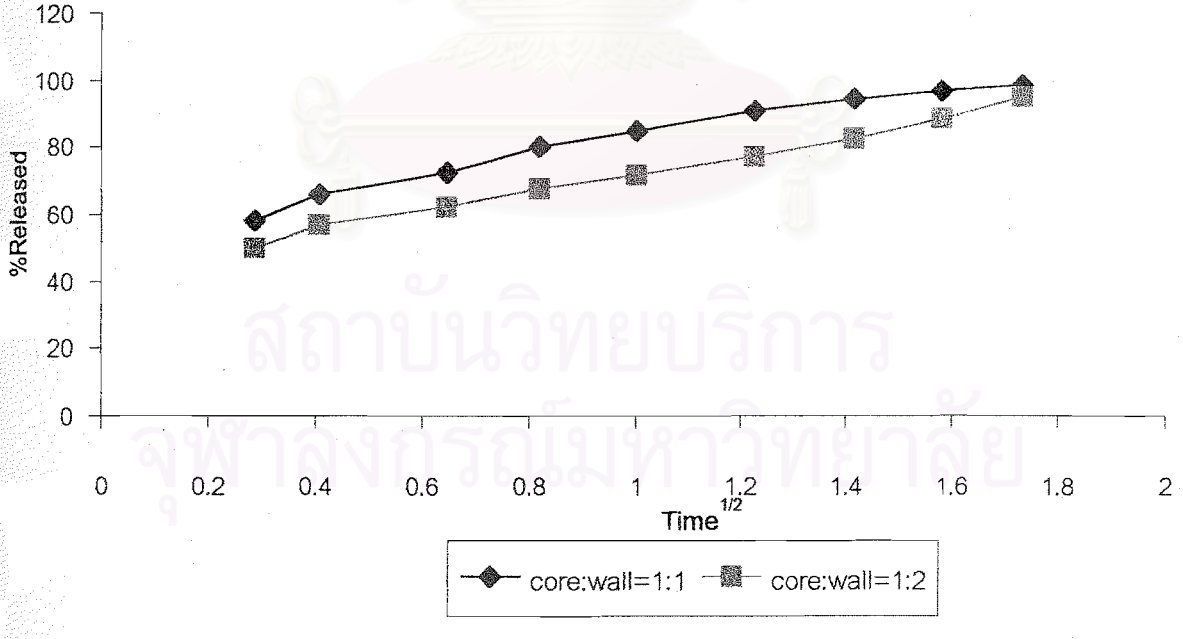


Figure 19. The release profiles of Higuchi's model of amoxycilin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

Table 19. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	18.6830	21.8890	17.7110
	2	18.8530	21.3270	20.5500
	3	18.7000	22.6830	20.9640
	Mean	18.7453	21.9663	19.7417
	S.D.	0.0936	0.6813	1.7707
R^2	1	0.9671	0.9798	0.9827
	2	0.9788	0.9822	0.9760
	3	0.9943	0.9640	0.9724
	Mean	0.9801	0.9753	0.9770
	S.D.	0.0136	0.0099	0.0052
T_{50}(hr)	1	0.0065	0.5393	0.8207
	2	0.0117	0.6956	0.6651
	3	0.0174	0.5814	0.5513
	Mean	0.0119	0.6054	0.6790
	S.D.	0.0055	0.0809	0.1353

Table 20. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	32.2950	24.4660	-
	2	33.0550	28.8970	-
	3	31.9350	27.7750	-
	Mean	32.4283	27.0460	-
	S.D.	0.5718	2.3037	-
R^2	1	0.9834	0.9750	-
	2	0.9801	0.9812	-
	3	0.9862	0.9879	-
	Mean	0.9832	0.9814	-
	S.D.	0.0031	0.0065	-
T_{50}(hr)	1	0.0057	0.0154	-
	2	0.0008	0.0374	-
	3	0.0018	0.0389	-
	Mean	0.0028	0.0306	-
	S.D.	0.0026	0.0131	-

Table 21. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	18.8900	21.8810	20.5630
	2	17.6400	21.7920	20.1970
	3	19.1740	21.8230	19.2520
	Mean	18.5680	21.8320	20.0040
	S.D.	0.8161	0.0452	0.6765
R^2	1	0.9644	0.9870	0.9906
	2	0.9533	0.9939	0.9923
	3	0.9727	0.9918	0.9935
	Mean	0.9635	0.9909	0.9921
	S.D.	0.0097	0.0035	0.0015
T_{50}(hr)	1	0.0153	0.5084	0.8598
	2	0.0303	0.6892	0.7940
	3	0.0106	0.5769	0.7347
	Mean	0.0187	0.5915	0.7962
	S.D.	0.0103	0.0913	0.0626

Table 22. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	27.4000	26.9140	-
	2	27.1000	30.6330	-
	3	27.8460	28.8890	-
	Mean	27.4487	28.8120	-
	S.D.	0.3754	1.8607	-
R^2	1	0.9702	0.9928	-
	2	0.9538	0.9856	-
	3	0.9617	0.9894	-
	Mean	0.9619	0.9893	-
	S.D.	0.0082	0.0036	-
T_{50}(hr)	1	0.0133	0.0309	-
	2	0.0574	0.0949	-
	3	0.0269	0.0381	-
	Mean	0.0325	0.0546	-
	S.D.	0.0225	0.0350	-

From the results of the yield, amoxycillin content, core entrapment, size, size distribution and the release rate constant, the 1:2 core to wall ratio of both walls was chosen for further study since it gave higher percent yield and core entrapment.

3.2. Effect of pH

From the investigation of core to wall ratio, the 1:2 core to wall was chosen for further studies. The microcapsules were prepared with various pH including 3.50, 3.75 and 4.0. It was found that the microcapsules prepared with gelatin-acacia had more percent yield than those prepared with gelatin-SCMC but the percent content and entrapment were similar (Table 23).

Table 23. The percent yield, content and entrapment amoxycillin microcapsules prepared by coacervation technique at various pH.

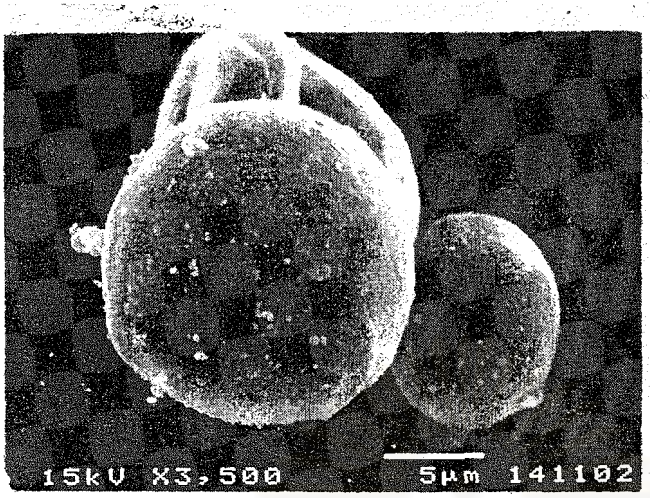
pH	% Yield		% Content		% Entrapment	
	G - A	G - S	G - A	G - S	G - A	G - S
3.5	87.86	83.61	29.72±1.78	28.55±1.12	89.17±5.48	85.66±4.72
3.75	88.06	84.72	29.57±0.84	29.26±0.36	88.72±3.06	87.79±2.16
4.0	87.71	84.11	28.91±0.17	28.91±0.19	86.74±2.02	86.74±2.06

The effect of pH on the size of microcapsules is shown in Table 24 and surface morphologies are shown in Figures 20 and 21. The frequency distribution curves is shown in Figure 22. The particle size of microcapsules prepared with gelatin-acacia was between 42.51-99.27 μm. The particle size of microcapsules prepared with gelatin-SCMC was between 551.85-904.18 μm. The microcapsules prepared with gelatin-SCMC at pH 3.5 had the particle size of 904.18±41.91 μm which were larger than those prepared at pH 3.75 and pH 4.0 (Table 24). The microcapsules prepared with gelatin-

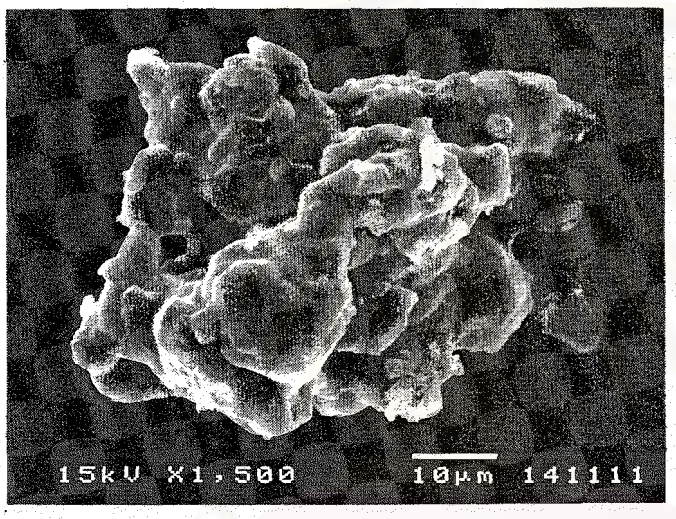
acacia at pH 3.5 had the particle size of 50.33±0.6 μm which were larger than those prepared at pH 3.75 (42.51±0.52) but at pH 4.0 showed the largest particle size with an average of 99.29±1.93 μm. This result was different from the report by Takenaka et al. (1980) that the pH was increased, the microcapsules size decreased. This result might be due to the electrophoretic characteristic of gelatin-acacia coacervates. Electrophoretic data of coacervates obtained previously (Takenaka et al., 1981) showed that, at a pH above 3.5, the coacervates were electronegatively charged and the charges increased with increasing pH. This finding indicate that, at the higher pH range, the small coacervates could be formed due to the strong repulsive force between the coacervates. In this study, at pH 4.0, the particle size of gelatin-acacia walled microcapsules was large, it might be because of aggregation of microcapsules (Figure 20).

Table 24. The particle sizes of amoxycillin microcapsules prepared by complex coacervation technique at various pH.

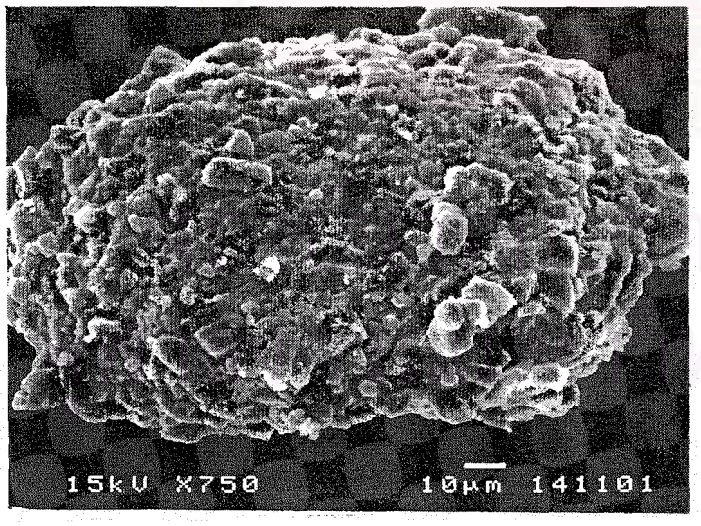
Polymer	No.	Particle size (μm)		
		3.5	3.75	4.0
Gelatin-Acacia	1	50.98	43.06	101.27
	2	50.24	42.46	99.10
	3	49.77	42.02	97.43
	Mean	50.33	42.51	99.27
	S.D.	0.61	0.52	1.93
Gelatin-SCMC	1	866.04	535.61	610.61
	2	897.44	551.92	659.13
	3	949.05	568.03	696.55
	Mean	904.18	551.85	655.43
	S.D.	41.91	16.21	43.09



A

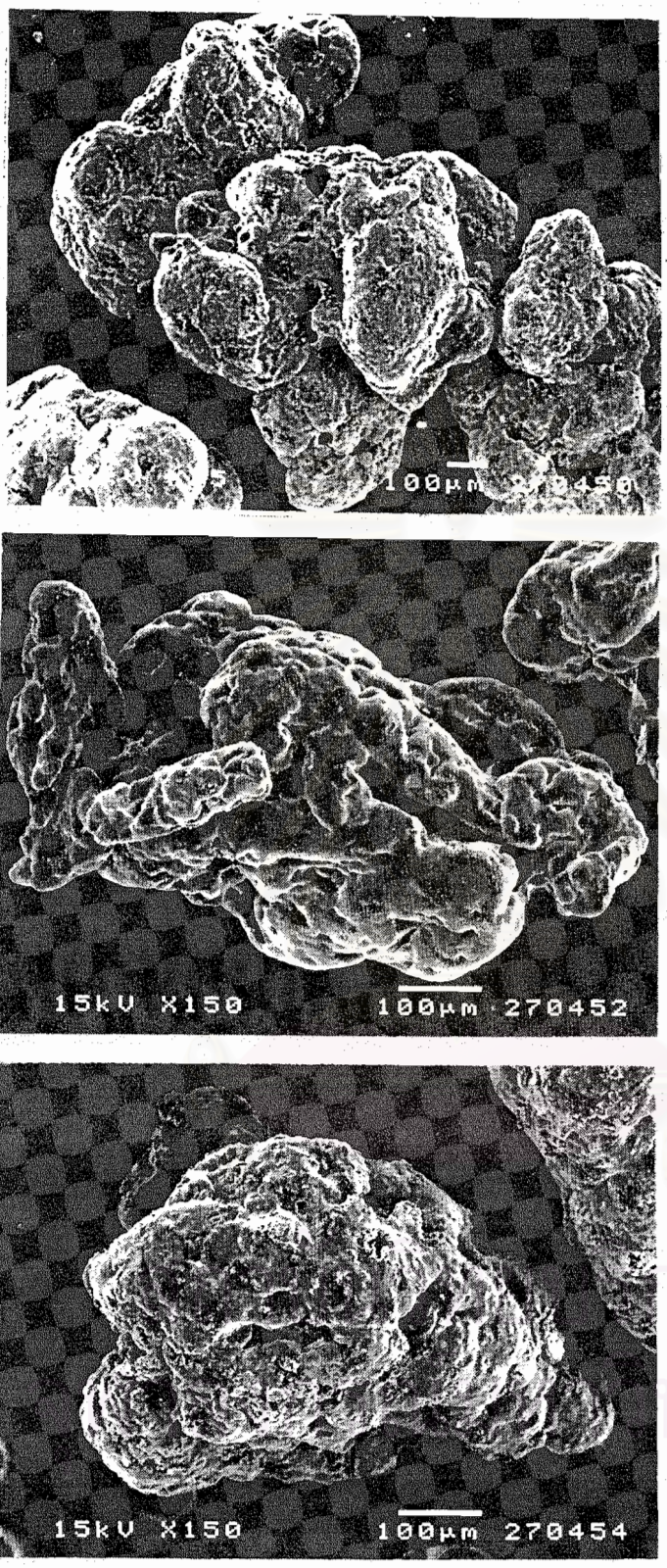


B



C

Figure 20. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various pH (A) 3.5 (B) 3.75 (C) 4.0. Magnification 3500x, 1500x and 750x respectively.



A

B

C

Figure 21. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various pH (A) 3.5 (B) 3.75 (C) 4.0. Magnification 75x, 150x and 150x respectively.

The effect of pH on the in vitro release is shown in Figures 23-30. It was observed that the initial drug release profile showed burst effect. The drug release profile obtained from microcapsules prepared using gelatin-acacia at pH 3.5 were lower than microcapsules prepared at pH 3.75 and pH 4.0. The drug release profile obtained from microcapsules prepared using gelatin-SCMC at pH 3.75 were lower than microcapsules prepared at pH 3.5 and pH 4.0. Among all of the models tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 153-156 (Appendix F). The value of the release rate constant (k_H) of gelatin-acacia walled microcapsules prepared at pH 3.5 was lower than at pH 3.75 and 4.0 respectively. The result of k_H in gelatin-SCMC walled microcapsules was also shown the correlation with the release profile. The time of 50% released of the amoxycillin microcapsules prepared at various pH were obtained from the release profile (Figures 25-30). From the time of 50% released, the amoxycillin microcapsules prepared by gelatin-acacia and gelatin-SCMC as the wall were significantly different in both media of pH 1.2 and pH 6.8 ($p<0.05$) whilst the release profile indicated that gelatin-acacia walled microcapsules gave lower percent released than gelatin-SCMC walled microcapsules. The time of 50% released of amoxycillin microcapsules prepared by the same wall at various pH were not significantly different in both media of pH 1.2 and pH 6.8 ($p>0.05$).

The results obtained from the yield, amoxycillin content, core entrapment, size, size distribution and the release rate constant. The pH 3.5 was chosen for preparation of gelatin-acacia walled microcapsules and pH 3.75 was chosen for preparation of gelatin-SCMC walled microcapsules because it exhibited slower release rate profile.

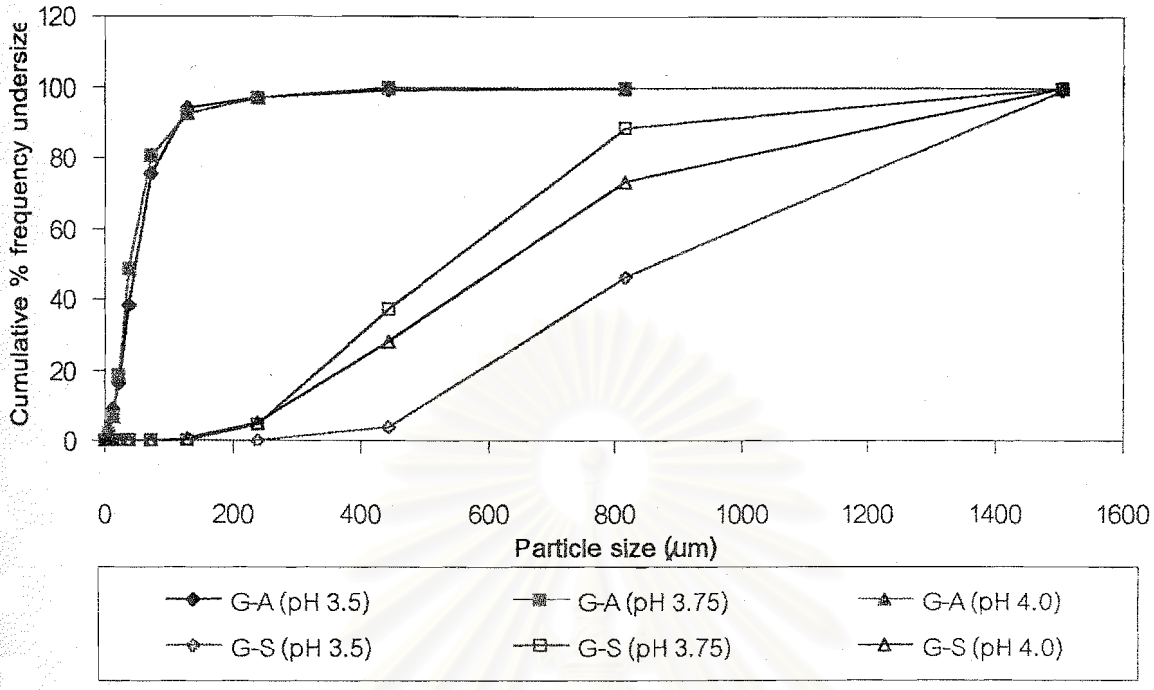


Figure 22. Cumulative % frequency undersize of amoxycillin microcapsules prepared by complex coacervation technique at various pH.

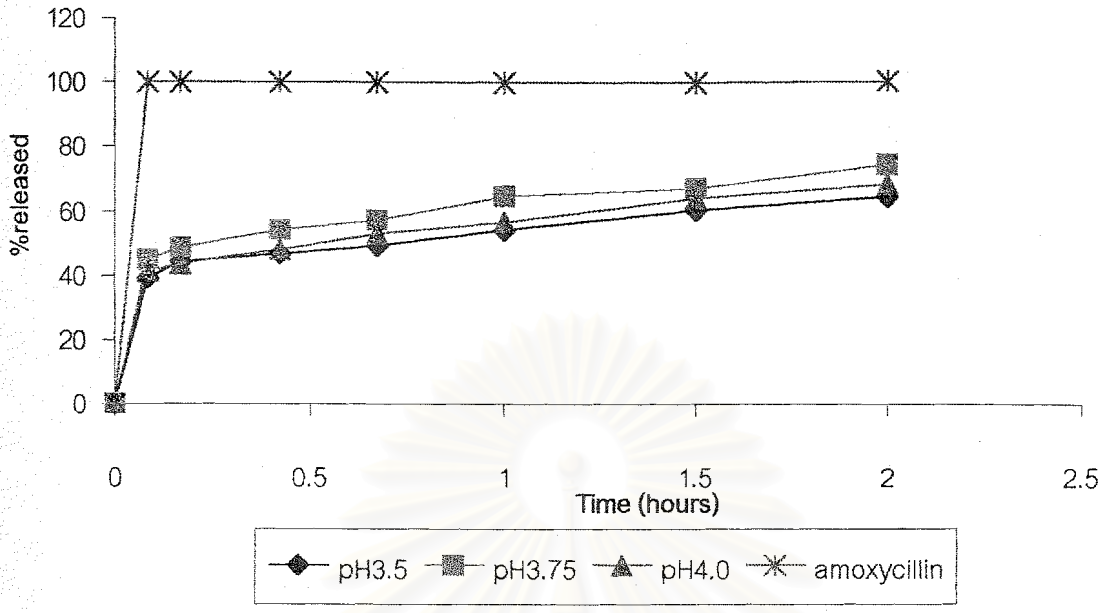


Figure 23. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated gastric fluid without pepsin pH 1.2.

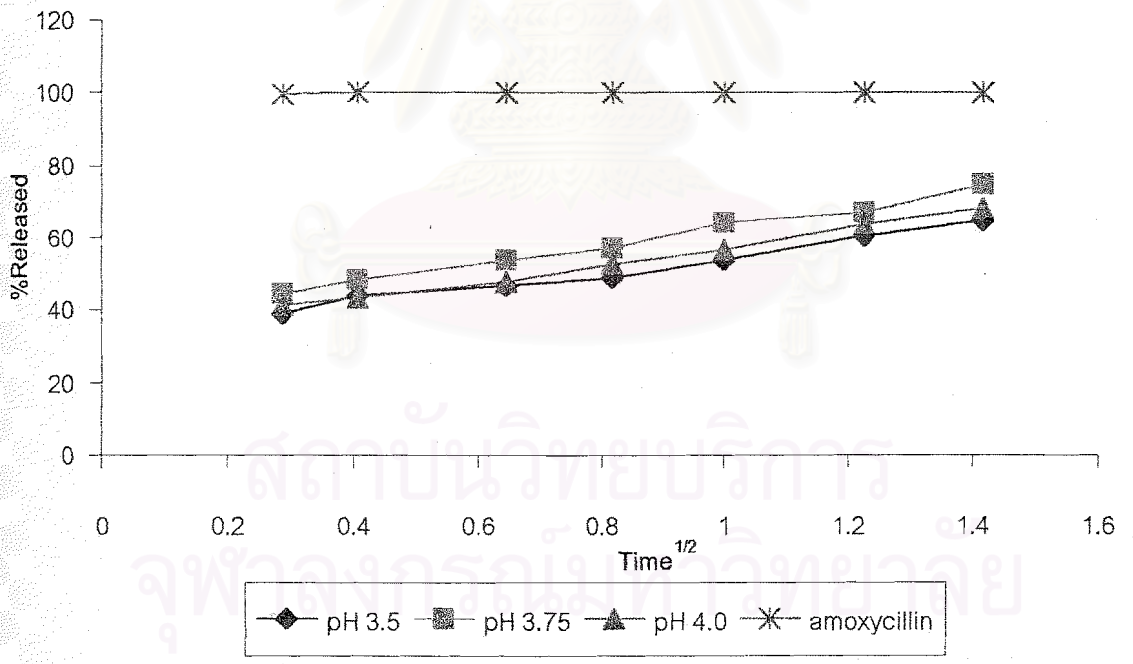


Figure 24. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated gastric fluid without pepsin pH 1.2.

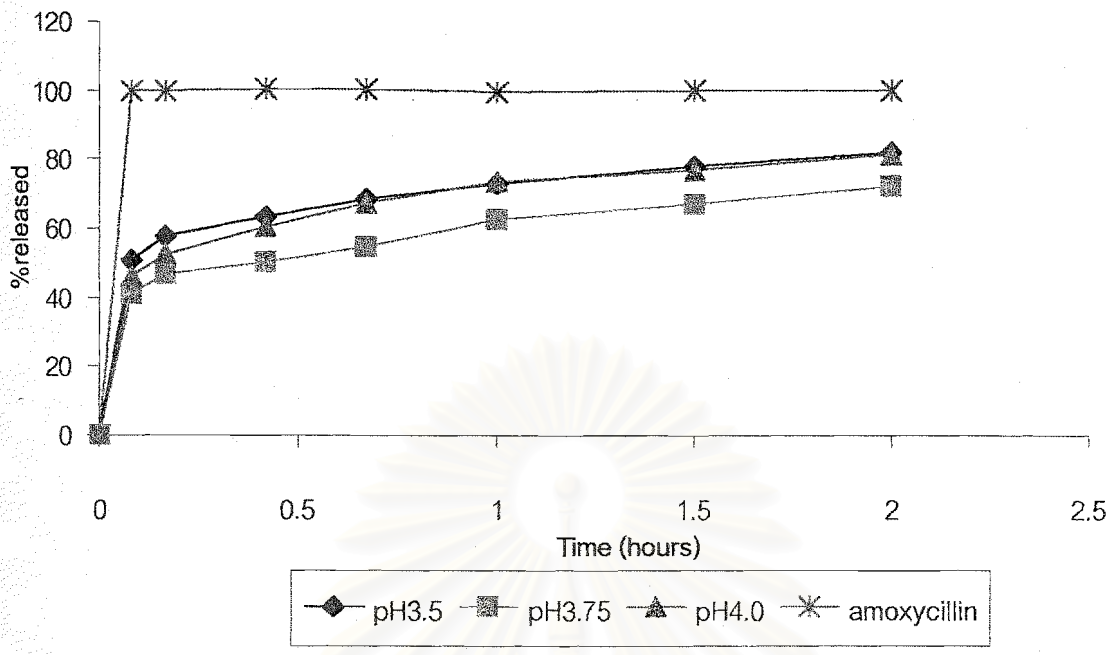


Figure 25. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated gastric fluid without pepsin pH 1.2.

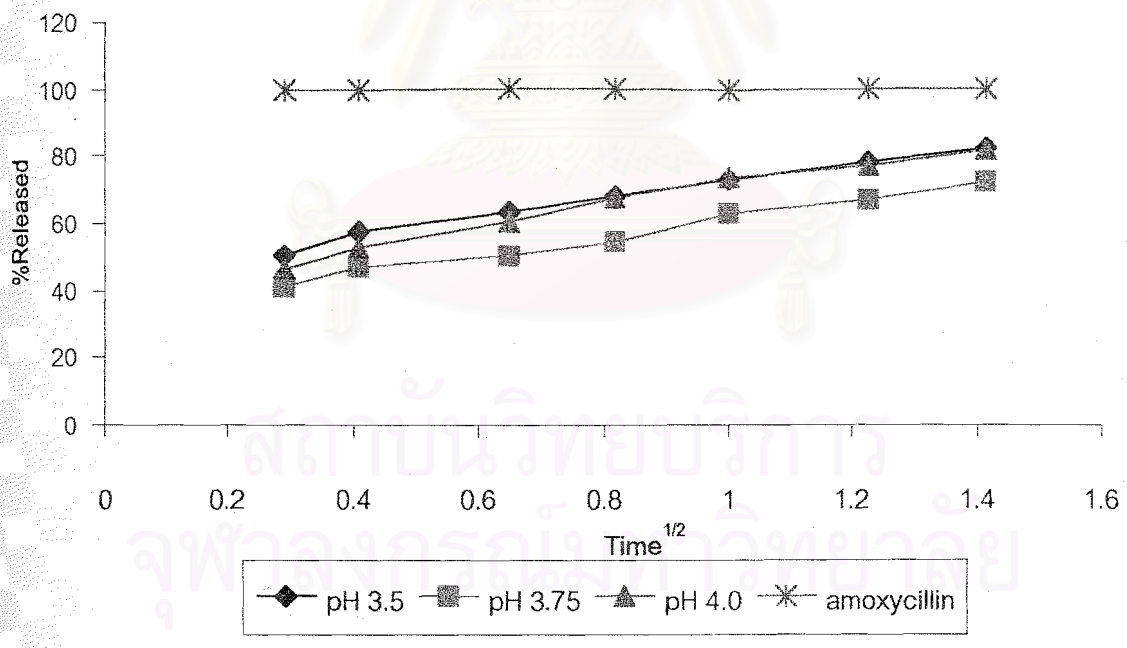


Figure 26. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated gastric fluid without pepsin pH 1.2.

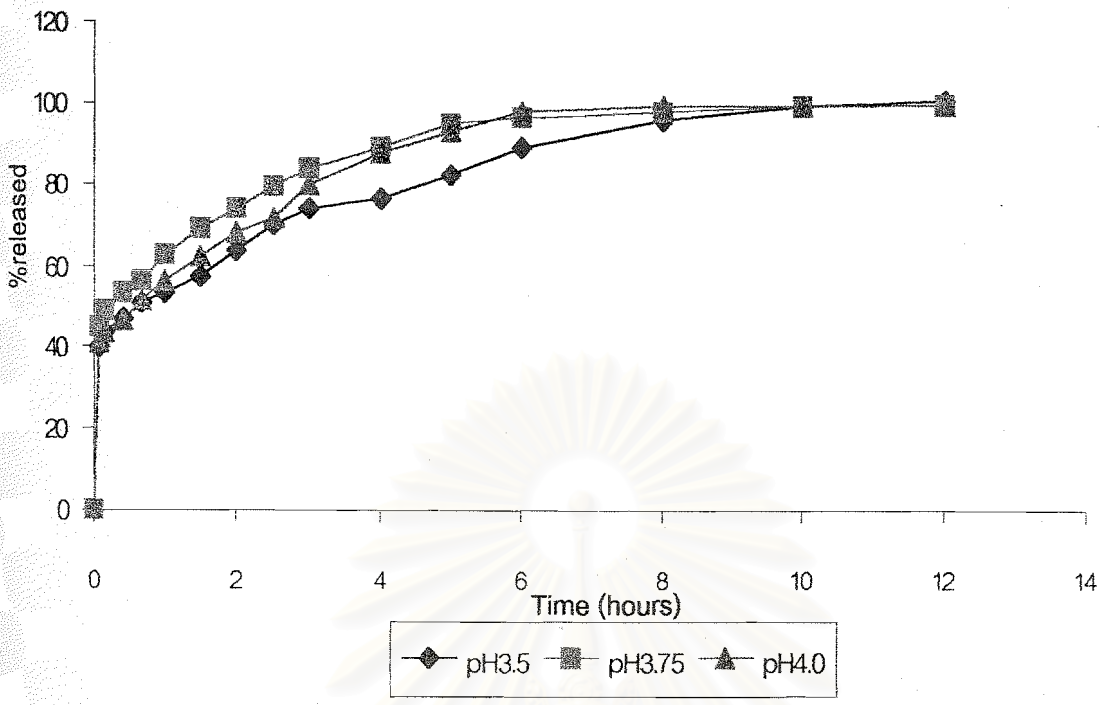


Figure 27. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

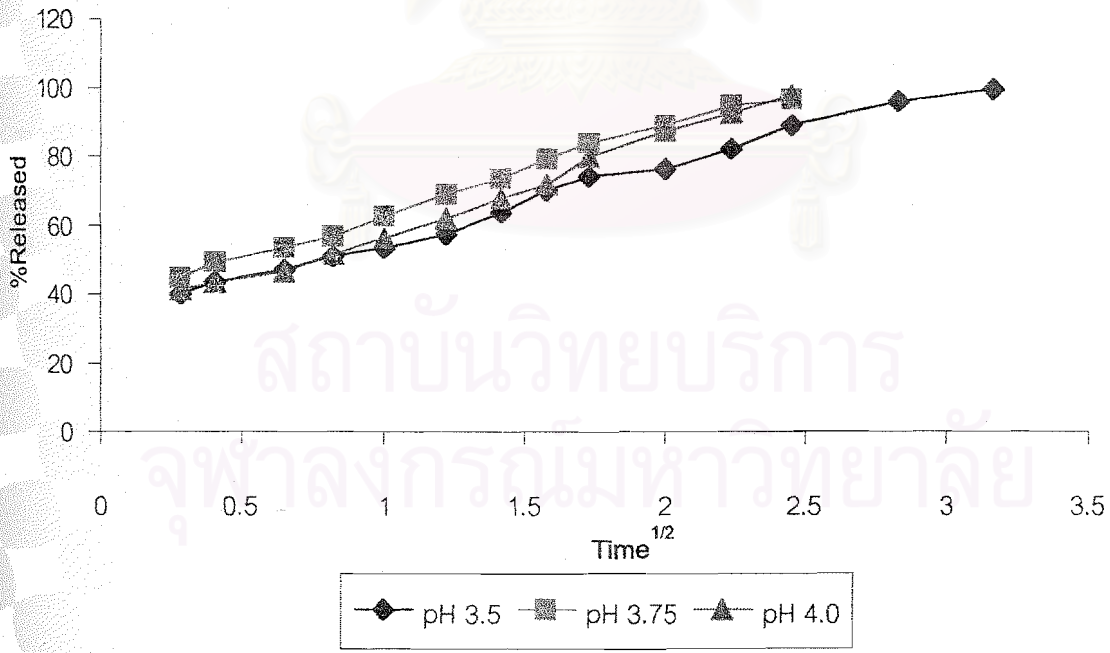


Figure 28. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

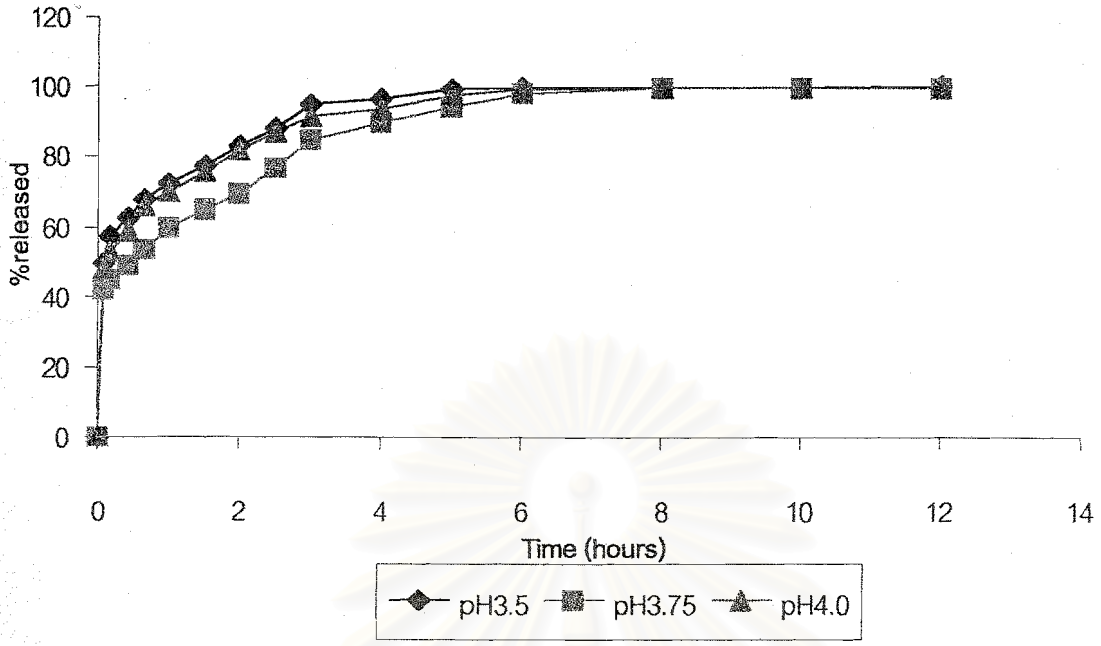


Figure 29. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

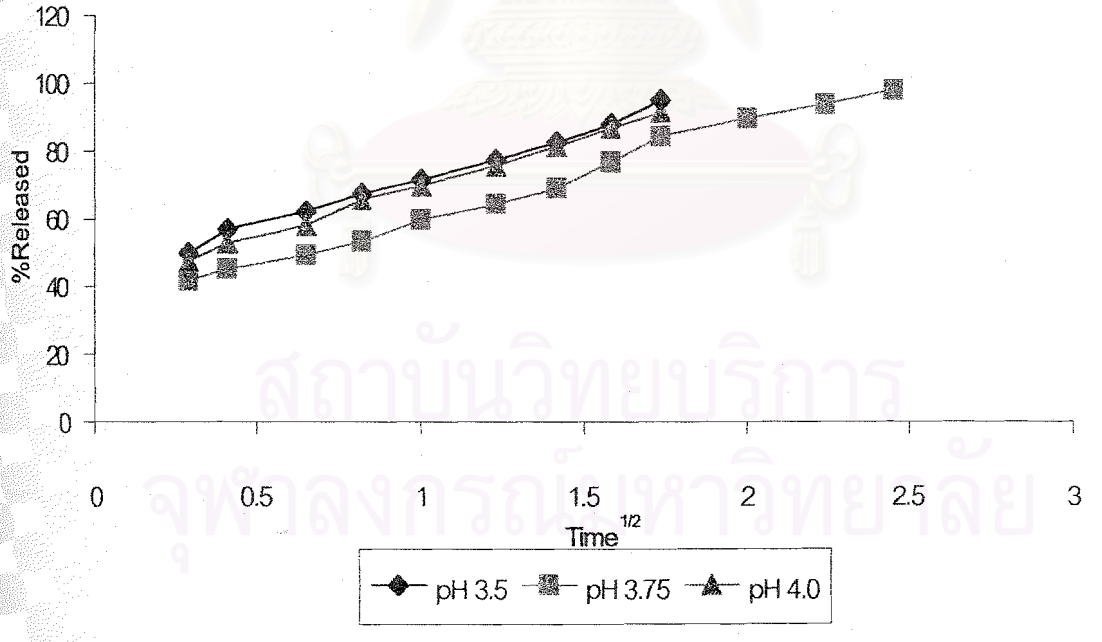


Figure 30. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

Table 25. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time for 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated gastric fluid without pepsin pH 1.2

Parameters	No.	pH		
		3.5	3.75	4.0
k_H ($hr^{-1/2}$)	1	21.8890	24.2760	24.0320
	2	21.3270	28.6370	23.7550
	3	22.6830	24.3360	26.2180
	Mean	21.9663	25.7497	24.6683
	S.D.	0.6813	2.5007	1.3492
R^2	1	0.9798	0.9940	0.9821
	2	0.9822	0.9732	0.9962
	3	0.9640	0.9906	0.9945
	Mean	0.9753	0.9859	0.9909
	S.D.	0.0099	0.0112	0.0077
T_{50}(hr)	1	0.5393	0.2530	0.5454
	2	0.6956	0.2598	0.4005
	3	0.5814	0.2026	0.4888
	Mean	0.6054	0.2385	0.4782
	S.D.	0.0809	0.0312	0.0730

Table 26. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time for 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated gastric fluid without pepsin pH 1.2

Parameters	No.	pH		
		3.5	3.75	4.0
k_H ($hr^{-1/2}$)	1	24.4660	26.2800	32.2280
	2	28.8970	28.8840	31.5100
	3	27.7750	27.6180	30.1610
	Mean	27.0460	27.5940	31.2997
	S.D.	2.3037	1.3022	1.0494
R^2	1	0.9750	0.9911	0.9685
	2	0.9812	0.9683	0.9602
	3	0.9879	0.9960	0.9895
	Mean	0.9814	0.9851	0.9727
	S.D.	0.0065	0.0148	0.0151
T_{50}(hr)	1	0.0154	0.4009	0.1015
	2	0.0374	0.3321	0.1088
	3	0.0389	0.3294	0.1086
	Mean	0.0306	0.3542	0.1063
	S.D.	0.0131	0.0405	0.0041

Table 27. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time for 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	pH		
		3.5	3.75	4.0
k_H ($hr^{-1/2}$)	1	21.8810	25.7580	27.6560
	2	21.7920	25.0870	27.2710
	3	21.8230	25.0870	28.0530
	Mean	21.8320	25.3107	27.6600
	S.D.	0.0452	0.3874	0.3910
R^2	1	0.9870	0.9920	0.9904
	2	0.9939	0.9937	0.9904
	3	0.9918	0.9904	0.9896
	Mean	0.9909	0.9920	0.9901
	S.D.	0.0035	0.0017	0.0005
T_{50}(hr)	1	0.5084	0.3071	0.5185
	2	0.6892	0.1676	0.4315
	3	0.5769	0.2277	0.5922
	Mean	0.5915	0.2341	0.5140
	S.D.	0.0913	0.0700	0.0805

Table 28. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time for 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation at various pH in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	pH		
		3.5	3.75	4.0
k_H ($hr^{-1/2}$)	1	26.9140	27.4150	28.8450
	2	30.6330	27.9250	30.5010
	3	28.8890	27.6760	29.9370
	Mean	28.8120	27.6720	29.7610
	S.D.	1.8607	0.2550	0.8419
R^2	1	0.9928	0.9931	0.9966
	2	0.9856	0.9873	0.9965
	3	0.9894	0.9870	0.9950
	Mean	0.9893	0.9891	0.9960
	S.D.	0.0036	0.0034	0.0009
T_{50}(hr)	1	0.0309	0.3904	0.0974
	2	0.0949	0.4230	0.1343
	3	0.0381	0.3831	0.1091
	Mean	0.0546	0.3988	0.1136
	S.D.	0.0350	0.0212	0.0189

3.3.Effect of concentration of wall

From the investigation of pH, the gelatin-acacia at pH 3.5 and gelatin-SCMC at pH 3.75 were chosen to prepare microcapsules. The microcapsules were prepared with various concentration of wall such as 1%, 1.5% and 2%. The effect of concentration of wall on percent yield, content and entrapment of amoxycillin microcapsules are shown in Table 29.

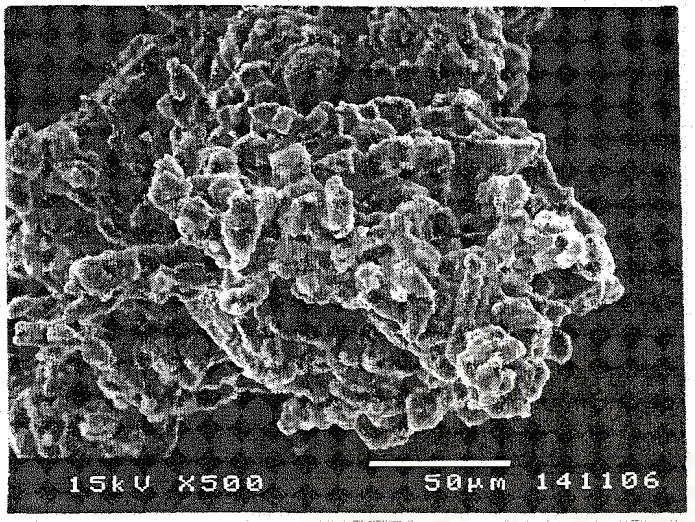
Table 29. The percent yield, content and entrapment of amoxycillin microcapsules prepared by coacervation technique with various concentration of wall.

Conc.	% Yield		% Content		% Entrapment	
of wall	G - A	G - S	G - A	G - S	G - A	G - S
1%	87.37	81.29	29.69±2.01	29.17±0.88	89.08±5.95	87.52±3.11
1.5%	87.86	84.72	29.72±1.78	29.26±0.36	89.17±5.48	87.79±2.16
2%	88.14	82.35	29.85±0.12	28.84±0.04	89.56±2.01	86.53±1.76

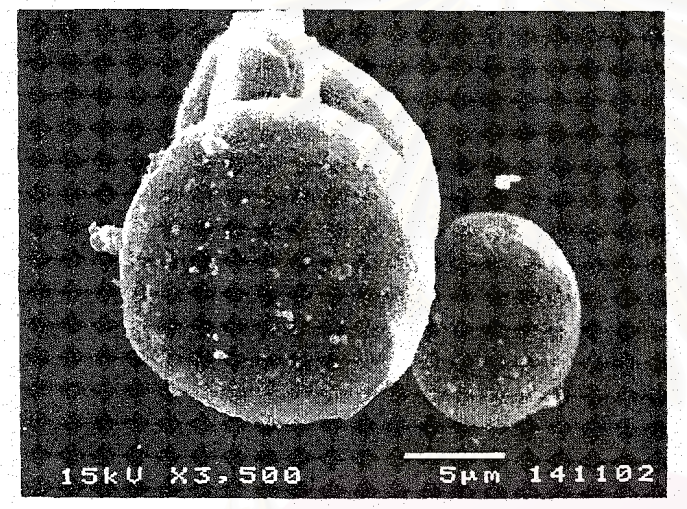
It was found that the concentration of 2% gelatin-acacia and 1.5% gelatin-SCMC gave the highest percent yield, but the drug content and core entrapment of the same wall were similar (Table 29). The increasing efficiency of coacervation with increasing wall concentration up to a maximum of 2% probably resulted from increased reactivity of the gelatin and acacia or gelatin and SCMC (Mcmullen et al., 1982). Above 2% of maximum wall concentration the decreasing efficiency of coacervation arises from an increasing salt or gegenion (e.g., Na^{+}, Ca^{2+}, Cl^{-}) concentration which insulates the oppositely charged of wall, suppressing coacervation and increasing the mutual solubilities of the coacervate and equilibrium solution phases (Mcmullen et al., 1982; Singh and Burgess, 1989). The effects of concentration of wall on the surface morphologies are shown in Figures 31 and 32. The size of microcapsules is shown in Table 30, and the frequency distribution curves are shown in Figure 33. The

microcapsules with 2% concentration of gelatin-acacia as wall and 1.5% concentration of gelatin-SCMC as wall had the largest particle size and in contrast, at 1% concentration of both walls gave the smallest particle size. The microcapsule sizes increased up on raising the concentration of wall. The result from this study agreed with a previous study by Nazik and Mohamed (1981).

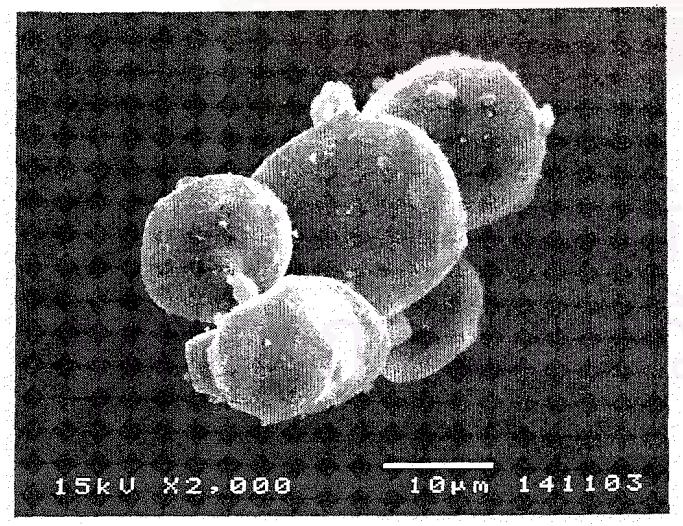
The effects of concentrations of wall on the in vitro drug release are shown in Figures 34-41. It was observed that the initial drug release profile showed burst effect. It was found that the concentration of 1% of both walls gave the fastest release profile in both media at pH 1.2 and pH 6.8 which correlated to the small particle size. Among all of the models tested, the Higuchi model appeared to provide the best fits for all of the investigated formulations as determined in Tables 157-160 (Appendix F). The release rate constant (k_H) of 1% gelatin-acacia and gelatin-SCMC walled microcapsules was high in a media of pH 1.2. The release of amoxycillin in the media of pH 6.8 showed burst released effect which resulted the higher value of k_H but it was lower than the estimated value because the total of drug almost came out and left small amount of drug in microcapsules. The time of 50% released of the amoxycillin microcapsules with various concentrations of wall was obtained from the release profiles (Figures 23-30). From the time of 50% released, the amoxycillin microcapsules prepared by gelatin-acacia and gelatin-SCMC as the wall were significantly difference in medium pH 1.2 ($p < 0.05$) but in the medium pH 6.8 were not significantly different ($p > 0.05$). The time of 50% released of amoxycillin microcapsules prepared by 1% of concentration of wall was the lowest than those of other concentrations of wall in both media at pH 1.2 and pH 6.8 ($p < 0.05$). The amoxycillin microcapsules prepared by gelatin-acacia and gelatin-SCMC showed fast release in medium pH 1.2 (2 hours) and slow release in medium pH 6.8 (12 hours).



A

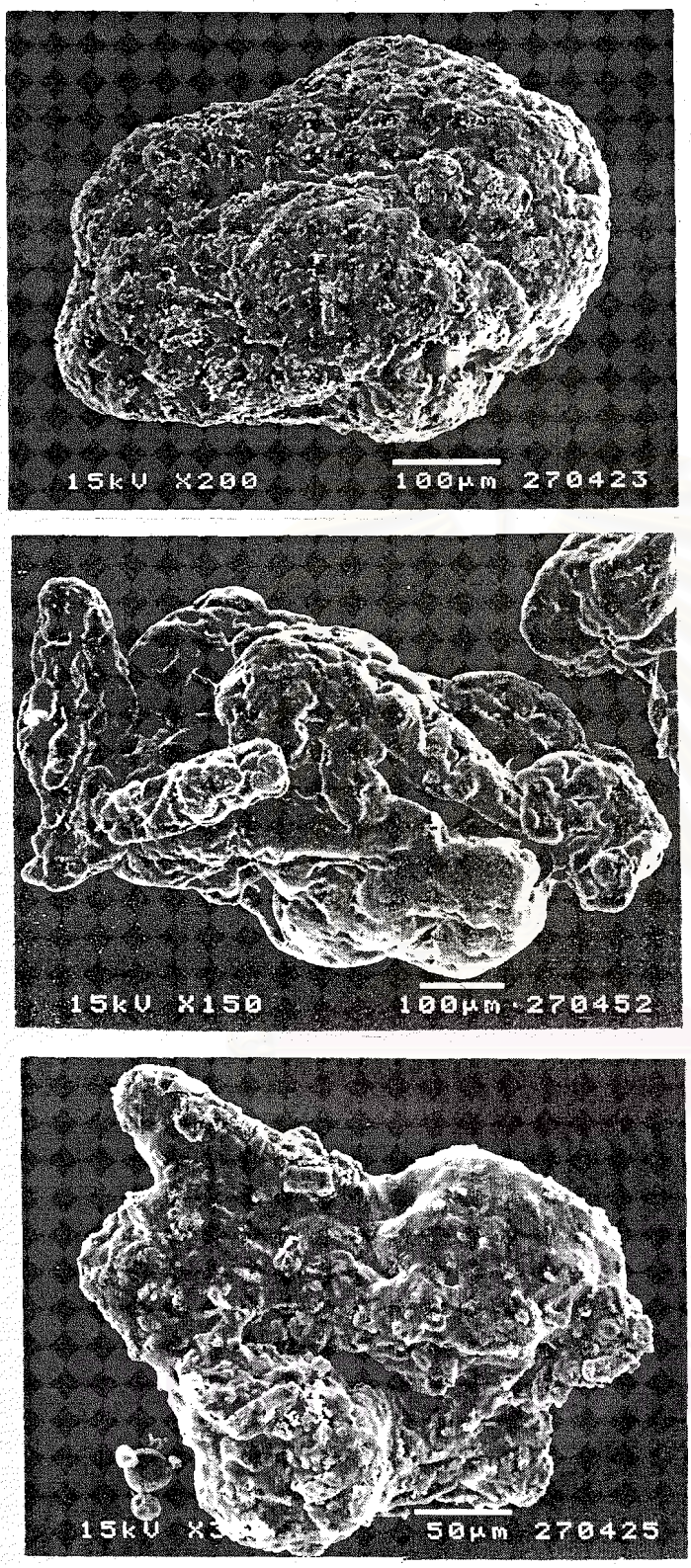


B



C

Figure 31. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various conc. of wall (A) 1% (B) 1.5% (C) 2%. Magnification 500x, 3500x and 2000x respectively.



A

B

C

Figure 32. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various conc. of wall (A) 1% (B) 1.5% (C) 2%. Magnification 200x, 150x and 350x respectively.

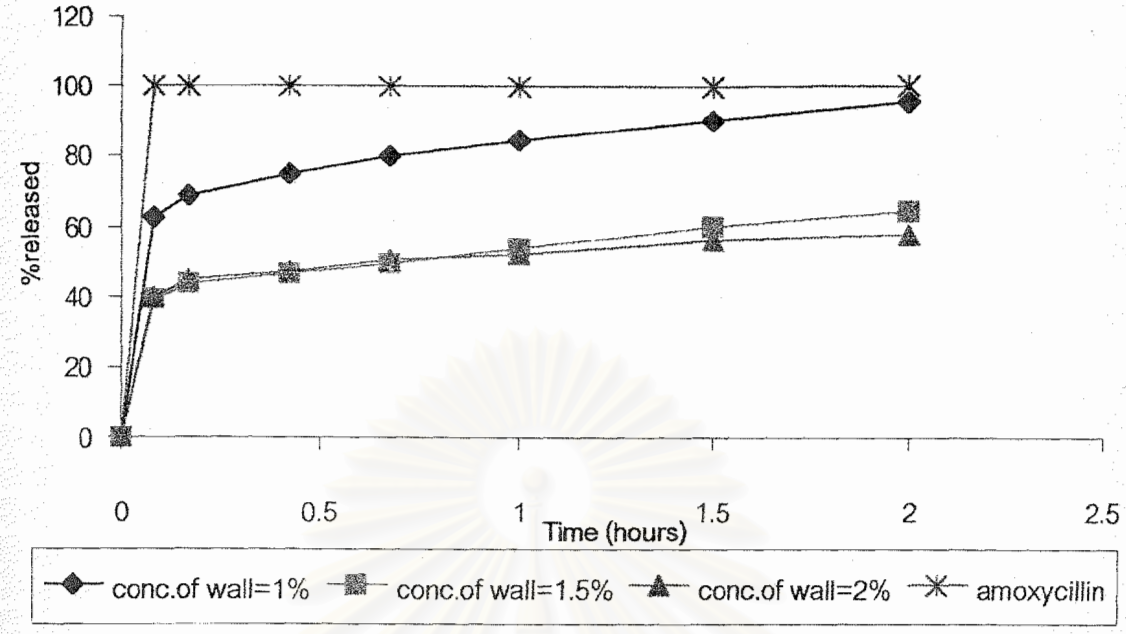


Figure 34. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

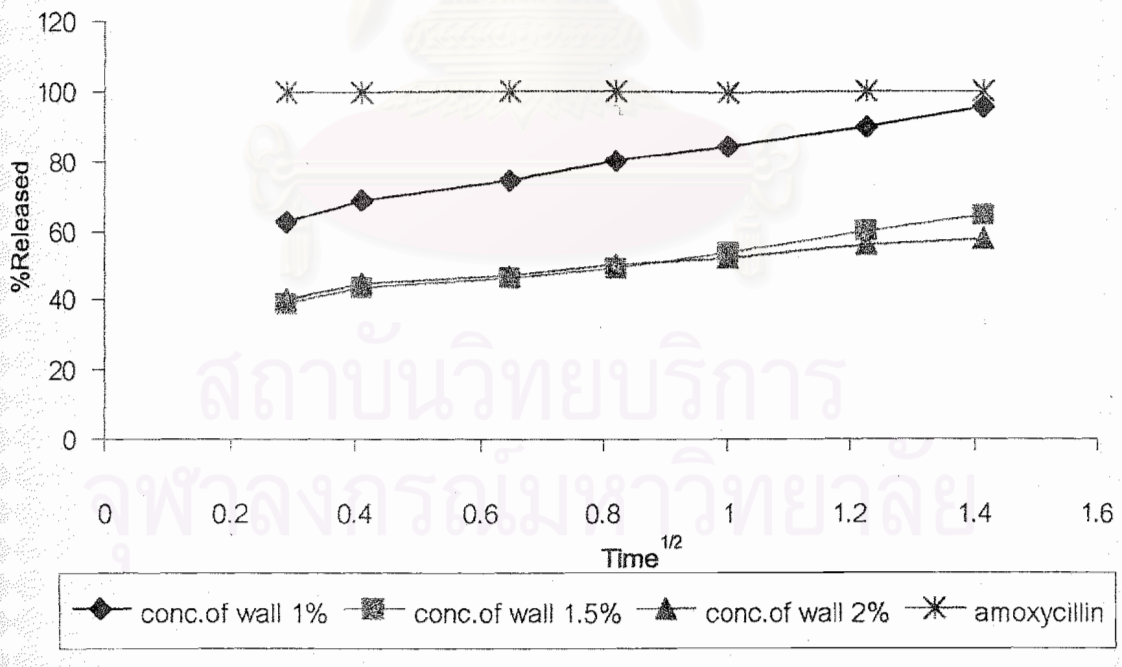


Figure 35. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

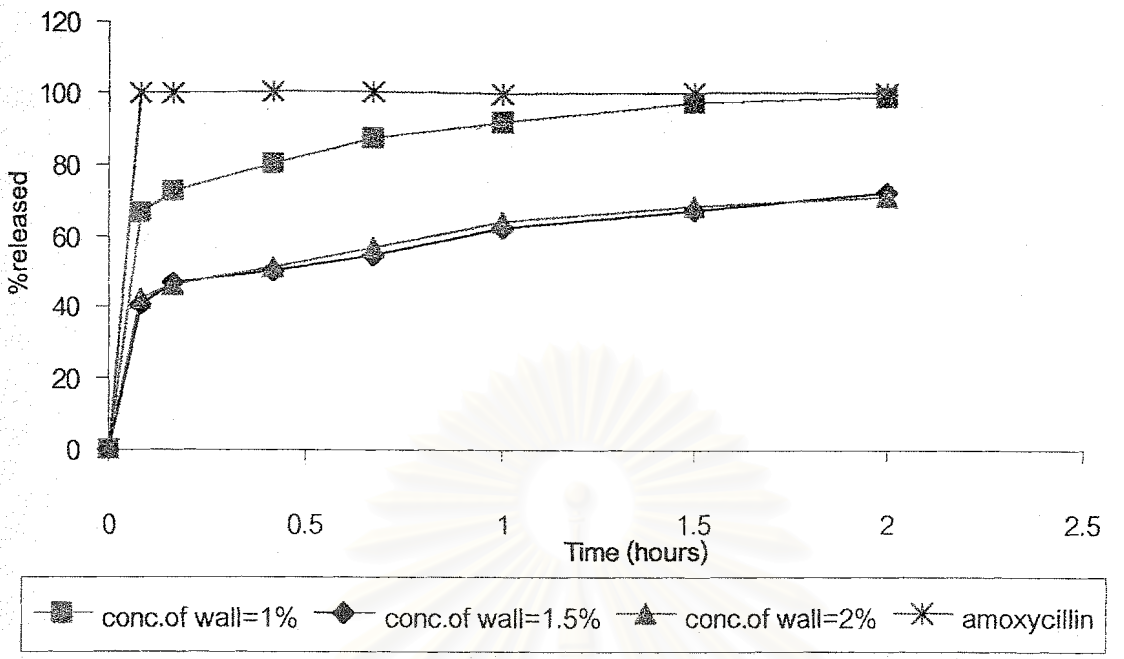


Figure 36. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

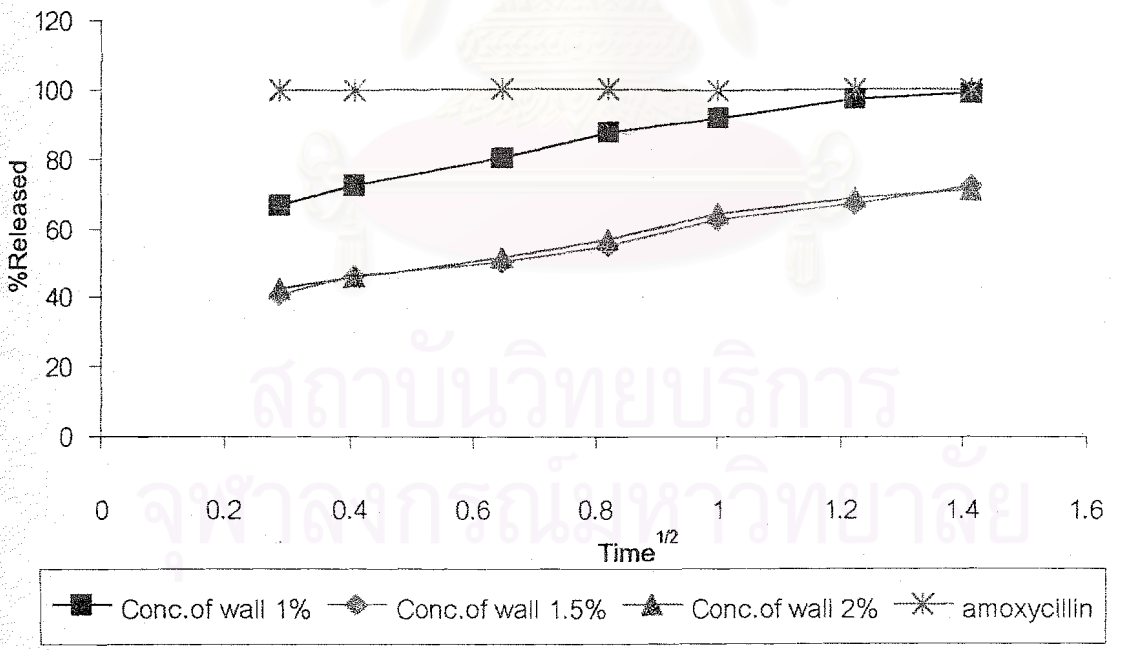


Figure 37. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

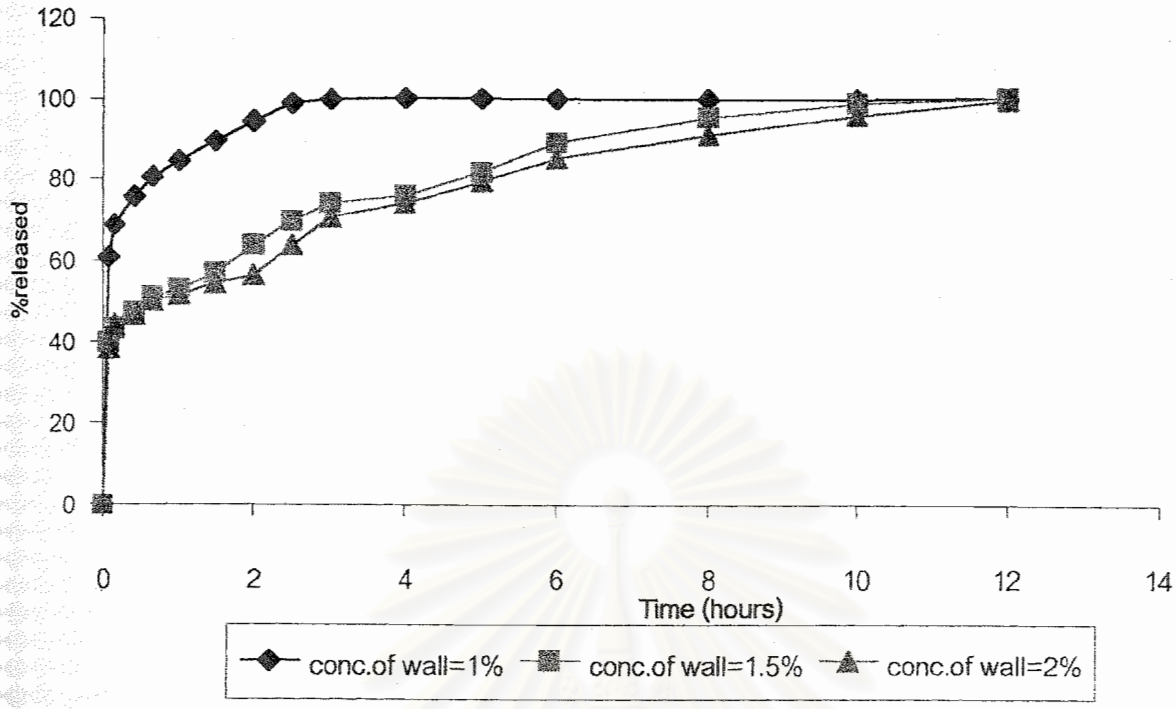


Figure 38. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

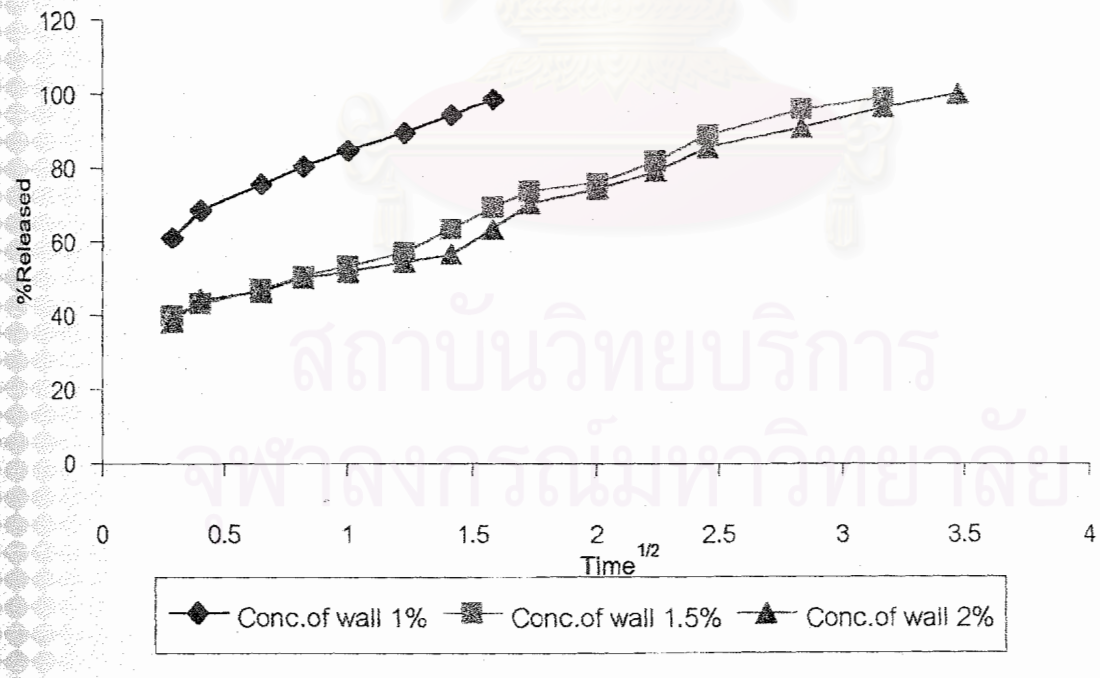


Figure 39. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

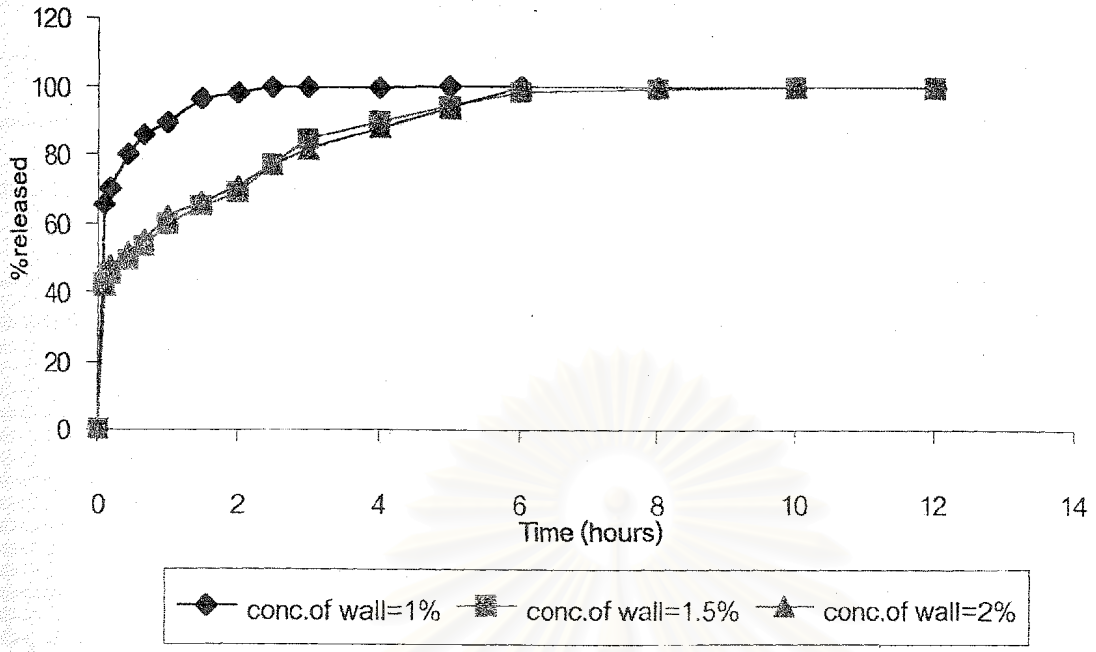


Figure 40. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

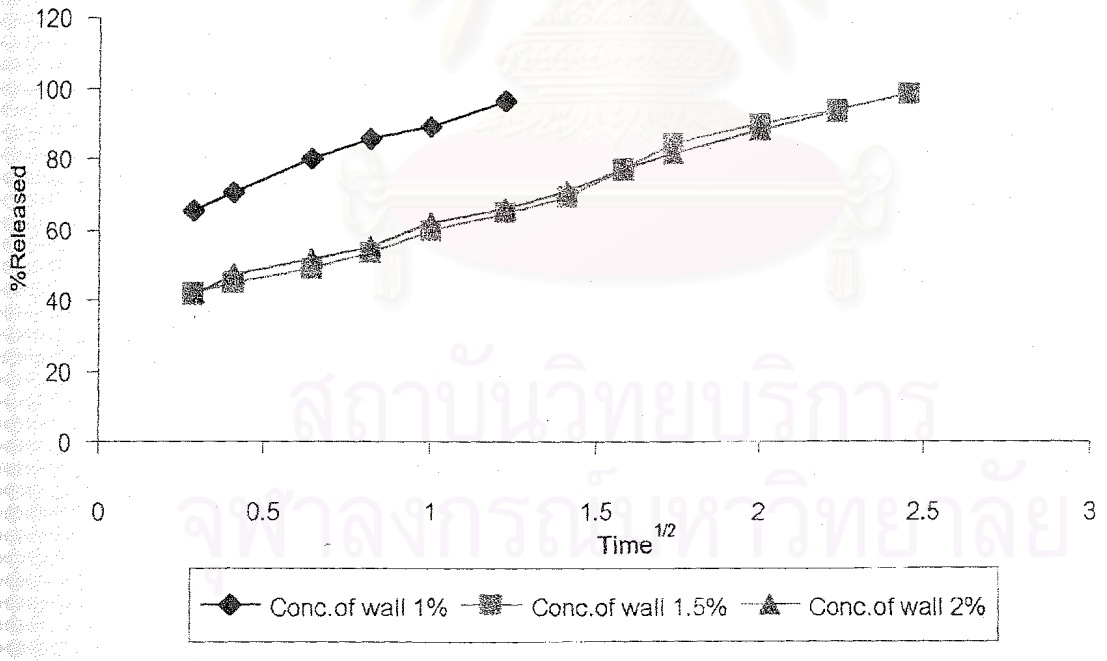


Figure 41. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

Table 31. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Concentration of wall		
		1%	1.5%	2%
k_H ($hr^{-1/2}$)	1	27.2850	21.8890	16.5540
	2	28.5880	21.3270	14.7340
	3	28.8360	22.6830	14.2390
	Mean	28.2363	21.9663	15.1757
	S.D.	0.8332	0.6813	1.2191
R^2	1	0.9867	0.9798	0.9908
	2	0.9938	0.9822	0.9524
	3	0.9867	0.9640	0.9658
	Mean	0.9891	0.9753	0.9697
	S.D.	0.0041	0.0099	0.0195
T_{50}(hr)	1	0.0779	0.5393	0.5865
	2	0.0498	0.6956	0.6849
	3	0.0270	0.5814	0.8752
	Mean	0.0515	0.6054	0.7156
	S.D.	0.0255	0.0809	0.1468

Table 32. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Concentration of wall		
		1%	1.5%	2%
k_H ($hr^{-1/2}$)	1	29.6820	26.2800	26.7860
	2	29.7690	28.8840	26.4640
	3	30.0670	27.6180	27.5600
	Mean	29.8393	27.5940	26.9367
	S.D.	0.2019	1.3022	0.5633
R^2	1	0.9698	0.9911	0.9763
	2	0.9723	0.9683	0.9838
	3	0.9658	0.9960	0.9900
	Mean	0.9693	0.9851	0.9834
	S.D.	0.0033	0.0148	0.0069
T_{50}(hr)	1	0.1513	0.4009	0.2755
	2	0.1281	0.3321	0.3377
	3	0.0947	0.3294	0.3141
	Mean	0.1247	0.3542	0.3091
	S.D.	0.0284	0.0405	0.0314

Table 33. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Concentration of wall		
		1%	1.5%	2%
k_H ($hr^{-1/2}$)	1	27.3140	21.8810	20.4450
	2	29.0570	21.7920	20.2720
	3	25.8840	21.8230	19.9430
	Mean	27.4183	21.8320	20.2200
	S.D.	1.5891	0.0452	0.2550
R^2	1	0.9922	0.9870	0.9848
	2	0.9730	0.9939	0.9839
	3	0.9677	0.9918	0.9859
	Mean	0.9776	0.9909	0.9849
	S.D.	0.0129	0.0035	0.0010
T_{50}(hr)	1	0.0750	0.5084	0.7054
	2	0.0219	0.6892	0.6263
	3	0.0850	0.5769	0.8060
	Mean	0.0607	0.5915	0.7125
	S.D.	0.0339	0.0913	0.0901

Table 34. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in simulated intestinal fluid without pancreatin pH 6.8.

Parameter	No.	Concentration of wall		
		1%	1.5%	2%
k_H ($hr^{-1/2}$)	1	32.2550	27.4150	26.9000
	2	32.9240	27.9250	26.2410
	3	33.2920	27.6760	26.6090
	Mean	32.8237	27.6720	26.5833
	S.D.	0.5257	0.2550	0.3302
R^2	1	0.9838	0.9931	0.9965
	2	0.9903	0.9873	0.9940
	3	0.9846	0.9870	0.9948
	Mean	0.9862	0.9891	0.9951
	S.D.	0.0035	0.0034	0.0013
T_{50}(hr)	1	0.0619	0.3904	0.3383
	2	0.0385	0.4230	0.3430
	3	0.0412	0.3831	0.3247
	Mean	0.0472	0.3988	0.3354
	S.D.	0.0128	0.0212	0.0095

The results were obtained from the yield, amoxycillin content, core entrapment, size, size distribution and the release rate constant. The 2% of wall concentration of gelatin-acacia and 1.5% of wall concentration of gelatin-SCMC were chosen because they gave higher percent yield and slower release profile.

3.3.Effect of stirring rate

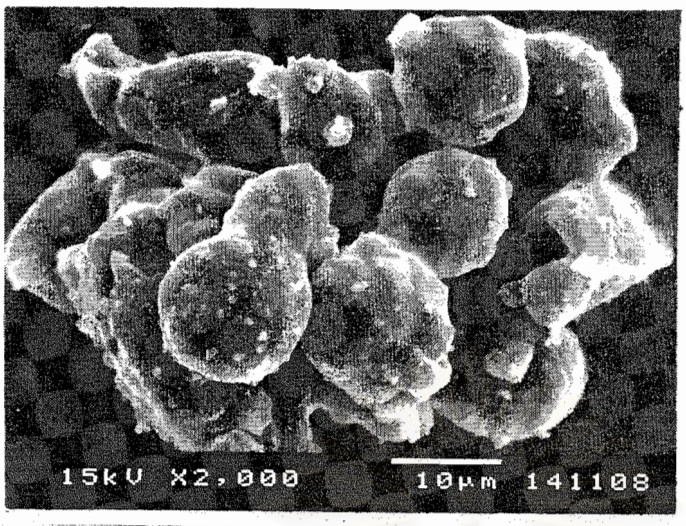
From the investigation of concentration of wall, 2% of gelatin and acacia and 1.5% of gelatin and SCMC were chosen to prepare microcapsules. The microcapsules were prepared with various stirring rates including 500, 700, and 900 rpm, respectively. It was found that the microcapsules prepared by gelatin-acacia had more percent yield than those prepared with gelatin-SCMC as wall, and the drug content and core entrapment were similar (Table 35).

Table 35. The percent yield, content and entrapment of amoxycillin microcapsules prepared by coacervation technique with various stirring rates.

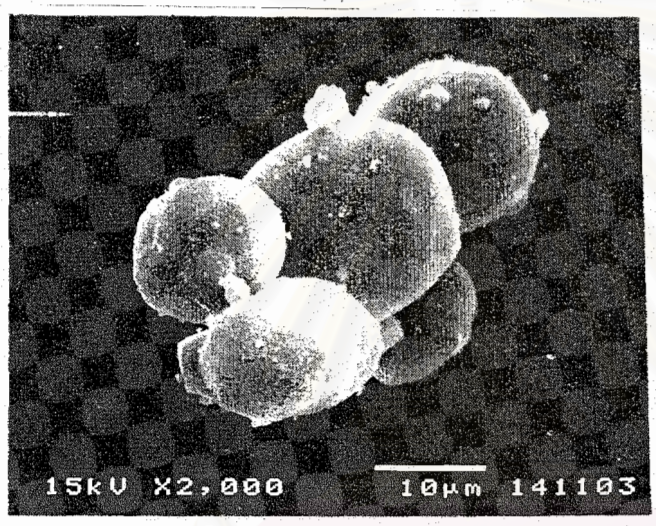
Stirring	% Yield		% Content		% Entrapment	
rate	G - A	G - S	G - A	G - S	G - A	G - S
500	86.75	83.44	29.57±0.19	28.77±0.08	88.72±2.06	86.32±1.84
700	88.14	84.72	29.85±0.12	29.26±0.36	89.56±2.01	87.79±2.16
900	88.98	84.53	29.78±0.27	29.09±0.16	89.35±2.14	87.28±2.02

The effects of stirring rates on the surface morphologies are shown in Figures 42 and 43. The size of microcapsules is shown in Table 36, and the frequency distribution curves are shown in Figure 44. The stirring rate exhibited the dramatic influence on the microcapsules size when the stirring rate was increased, the microcapsules became smaller. At stirring rate of 500 rpm, the mean diameter of gelatin-acacia walled microcapsules was 109.9±2.21 μm while the stirring rate of 900 rpm the mean diameter was reduced to 28.40±0.35 μm. This phenomena was the same as in gelatin-SCMC walled microcapsules that the particle size was reduced from 584.66±28.59 μm to 470.52±29.82 μm. This could be explained by the fact that the stirring rate provided the energy to shearing forces during preparation and prevented aggregates of small microcapsules forming. The result from this study agreed with a previous study by Nazik and Mohamed (1981).

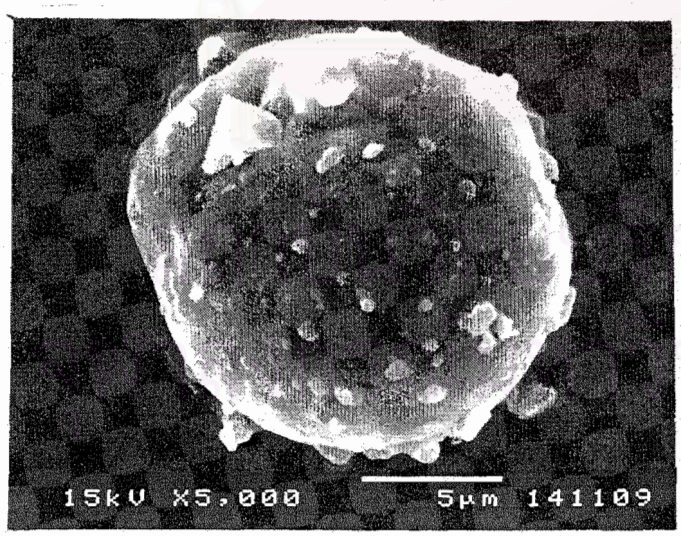
The effects of stirring rate on the in vitro drug relelase are shown in Figures 45-52. It could be observed that the drug release profiles of microcapsules prepared using stirring rate at 900 rpm were faster than microcapsules prepared using stirring rate at 500, and 700 rpm. Since the higher stirring rate produced the smaller particle size thus it resulted in a higher surface area available for drug release. Among all of the models tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 161-164 (Appendix F). The time of 50% released of amoxycillin microcapsules prepared with various stirring rates were obtained from the release profiles (Tables 37-40). The time of 50% released of amoxycillin microcapsules prepared with 900 rpm of stirring rate was the lowest ($p<0.05$), whereas T_{50} of those prepared using 700 rpm of stirring rate were the highest in both media of pH 1.2 and pH 6.8 ($p<0.05$).



A

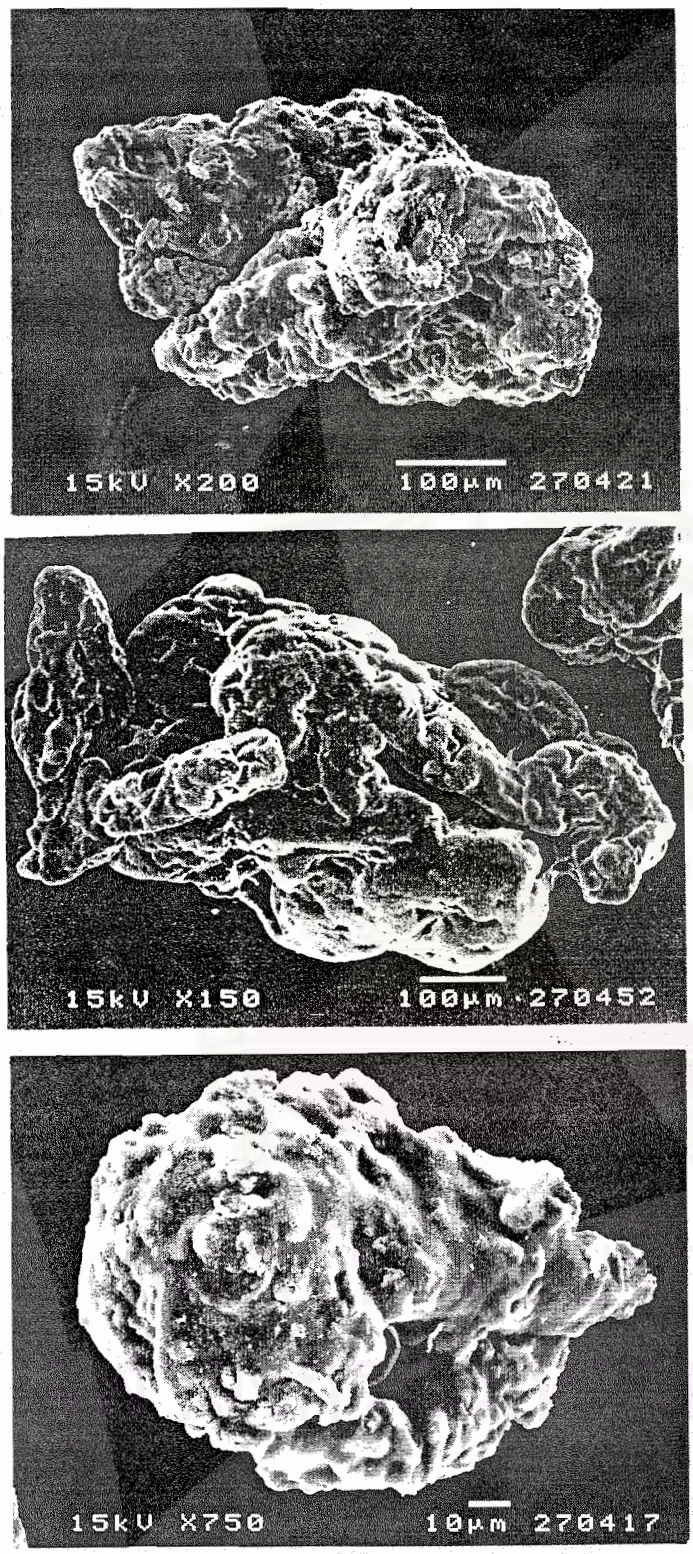


B



C

Figure 42. Scanning electron micrographsof amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rate (rpm) (A) 500 (B) 700 (C) 900. Magnification 2000x, 2000x and 5000x respectively.



A

B

C

Figure 43. Scanning electron micrographs of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rate (rpm) (A) 500 (B) 700 (C) 900. Magnification 200x, 150x and 750x respectively.

Table 36. The particle sizes of amoxycillin microcapsules prepared by coacervation technique with various stirring rates.

Polymer	No.	Particle size (μm)		
		500	700	900
Gelatin-Acacia	1	112.44	59.83	28.53
	2	108.38	61.96	28.66
	3	108.88	61.27	28.00
	Mean	109.90	61.02	28.40
	S.D.	2.21	1.09	0.35
Gelatin-SCMC	1	553.72	535.61	436.49
	2	590.17	551.92	482.98
	3	610.10	568.03	492.08
	Mean	584.66	551.85	470.52
	S.D.	28.59	16.21	29.82

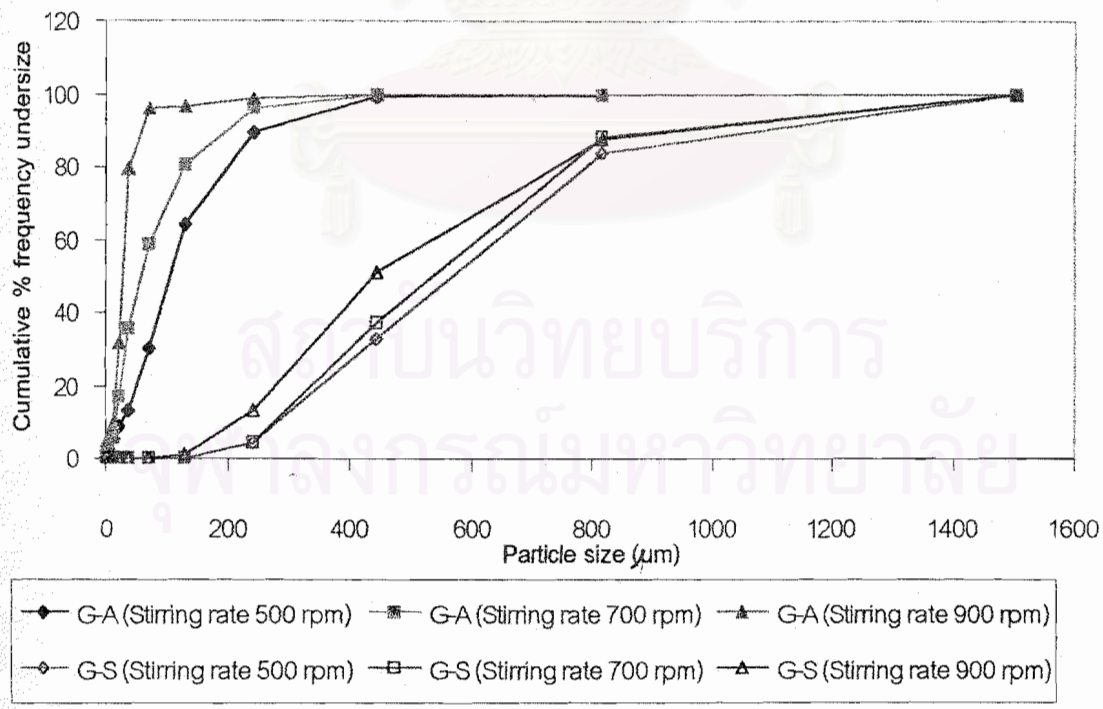


Figure 44. Cumulative % frequency undersize of amoxycillin microcapsules prepared by complex coacervation technique with various stirring rate.

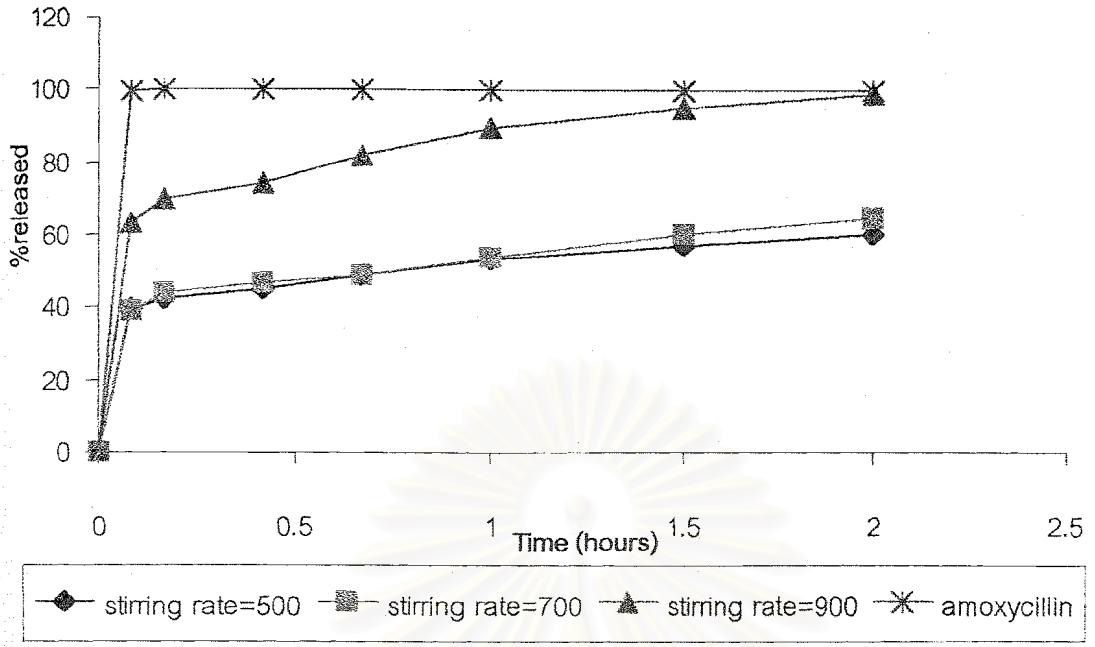


Figure 45. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

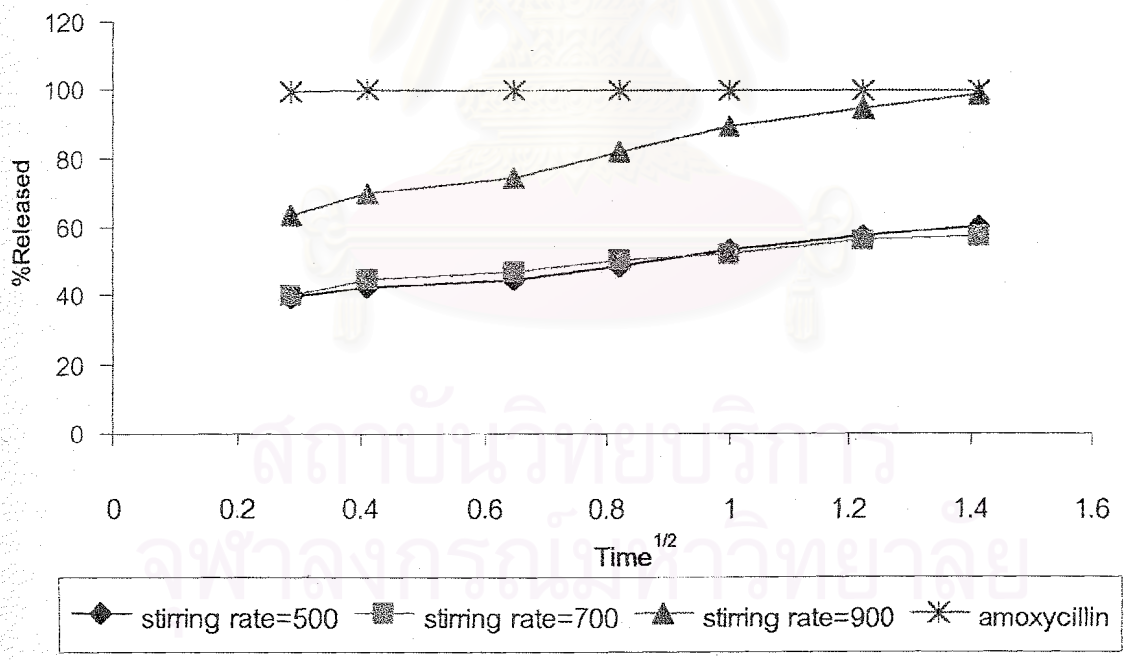


Figure 46. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

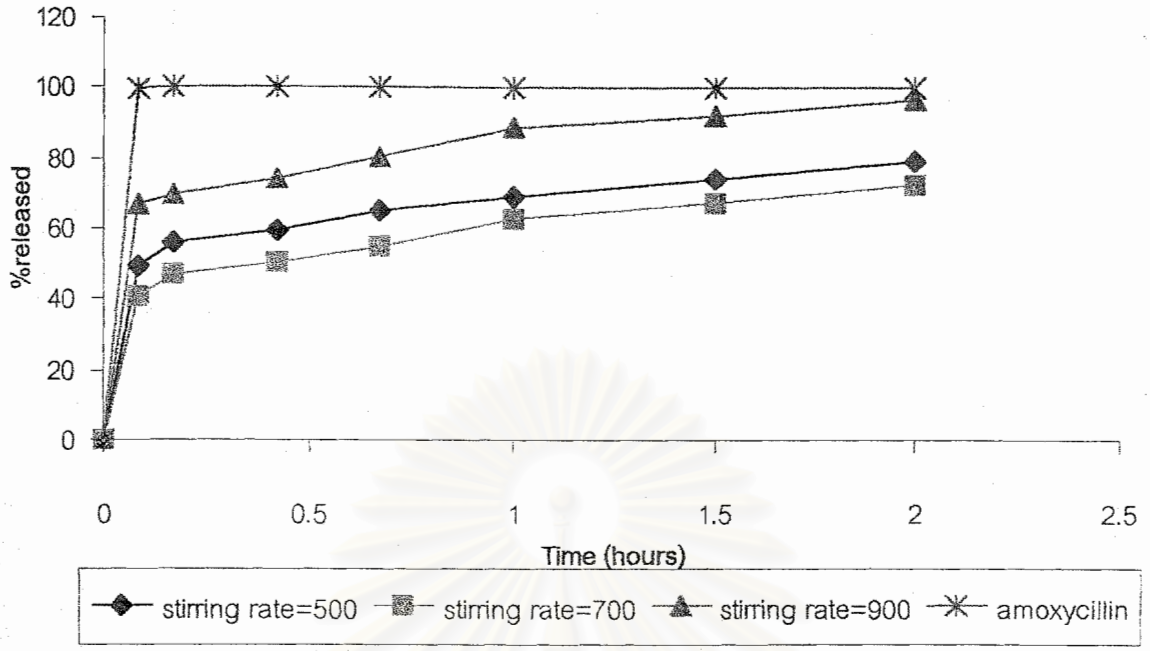


Figure 47. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

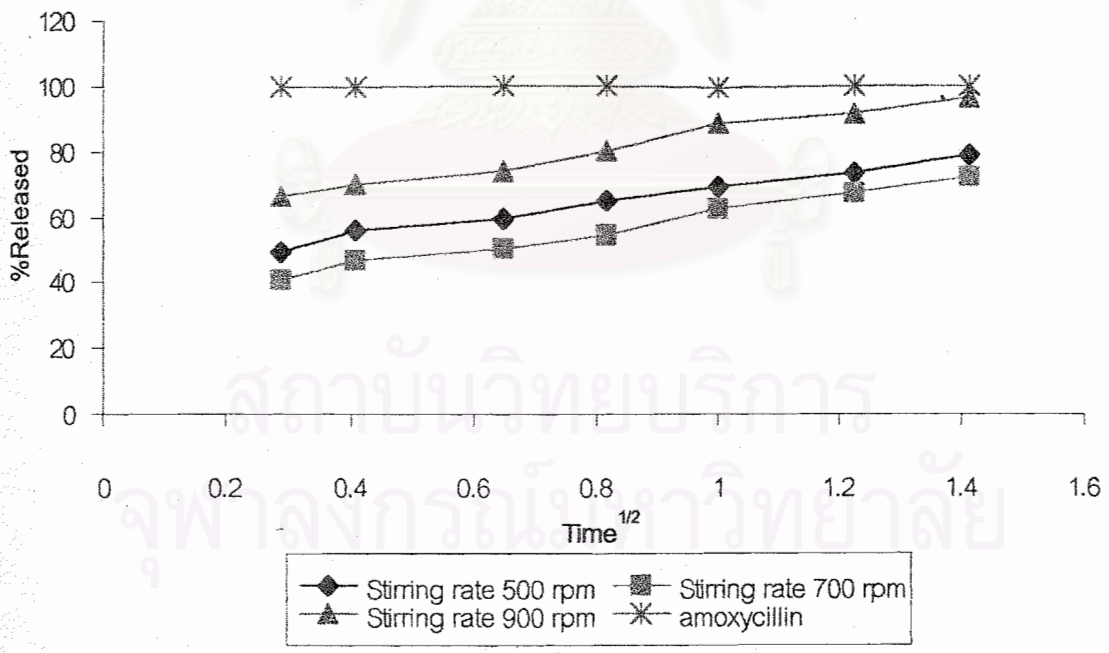


Figure 48. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

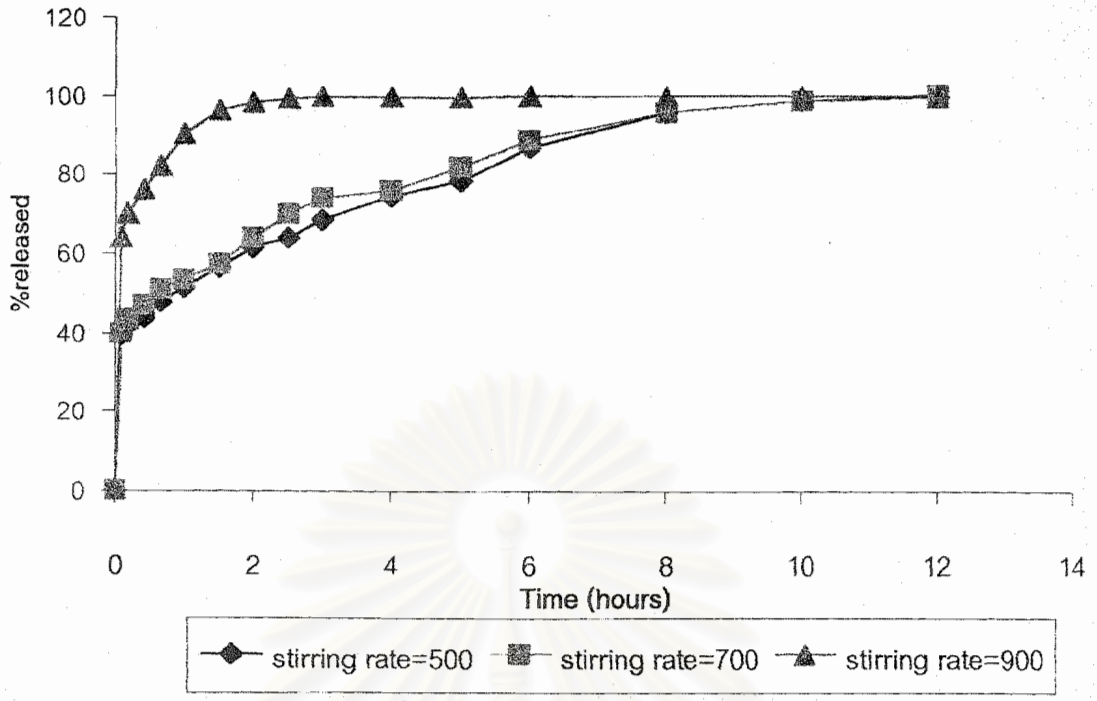


Figure 49. The release profiles of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rates in simulated intestinal fluid without pancreatin pH 6.8.

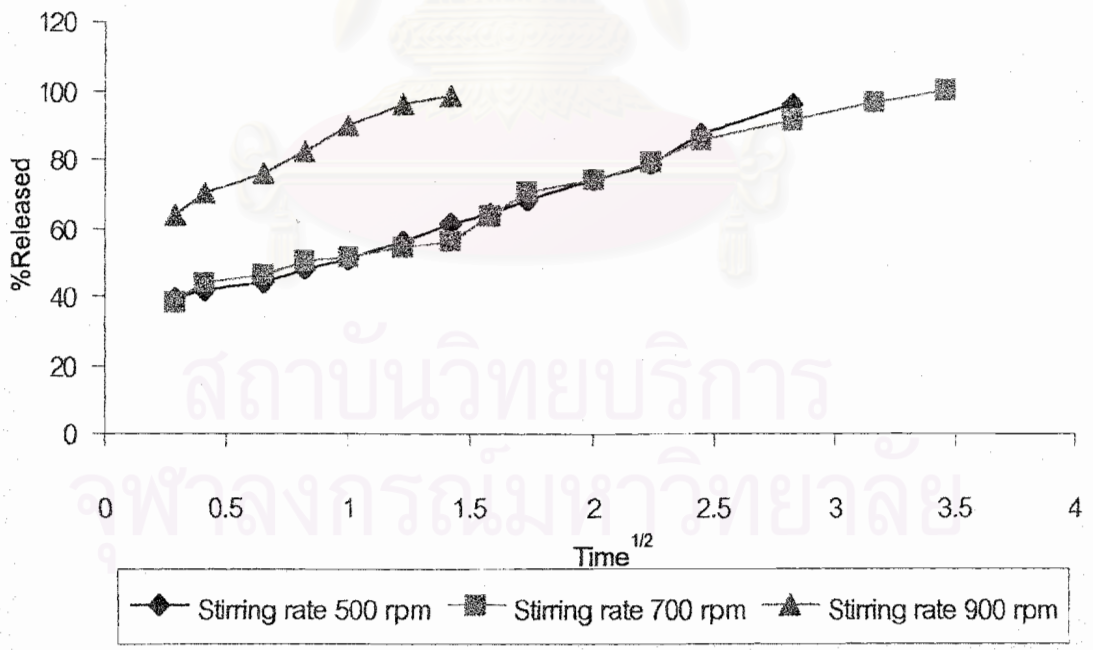


Figure 50. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rates in simulated intestinal fluid without pancreatin pH 6.8.

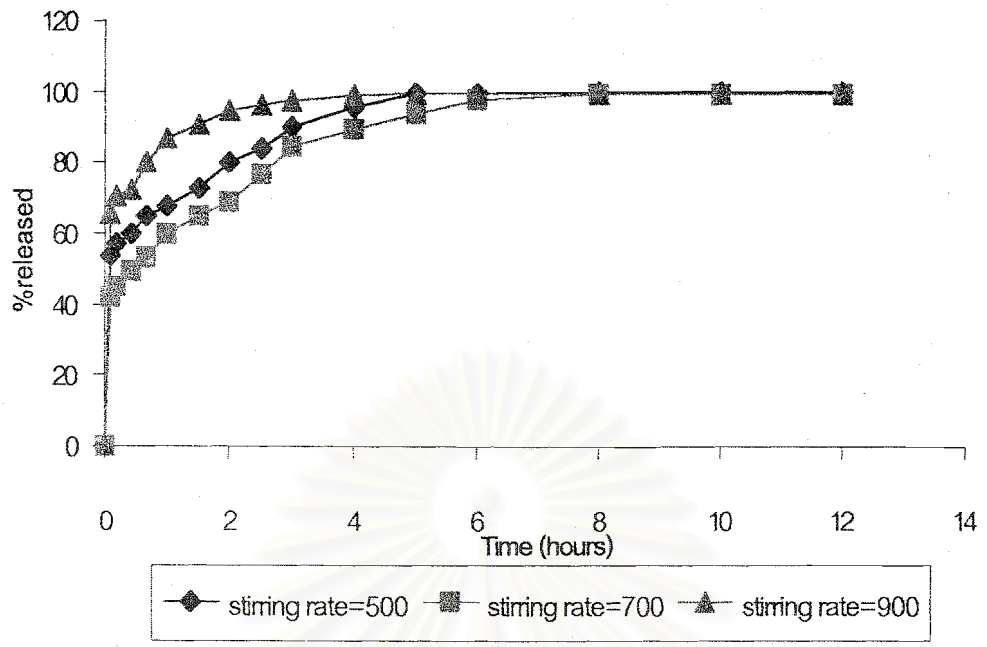


Figure 51. The release profiles of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rates in simulated intestinal fluid without pancreatin pH 6.8.

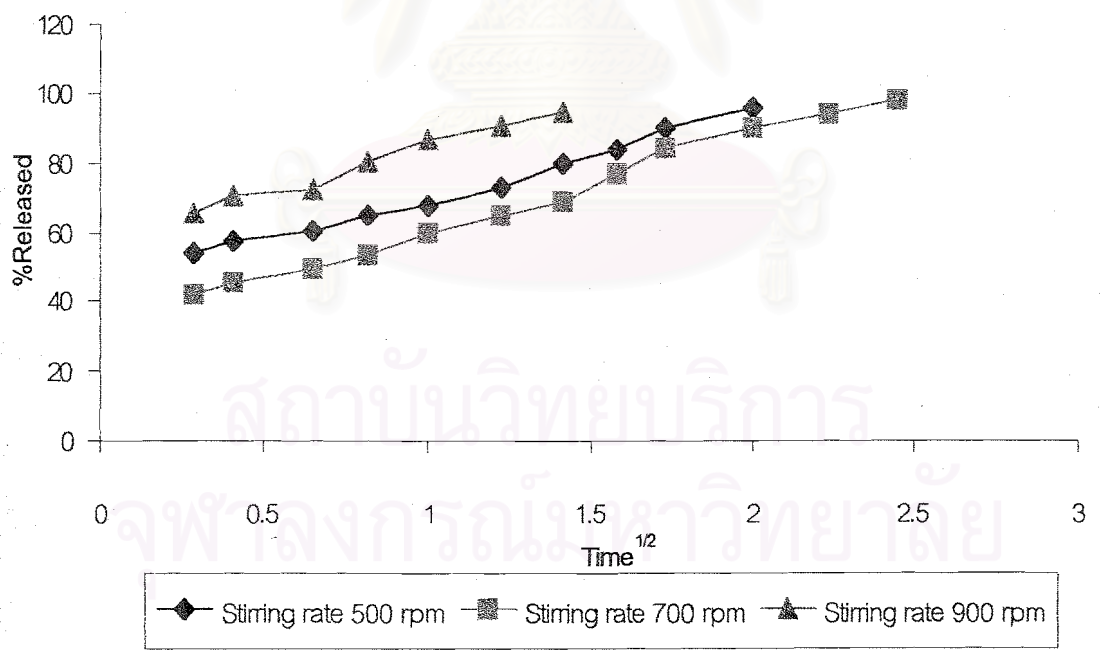


Figure 52. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rates in simulated intestinal fluid without pancreatin pH 6.8.

Table 37. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Stirring rates(rpm)		
		500	700	900
k_H ($hr^{-1/2}$)	1	18.5270	16.5540	32.3110
	2	19.4980	14.7340	31.7290
	3	18.9210	14.2390	32.2160
	Mean	18.9820	15.1757	32.0853
	S.D.	0.4884	1.2191	0.3122
R^2	1	0.9784	0.9908	0.9867
	2	0.9945	0.9524	0.9852
	3	0.9840	0.9658	0.9871
	Mean	0.9856	0.9697	0.9863
	S.D.	0.0082	0.0195	0.0010
T_{50}(hr)	1	0.6470	0.5865	0.0137
	2	0.6092	0.6849	0.0480
	3	0.6240	0.8752	0.0260
	Mean	0.6267	0.7156	0.0292
	S.D.	0.0190	0.1468	0.0174

Table 38. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rates in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Stirring rates(rpm)		
		500	700	900
k_H ($hr^{-1/2}$)	1	24.2390	26.2800	27.9990
	2	24.0680	28.8840	28.7850
	3	24.2390	27.6180	27.1060
	Mean	24.1820	27.5940	27.9633
	S.D.	0.0987	1.3022	0.8401
R^2	1	0.9883	0.9911	0.9812
	2	0.9872	0.9683	0.9893
	3	0.9928	0.9960	0.9819
	Mean	0.9894	0.9851	0.9841
	S.D.	0.0030	0.0148	0.0045
T_{50}(hr)	1	0.1558	0.4009	0.1044
	2	0.1688	0.3321	0.0665
	3	0.1558	0.3294	0.0847
	Mean	0.1602	0.3542	0.0852
	S.D.	0.0075	0.0405	0.0190

Table 39. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-acacia with various stirring rate in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Stirring rate (rpm)		
		500	700	900
k_H ($hr^{-1/2}$)	1	22.9780	20.4450	30.7990
	2	22.1110	20.2720	31.7110
	3	22.4320	19.9430	32.1080
	Mean	22.5070	20.2200	31.5393
	S.D.	0.4383	0.2550	0.6712
R^2	1	0.9865	0.9848	0.9864
	2	0.9921	0.9839	0.9774
	3	0.9888	0.9859	0.9838
	Mean	0.9891	0.9849	0.9825
	S.D.	0.0028	0.0010	0.0046
T_{50}(hr)	1	0.5869	0.7054	0.0394
	2	0.6958	0.6263	0.0411
	3	0.5404	0.8060	0.0398
	Mean	0.6077	0.7125	0.0401
	S.D.	0.0798	0.0901	0.0009

Table 40. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by gelatin-SCMC with various stirring rate in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Stirring rate (rpm)		
		500	700	900
k_H ($hr^{-1/2}$)	1	24.7240	27.4150	25.6280
	2	23.5680	27.9250	27.3880
	3	25.9060	27.6760	26.0040
	Mean	24.7327	27.6720	26.3400
	S.D.	1.1690	0.2550	0.9269
R^2	1	0.9893	0.9931	0.9699
	2	0.9843	0.9873	0.9817
	3	0.9793	0.9870	0.9781
	Mean	0.9843	0.9891	0.9766
	S.D.	0.0050	0.0034	0.0060
T_{50}(hr)	1	0.1553	0.3904	0.1359
	2	0.2052	0.4230	0.0740
	3	0.1818	0.3831	0.0998
	Mean	0.1808	0.3988	0.1032
	S.D.	0.0250	0.0212	0.0311

4. Preparation of amoxycillin microcapsules by spray-drying technique

Amoxycillin microcapsules were prepared by spray-drying method described in chapter II. This process gave a less yellow colour, fine powder. The percent yield was about 50% because the smaller spray dried particles were carried by the cyclone system to the collector while the larger (more heavy) retained particles in the chamber thus it lost about 50%.

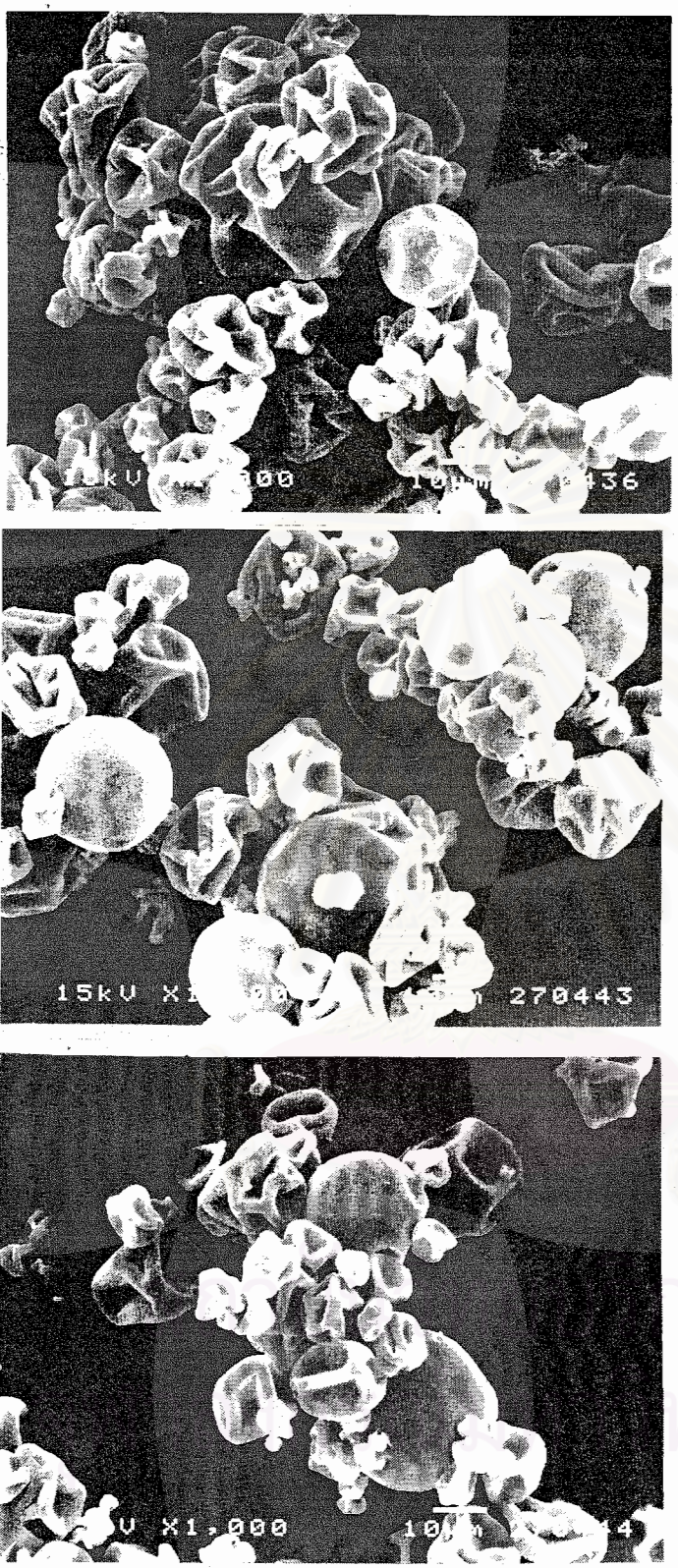
4.1.Effect of core to wall ratio.

The microcapsules containing amoxycillin were prepared using spray-drying technique with varied core to wall ratios from 1:1, 1:2, and 1:3, respectively. The percent yield, amoxycillin content, and core entrapment are shown in Table 41. It was found that the microcapsules prepared with 1:2 core to wall ratio gave the highest yield and core entrapment.

Table 41. The percent yield, content and entrapment of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios.

Core:wall ratio	% Yield	% Content	% Entrapment
1:1	57.15	35.42±0.12	70.84±1.98
1:2	59.57	25.56±0.18	76.69±2.04
1:3	55.23	18.06±0.11	72.24±1.96

The effects of core to wall ratios on the surface morphologies are shown in Figure 53. The sizes of microcapsules are shown in Table 42, and the frequency distribution curves are shown in Figure 54. The microcapsules size tended to increase with increasing the amount of wall. Kawashima et al. (1972) indicated that the main



A

B

C

Figure 53. Scanning electron micrographs of amoxycillin microcapsules prepared by spray-dried technique with various core to wall ratio (A) 1:1 (B) 1:2 (C) 1:3. Magnification 1000x, 1000x and 1000x respectively.

Table 42. The particle sizes of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios.

No.	Particle size (μm)		
	1:1	1:2	1:3
1	26.67	27.30	28.89
2	25.89	26.53	27.86
3	25.88	26.07	27.42
Mean	26.15	26.63	28.06
S.D.	0.45	0.62	0.75

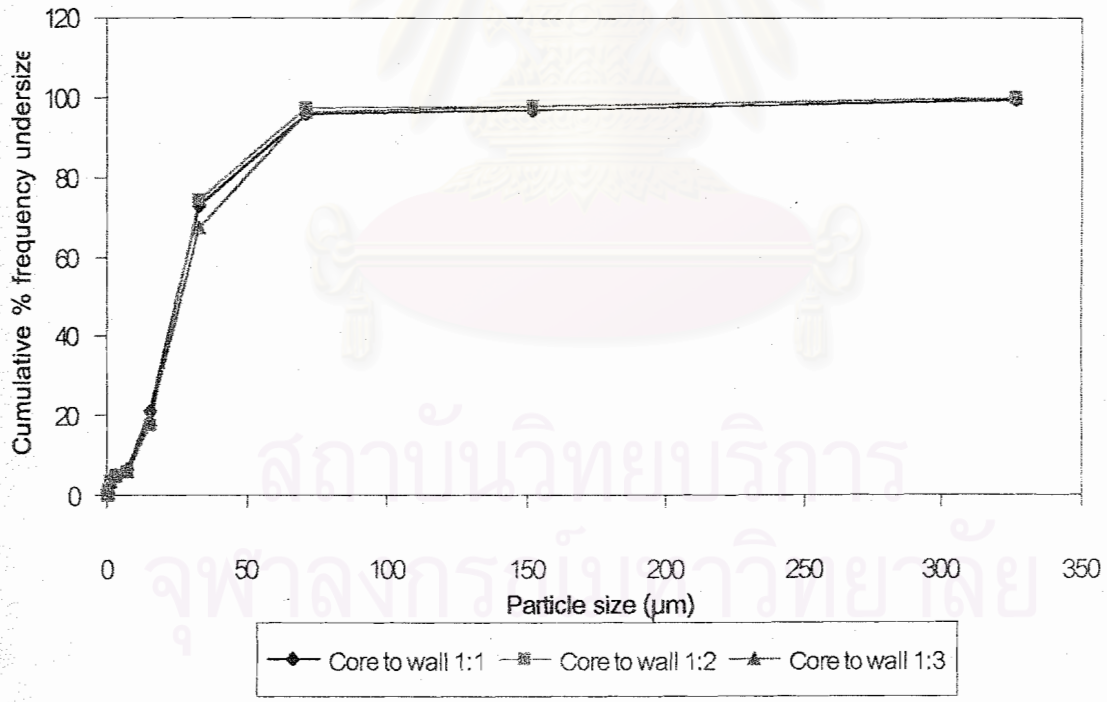


Figure 54. Cumulative % frequency undersize of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios.

factors determinining the size of microparticles were the concentrations of the drug and the polymer in the formulation. The average diameter of microcapsules gradually increased with the weight ratio of polymer to drug in the system increased.

The effects of core to wall ratios on the in vitro drug release are shown in Figures 52-58. It was observed that the initial drug release profile showed burst effect. The core to wall ratio of 1:1 gave the fastest release profile in a both of media at pH 1.2 and pH 6.8 because the mirocapsules with 1:1 core to wall ratio had a smaller size which resulted in a higher surface area and less wall thickness than the other ratios.

From the drug release profile, the data were analyzed according to different models to obtain the release rate constant (k) and the regression coefficient or coefficient of determination (R^2) which was determined to present the linearity as shown in Tables 43 and 44. Among all of the models tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 165-166 (Appendix F). The time of 50% released of the amoxycillin microcapsules with various core to wall ratios were obtained from the release profiles (Figures 56 and 58). The time of 50% released of the spray-dried microcapsules prepared with 1:1 core to wall ratio was the lowest in both media of pH 1.2 and pH 6.8 ($p<0.05$). But in the medium pH 6.8, the time of 50% released of the spray-dried microcapsules prepared with 1:3 core to wall ratio was the highest ($p<0.05$).

From the results obtained from the yield, amoxycillin content, core entrapment, size, size distribution and rate constant. The 1:2 core to wall ratio was chosen for further study due to the highest percent yield, and core entrapment eventhough the T_{50} of 1:2 core to wall ratio did not show the highest value but it closed to T_{50} of 1:3 core to wall ratio.

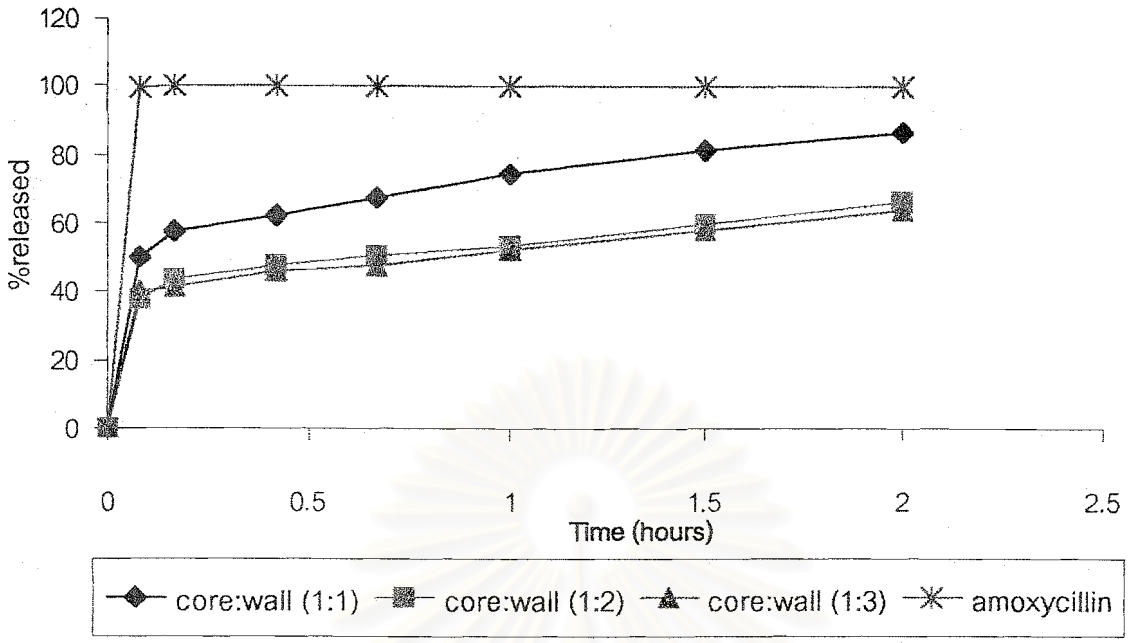


Figure 55. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

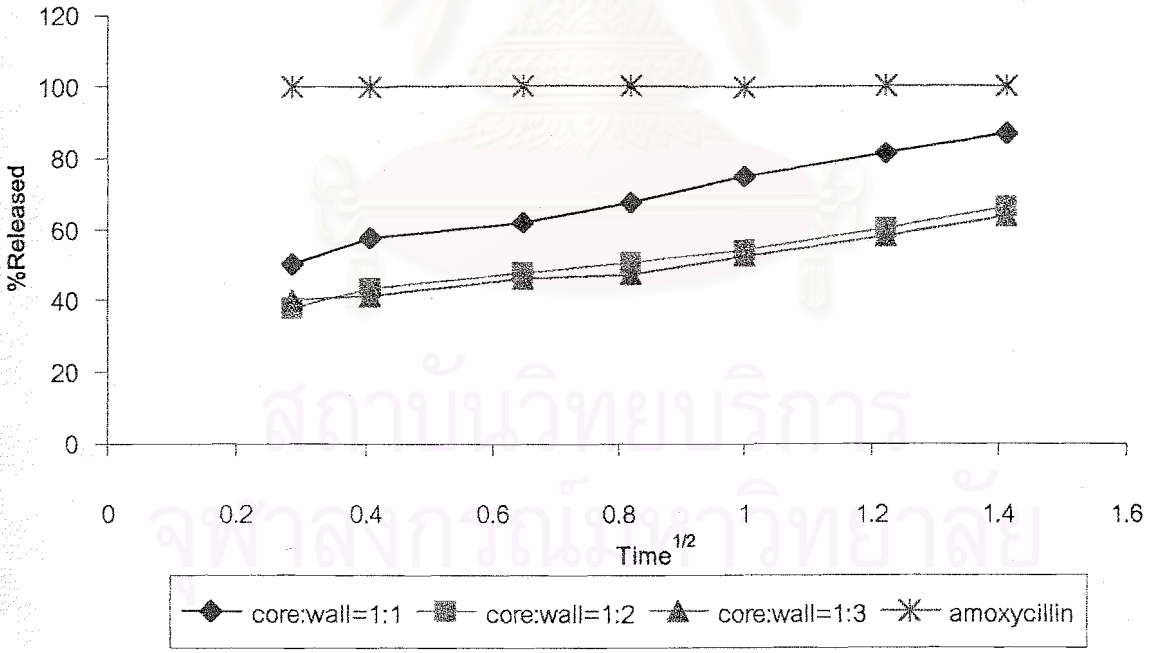


Figure 56. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

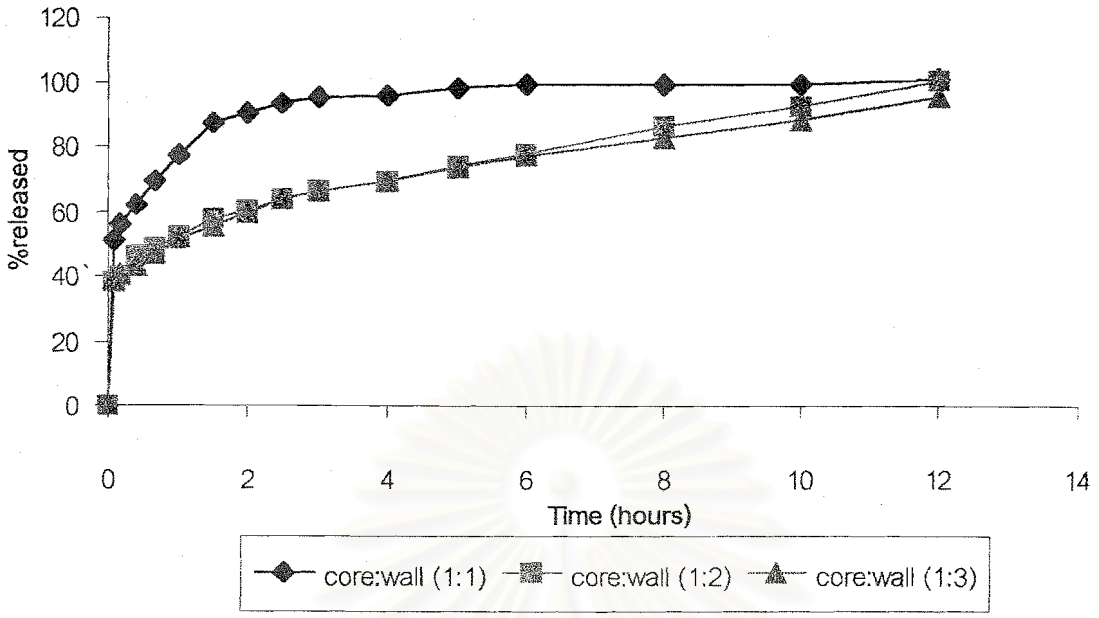


Figure 57. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

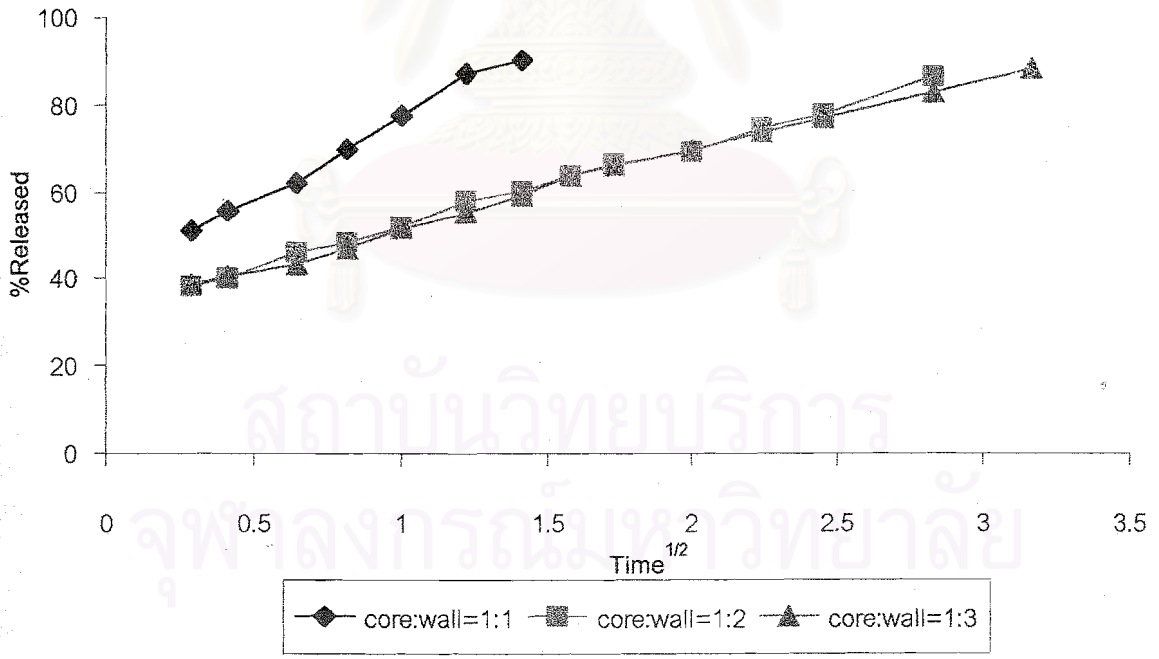


Figure 58. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

Table 43. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	32.1470	23.6770	21.3970
	2	32.2730	21.1890	19.8020
	3	29.9370	24.5190	21.6320
	Mean	31.4523	23.1283	20.9437
	S.D.	1.3138	1.7315	0.9957
R^2	1	0.9902	0.9835	0.9668
	2	0.9921	0.9715	0.9655
	3	0.9921	0.9914	0.9878
	Mean	0.9915	0.9821	0.9734
	S.D.	0.0011	0.0100	0.0125
T_{50}(hr)	1	0.0550	0.5089	0.6621
	2	0.0557	0.6135	0.7784
	3	0.0569	0.6365	0.6450
	Mean	0.0558	0.5863	0.6952
	S.D.	0.0010	0.0680	0.0726

Table 44. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various core to wall ratios in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Core to wall ratios		
		1:1	1:2	1:3
k_H ($hr^{-1/2}$)	1	36.5780	18.4480	16.7130
	2	37.2080	19.0730	18.2390
	3	35.9930	18.1620	18.5650
	Mean	36.5930	18.5610	17.8390
	S.D.	0.6076	0.4659	0.9887
R^2	1	0.9937	0.9928	0.9896
	2	0.9821	0.9914	0.9949
	3	0.9907	0.9962	0.9921
	Mean	0.9888	0.9935	0.9922
	S.D.	0.0060	0.0025	0.0027
T_{50}(hr)	1	0.0562	0.7945	0.7934
	2	0.0848	0.7482	0.8958
	3	0.0726	0.7901	0.8513
	Mean	0.0712	0.7776	0.8468
	S.D.	0.0143	0.0256	0.0514

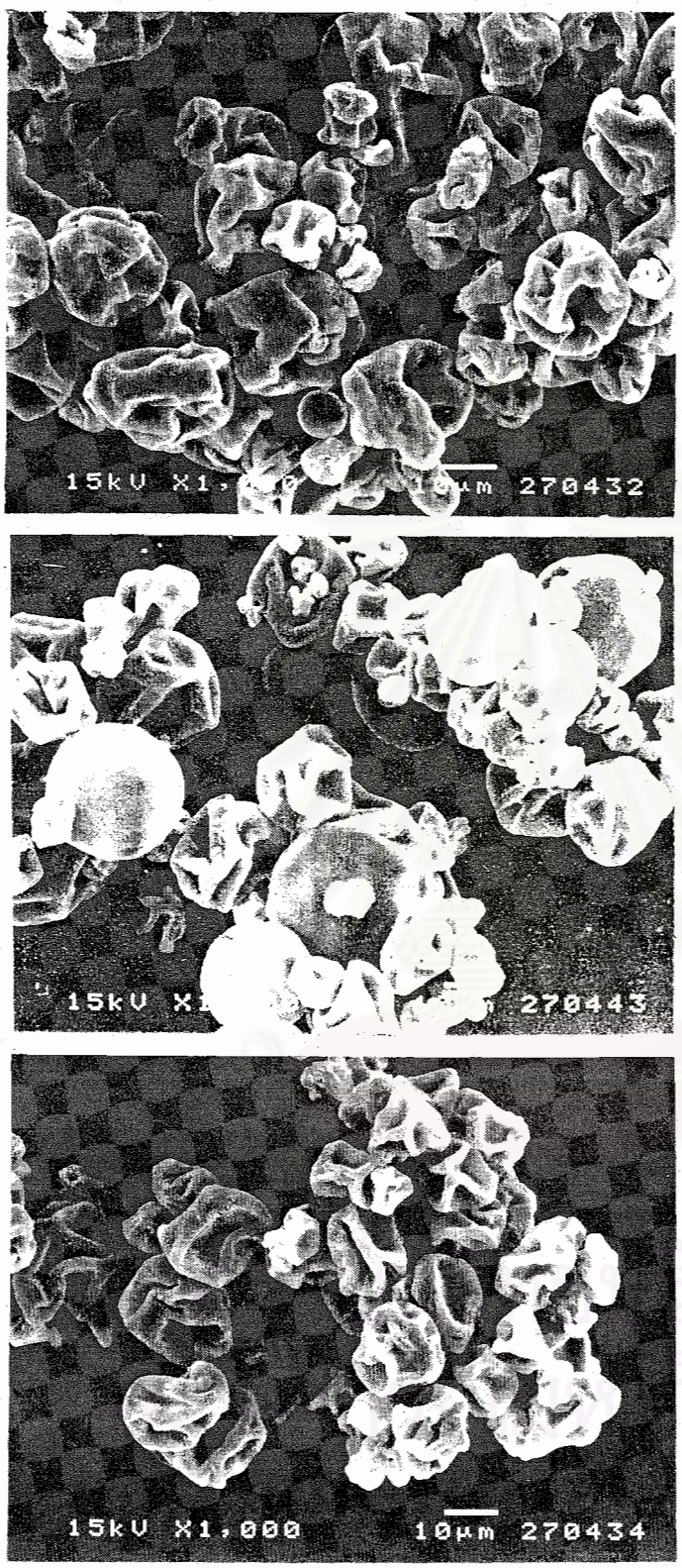
4.2.Effect of inlet air temperature

From the investigation of core to wall ratios, the 1:2 core to wall ratio was chosen for further studies. The microcapsules were prepared with various inlet air temperature including 110°C, 120°C, and 130°C, respectively. It was found that the microcapsules prepared by maintaining the inlet air temperature at 120°C gave the highest percent yield, amoxycillin content and core entrapment while the inlet air temperature was maintained at 110°C gave the lowest percent yield, amoxycillin content and core entrapment (Table 45).

The effects of inlet air temperature on the surface and morphologies of microcapsules are shown in Figure 59. The sizes of microcapsules are shown in Table 46, and the frequency distribution curves are displayed in Figure 60. The microcapsule sizes tend to be smaller when inlet air temperature was increased in the process. This result was in agreement with the other investigations (Masters, 1979).

Table 45. The percent yield, content and entrapment of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures.

Inlet air temp.	%Yield	% Content	% Entrapment
110°C	43.42	23.28±0.11	69.85±1.96
120°C	59.57	25.56±0.18	76.69±2.04
130°C	50.68	24.69±0.21	74.08±2.87



A

B

C

Figure 59. Scanning electron micrographs of amoxycillin microcapsules prepared by spray-dried technique with various inlet air temperatures (°C) (A) 110 (B) 120 (C) 130. Magnification 1000x, 1000x and 1000x respectively.

Table 46. The particle sizes of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures.

No.	Particle size (μm)		
	110 °C	120 °C	130 °C
1	27.29	27.30	26.05
2	26.84	26.53	25.64
3	26.19	26.07	25.28
Mean	26.77	26.63	25.66
S.D.	0.55	0.62	0.39

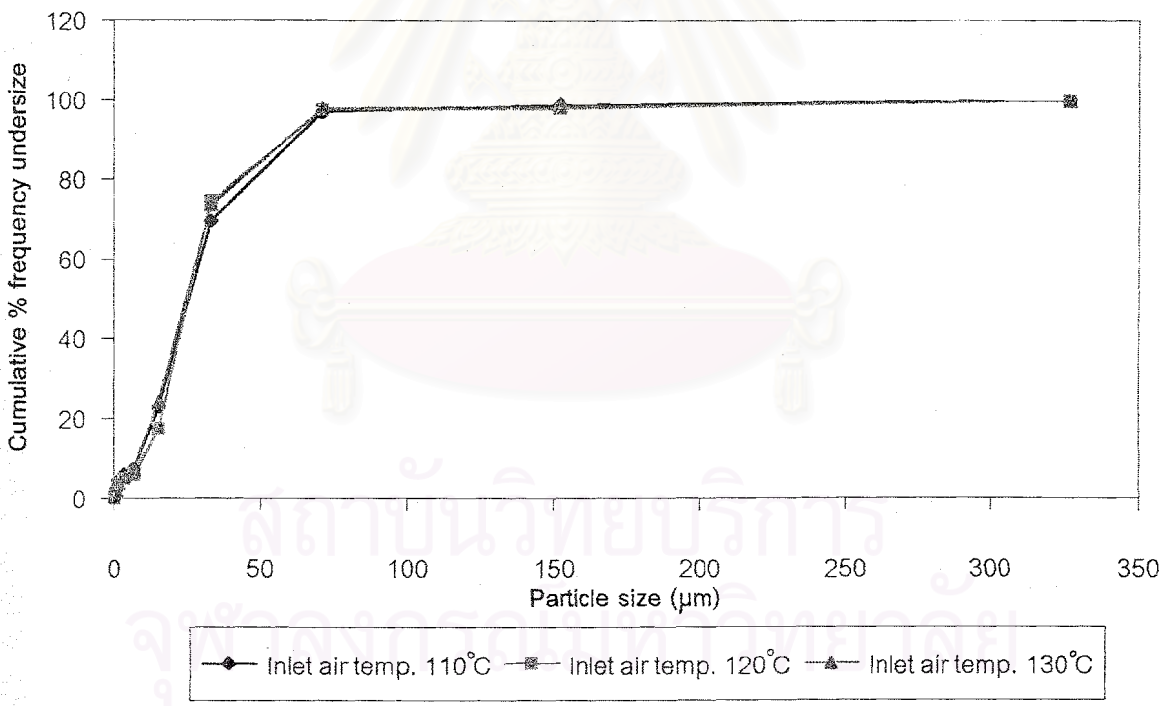


Figure 60. Cumulative % frequency undersize of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures.

The effects of inlet air temperature on the in vitro drug release are shown in Figures 61-64. It was observed that the initial drug release profile showed burst effect because the surface of microcapsules had a drug crystal adhering on the wall (Figure 59). It was found that the release profiles of microcapsules prepared by maintaining the inlet air temperature at 110, 120 and 130°C, respectively, showed similar characteristics due to similarity of small particle size as shown in Table 46. Among all of the models tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 167-168 (Appendix F). The time of 50% released of the amoxycillin microcapsules prepared with various inlet air temperatures was obtained from the release profile. The time of 50% release of the spray-drying microcapsules prepared by the inlet air temperature of 130°C was the lowest among those of other inlet air temperatures in both media at pH 1.2 and pH 6.8 ($p<0.05$). In the medium pH 6.8, the time of 50% release of amoxycillin microcapsules prepared by inlet air temperature of 120°C was the highest ($p<0.05$).

From the results obtained from the yield, amoxycillin content, core entrapment, size, size distribution and the release rate constant. The inlet air temperature of 120°C was chosen for further study since it gave the highest percent yield, amoxycillin content, and core entrapment.

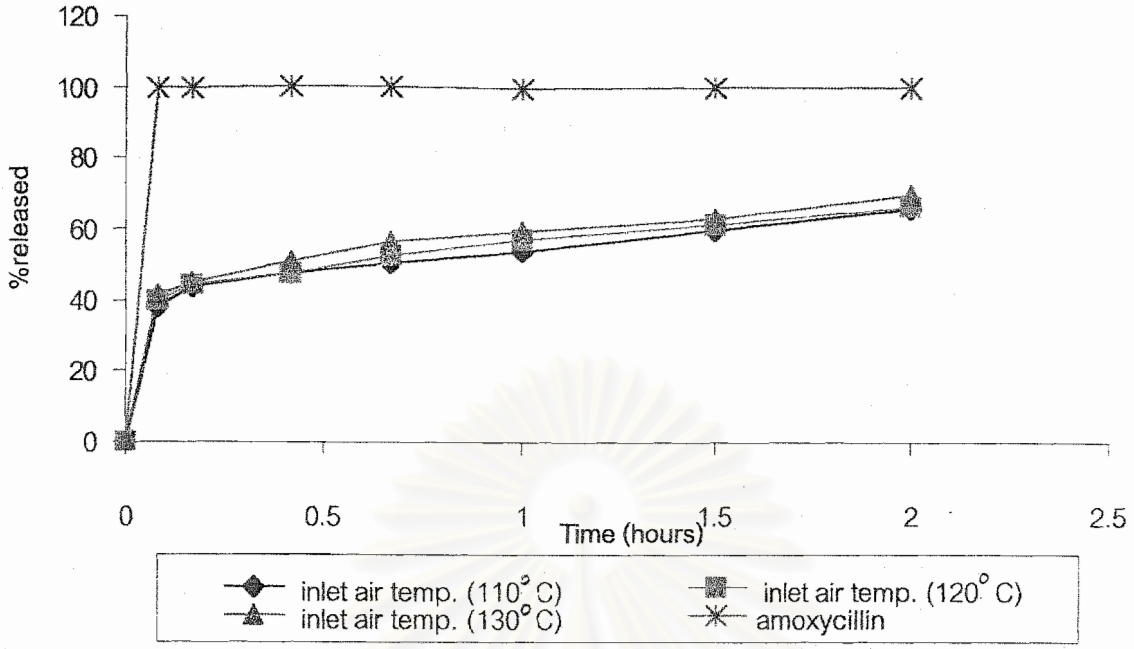


Figure 61. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated gastric fluid without pepsin pH 1.2.

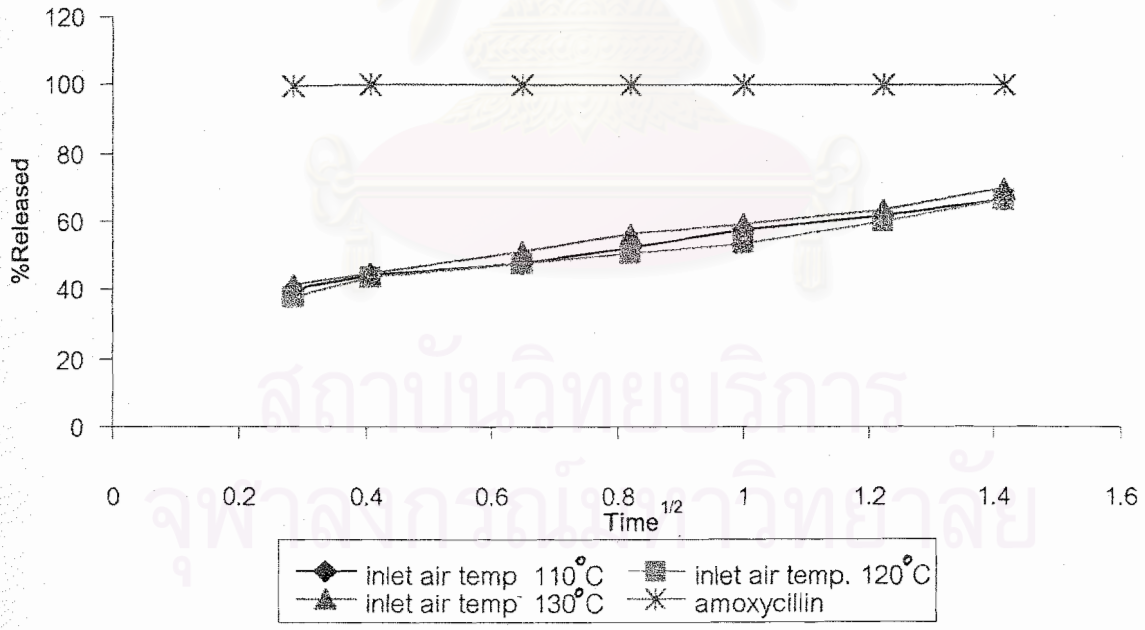


Figure 62. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated gastric fluid without pepsin pH 1.2.

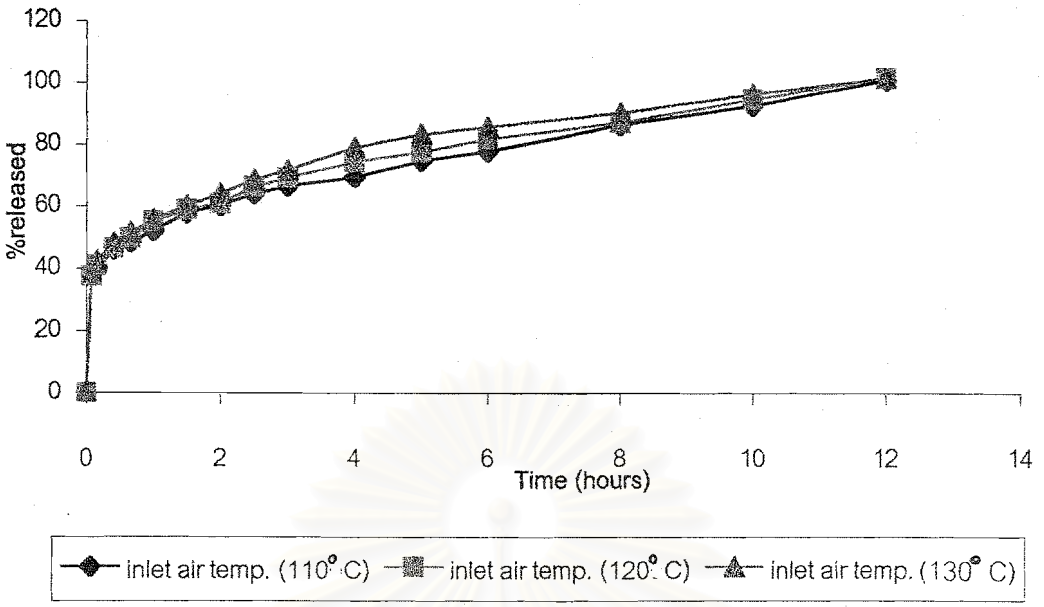


Figure 63. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated intestinal fluid without pancreatin pH 6.8.

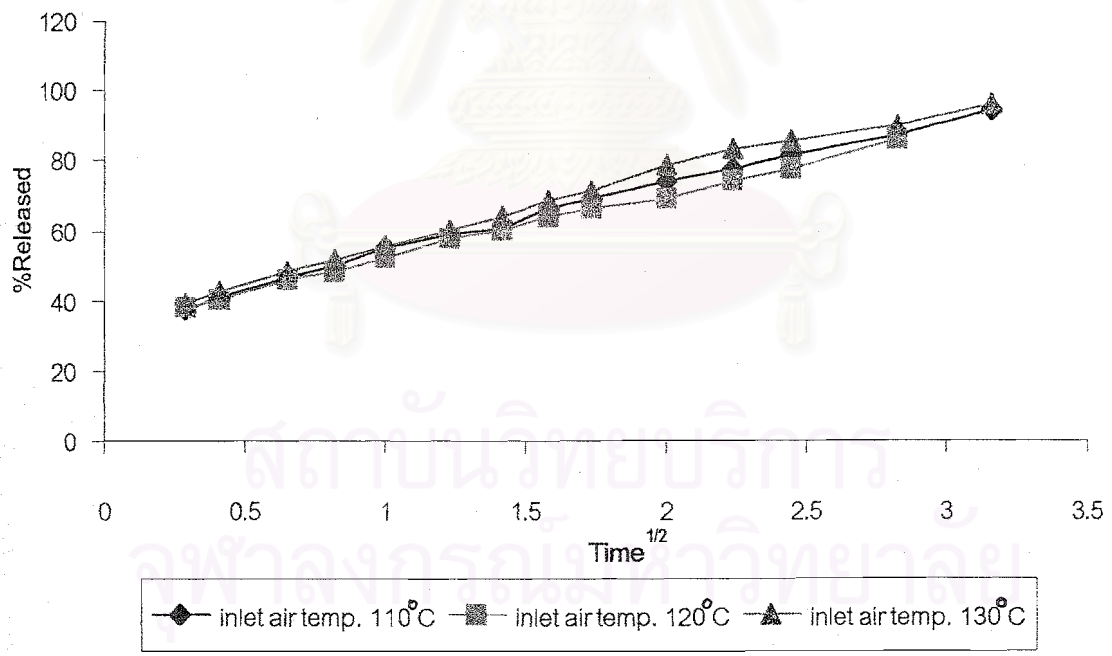


Figure 64. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated intestinal fluid without pancreatin pH 6.8.

Table 47. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Inlet air temperature		
		110°C	120°C	130°C
k_H ($hr^{-1/2}$)	1	22.9220	23.6770	21.9400
	2	23.6560	21.1890	25.8600
	3	23.3120	24.5190	25.3520
	Mean	23.2967	23.1283	24.3840
	S.D.	0.3672	1.7315	2.1318
R^2	1	0.9937	0.9835	0.9731
	2	0.9833	0.9715	0.9885
	3	0.9930	0.9914	0.9950
	Mean	0.9900	0.9821	0.9855
	S.D.	0.0058	0.0100	0.0112
T_{50}(hr)	1	0.4450	0.5089	0.3641
	2	0.5026	0.6135	0.3520
	3	0.5381	0.6365	0.4033
	Mean	0.4952	0.5863	0.3732
	S.D.	0.0470	0.0680	0.0268

Table 48. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various inlet air temperatures in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Inlet air temperature		
		110 °C	120 °C	130 °C
k_H ($hr^{-1/2}$)	1	19.8140	18.4480	20.0720
	2	19.3030	19.0730	20.9580
	3	19.4600	18.1620	20.3010
	Mean	19.5257	18.5610	20.4437
	S.D.	0.2618	0.4659	0.4599
R^2	1	0.9966	0.9928	0.9903
	2	0.9892	0.9914	0.9883
	3	0.9922	0.9962	0.9905
	Mean	0.9927	0.9935	0.9897
	S.D.	0.0037	0.0025	0.0012
T_{50}(hr)	1	0.7140	0.7945	0.5465
	2	0.6661	0.7482	0.5148
	3	0.6229	0.7901	0.5157
	Mean	0.6676	0.7776	0.5256
	S.D.	0.0456	0.0256	0.0181

4.3.Effect of feed rate

From the investigation of inlet air temperature, the 120°C of inlet air temperature was chosen for further studies. The microcapsules were prepared with various feed rates such as 18, 24, and 30 mL/min.

It was found that the microcapsules prepared by using 24 mL/min of feed rate had the highest percent yield whereas amoxycillin content and core entrapment had a similar value (Table 49).

The effects of feed rate on the surface morphologies of microcapsules are shown in Figure 65. The size of microcapsules is shown in Table 50, and the frequency distribution curves are displayed in Figure 66. The 30 mL/min of feed rate gave the largest microcapsules size but size distribution was not different. The microcapsule sizes were not affected by the feed rate. This result was not agreed with a report by Master (1979) that spray dried particles were larger as the feed rate was increased. From the scanning electron microphotographs in Figure 65, the microcapsules prepared with 18 mL/min of feed rate had smaller particles with aggregation due to more cohesive forces formed during spray-drying process.

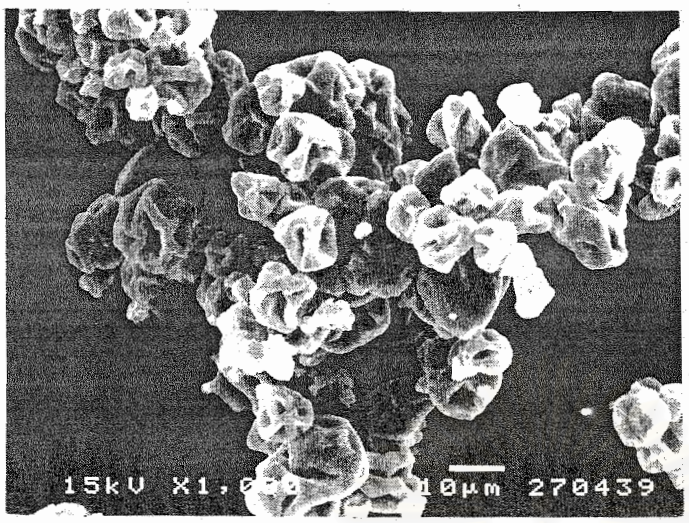
Table 49. The percent yield, content and entrapment of amoxycillin microcapsules prepared by spray-drying technique with various feed rates.

Feed rate	%Yield	% Content	% Entrapment
18 mL/min	58.95	25.34±0.16	76.03±2.02
24 mL/min	59.57	25.56±0.18	76.69±2.04
30 mL/min	58.34	25.58±0.11	76.77±1.96

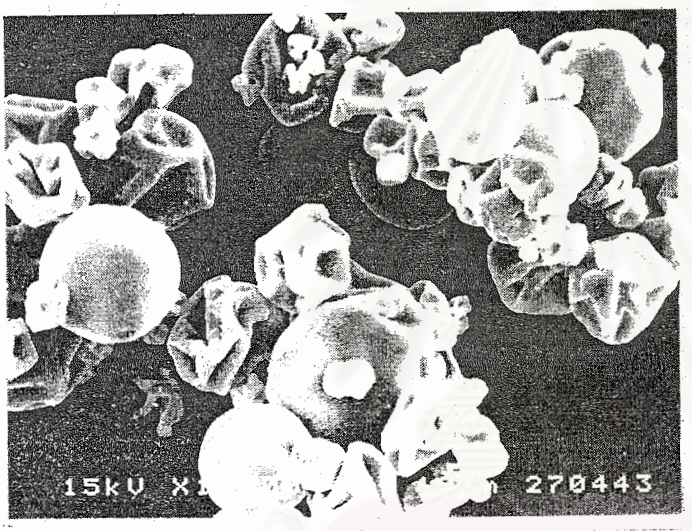
The effects of feed rates on the in vitro drug release are shown in Figures 67-70. It was observed that the initial drug release profile showed burst effect. The feed rate of 18 mL/min gave the fastest release profile in both media at pH 1.2 and 6.8. The microcapsules prepared by using 24 and 30 mL/min of feed rate showed similar release profile. The 18 mL/min of feed rate showed the agglomeration of small particles which resulted in larger particle sizes as shown in Table 50, therefore it disintegrated in the media which resulted in high surface area.

Among all of the model tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 169-170 (Appendix F). The time of 50% released of the microcapsules prepared with various feed rate were obtained from Higuchi equation. The time of 50% released of spray-dried microcapsules with 30 mL/min was the highest in both media, pH 1.2 and pH 6.8 ($p<0.05$).

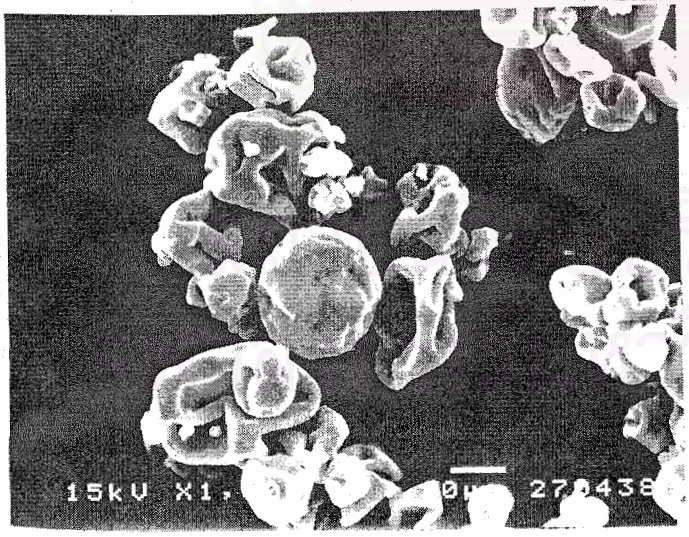
From the results obtained from the yield, amoxycillin content, core entrapment, size, size distribution and the release rate constant, the process using 24 mL/min of feed rate was chosen for further study since it gave the highest percent yield and the slower release profile.



A



B



C

Figure 65. Scanning electron micrographs of amoxycillin microcapsules prepared by spray-dried technique with various feed rates (mL/min) (A) 18 (B) 24 (C) 30. Magnification 1000x, 1000x and 1000x respectively.

Table 50. The particle sizes of amoxycillin microcapsules prepared by spray-drying technique with various feed rates.

	Particle size (μm)		
	18 mL/min	24 mL/min	30 mL/min
1	27.09	27.30	29.55
2	27.94	26.53	29.71
3	28.60	26.07	28.99
Mean	27.88	26.63	29.42
S.D.	0.76	0.62	0.38

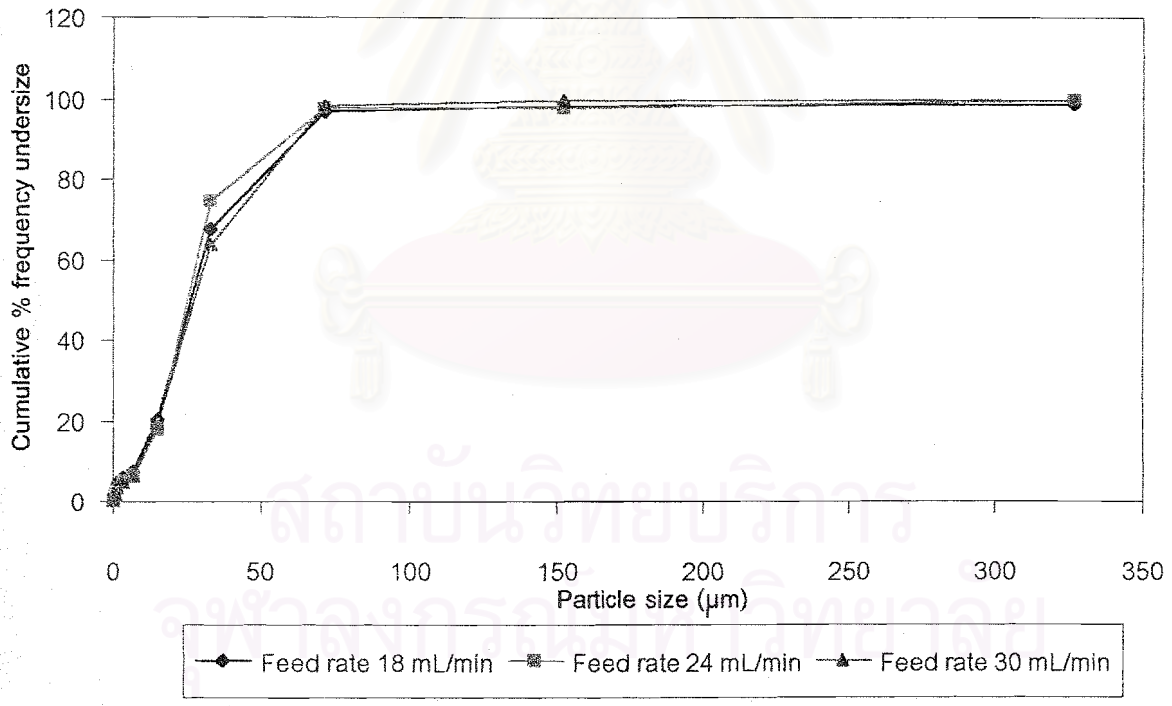


Figure 66. Cumulative % frequency undersize of amoxycillin microcapsules prepared by spray-drying technique with various feed rates.

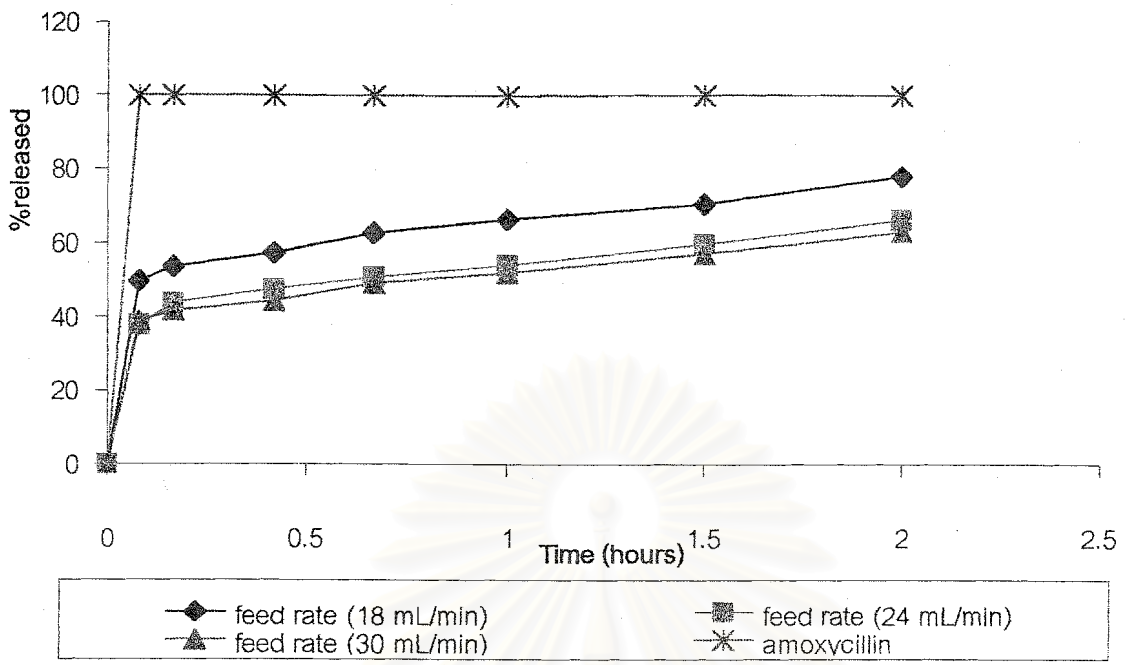


Figure 67. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated gastric fluid without pepsin pH 1.2.

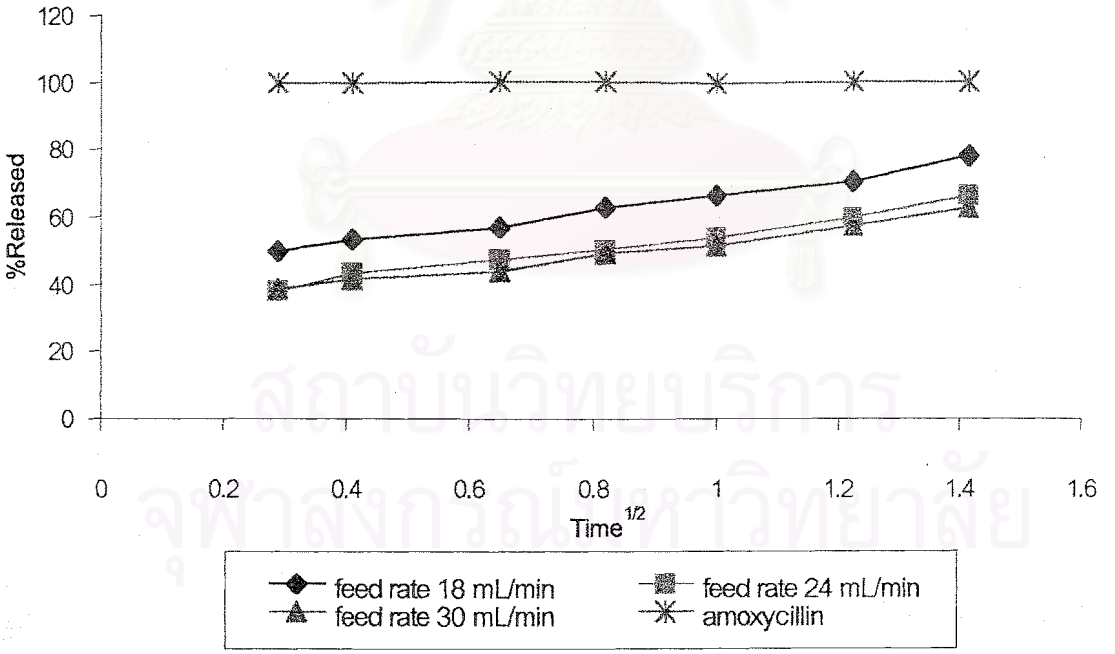


Figure 68. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated gastric fluid without pepsin pH 1.2.

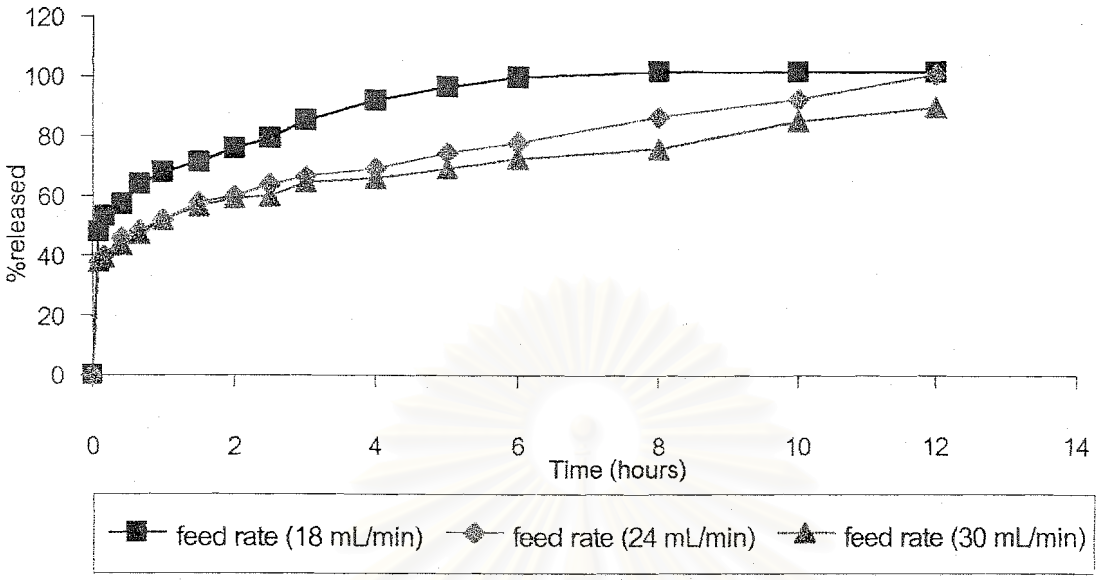


Figure 69. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated intestinal fluid without pancreatin pH 6.8.

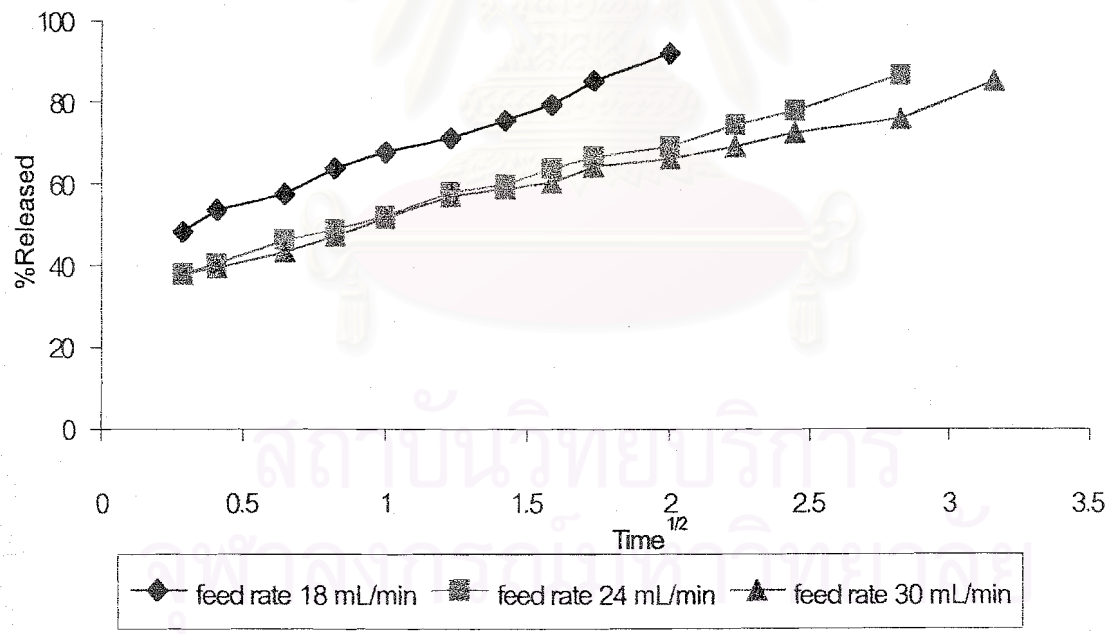


Figure 70. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated intestinal fluid without pancreatin pH 6.8.

Table 51. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Feed rates		
		18 mL/min	24 mL/min	30 mL/min
k_H ($hr^{-1/2}$)	1	23.3630	23.6770	20.8800
	2	25.1550	21.1890	20.3520
	3	24.3790	24.5190	21.5200
	Mean	24.2990	23.1283	20.9173
	S.D.	0.8987	1.7315	0.5849
R^2	1	0.9726	0.9835	0.9615
	2	0.9817	0.9715	0.9860
	3	0.9633	0.9914	0.9727
	Mean	0.9725	0.9821	0.9734
	S.D.	0.0092	0.0100	0.0123
T_{50}(hr)	1	0.0864	0.5089	0.7061
	2	0.0991	0.6135	0.7538
	3	0.0922	0.6365	0.7460
	Mean	0.0925	0.5863	0.7353
	S.D.	0.0063	0.0680	0.0256

Table 52. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various feed rates in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Feed rates		
		18 mL/min	24 mL/min	30 mL/min
k_H ($hr^{-1/2}$)	1	24.0660	18.4480	15.1740
	2	24.7360	19.0730	16.3300
	3	24.4520	18.1620	15.8200
	Mean	24.4180	18.5610	15.7747
	S.D.	0.3363	0.4659	0.5793
R^2	1	0.9916	0.9928	0.9883
	2	0.9938	0.9914	0.9812
	3	0.9902	0.9962	0.9859
	Mean	0.9919	0.9935	0.9851
	S.D.	0.0018	0.0025	0.0036
T_{50}(hr)	1	0.1237	0.7945	0.8471
	2	0.0757	0.7482	1.0045
	3	0.0989	0.7901	0.9279
	Mean	0.0994	0.7776	0.9265
	S.D.	0.0240	0.0256	0.0787

4.4. Effect of solid content

From the investigation of feed rate, the 24 mL/min of feed rate was chosen for further studies. The microcapsules were prepared with various solid contents including 5%, 7%, and 10%, respectively. It was found that the microcapsules prepared by using 5% of solid content gave the lowest percent yield, amoxycillin content and core entrapment. The 7% and 10% of solid content gave a similar high percent yield, amoxycillin content and core entrapment (Table 53).

Table 53. The percent yield, content and entrapment of amoxycillin microcapsules prepared by spray-drying technique with various solid contents.

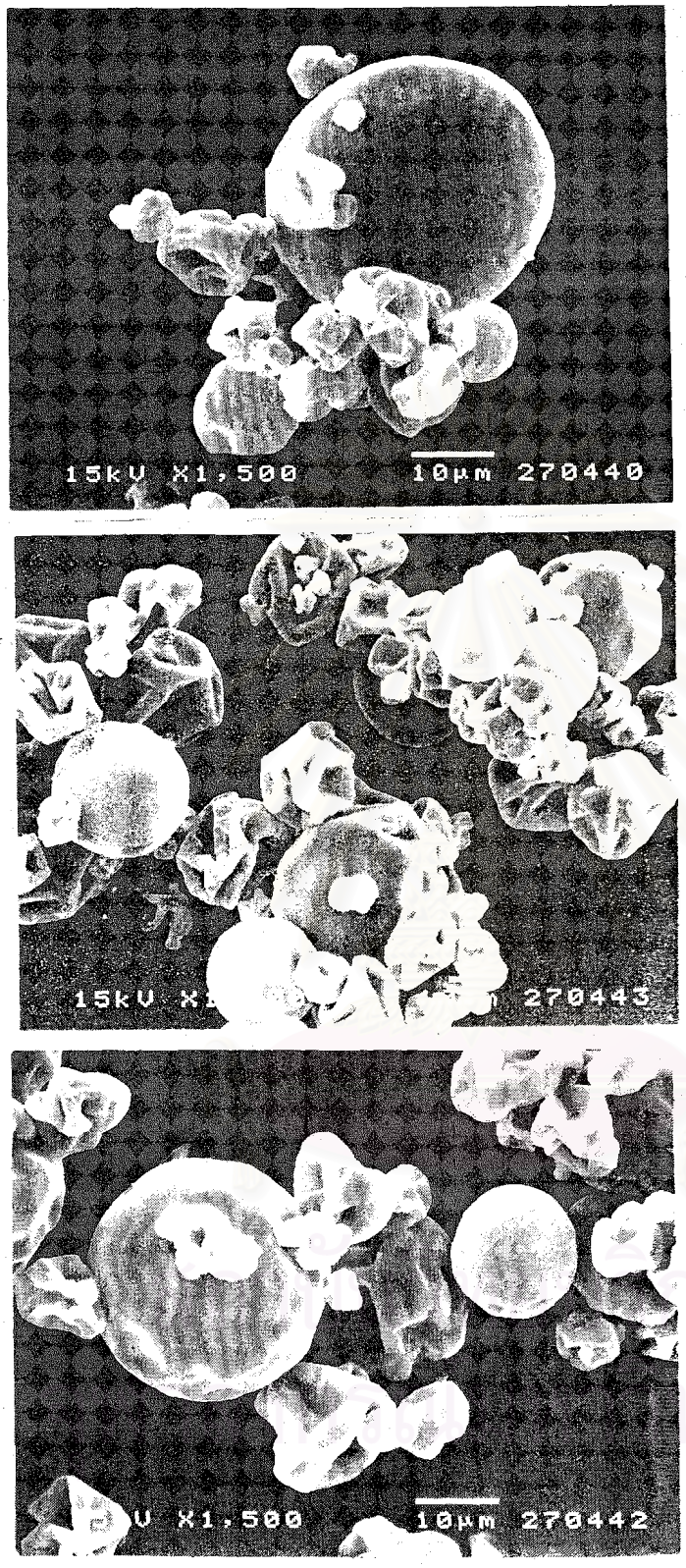
Solid content	%Yield	% Content	% Entrapment
5%	56.21	24.72±0.11	74.17±1.96
7%	59.57	25.56±0.18	76.69±2.04
10%	59.62	25.41±0.14	76.24±2.01

The effect of solid content on the surface morphologies of microcapsules is shown in Figure 71. The size of microcapsules is shown in Table 54, and the frequency distribution curves are shown in Figure 72. The microcapsules size was not affected by the solid content, because the solid content was varied in narrow range between 5 to 10%. While the different result was reported by Master (1979) and Vipaluk (2536) as they reported that the higher concentration of solution yielded larger spray dried particles, the concentration of solution was varied between 10-25% which was varied in wide range.

The effects of solid content on the in vitro drug release are shown in Figures 73-76. It was found that the microcapsules prepared with 5% of solid content which showed

mean size diameter of 29.05±0.49 μm gave the fastest release profile while the microcapsules prepared with 7% and 10% of solid content which showed mean diameter of 26.63±0.62 and 27.96±0.66 μm gave the slower release profile because of the aggregation of microcapsules as shown in Figure 71. The higher solid content that more aggregation was obtained.

Among all of the model tested, the Higuchi's model appeared to provide the best fits for all of the investigated formulations as determined in Tables 171-172 (Appendix F). The time of 50% released of the amoxycillin microcapsules prepared with various solid contents were obtained from the release profiles. The drug release rate constants of the spray-dried microcapsules having various solid contents were obtained from Higuchi equation. The time of 50% released of the spray-dried microcapsules prepared at 5% of solid content was the lowest significantly in both media of pH 1.2 and pH 6.8 ($p<0.05$). But in the medium pH 6.8, the time of 50% released of the spray-dried microcapsules prepared with 10% of solid content was the highest ($p<0.05$).



A

B

C

Figure 71. Scanning electron micrographs of amoxycillin microcapsules prepared by spray-dried technique with various solid contents (A) 5% (B) 7% (C) 10%. Magnification 1500x, 1000x and 1500x respectively.

Table 54. The particle size of amoxycillin microcapsules prepared by spray-drying technique with various solid contents.

No.	Particle size (μm)		
	5%	7%	10%
1	29.60	27.30	27.88
2	28.65	26.53	28.66
3	28.90	26.07	27.35
Mean	29.05	26.63	27.96
S.D.	0.49	0.62	0.66

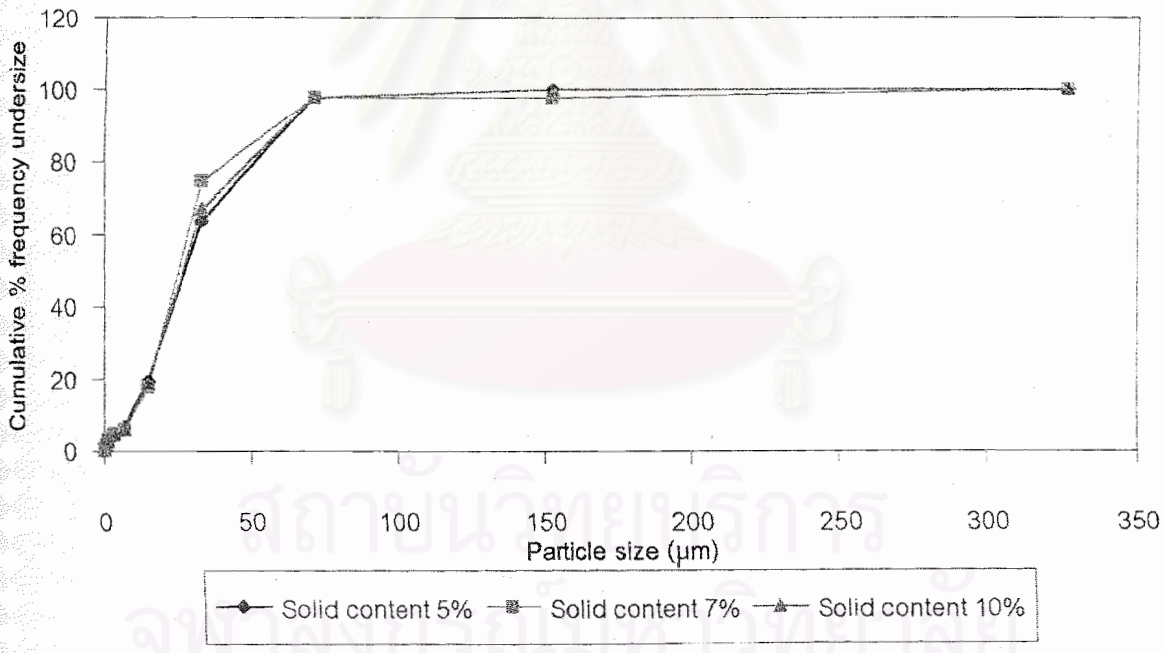


Figure 72. Cumulative % frequency undersize of amoxycillin microcapsules solid prepared by spray-drying technique with various solid contents.

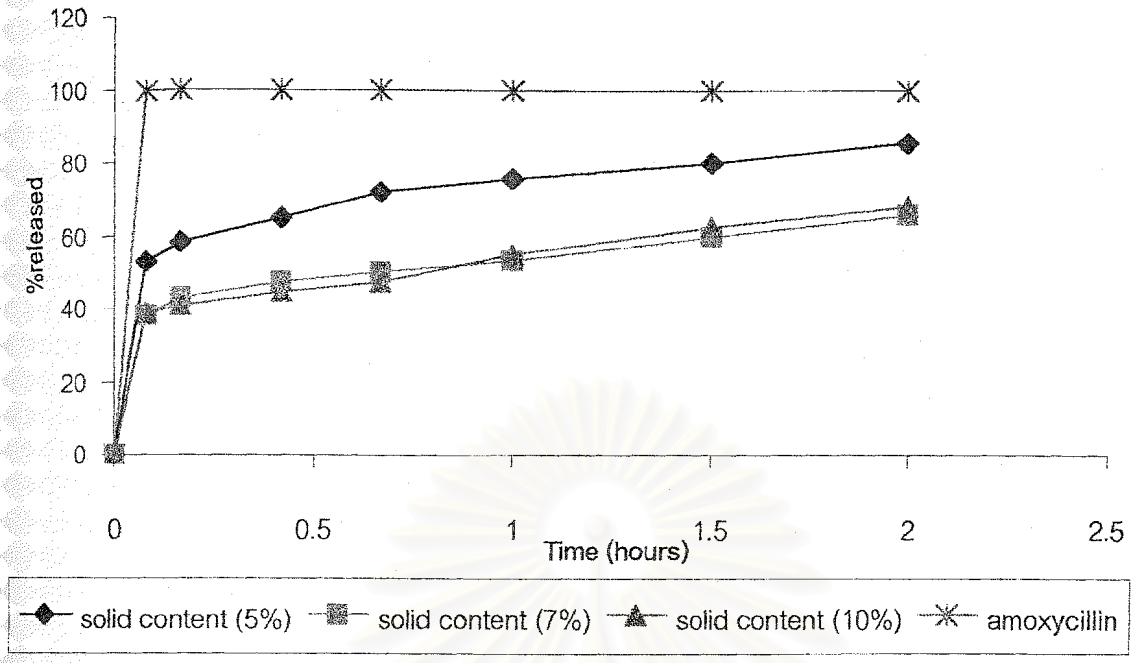


Figure 73. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated gastric fluid without pepsin pH 1.2.

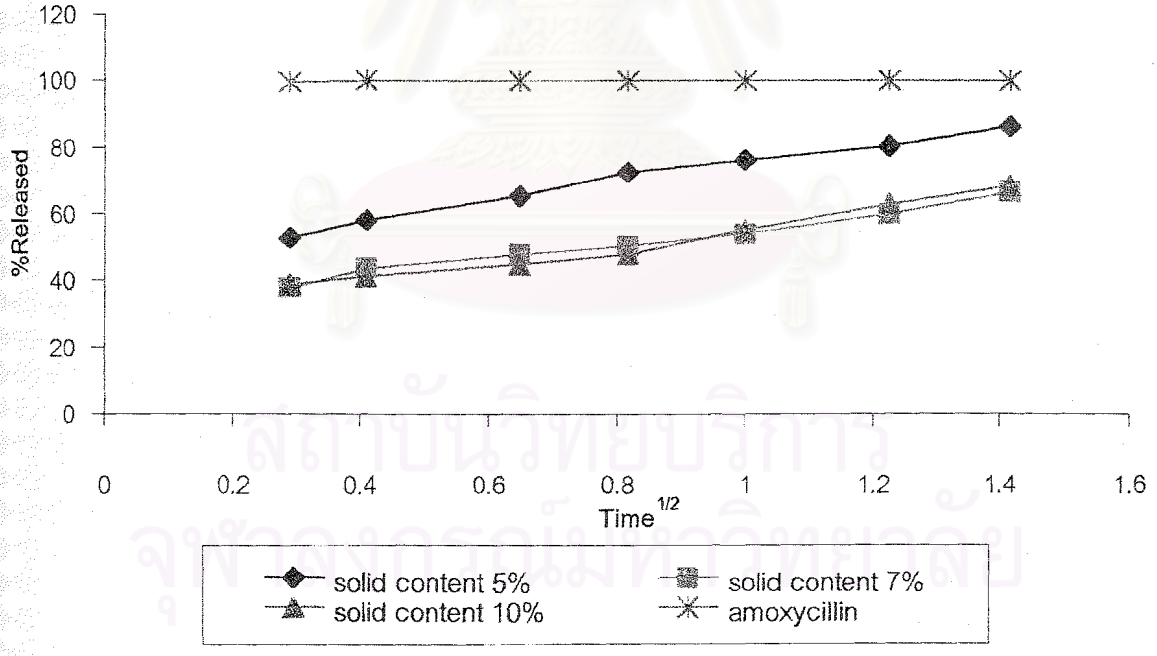


Figure 74. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated gastric fluid without pepsin pH 1.2.

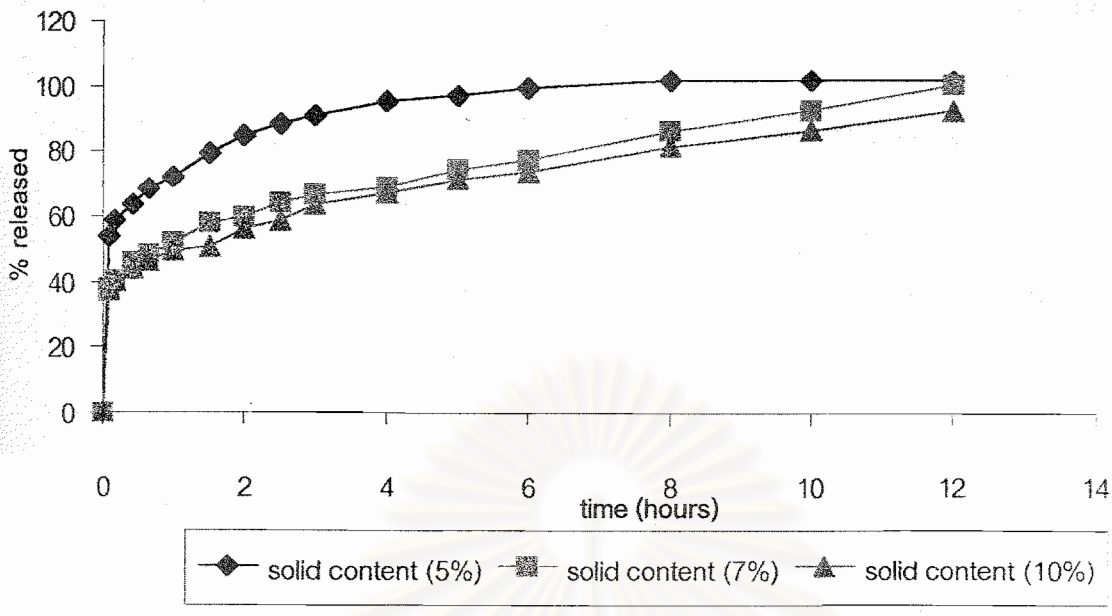


Figure 75. The release profiles of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated intestinal fluid without pancreatin pH 6.8.

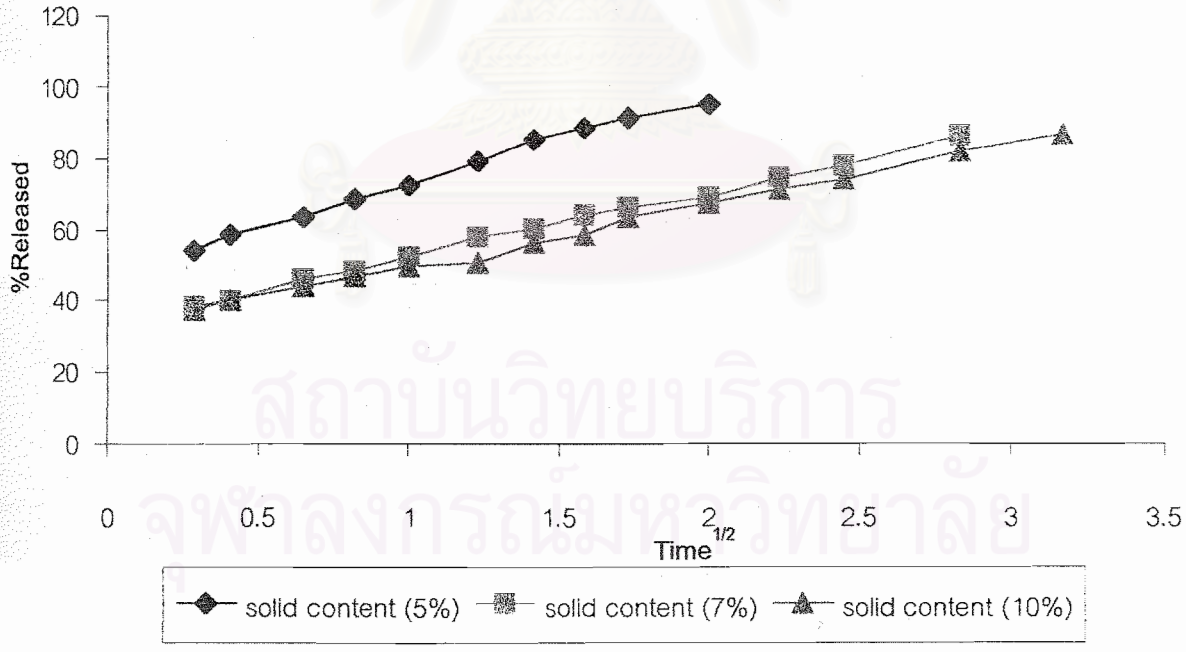


Figure 76. The release profiles of Higuchi's model of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated intestinal fluid without pancreatin pH 6.8.

Table 55. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated gastric fluid without pepsin pH 1.2.

Parameters	No.	Solid content		
		5%	7%	10%
k_H ($hr^{-1/2}$)	1	27.2644	23.6770	26.2820
	2	31.0270	21.1890	25.4660
	3	27.9320	24.5190	27.7320
	Mean	28.7411	23.1283	26.4933
	S.D.	2.0076	1.7315	1.1477
R^2	1	0.9789	0.9835	0.9679
	2	0.9802	0.9715	0.9816
	3	0.9901	0.9914	0.9612
	Mean	0.9831	0.9821	0.9702
	S.D.	0.0061	0.0100	0.0104
T_{50}(hr)	1	0.0047	0.5089	0.6955
	2	0.0301	0.6135	0.5650
	3	0.0144	0.6365	0.5634
	Mean	0.0164	0.5863	0.6080
	S.D.	0.0128	0.0680	0.0758

Table 56. The release rate constants of Higuchi model (k_H), the coefficient of determination (R^2) and the time of 50% released (T_{50}) of amoxycillin microcapsules prepared by spray-drying technique with various solid contents in simulated intestinal fluid without pancreatin pH 6.8.

Parameters	No.	Solid content		
		5%	7%	10%
k_H ($hr^{-1/2}$)	1	25.2440	18.4480	17.4030
	2	25.1690	19.0730	17.1910
	3	24.7380	18.1620	17.3460
	Mean	25.0503	18.5610	17.3133
	S.D.	0.2731	0.4659	0.1097
R^2	1	0.9895	0.9928	0.9937
	2	0.9906	0.9914	0.9950
	3	0.9911	0.9962	0.9931
	Mean	0.9904	0.9935	0.9939
	S.D.	0.0008	0.0025	0.0010
T_{50}(hr)	1	0.0038	0.7945	1.0185
	2	0.0176	0.7482	1.1582
	3	0.0027	0.7901	0.9664
	Mean	0.0080	0.7776	1.0477
	S.D.	0.0083	0.0256	0.0992

Formulation was selected by consideration of time of 50% released of amoxycillin microcapsules. The microcapsules prepared by complex coacervation technique with gelatin-acacia as wall (1:2 core to wall ratio, pH of medium 3.5, 2% of concentration of wall and 700 rpm of stirring rate) and gelatin-SCMC as wall (1:2 core to wall ratio, pH of medium 3.75, 1.5% of concentration of wall and 700 rpm of stirring rate) were compared with amoxycillin microcapsules prepared by spray-drying technique with polyvinyl acetate as wall(1:2 core to wall ratio, 120°C of inlet air temperature, 24 mL/min of feed rate and 10% of solid content). It was found that, in gastric fluid without pepsin pH 1.2, the time of 50% released of formulation of amoxycillin microcapsules prepared by gelatin-SCMC coacervation technique was the lowest ($p<0.05$). In medium pH 6.8, the time of 50% released of amoxycillin microcapsules prepared by spray-drying technique was the highest ($p<0.05$). Then, from the kinetic parameters, amoxycillin microcapsules prepared by spray-drying technique was selected to determine the micromeritic properties compared with amoxycillin powder as shown in Table 57.

Micromeritic properties of amoxycillin microcapsules prepared by spray-drying technique.

From the results of these investigation, the microcapsules prepared by spray-drying technique with 1:2 core to wall ratio, 10% of solid content, and the inlet air temperature at 120°C and 24 mL/min of feed rate were used to investigate micromeritic properties. The bulk density of microcapsules was reduced from 0.45 g/mL of pure powder to 0.16 g/mL and the angle of repose was also reduced (Table 57) resulted in more free-flowing property of amoxycyllin microcapsules than free-flowing properties of pure amoxycillin. The uniform distribution within a narrow particle size range and free-flowing properties will allow better control of weight and size of compress tablets or capsules.

Table 57. Micromeristic properties of pure amoxycillin and amoxycillin microcapsules.

Drug	Bulk density (g/mL)	Tap density (g/mL)	Angle of repose (degree)
Amoxycillin	0.45±0.03	0.63±0.04	19.27±2.05
Amoxycillin. MC	0.16±0.01	0.19±0.01	15.46±1.11

The time of 100% released of amoxycillin microcapsules was calculated from Higuchi's equation (Tables 58 and 59). In simulated gastric fluid without pepsin pH 1.2, the time of 100% release of amoxycillin microcapsules prepared by gelatin-acacia coacervation was higher than those of other microcapsules and in simulated intestinal fluid without pancreatin pH 6.8, the time of 100% release of amoxycillin microcapsules prepared by spray-drying technique with polyvinyl acetate as wall was higher than those of other microcapsules.

Table 58. Comparative time of 100% released of amoxycillin microcapsules in simulated gastric fluid without pepsin pH1.2 calculated from Higuchi's equation.

Polymer	Microencapsulation technique	Time of 100% released (hours)
Gelatin-acacia	Coacervation	8.3099±2.7554
Gelatin-SCMC	Coacervation	5.8131±0.5641
Polyvinyl acetate	Spray-drying	7.1268±0.5281

Table 59. Comparative time of 100% released of amoxycillin microcapsules in simulated intestinal fluid without pancreatin pH 6.8 calculated from Higuchi's equation.

Polymer	Microencapsulation technique	Time of 100% released (hours)
Gelatin-acacia	Coacervation	11.0004±0.0528
Gelatin-SCMC	Coacervation	8.9456±0.3299
Polyvinyl acetate	Spray-drying	15.2975±0.4175

CHAPTER V

CONCLUSIONS

The present study, the factors influencing microencapsulation of amoxycillin, i.e. the core to wall ratio, pH, concentration of wall and stirring rate on the complex coacervation of gelatin-acacia and gelatin-SCMC were studied, and the core to wall ratio, inlet air temperature, feed rate and solid content on the spray-drying technique were also investigated. The physicochemical properties of the microcapsules were evaluated including percent yield, drug content, core entrapment, size and the drug release properties. The results of the investigation are concluded as follows:

The optimum condition of preparation of amoxycillin microcapsules by complex coacervation of gelatin-acacia was selected from percent yield, drug content, entrapment and release rate profile. It was found that the core to wall ratio of 1:2 with 2% wall concentration, pH 3.5 and the stirring rate at 700 rpm were the suitable condition. The release of amoxycillin was 57.82% in 2 hours in simulated gastric fluid without pepsin pH 1.2 and 100% in 12 hours in simulated intestinal fluid without pancreatin pH 6.8.

The optimum condition of preparation of amoxycillin microcapsules by complex coacervation of gelatin-SCMC was selected from percent yield, drug content, entrapment and release rate profile. It was found that the core to wall ratio of 1:2 with 1.5% wall concentration, pH 3.75 and the stirring rate at 700 rpm were the suitable condition. The release of amoxycillin was 72.47% in 2 hours in simulated gastric fluid without pepsin at pH 1.2 and was 100% in 8 hours in simulated intestinal fluid without pancreatin pH 6.8.

The optimum condition of preparation of amoxycillin microcapsules by spray-drying technique with polyvinyl acetate as wall was selected from percent yield, drug content, entrapment and release rate profile. It was found that the core to wall ratio of 1:2 with 10% solid content, inlet air temperature 120°C and the feed rate at 24 mL/min were

the suitable condition. The release of amoxycillin was 68.22% in 2 hours in simulated gastric fluid without pepsin at pH 1.2 and was 93.09% in 12 hours in simulated intestinal fluid wihtout pancreatin pH 6.8.

The time of 50% released of amoxycillin microcapsules prepared by gelatin-acacia as wall had higher value than gelatin-SCMC as wall resulted in slow release of amoxycillin from gelatin-acacia walled microcapsules.

Amoxycillin microcapsules prepared by spray-drying technique with polyvinyl acetate as wall showed prolonged release in simulated gastric fluid without pepsin pH 1.2 calculated from Higuchi's equation which 100% of amoxycillin was released within 7.13 hours and in simulated intestinal fluid without pancreatin pH 6.8, 100% of amoxycillin was released within 15.30 hours.

The particle size of amoxycillin microcapsules prepared by spray-drying method was within narrow range. The mean sizes were between 25-30 μm. The bulk density was reduced to 0.16 g/mL and the angle of repose was reduced to $15.46 \pm 1.11^{\circ}$. This outcomes showed more free-flowing property of amoxycillin microcapsules than pure amoxycillin which resulted in more uniform distribution within a narrow particle size range.

The percent yield of microcapsules prepared by spray-drying method was low because the batch size of each preparation was 1.0 litre while the capacity of drying instrument was 1-6 kg water evaporation/hours. The increase in batch size might be result in the increase in the percent yield because the amount of microcapsules retained in the chamber is constant.

This research work gives the opportunity to select the method for preparation of amoxycillin microcapsules for sustained release in simulated gastric fluid without pepsin pH 1.2 and simulated intestinal fluid without pancreatin pH 6.8.

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APPENDIX A

Details of amoxycillin, and walls used

AMOXYCILLIN

(Albert, 1994; and Martindale, 1996)

Amoxycillin is a broad spectrum penicillin antibiotic. A co-formulation with potassium clavulanate, extended the antibacterial spectrum to include β–lactamase producing organisms. Amoxycillin is on the World Health Organisation's list of essential drugs. Amoxycillin is used as the trihydrate in oral products and as the sodium salt in parenteral products. Many other salts that are not used clinically.

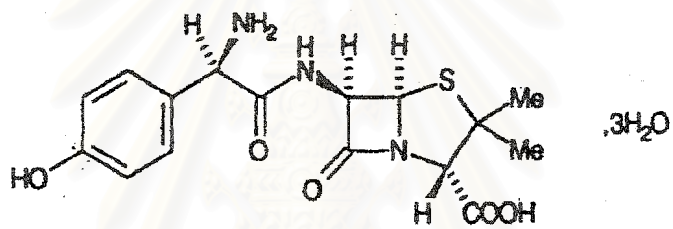

Figure 77. Chemical structure of amoxycillin trihydrate.

Formula: $C_{16}H_{19}N_3O_5S.3H_2O$

Molecular weight: 419.45

Appearance: Amoxycillin trihydrate is a white or almost white crystalline powder, have the slightly sulphurous odour that is typical of many penicillins.

Solubility: Amoxycillin trihydrate is soluble 1 in 400 of water, 1 in 1000 of ethanol, and 1 in 200 of methanol; practically insoluble in chloroform and in ether; dissolves in dilute solutions of acids and alkali hydroxides.

Stability in aqueous solution: At constant pH degradation followed first order or pseudo first order kinetics, with a minimum rate at about pH 6. Degradation was subjected to general acid base catalysis by citrate and phosphate buffers.

Stability in the solid state: The trihydrate showed first order kinetics at 37 and 50°C but at the higher temperatures its degradation rate was consistent with formation of a solid plus a gas.

Pharmacokinetics: Amoxycillin is active against a wide range of gram positive and gram negative pathogens, but is inacitivated by β-lactamase producing bacteria. However, it is active against such bacteira when co-administered with the β–lactamase inhibitor, potassium clavulanate. It is more rapidly and more completely absorbed than ampicillin when given by mouth and is reported to produce peak antibiotic plasma concentrations at least twice those from a similar dose of ampicillin. Plasma half-life is 1 to 1.5 hours.

Adverse effect: The incidence of diarrhoea is less with amoxycillin than ampicillin.

Administration and dosage: The usual oral dose is amoxycillin 250 to 500 mg every 8 hours. Children up to 10 years of age may be given 125 to 250 mg every 8 hours; under 20 kg body-weight a dose of 20 to 40 mg per kg daily has been suggested.

GELATIN

Appearance, color, odor, and taste: Gelatin is nearly tasteless and odorless. It is a vitreous, brittle solid, and is faintly yellow in color.

Amphoteric character: Gelatin, a typical protein, acts both as an acid and as a base. Thus, it is an amphoteric substance and can be titrated with acids and with alkalis.

Isoelectric point: In a strongly acidic solution, an ampholite such as gelatin is positively charged and migrates as a cation in an electric field. In a strongly alkaline solution, it is negatively charged and migrates as an anion. There is an intermediate point where the net charge is zero and no movement occurs. This point is known as the isoelectric point (IEP) and is designated in pH units.

Gelatin as a colloid: A very important, characteristic property of gelatin is its ability to form a gel or jelly in aqueous solution at temperatures below 35-40°C. At higher temperatures, the system exists as a sol. The gel-sol system is heat reversible, the melting temperature being slightly higher than the setting point.

Viscosity: In certain applications the viscosity of a solution of gelatin in water is as important as the ability of the solution to form a gel.

Table 60. General physical properties of gelatin.

Property	Type A	Type B
pH (1% solution at 25°C)	3.8-6.0	5.0-7.4
Isoelectric point		
USP method	9.0-9.2	4.8-5.0
BP method	8.9-9.2	4.8-5.2
Gel strength, Bloomgrams		
USP method	75-300	75-275
BP method	50-320	50-300
Viscosity, cP	2.0-7.5	2.0-7.5

Solubility: (a) In water-at 25°C, absorbs up to 10 times its volume of water but does not dissolve; at 37°C, up to 20% readily dissolves; at 100°C, slowly breaks down in solution, with changes in viscosity and other physical properties. Up to 50% can be dispersed. (b) in other solvents: ethanol-insoluble; isopropanol-insoluble; depending on molecular weight of gelatin; methanol-insoluble; acetone-insoluble; acids and alkalis-acetic acid will dissolve at least 5%. Strong acid and alkali tend to precipitate.

Applications of gelatin in pharmaceutical formulation:

Encapsulating agent; suspending agent; tablet binder and coating agent.

ACACIA

Appearance: Thin flakes, spheroidal tears, or in powdered or granular form; white or yellowish-white color; odorless, and bland taste.

Solubility: 1 g in 2.7 mL of water; alcohol insoluble; 1 g in 20 mL of glycerin; 1 g in 20 mL of propylene glycol.

pH (5% solution): 4.5-5 0

Specific gravity: 1.35-1.49

Viscosity of solutions: Variable depending upon the source of the material, processing, storage conditions, pH and the presence of salts. Prolonged heating of acacia solutions results in a decrease of viscosity due to depolymerization or particle agglomeration. The solutions exhibit Newtonian behavior.

Table 61. Applications of acacia in pharmaceutical formulation.

Use	Concentration (%)
Emulsifying agent	5.0-10.0
Suspending agent	5.0-10.0
Table binder	1.0-5.0

CARBOXYMETHYCELLULOSE SODIUM (SCMC)

Appearance: White to faintly yellow, odorless, hygroscopic powder or granular material having a faint paper-like taste.

Typical properties

Browning temperature: Approximately 227°C

Bulk density: 0.75 g/cm^3

Charring temperature: Approximately 252°C

Solubility: Soluble in water at all temperatures, giving a clear solution; practically insoluble in most organic solvents.

Viscosity: Aqueous solutions of SCMC exhibit pseudoplastic flow behavior. The material is supplied in various viscosity grades (H, M, or L), the viscosity being directly proportional to the degree of polymerization.

Table 62. Applications of SCMC in pharmaceutical formulations.

Use	Concentration (%)
Emulsifying agent	0.25-1.0
Gel-forming agent	4.0-6.0
Binding agent	1-6% in solution or as solid as required

POLYVINYL ACETATE (Kollicoat® SR30 D)

Kollicoat® SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate.

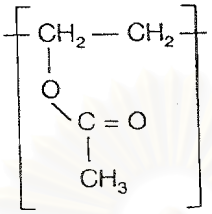

Figure 78. Chemical structure of polyvinyl acetate.

Commercial formulation: Kollicoat SR 30 D is an aqueous dispersion with a solids content of 30%. The low viscosity product has a weak characteristic odour and a milky white or slightly yellowish appearance.

Specifications and properties

Description: The dispersion consists of about 27% polyvinyl acetate, 2.5% povidone and 0.3% sodium lauryl sulfate.

Physical and chemical properties:

Identification	Conforms
Film formulation	Conforms
Solubility	Conforms
pH	3.5-5.5
Relative density	1.045-1.065
Viscosity	<100mPas
Coagulate content	<0.5%
Solids content	28.5-31.5%
Sulfated ash	<0.5%

Heavy metals	<20 ppm
Monomers	<100ppm
Microbiological status	Conforms

Solubility: Kollicoat® SR 30 D is miscible with water in any ratio while retaining its milky-white appearance. Mixing the product with ethanol or isopropyl alcohol in a 1:5 ratio produces a slightly turbid and somewhat viscous solution; a solution in acetone is more turbid. On addition of organic solvents the polymer precipitates out but then dissolves when further solvent is added.

APPENDIX B

Data of the analysis of amoxycillin by HPLC method

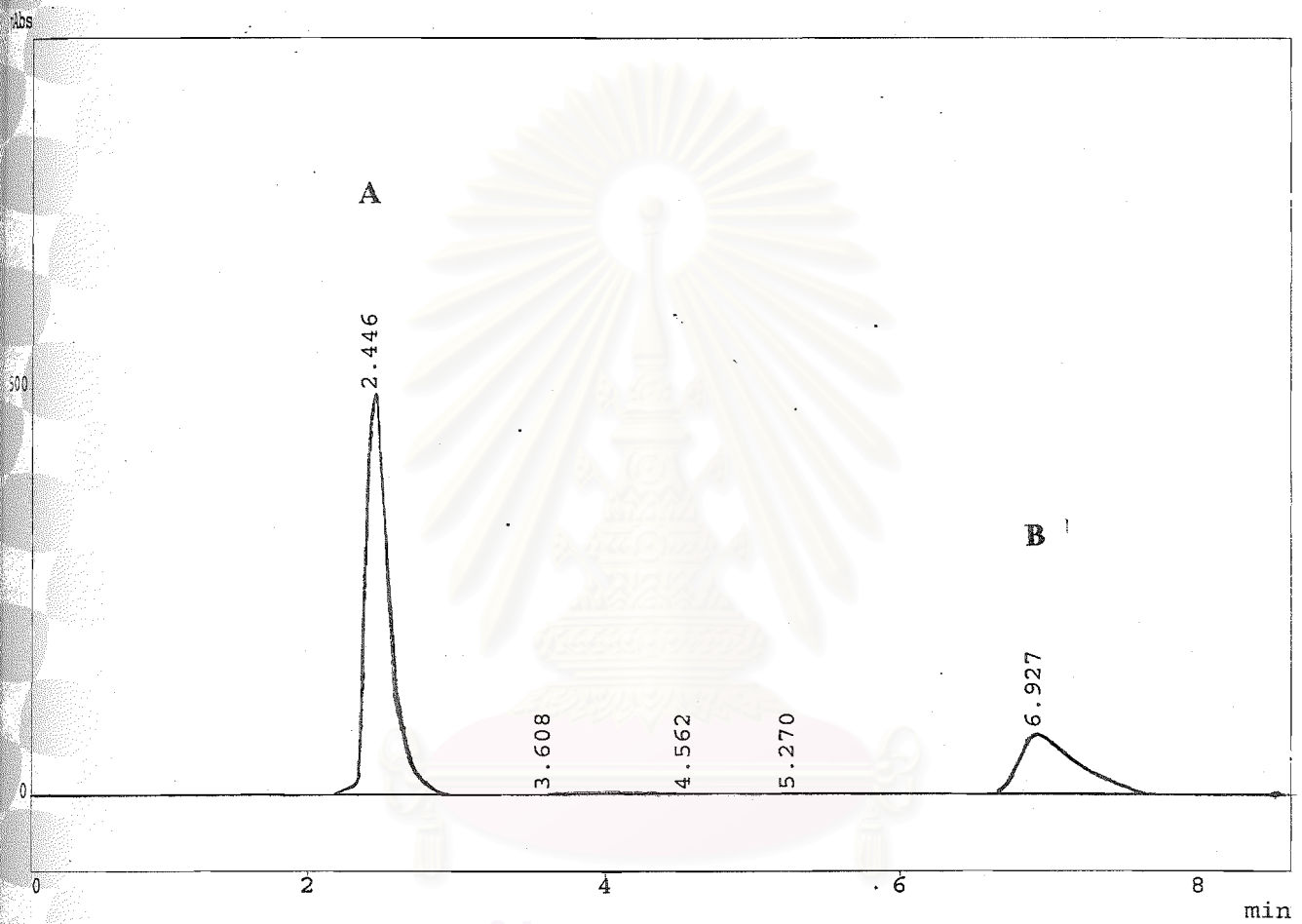

Figure 79. Chromatogram of amoxycillin (retention time = 2.4 min) (A) and cloxacillin (retention time = 6.9 min) (B) assayed by HPLC method.

Table 63. Calibration curve data of amoxycillin assayed by HPLC method.

Standard solution number	Concentration (μg/mL)	Peak area ratio (PAR)
1	100	0.702
2	200	1.356
3	300	1.981
4	400	2.670
5	500	3.339
6	600	3.966
7	700	4.608

Table 64. The percent analytical recoveries of the analysis of amoxycillin by HPLC method.

Concentration (μg/mL)	Peak are ratio (PAR)	Inversely estimated concentration (μg/mL)	%Recovery
100	0.699	100.385	100.38
200	1.343	199.477	99.74
300	1.965	295.262	98.42
400	2.678	404.923	101.23
500	3.319	503.569	100.71
600	3.917	595.538	99.26
700	4.597	700.062	100.01
		mean	99.96
		S.D.	0.94
		%C.V.	0.94

Table 65. The within-run precision of amoxycillin by HPLC method.

Concentration (μg/mL)	PAR			mean	S.D.	%C.V.
	Inj1	Inj2	Inj3			
100	0.702	0.685	0.711	0.699	0.013	1.862
200	1.356	1.302	1.328	1.329	0.027	2.017
300	1.981	1.911	1.853	1.915	0.064	3.337
400	2.670	2.599	2.628	2.632	0.036	1.368
500	3.339	3.310	3.356	3.335	0.023	0.691
600	3.966	3.885	3.931	3.927	0.040	1.029
700	4.608	4.589	4.626	4.608	0.019	0.405

Table 66. The between-run precision of amoxycillin by HPLC method.

Concentration (μg/mL)	PAR			Mean	S.D.	%C.V.
	day1	day2	day3			
100	0.702	0.680	0.698	0.693	0.011	1.652
200	1.356	1.336	1.370	1.354	0.017	1.258
300	1.981	1.970	1.972	1.974	0.006	0.293
400	2.670	2.644	2.695	2.670	0.026	0.957
500	3.339	3.319	3.345	3.334	0.014	0.412
600	3.966	3.959	3.927	3.950	0.021	0.529
700	4.608	4.545	4.614	4.589	0.038	0.834

APPENDIX C

Data of the analysis of amoxycillin by UV method

1. Accuracy.

Table 67. Accuracy of analytical method for determination of amoxycillin in simulated gastric fluid without pepsin pH 1.2 assayed by UV/visible spectrophotometer at λ = 229 nm.

Concentration (μg/mL)	Absorbance	Inversely estimated concentration (μg/mL)	%Recovery
10.03	0.218	9.90	98.75
15.05	0.335	15.20	100.99
20.06	0.438	19.86	99.00
25.08	0.556	25.20	100.47
30.09	0.669	30.31	100.74
40.12	0.882	39.95	99.58

Table 68. Accuracy of analytical method for determination of amoxycillin in simulated intestinal fluid without pancreatin pH 6.8 assayed by UV/visible spectrophotometer at λ = 229 nm.

Concentration (μg/mL)	Absorbance	Inversely estimated concentration (μg/mL)	%Recovery
10.03	0.218	9.90	98.75
15.05	0.334	15.15	100.69
20.06	0.444	20.13	100.36
25.08	0.552	25.02	99.75
30.09	0.660	29.90	99.39
40.12	0.890	40.31	100.48

2. Precision.

2.1. Within run precision.

Table 69. Within run precison of analytical method for determination of amoxycillin in simulated gastric fluid without pepsin pH 1.2 at λ = 229 nm.

Concentration	Absorbance			Mean	S.D.	%C.V.
(μg/mL)	1	2	3			
10.03	0.218	0.211	0.215	0.21	0.004	1.64
15.05	0.335	0.328	0.330	0.33	0.004	1.09
20.06	0.438	0.431	0.430	0.43	0.004	1.01
25.08	0.556	0.558	0.551	0.56	0.004	0.65
30.09	0.669	0.667	0.663	0.67	0.003	0.46
40.12	0.882	0.878	0.880	0.88	0.002	0.23

Table 70. Within run precison of analytical method for determination of amoxycillin in simulated intestinal fluid without pancreatin pH 6.8 at λ = 229 nm.

Concentration	Absorbance			Mean	S.D.	%C.V.
(μg/mL)	1	2	3			
10.03	0.218	0.223	0.221	0.22	0.003	1.14
15.05	0.334	0.331	0.337	0.33	0.003	0.90
20.06	0.444	0.450	0.447	0.45	0.003	0.67
25.08	0.552	0.559	0.562	0.56	0.005	0.92
30.09	0.66	0.670	0.665	0.67	0.005	0.75
40.12	0.89	0.888	0.884	0.89	0.003	0.34

2.2. Between run precison.

Table 71. Between run precision of analytical method for determination of amoxycillin in simulated gastric fluid without pepsin pH 1.2 at λ = 229 nm.

Concentration	Absorbance			Mean	S.D.	%C.V.
(μg/mL)	1	2	3			
10.03	0.218	0.221	0.214	0.22	0.004	1.61
15.05	0.335	0.337	0.340	0.34	0.003	0.75
20.06	0.438	0.435	0.430	0.43	0.004	0.93
25.08	0.556	0.552	0.558	0.56	0.003	0.55
30.09	0.669	0.670	0.672	0.67	0.002	0.23
40.12	0.882	0.886	0.889	0.89	0.004	0.40

Table 72. Between run precision of analytical method for determination of amoxycillin in simulated intestinal fluid without pancreatin pH 6.8 at λ=229 nm.

Concentration	Absorbance			Mean	S.D.	%C.V.
(μg/mL)	1	2	3			
10.03	0.218	0.214	0.210	0.21	0.004	1.87
15.05	0.334	0.331	0.339	0.33	0.004	1.21
20.06	0.444	0.438	0.450	0.44	0.006	1.35
25.08	0.552	0.556	0.551	0.55	0.003	0.48
30.09	0.66	0.664	0.669	0.66	0.005	0.68
40.12	0.89	0.887	0.898	0.89	0.006	0.64

Table 73. Calibration curve data of amoxycillin in simulated gastric fluid without pepsin pH 1.2 assayed by UV/visible spectrophotometer.

Standard solution no.	Concentraiton (μg/mL)	Absorbance at 229 nm
1	10.03	0.218
2	15.05	0.335
3	20.06	0.438
4	25.08	0.556
5	30.09	0.669
6	40.12	0.882

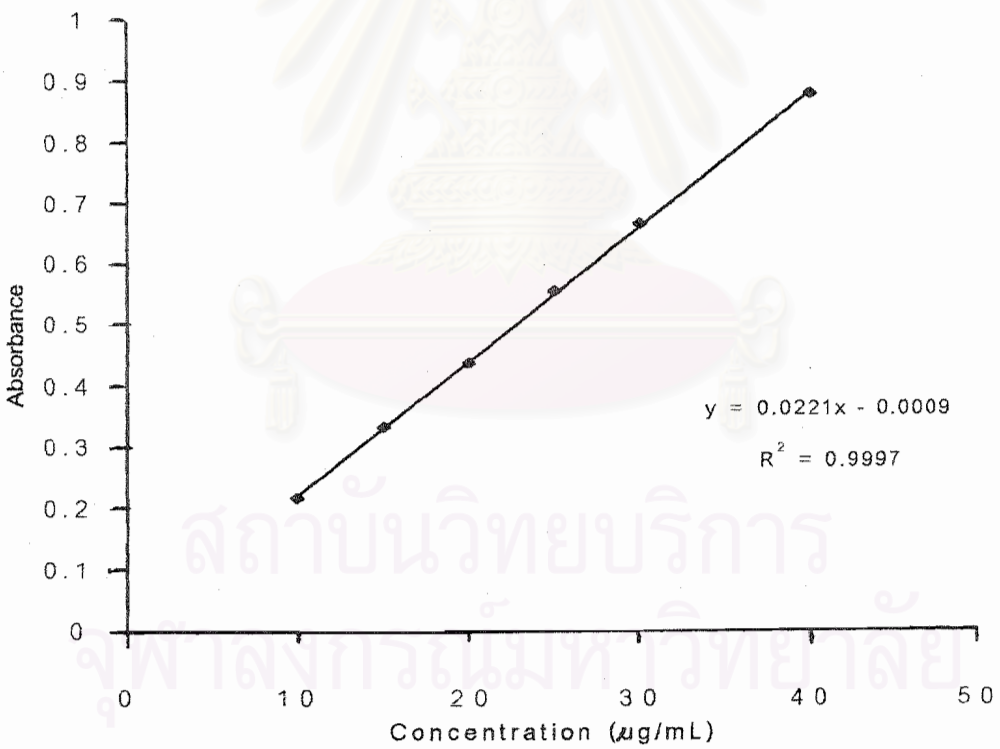

Figure 80. The calibration curve of amoxycillin standard in simulated gastric fluid without pepsin pH 1.2 assayed by UV/visible spectrophotometer.

Table 74. Calibration curve data of amoxycillin in simulated intestinal fluid without pancreatin pH 6.8 assayed by UV/visible spectrophotometer.

Standard solution no.	Concentraiton (μg/mL)	Absorbance at 229 nm
1	10.03	0.218
2	15.05	0.334
3	20.06	0.444
4	25.08	0.552
5	30.39	0.66
6	40.12	0.89

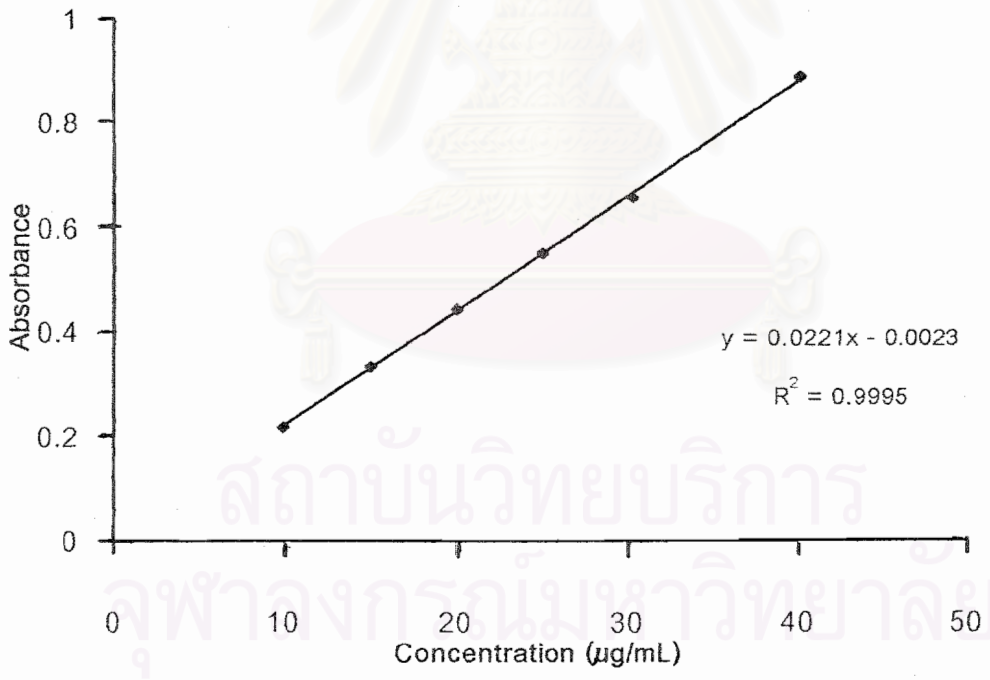

Figure 81. The calibration curve of amoxycillin standard in simulated intestinal fluid without pancreatin pH 6.8±0.1 assayed by UV/visible spectrophotometer.

APPENDIX D

Data of comparative percent yield, content, entrapment, and particle size of amoxycillin microcapsules

Table 75. Comparative percent yield of amoxycillin microcapsules.

Wall type	Core to wall ratio	Microencapsulation technique	%Yield
gelatin-acacia	1:1	Coacervation	88.25
gelatin-acacia	1:2	Coacervation	87.86
gelatin-acacia	1:3	Coacervation	87.59
gelatin-SCMC	1:1	Coacervation	82.27
gelatin-SCMC	1:2	Coacervation	83.61
gelatin-SCMC	1:3	Coacervation	-
Wall type	**pH**	**Microencapsulation technique**	**%Yield**
gelatin-acacia	3.5	Coacervation	87.86
gelatin-acacia	3.75	Coacervation	88.06
gelatin-acacia	4.0	Coacervation	87.71
gelatin-SCMC	3.5	Coacervation	83.61
gelatin-SCMC	3.75	Coacervation	84.72
gelatin-SCMC	4.0	Coacervation	84.11
Wall type	**Conc. of wall**	**Microencapsulation technique**	**%Yield**
gelatin-acacia	1%	Coacervation	87.37
gelatin-acacia	1.5%	Coacervation	87.86
gelatin-acacia	2%	Coacervation	88.14
gelatin-SCMC	1%	Coacervation	81.29
gelatin-SCMC	1.5%	Coacervation	84.72
gelatin-SCMC	2%	Coacervation	82.35

Table 75. Comparative percent yield of amoxycillin microcapsules. (continued)

Wall type	**Stirring rate**	**Microencapsulation technique**	**%Yield**
gelatin-acacia	500	Coacervation	86.75
gelatin-acacia	700	Coacervation	88.14
gelatin-acacia	900	Coacervation	88.98
gelatin-SCMC	500	Coacervation	83.44
gelatin-SCMC	700	Coacervation	84.72
gelatin-SCMC	900	Coacervation	84.53
Wall type	**Core to wall ratio**	**Microencapsulation technique**	**%Yield**
Polyvinyl acetate	1:1	Spray-drying	57.15
Polyvinyl acetate	1:2	Spray-drying	59.57
Polyvinyl acetate	1:3	Spray-drying	55.23
Wall type	**Inlet air temperature**	**Microencapsulation technique**	**%Yield**
Polyvinyl acetate	110°C	Spray-drying	43.42
Polyvinyl acetate	120°C	Spray-drying	59.57
Polyvinyl acetate	130°C	Spray-drying	50.68
Wall type	**Feed rate**	**Microencapsulation technique**	**%Yield**
Polyvinyl acetate	18 mL/min	Spray-drying	58.95
Polyvinyl acetate	24 mL/min	Spray-drying	59.57
Polyvinyl acetate	30 mL/min	Spray-drying	58.34
Wall type	**Solid content**	**Microencapsulation technique**	**%Yield**
Polyvinyl acetate	5%	Spray-drying	56.21
Polyvinyl acetate	7%	Spray-drying	59.57
Polyvinyl acetate	10%	Spray-drying	59.62

Table 76. Comparative percent content of amoxycillin microcapsules.

Wall type	Core to wall ratio	Microencapsulation technique	%Content
gelatin-acacia	1:1	Coacervation	38.53±0.98
gelatin-acacia	1:2	Coacervation	29.72±1.78
gelatin-acacia	1:3	Coacervation	22.52±0.02
gelatin-SCMC	1:1	Coacervation	39.63±0.25
gelatin-SCMC	1:2	Coacervation	28.55±1.12
gelatin-SCMC	1:3	Coacervation	-
Wall type	**pH**	**Microencapsulation technique**	**%Content**
gelatin-acacia	3.5	Coacervation	29.72±1.78
gelatin-acacia	3.75	Coacervation	29.57±0.84
gelatin-acacia	4.0	Coacervation	28.91±0.17
gelatin-SCMC	3.5	Coacervation	28.55±1.12
gelatin-SCMC	3.75	Coacervation	29.26±0.36
gelatin-SCMC	4.0	Coacervation	28.91±0.19
Wall type	**Conc. of wall**	**Microencapsulation technique**	**%Content**
gelatin-acacia	1%	Coacervation	29.69±2.01
gelatin-acacia	1.5%	Coacervation	29.72±1.78
gelatin-acacia	2%	Coacervation	29.85±0.12
gelatin-SCMC	1%	Coacervation	29.17±0.88
gelatin-SCMC	1.5%	Coacervation	29.526±0.36
gelatin-SCMC	2%	Coacervation	28.84±0.04

Table 76. Comparative percent content of amoxycillin microcapsules. (continued)

Wall type	Stirring rate	Microencapsulation technique	%Content
gelatin-acacia	500	Coacervation	29.57±0.19
gelatin-acacia	700	Coacervation	29.85±0.12
gelatin-acacia	900	Coacervation	29.78±0.27
gelatin-SCMC	500	Coacervation	28.77±0.08
gelatin-SCMC	700	Coacervation	29.26±0.36
gelatin-SCMC	900	Coacervation	29.09±0.16
Wall type	**Core to wall ratio**	**Microencapsulation technique**	**%Content**
Polyvinyl acetate	1:1	Spray-drying	35.42±0.12
Polyvinyl acetate	1:2	Spray-drying	25.56±0.18
Polyvinyl acetate	1:3	Spray-drying	18.06±0.11
Wall type	**Inlet air temperature**	**Microencapsulation technique**	**%Content**
Polyvinyl acetate	110°C	Spray-drying	23.28±0.11
Polyvinyl acetate	120°C	Spray-drying	25.56±0.18
Polyvinyl acetate	130°C	Spray-drying	24.69±0.21
Wall type	**Feed rate**	**Microencapsulation technique**	**%Content**
Polyvinyl acetate	18 mL/min	Spray-drying	25.34±0.16
Polyvinyl acetate	24 mL/min	Spray-drying	25.56±0.18
Polyvinyl acetate	30 mL/min	Spray-drying	25.58±0.11
Wall type	**Solid content**	**Microencapsulation technique**	**%Content**
Polyvinyl acetate	5%	Spray-drying	24.72±0.11
Polyvinyl acetate	7%	Spray-drying	25.56±0.18
Polyvinyl acetate	10%	Spray-drying	25.41±0.14

Table 77. Comparative percent entrapment of amoxycillin microcapsules.

Wall type	Core to wall ratio	Microencapsulation technique	%Entrapment
gelatin-acacia	1:1	Coacervation	77.06±3.46
gelatin-acacia	1:2	Coacervation	89.17±5.48
gelatin-acacia	1:3	Coacervation	90.08±1.37
gelatin-SCMC	1:1	Coacervation	79.26±2.54
gelatin-SCMC	1:2	Coacervation	85.66±4.96
gelatin-SCMC	1:3	Coacervation	-
Wall type	**pH**	**Microencapsulation technique**	**%Entrapment**
gelatin-acacia	3.5	Coacervation	89.17±5.48
gelatin-acacia	3.75	Coacervation	88.72±3.06
gelatin-acacia	4.0	Coacervation	86.74±2.02
gelatin-SCMC	3.5	Coacervation	85.66±4.72
gelatin-SCMC	3.75	Coacervation	87.79±2.16
gelatin-SCMC	4.0	Coacervation	86.74±2.06
Wall type	**Conc. of wall**	**Microencapsulation technique**	**%Entrapment**
gelatin-acacia	1%	Coacervation	89.08±5.95
gelatin-acacia	1.5%	Coacervation	89.17±5.48
gelatin-acacia	2%	Coacervation	89.56±2.01
gelatin-SCMC	1%	Coacervation	87.52±3.11
gelatin-SCMC	1.5%	Coacervation	87.79±2.16
gelatin-SCMC	2%	Coacervation	86.53±1.76

Table 77. Comparative percent entrapment of amoxycillin microcapsule.(continued)

Wall type	**Stirring rate**	**Microencapsulation technique**	**%Entrapment**
gelatin-acacia	500	Coacervation	88.72±2.06
gelatin-acacia	700	Coacervation	89.56±2.01
gelatin-acacia	900	Coacervation	89.35±2.14
gelatin-SCMC	500	Coacervation	86.32±1.84
gelatin-SCMC	700	Coacervation	87.79±2.16
gelatin-SCMC	900	Coacervation	87.28±2.02
Wall type	**Core to wall ratio**	**Microencapsulation technique**	**%Entrapment**
Polyvinyl acetate	1:1	Spray-drying	70.84±1.98
Polyvinyl acetate	1:2	Spray-drying	76.69±2.04
Polyvinyl acetate	1:3	Spray-drying	72.24±1.96
Wall type	**Inlet air temperature**	**Microencapsulation technique**	**%Entrapment**
Polyvinyl acetate	110°C	Spray-drying	69.85±1.96
Polyvinyl acetate	120°C	Spray-drying	76.69±2.04
Polyvinyl acetate	130°C	Spray-drying	74.08±2.87
Wall type	**Feed rate**	**Microencapsulation technique**	**%Entrapment**
Polyvinyl acetate	18 mL/min	Spray-drying	76.03±2.02
Polyvinyl acetate	24 mL/min	Spray-drying	76.69±2.04
Polyvinyl acetate	30 mL/min	Spray-drying	76.77±1.96
Wall type	**Solid content**	**Microencapsulation technique**	**%Entrapment**
Polyvinyl acetate	5%	Spray-drying	74.17±1.96
Polyvinyl acetate	7%	Spray-drying	76.69±2.04
Polyvinyl acetate	10%	Spray-drying	76.24±2.01

Table 78. Comparative particle sizes of amoxycillin microcapsules. (continued)

Wall type	**Stirring rate**	**Microencapsulation technique**	**Particle size**
gelatin-acacia	500	Coacervation	109.90±2.21
gelatin-acacia	700	Coacervation	61.02±1.09
gelatin-acacia	900	Coacervation	28.40±0.35
gelatin-SCMC	500	Coacervation	584.66±28.59
gelatin-SCMC	700	Coacervation	551.85±16.21
gelatin-SCMC	900	Coacervation	470.52±29.82
Wall type	**Core to wall ratio**	**Microencapsulation technique**	**Particle size**
Polyvinyl acetate	1:1	Spray-drying	26.15±0.45
Polyvinyl acetate	1:2	Spray-drying	26.63±0.62
Polyvinyl acetate	1:3	Spray-drying	28.06±0.75
Wall type	**Inlet air temperature**	**Microencapsulation technique**	**Particle size**
Polyvinyl acetate	110°C	Spray-drying	26.77±0.55
Polyvinyl acetate	120°C	Spray-drying	26.63±0.62
Polyvinyl acetate	130°C	Spray-drying	25.66±0.39
Wall type	**Feed rate**	**Microencapsulation technique**	**Particle size**
Polyvinyl acetate	18 mL/min	Spray-drying	27.88±0.76
Polyvinyl acetate	24 mL/min	Spray-drying	26.63±0.62
Polyvinyl acetate	30 mL/min	Spray-drying	29.42±0.38
Wall type	**Solid content**	**Microencapsulation technique**	**Particle size**
Polyvinyl acetate	5%	Spray-drying	29.05±0.49
Polyvinyl acetate	7%	Spray-drying	26.63±0.62
Polyvinyl acetate	10%	Spray-drying	27.96±0.66

APPENDIX E

Data of amoxycillin released from microcapsules

Table 79. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:1 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	77.67	78.57	76.23	77.49	1.18
0.17	83.41	81.43	81.97	82.27	1.02
0.42	86.82	85.92	83.95	85.56	1.47
0.67	90.76	88.07	86.46	88.43	2.17
1.00	94.89	92.91	90.94	92.91	1.97
1.50	96.32	95.61	94.89	95.61	0.72
2.00	100.09	100.27	99.19	99.85	0.58

Table 80. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:2 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	39.10	38.21	39.10	0.90
0.17	43.59	45.20	42.87	43.89	1.19
0.42	46.82	47.53	45.20	46.52	1.19
0.67	49.33	50.22	48.07	49.21	1.08
1.00	52.56	56.50	53.09	54.05	2.14
1.50	62.06	60.99	58.30	60.45	1.94
2.00	66.19	64.93	63.50	64.87	1.35

Table 81. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:3 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.90	40.00	39.28	40.06	0.81
0.17	45.02	42.69	41.79	43.17	1.67
0.42	46.28	43.77	45.20	45.08	1.26
0.67	49.51	50.22	47.53	49.09	1.39
1.00	55.43	53.45	52.02	53.63	1.71
1.50	60.45	59.37	54.17	58.00	3.36
2.00	65.11	62.42	60.45	62.66	2.34

Table 82. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 3.5 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	39.10	38.21	39.10	0.90
0.17	43.59	45.20	42.87	43.89	1.19
0.42	46.82	47.53	45.20	46.52	1.19
0.67	49.33	50.22	48.07	49.21	1.08
1.00	52.56	56.50	53.09	54.05	2.14
1.50	62.06	60.99	58.30	60.45	1.94
2.00	66.19	64.93	63.50	64.87	1.35

Table 83. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 3.75 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	45.02	46.64	42.69	44.78	1.98
0.17	48.07	48.25	49.15	48.49	0.58
0.42	52.56	55.07	54.17	53.93	1.27
0.67	57.22	58.48	56.32	57.34	1.08
1.00	63.32	64.57	66.01	64.63	1.35
1.50	66.73	67.26	68.16	67.38	0.72
2.00	72.47	74.26	77.49	74.74	2.55

Table 84. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 4.0 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	41.79	40.18	41.08	41.02	0.81
0.17	45.20	42.69	41.79	43.23	1.77
0.42	50.04	47.17	46.28	47.83	1.97
0.67	54.17	52.91	51.48	52.86	1.35
1.00	57.94	57.40	54.71	56.68	1.73
1.50	65.11	64.22	62.96	64.10	1.08
2.00	68.34	69.24	66.91	68.16	1.18

Table 85. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 1% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	63.14	60.99	63.32	62.48	1.30
0.17	69.60	67.09	70.49	69.06	1.77
0.42	74.80	74.08	75.87	74.92	0.90
0.67	79.82	80.54	80.90	80.42	0.55
1.00	85.20	83.95	84.66	84.60	0.63
1.50	91.84	88.97	89.87	90.22	1.47
2.00	96.14	94.89	96.50	95.84	0.85

Table 86. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 1.5% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	39.10	38.21	39.10	0.90
0.17	43.59	45.20	42.87	43.89	1.19
0.42	46.82	47.53	45.20	46.52	1.19
0.67	49.33	50.22	48.07	49.21	1.08
1.00	52.56	56.50	53.09	54.05	2.14
1.50	62.06	60.99	58.30	60.45	1.94
2.00	66.19	64.93	63.50	64.87	1.35

Table 87. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 2% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.92	39.82	41.08	39.94	1.08
0.17	43.59	45.92	44.66	44.72	1.17
0.42	46.28	47.35	48.07	47.23	0.90
0.67	49.51	50.58	51.48	50.52	0.99
1.00	50.76	52.20	54.17	52.38	1.71
1.50	54.53	56.50	57.94	56.32	1.71
2.00	55.78	57.76	59.91	57.82	2.06

Table 88. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 500 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.21	39.82	40.54	39.52	1.19
0.17	41.43	42.51	43.41	42.45	0.99
0.42	44.48	45.02	45.92	45.14	0.72
0.67	48.97	48.79	49.87	49.21	0.58
1.00	52.20	53.09	55.07	53.45	1.47
1.50	57.40	58.83	56.14	57.46	1.35
2.00	59.91	60.09	62.24	60.75	1.30

Table 89. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 700 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.92	39.82	41.08	39.94	1.08
0.17	43.59	45.92	44.66	44.72	1.17
0.42	46.28	47.35	48.07	47.23	0.90
0.67	49.51	50.58	51.48	50.52	0.99
1.00	50.76	52.20	54.17	52.38	1.71
1.50	54.53	56.50	57.94	56.32	1.71
2.00	55.78	57.76	59.91	57.82	2.06

Table 90. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 900 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	63.32	64.75	61.88	63.32	1.43
0.17	69.78	70.49	68.70	69.66	0.90
0.42	74.08	76.41	73.18	74.56	1.67
0.67	82.51	84.13	79.82	82.15	2.17
1.00	89.15	90.94	88.43	89.51	1.29
1.50	95.25	96.50	93.81	95.19	1.35
2.00	99.19	99.55	98.12	98.95	0.75

Table 91. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with core to wall ratio 1:1 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	56.14	59.37	59.73	58.42	1.98
0.17	62.96	64.22	66.37	64.51	1.72
0.42	70.49	71.39	72.65	71.51	1.08
0.67	78.74	79.46	80.90	79.70	1.10
1.00	84.30	85.02	86.82	85.38	1.29
1.50	88.97	91.12	92.02	90.70	1.57
2.00	93.63	94.17	95.96	94.59	1.22

Table 92. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with core to wall ratio 1:2 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	50.76	49.87	51.12	50.58	0.65
0.17	57.04	57.94	58.65	57.88	0.81
0.42	61.88	63.50	64.75	63.38	1.44
0.67	68.70	69.78	66.91	68.46	1.45
1.00	73.36	74.08	71.75	73.06	1.19
1.50	78.57	79.28	76.77	78.21	1.29
2.00	82.51	84.13	80.72	82.45	1.70

Table 93. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 3.5 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	50.76	49.87	51.12	50.58	0.65
0.17	57.04	57.94	58.65	57.88	0.81
0.42	61.88	63.50	64.75	63.38	1.44
0.67	68.70	69.78	66.91	68.46	1.45
1.00	73.36	74.08	71.75	73.06	1.19
1.50	78.57	79.28	76.77	78.21	1.29
2.00	82.51	84.13	80.72	82.45	1.70

Table 94. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 3.75 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	41.61	40.90	40.84	0.81
0.17	45.74	46.28	48.25	46.76	1.32
0.42	49.87	51.48	49.51	50.28	1.05
0.67	53.81	56.32	54.71	54.95	1.27
1.00	60.81	62.96	64.57	62.78	1.89
1.50	65.29	67.44	69.42	67.38	2.06
2.00	70.49	73.18	73.72	72.47	1.73

Table 95. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 4.0 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	47.17	46.28	45.38	46.28	0.90
0.17	52.91	51.30	53.99	52.74	1.35
0.42	59.37	60.63	62.24	60.75	1.44
0.67	66.01	69.42	67.09	67.50	1.74
1.00	72.11	73.90	75.16	73.72	1.53
1.50	76.41	77.67	78.39	77.49	1.00
2.00	81.43	80.90	82.87	81.73	1.02

Table 96. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 1% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	65.11	66.73	67.80	66.55	1.35
0.17	71.39	72.83	73.54	72.59	1.10
0.42	79.64	80.36	80.90	80.30	0.63
0.67	86.64	87.89	88.79	87.77	1.08
1.00	91.30	92.20	92.91	92.14	0.81
1.50	96.86	97.40	98.83	97.70	1.02
2.00	98.30	99.91	100.27	99.49	1.05

Table 97. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 1.5% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	41.61	40.90	40.84	0.81
0.17	45.74	46.28	48.25	46.76	1.32
0.42	49.87	51.48	49.51	50.28	1.05
0.67	53.81	56.32	54.71	54.95	1.27
1.00	60.81	62.96	64.57	62.78	1.89
1.50	65.29	67.44	69.42	67.38	2.06
2.00	70.49	73.18	73.72	72.47	1.73

Table 98. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 2% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	41.79	42.69	43.05	42.51	0.65
0.17	46.46	45.38	46.82	46.22	0.75
0.42	50.58	51.48	52.20	51.42	0.81
0.67	55.07	57.04	58.12	56.74	1.55
1.00	63.32	64.22	65.83	64.45	1.27
1.50	67.98	68.88	69.60	68.82	0.81
2.00	70.67	72.11	71.39	71.39	0.72

Table 99. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 500 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	50.76	49.69	48.07	49.51	1.35
0.17	57.22	55.25	56.50	56.32	1.00
0.42	60.63	59.55	58.83	59.67	0.90
0.67	65.83	64.22	65.11	65.05	0.81
1.00	69.96	68.70	69.06	69.24	0.65
1.50	74.62	73.00	74.08	73.90	0.82
2.00	79.64	78.03	80.36	79.34	1.19

Table 100. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 700 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	41.61	40.90	40.84	0.81
0.17	45.74	46.28	48.25	46.76	1.32
0.42	49.87	51.48	49.51	50.28	1.05
0.67	53.81	56.32	54.71	54.95	1.27
1.00	60.81	62.96	64.57	62.78	1.89
1.50	65.29	67.44	69.42	67.38	2.06
2.00	70.49	73.18	73.72	72.47	1.73

Table 101. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 900 rpm in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	66.55	65.29	67.80	66.55	1.26
0.17	69.06	69.96	70.49	69.84	0.72
0.42	73.18	74.44	74.98	74.20	0.92
0.67	79.46	81.08	81.43	80.66	1.05
1.00	87.71	88.43	90.04	88.73	1.19
1.50	90.76	92.56	93.27	92.20	1.29
2.00	95.78	97.22	97.76	96.92	1.02

Table 102. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:1 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	50.22	51.84	48.97	50.34	1.44
0.17	57.94	56.50	58.83	57.76	1.18
0.42	62.96	60.99	62.24	62.06	1.00
0.67	67.98	65.65	68.70	67.44	1.59
1.00	74.80	73.18	75.70	74.56	1.27
1.50	81.79	79.64	83.05	81.49	1.72
2.00	88.07	85.92	86.46	86.82	1.12

Table 103. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:2 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.95	38.21	39.10	38.09	1.08
0.17	41.97	44.13	44.48	43.53	1.36
0.42	46.46	47.89	48.97	47.77	1.26
0.67	49.51	50.40	51.84	50.58	1.18
1.00	53.99	52.38	55.25	53.87	1.44
1.50	60.45	59.01	61.35	60.27	1.18
2.00	66.01	64.75	68.16	66.31	1.72

Table 104. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:3 in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	39.28	39.82	41.08	40.06	0.92
0.17	42.51	41.08	40.00	41.20	1.26
0.42	46.28	45.02	47.00	46.10	1.00
0.67	48.79	46.10	48.25	47.71	1.42
1.00	53.27	51.30	52.74	52.44	1.02
1.50	59.55	56.86	58.48	58.30	1.35
2.00	64.22	62.42	64.75	63.80	1.22

Table 105. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 110°C in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.57	40.00	41.26	39.94	1.35
0.17	43.23	45.02	44.48	44.25	0.92
0.42	47.89	47.00	48.25	47.71	0.65
0.67	52.20	51.48	53.81	52.50	1.19
1.00	57.40	56.32	58.65	57.46	1.17
1.50	60.63	62.24	62.96	61.94	1.19
2.00	65.65	67.80	66.55	66.67	1.08

Table 106. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 120°C in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.95	38.21	39.10	38.09	1.08
0.17	41.97	44.13	44.48	43.53	1.36
0.42	46.46	47.89	48.97	47.77	1.26
0.67	49.51	50.40	51.84	50.58	1.18
1.00	53.99	52.38	55.25	53.87	1.44
1.50	60.45	59.01	61.35	60.27	1.18
2.00	66.01	64.75	68.16	66.31	1.72

Table 107. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 130°C in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.00	41.61	42.69	41.43	1.35
0.17	44.84	46.28	44.30	45.14	1.02
0.42	50.94	50.04	52.20	51.06	1.08
0.67	55.43	57.04	57.22	56.56	0.99
1.00	59.19	60.81	57.94	59.31	1.44
1.50	64.22	64.75	61.88	63.62	1.53
2.00	69.78	72.11	68.16	70.01	1.98

Table 108. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 18 mL/min in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	48.25	49.69	50.94	49.63	1.35
0.17	53.09	53.45	54.35	53.63	0.65
0.42	57.40	58.30	55.78	57.16	1.27
0.67	64.75	62.24	61.35	62.78	1.77
1.00	68.16	66.91	64.93	66.67	1.63
1.50	70.85	68.88	72.83	70.85	1.97
2.00	78.03	80.18	77.31	78.51	1.49

Table 109. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 24 mL/min in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.95	38.21	39.10	38.09	1.08
0.17	41.97	44.13	44.48	43.53	1.36
0.42	46.46	47.89	48.97	47.77	1.26
0.67	49.51	50.40	51.84	50.58	1.18
1.00	53.99	52.38	55.25	53.87	1.44
1.50	60.45	59.01	61.35	60.27	1.18
2.00	66.01	64.75	68.16	66.31	1.72

Table 110. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 30 mL/min in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.74	37.31	40.00	38.68	1.35
0.17	41.61	41.97	41.43	41.67	0.27
0.42	42.87	44.30	45.20	44.13	1.18
0.67	48.43	49.87	48.97	49.09	0.72
1.00	51.66	53.27	50.58	51.84	1.35
1.50	58.30	56.32	57.58	57.40	1.00
2.00	63.14	61.35	64.57	63.02	1.62

Table 111. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 5% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	53.27	51.84	53.81	52.97	1.02
0.17	58.30	57.58	59.55	58.48	1.00
0.42	65.29	64.04	66.19	65.17	1.08
0.67	71.21	73.72	72.29	72.41	1.26
1.00	75.16	76.23	77.49	76.29	1.17
1.50	79.28	81.26	80.90	80.48	1.05
2.00	86.10	87.71	84.84	86.22	1.44

Table 112. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 7% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.95	38.21	39.10	38.09	1.08
0.17	41.97	44.13	44.48	43.53	1.36
0.42	46.46	47.89	48.97	47.77	1.26
0.67	49.51	50.40	51.84	50.58	1.18
1.00	53.99	52.38	55.25	53.87	1.44
1.50	60.45	59.01	61.35	60.27	1.18
2.00	66.01	64.75	68.16	66.31	1.72

Table 113. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 10% in simulated gastric fluid without pepsin pH 1.2.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.92	40.00	37.85	38.92	1.08
0.17	42.51	41.43	39.64	41.20	1.45
0.42	47.00	44.30	43.41	44.90	1.87
0.67	48.97	48.61	46.10	47.89	1.56
1.00	55.43	56.50	54.17	55.37	1.17
1.50	63.14	64.22	61.17	62.84	1.55
2.00	67.80	70.13	66.73	68.22	1.74

Table 114. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:1 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	76.23	80.54	75.52	77.43	2.72
0.17	82.33	84.30	81.08	82.57	1.63
0.42	84.66	85.38	83.23	84.42	1.10
0.67	88.07	87.17	85.92	87.06	1.08
1.00	88.97	91.30	88.43	89.57	1.53
1.50	96.32	98.12	95.07	96.50	1.53
2.00	99.37	100.81	98.83	99.67	1.02
2.50	100.63	100.99	99.73	100.45	0.65
3.00	100.99	101.17	100.99	101.05	0.10
4.00	101.17	100.99	101.35	101.17	0.18
5.00	101.52	101.35	101.35	101.41	0.10
6.00	101.17	100.99	101.17	101.11	0.10
8.00	100.99	101.17	101.35	101.17	0.18
10.00	101.17	100.99	100.99	101.05	0.10
12.00	101.52	100.99	100.99	101.17	0.31

Table 115. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:2 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.57	40.18	41.43	40.06	1.44
0.17	42.87	43.77	43.41	43.35	0.45
0.42	46.28	48.43	46.46	47.06	1.19
0.67	49.69	51.30	52.02	51.00	1.19
1.00	52.38	52.74	54.71	53.27	1.26
1.50	55.78	57.04	59.01	57.28	1.63
2.00	62.06	64.22	65.11	63.80	1.57
2.50	66.01	67.26	70.31	67.86	2.21
3.00	70.85	73.54	77.67	74.02	3.43
4.00	74.44	76.77	77.85	76.35	1.74
5.00	80.54	81.79	84.13	82.15	1.82
6.00	87.89	90.04	89.87	89.27	1.19
8.00	95.25	96.14	97.04	96.14	0.90
10.00	99.01	100.27	99.37	99.55	0.65
12.00	100.63	100.99	101.17	100.93	0.27

Table 116. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with core to wall ratio 1:3 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.54	39.28	37.85	39.22	1.35
0.17	42.69	41.61	40.00	41.43	1.35
0.42	44.84	45.92	47.00	45.92	1.08
0.67	47.00	48.43	48.07	47.83	0.75
1.00	51.48	50.40	48.97	50.28	1.26
1.50	54.17	53.63	55.07	54.29	0.72
2.00	60.81	58.83	58.12	59.25	1.39
2.50	65.83	64.04	60.99	63.62	2.45
3.00	69.24	67.26	66.01	67.50	1.63
4.00	72.47	71.03	71.75	71.75	0.72
5.00	76.95	78.03	78.57	77.85	0.82
6.00	81.26	84.13	81.08	82.15	1.71
8.00	88.61	91.12	93.09	90.94	2.25
10.00	94.17	97.22	97.40	96.26	1.81
12.00	98.65	99.19	99.37	99.07	0.37

Table 117. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 3.5 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.57	40.18	41.43	40.06	1.44
0.17	42.87	43.77	43.41	43.35	0.45
0.42	46.28	48.43	46.46	47.06	1.19
0.67	49.69	51.30	52.02	51.00	1.19
1.00	52.38	52.74	54.71	53.27	1.26
1.50	55.78	57.04	59.01	57.28	1.63
2.00	62.06	64.22	65.11	63.80	1.57
2.50	66.01	67.26	70.31	67.86	2.21
3.00	70.85	73.54	77.67	74.02	3.43
4.00	74.44	76.77	77.85	76.35	1.74
5.00	80.54	81.79	84.13	82.15	1.82
6.00	87.89	90.04	89.87	89.27	1.19
8.00	95.25	96.14	97.04	96.14	0.90
10.00	99.01	100.27	99.37	99.55	0.65
12.00	100.63	100.99	101.17	100.93	0.27

Table 118. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 3.75 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	44.48	46.46	43.59	44.84	1.47
0.17	49.33	50.40	47.89	49.21	1.26
0.42	53.27	55.96	50.94	53.39	2.51
0.67	56.32	59.01	54.35	56.56	2.34
1.00	64.39	62.96	60.99	62.78	1.71
1.50	68.52	71.21	66.91	68.88	2.17
2.00	73.36	76.05	72.29	73.90	1.94
2.50	79.10	80.90	78.03	79.34	1.45
3.00	84.13	85.38	82.33	83.95	1.53
4.00	88.61	90.76	87.89	89.09	1.49
5.00	95.43	95.61	94.71	95.25	0.47
6.00	95.78	98.48	95.78	96.68	1.55
8.00	98.48	99.19	96.68	98.12	1.29
10.00	99.37	100.27	98.83	99.49	0.72
12.00	100.27	99.91	99.73	99.97	0.27

Table 119. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation at pH 4.0 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	42.33	40.72	40.00	41.02	1.19
0.17	44.66	43.59	41.79	43.35	1.45
0.42	48.43	46.28	44.84	46.52	1.81
0.67	53.45	51.48	49.69	51.54	1.88
1.00	58.12	57.40	53.99	56.50	2.20
1.50	64.39	61.88	60.09	62.12	2.16
2.00	68.70	67.26	68.34	68.10	0.75
2.50	72.65	71.21	71.39	71.75	0.78
3.00	81.79	79.46	78.74	80.00	1.59
4.00	89.51	87.89	85.74	87.71	1.89
5.00	93.99	92.02	93.09	93.03	0.99
6.00	97.94	98.83	96.50	97.76	1.18
8.00	99.19	99.37	99.19	99.25	0.10
10.00	99.01	99.19	99.55	99.25	0.27
12.00	99.55	100.27	100.09	99.97	0.37

Table 120. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 1% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	63.50	58.12	61.17	60.93	2.70
0.17	69.96	67.98	68.70	68.88	1.00
0.42	74.62	75.70	76.59	75.64	0.99
0.67	80.72	79.82	81.43	80.66	0.81
1.00	85.74	83.59	84.84	84.72	1.08
1.50	91.30	89.87	88.07	89.75	1.62
2.00	96.32	95.07	92.38	94.59	2.02
2.50	99.37	98.83	98.30	98.83	0.54
3.00	99.91	99.19	99.37	99.49	0.37
4.00	100.27	100.09	100.27	100.21	0.10
5.00	99.73	100.27	100.45	100.15	0.37
6.00	100.09	100.45	100.27	100.27	0.18
8.00	100.27	100.27	100.63	100.39	0.21
10.00	100.27	100.63	100.63	100.51	0.21
12.00	100.09	100.63	101.17	100.63	0.54

Table 121. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 1.5% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.57	40.18	41.43	40.06	1.44
0.17	42.87	43.77	43.41	43.35	0.45
0.42	46.28	48.43	46.46	47.06	1.19
0.67	49.69	51.30	52.02	51.00	1.19
1.00	52.38	52.74	54.71	53.27	1.26
1.50	55.78	57.04	59.01	57.28	1.63
2.00	62.06	64.22	65.11	63.80	1.57
2.50	66.01	67.26	70.31	67.86	2.21
3.00	70.85	73.54	77.67	74.02	3.43
4.00	74.44	76.77	77.85	76.35	1.74
5.00	80.54	81.79	84.13	82.15	1.82
6.00	87.89	90.04	89.87	89.27	1.19
8.00	95.25	96.14	97.04	96.14	0.90
10.00	99.01	100.27	99.37	99.55	0.65
12.00	100.63	100.99	101.17	100.93	0.27

Table 122. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with concentration of wall 2% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.21	39.28	37.31	38.27	0.99
0.17	44.30	43.05	45.38	44.25	1.17
0.42	46.46	45.38	47.71	46.52	1.17
0.67	50.40	47.89	52.20	50.16	2.16
1.00	51.48	50.04	53.81	51.78	1.90
1.50	54.71	52.91	55.43	54.35	1.29
2.00	56.32	55.25	57.94	56.50	1.35
2.50	64.39	62.96	64.57	63.98	0.88
3.00	70.85	69.24	72.65	70.91	1.70
4.00	74.62	73.36	75.52	74.50	1.08
5.00	80.72	77.85	80.18	79.58	1.53
6.00	86.46	84.13	86.82	85.80	1.46
8.00	92.02	89.69	93.09	91.60	1.74
10.00	97.04	94.89	97.76	96.56	1.49
12.00	100.81	99.19	100.99	100.33	0.99

Table 123. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 500 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	39.82	39.46	38.21	39.16	0.85
0.17	41.79	41.43	42.51	41.91	0.55
0.42	44.66	43.59	43.05	43.77	0.82
0.67	48.43	46.28	48.97	47.89	1.42
1.00	50.94	52.38	50.58	51.30	0.95
1.50	56.32	57.04	55.78	56.38	0.63
2.00	61.17	62.24	60.45	61.29	0.90
2.50	64.39	65.11	63.14	64.22	1.00
3.00	69.96	68.34	66.91	68.40	1.53
4.00	73.90	74.08	75.16	74.38	0.68
5.00	78.57	77.85	80.18	78.86	1.19
6.00	88.07	86.10	88.25	87.47	1.19
8.00	96.50	95.25	97.04	96.26	0.92
10.00	99.37	99.55	99.73	99.55	0.18
12.00	100.27	100.45	99.91	100.21	0.27

Table 124. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 700 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.21	39.28	37.31	38.27	0.99
0.17	44.30	43.05	45.38	44.25	1.17
0.42	46.46	45.38	47.71	46.52	1.17
0.67	50.40	47.89	52.20	50.16	2.16
1.00	51.48	50.04	53.81	51.78	1.90
1.50	54.71	52.91	55.43	54.35	1.29
2.00	56.32	55.25	57.94	56.50	1.35
2.50	64.39	62.96	64.57	63.98	0.88
3.00	70.85	69.24	72.65	70.91	1.70
4.00	74.62	73.36	75.52	74.50	1.08
5.00	80.72	77.85	80.18	79.58	1.53
6.00	86.46	84.13	86.82	85.80	1.46
8.00	92.02	89.69	93.09	91.60	1.74
10.00	97.04	94.89	97.76	96.56	1.49
12.00	100.81	99.19	100.99	100.33	0.99

Table 125. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-acacia coacervation with stirring rate 900 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	63.68	62.78	64.93	63.80	1.08
0.17	69.24	71.57	69.60	70.13	1.26
0.42	75.16	76.41	77.13	76.23	1.00
0.67	82.33	83.05	81.79	82.39	0.63
1.00	89.15	90.04	90.94	90.04	0.90
1.50	94.35	96.32	97.58	96.08	1.63
2.00	97.58	98.83	99.19	98.54	0.85
2.50	99.19	99.37	99.37	99.31	0.10
3.00	99.55	99.73	99.55	99.61	0.10
4.00	100.09	99.73	100.09	99.97	0.21
5.00	99.73	100.27	99.73	99.91	0.31
6.00	100.27	99.91	100.27	100.15	0.21
8.00	100.45	99.73	100.09	100.09	0.36
10.00	100.27	100.27	99.91	100.15	0.21
12.00	100.27	100.09	100.09	100.15	0.10

Table 126. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with core to wall ratio 1:1 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	57.22	58.12	59.19	58.18	0.99
0.17	64.57	65.83	67.26	65.89	1.35
0.42	70.67	72.47	74.98	72.71	2.16
0.67	78.03	80.90	82.51	80.48	2.27
1.00	83.23	85.38	86.10	84.90	1.49
1.50	89.87	91.30	92.38	91.18	1.26
2.00	92.20	94.71	95.61	94.17	1.77
2.50	94.35	97.22	98.30	96.62	2.04
3.00	98.12	99.01	99.19	98.77	0.58
4.00	99.37	100.09	99.73	99.73	0.36
5.00	99.91	100.27	100.09	100.09	0.18
6.00	100.09	99.91	100.27	100.09	0.18
8.00	100.27	100.27	100.45	100.33	0.10
10.00	100.45	100.27	100.27	100.33	0.10
12.00	100.27	100.45	100.27	100.33	0.10

Table 127. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with core to wall ratio 1:2 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	52.20	49.69	47.35	49.75	2.42
0.17	57.40	58.12	56.14	57.22	1.00
0.42	63.14	63.86	60.63	62.54	1.70
0.67	67.98	69.06	66.73	67.92	1.17
1.00	71.75	74.26	69.96	71.99	2.16
1.50	77.31	78.92	76.23	77.49	1.35
2.00	81.26	84.66	82.69	82.87	1.71
2.50	88.07	88.79	88.25	88.37	0.37
3.00	93.63	95.25	96.32	95.07	1.35
4.00	96.14	99.01	95.25	96.80	1.97
5.00	99.19	99.91	98.65	99.25	0.63
6.00	99.73	100.09	99.91	99.91	0.18
8.00	100.09	100.27	99.91	100.09	0.18
10.00	100.27	100.27	100.09	100.21	0.10
12.00	100.45	100.45	100.27	100.39	0.10

Table 128. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 3.5 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	52.20	49.69	47.35	49.75	2.42
0.17	57.40	58.12	56.14	57.22	1.00
0.42	63.14	63.86	60.63	62.54	1.70
0.67	67.98	69.06	66.73	67.92	1.17
1.00	71.75	74.26	69.96	71.99	2.16
1.50	77.31	78.92	76.23	77.49	1.35
2.00	81.26	84.66	82.69	82.87	1.71
2.50	88.07	88.79	88.25	88.37	0.37
3.00	93.63	95.25	96.32	95.07	1.35
4.00	96.14	99.01	95.25	96.80	1.97
5.00	99.19	99.91	98.65	99.25	0.63
6.00	99.73	100.09	99.91	99.91	0.18
8.00	100.09	100.27	99.91	100.09	0.18
10.00	100.27	100.27	100.09	100.21	0.10
12.00	100.45	100.45	100.27	100.39	0.10

Table 129. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 3.75 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.90	41.79	43.41	42.03	1.27
0.17	46.10	44.30	45.02	45.14	0.90
0.42	49.51	48.79	49.15	49.15	0.36
0.67	54.17	52.38	53.27	53.27	0.90
1.00	59.73	59.37	60.45	59.85	0.55
1.50	65.29	64.04	65.47	64.93	0.78
2.00	69.96	68.88	68.52	69.12	0.75
2.50	76.59	76.95	77.49	77.01	0.45
3.00	84.13	84.48	84.84	84.48	0.36
4.00	88.79	90.40	90.76	89.99	1.05
5.00	93.81	94.35	94.53	94.23	0.37
6.00	98.65	97.58	98.83	98.36	0.68
8.00	99.91	99.73	99.91	99.85	0.10
10.00	100.09	99.91	100.27	100.09	0.18
12.00	100.09	100.27	99.91	100.09	0.18

Table 130. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation at pH 4.0 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	48.43	46.82	47.89	47.71	0.82
0.17	53.45	52.20	52.74	52.80	0.63
0.42	58.65	57.58	59.01	58.42	0.75
0.67	66.19	64.75	67.09	66.01	1.18
1.00	70.31	69.96	69.42	69.90	0.45
1.50	76.23	75.52	75.87	75.87	0.36
2.00	80.90	82.69	81.79	81.79	0.90
2.50	87.00	85.74	88.25	87.00	1.26
3.00	90.76	92.20	91.84	91.60	0.75
4.00	93.81	94.35	93.45	93.87	0.45
5.00	97.04	98.83	98.12	98.00	0.90
6.00	99.19	100.27	99.91	99.79	0.55
8.00	100.09	100.09	100.09	100.09	0.00
10.00	100.27	99.91	100.27	100.15	0.21
12.00	100.45	100.27	100.09	100.27	0.18

Table 131. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 1% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	66.01	64.75	64.93	65.23	0.68
0.17	70.67	69.96	70.13	70.25	0.37
0.42	80.54	79.10	79.64	79.76	0.72
0.67	86.46	84.84	86.28	85.86	0.88
1.00	89.87	88.25	89.33	89.15	0.82
1.50	96.14	96.32	96.32	96.26	0.10
2.00	97.76	98.83	97.40	98.00	0.75
2.50	99.19	99.37	99.73	99.43	0.27
3.00	99.73	99.55	99.73	99.67	0.10
4.00	100.09	99.91	99.91	99.97	0.10
5.00	100.27	100.27	100.09	100.21	0.10
6.00	100.45	100.09	100.27	100.27	0.18
8.00	100.09	100.27	100.09	100.15	0.10
10.00	100.27	100.45	100.45	100.39	0.10
12.00	100.27	100.09	100.45	100.27	0.18

Table 132. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 1.5% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.90	41.79	43.41	42.03	1.27
0.17	46.10	44.30	45.02	45.14	0.90
0.42	49.51	48.79	49.15	49.15	0.36
0.67	54.17	52.38	53.27	53.27	0.90
1.00	59.73	59.37	60.45	59.85	0.55
1.50	65.29	64.04	65.47	64.93	0.78
2.00	69.96	68.88	68.52	69.12	0.75
2.50	76.59	76.95	77.49	77.01	0.45
3.00	84.13	84.48	84.84	84.48	0.36
4.00	88.79	90.40	90.76	89.99	1.05
5.00	93.81	94.35	94.53	94.23	0.37
6.00	98.65	97.58	98.83	98.36	0.68
8.00	99.91	99.73	99.91	99.85	0.10
10.00	100.09	99.91	100.27	100.09	0.18
12.00	100.09	100.27	99.91	100.09	0.18

Table 133. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with concentration of wall 2% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	41.43	41.97	41.43	41.61	0.31
0.17	47.00	47.89	47.35	47.41	0.45
0.42	50.94	52.20	52.02	51.72	0.68
0.67	55.07	54.35	56.14	55.19	0.90
1.00	62.60	62.24	61.17	62.00	0.75
1.50	66.91	66.55	64.04	65.83	1.56
2.00	71.39	71.21	70.13	70.91	0.68
2.50	77.85	77.31	76.23	77.13	0.82
3.00	81.61	82.15	81.26	81.67	0.45
4.00	88.43	88.61	88.07	88.37	0.27
5.00	93.81	93.99	93.45	93.75	0.27
6.00	99.91	100.27	99.91	100.03	0.21
8.00	100.27	100.09	100.09	100.15	0.10
10.00	100.45	100.09	100.27	100.27	0.18
12.00	100.45	100.27	100.27	100.33	0.10

Table 134. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 500 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	53.45	55.78	52.20	53.81	1.82
0.17	58.65	57.40	56.14	57.40	1.26
0.42	61.35	59.73	59.01	60.03	1.19
0.67	66.55	64.57	63.32	64.81	1.63
1.00	69.60	68.16	66.19	67.98	1.71
1.50	74.62	73.00	70.67	72.77	1.98
2.00	80.72	79.46	79.64	79.94	0.68
2.50	85.02	83.41	83.77	84.07	0.85
3.00	91.84	88.97	90.04	90.28	1.45
4.00	95.61	94.71	96.50	95.61	0.90
5.00	99.37	99.73	99.91	99.67	0.27
6.00	99.91	100.09	100.09	100.03	0.10
8.00	100.27	100.09	100.27	100.21	0.10
10.00	100.27	100.27	99.91	100.15	0.21
12.00	100.45	100.27	100.09	100.27	0.18

Table 135. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 700 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	SD
0.00	0.00	0.00	0.00	0.00	0.00
0.08	40.90	41.79	43.41	42.03	1.27
0.17	46.10	44.30	45.02	45.14	0.90
0.42	49.51	48.79	49.15	49.15	0.36
0.67	54.17	52.38	53.27	53.27	0.90
1.00	59.73	59.37	60.45	59.85	0.55
1.50	65.29	64.04	65.47	64.93	0.78
2.00	69.96	68.88	68.52	69.12	0.75
2.50	76.59	76.95	77.49	77.01	0.45
3.00	84.13	84.48	84.84	84.48	0.36
4.00	88.79	90.40	90.76	89.99	1.05
5.00	93.81	94.35	94.53	94.23	0.37
6.00	98.65	97.58	98.83	98.36	0.68
8.00	99.91	99.73	99.91	99.85	0.10
10.00	100.09	99.91	100.27	100.09	0.18
12.00	100.09	100.27	99.91	100.09	0.18

Table 136. The percent release of amoxycillin from amoxycillin microcapsules prepared by gelatin-SCMC coacervation with stirring rate 900 rpm in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	66.19	64.75	65.83	65.59	0.75
0.17	71.75	70.13	70.31	70.73	0.88
0.42	72.83	72.47	72.11	72.47	0.36
0.67	80.90	80.90	79.10	80.30	1.04
1.00	87.89	86.10	86.28	86.76	0.99
1.50	90.40	91.66	90.22	90.76	0.78
2.00	94.89	95.07	94.53	94.83	0.27
2.50	97.22	96.14	96.68	96.68	0.54
3.00	98.12	97.40	97.58	97.70	0.37
4.00	99.19	99.37	99.73	99.43	0.27
5.00	99.55	99.73	99.55	99.61	0.10
6.00	99.91	100.09	99.91	99.97	0.10
8.00	99.73	99.91	100.09	99.91	0.18
10.00	100.09	100.09	99.91	100.03	0.10
12.00	100.27	100.09	99.91	100.09	0.18

Table 137. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:1 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	52.02	50.58	50.76	51.12	0.78
0.17	57.22	53.99	56.14	55.78	1.64
0.42	63.14	61.17	61.88	62.06	1.00
0.67	70.85	70.13	68.34	69.78	1.29
1.00	78.57	76.95	77.85	77.79	0.81
1.50	87.71	88.25	85.92	87.29	1.22
2.00	92.02	88.97	90.04	90.34	1.55
2.50	92.20	94.89	93.81	93.63	1.35
3.00	94.89	96.50	95.07	95.49	0.88
4.00	95.78	97.40	95.61	96.26	0.99
5.00	97.40	98.30	99.01	98.24	0.81
6.00	99.01	100.45	99.55	99.67	0.72
8.00	99.73	98.30	100.27	99.43	1.02
10.00	99.91	99.19	100.63	99.91	0.72
12.00	102.06	100.81	101.17	101.35	0.65

Table 138. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:2 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.59	38.39	39.82	38.27	1 62
0.17	39.28	41.61	40.00	40.30	1.19
0.42	47.89	44.84	45.92	46.22	1.55
0.67	49.69	48.79	47.17	48.55	1.27
1.00	53.45	51.48	51.84	52.26	1.05
1.50	58.65	57.22	57.94	57.94	0.72
2.00	60.45	60.09	60.09	60.21	0.21
2.50	64.39	63.50	64.22	64.04	0.47
3.00	67.98	66.73	65.11	66.61	1.44
4.00	70.67	69.42	67.98	69.36	1.35
5.00	75.87	73.36	74.98	74.74	1.27
6.00	78.74	77.13	77.85	77.91	0.81
8.00	87.17	85.92	87.00	86.70	0.68
10.00	90.58	93.45	94.89	92.97	2.19
12.00	102.60	99.55	101.17	101.11	1.53

Table 139. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with core to wall ratio 1:3 in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.57	37.67	40.18	38.80	1.27
0.17	40.90	39.64	41.79	40.78	1.08
0.42	42.69	43.95	43.05	43.23	0.65
0.67	45.56	47.00	48.61	47.06	1.53
1.00	52.38	51.84	50.76	51.66	0.82
1.50	55.78	53.45	56.32	55.19	1.53
2.00	59.19	58.30	60.81	59.43	1.27
2.50	64.04	62.78	64.57	63.80	0.92
3.00	66.55	66.37	65.65	66.19	0.47
4.00	69.60	71.03	68.52	69.72	1.26
5.00	76.59	74.26	70.67	73.84	2.98
6.00	79.10	77.49	75.16	77.25	1.98
8.00	84.13	83.05	82.15	83.11	0.99
10.00	89.69	88.97	87.53	88.73	1.10
12.00	96.14	96.50	95.78	96.14	0.36

Table 140. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 110°C in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	38.21	37.85	36.95	37.67	0.65
0.17	41.26	39.46	42.51	41.08	1.53
0.42	45.56	45.92	48.25	46.58	1.46
0.67	47.89	50.22	51.66	49.93	1.90
1.00	53.81	54.71	56.50	55.01	1.37
1.50	58.30	59.73	58.65	58.89	0.75
2.00	60.63	61.88	60.45	60.99	0.78
2.50	66.73	67.80	64.75	66.43	1.55
3.00	69.06	68.52	70.13	69.24	0.82
4.00	73.36	74.44	75.16	74.32	0.90
5.00	77.49	78.57	76.95	77.67	0.82
6.00	81.79	81.61	82.69	82.03	0.58
8.00	88.07	85.92	88.43	87.47	1.36
10.00	95.25	93.45	95.96	94.89	1.29
12.00	102.24	100.81	102.60	101.88	0.95

Table 141. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 120°C in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.59	38.39	39.82	38.27	1.62
0.17	39.28	41.61	40.00	40.30	1.19
0.42	47.89	44.84	45.92	46.22	1.55
0.67	49.69	48.79	47.17	48.55	1.27
1.00	53.45	51.48	51.84	52.26	1.05
1.50	58.65	57.22	57.94	57.94	0.72
2.00	60.45	60.09	60.09	60.21	0.21
2.50	64.39	63.50	64.22	64.04	0.47
3.00	67.98	66.73	65.11	66.61	1.44
4.00	70.67	69.42	67.98	69.36	1.35
5.00	75.87	73.36	74.98	74.74	1.27
6.00	78.74	77.13	77.85	77.91	0.81
8.00	87.17	85.92	87.00	86.70	0.68
10.00	90.58	93.45	94.89	92.97	2.19
12.00	102.60	99.55	101.17	101.11	1.53

Table 142. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique at inlet air temperature 130°C in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	39.82	37.85	39.46	39.04	1.05
0.17	42.15	43.05	42.69	42.63	0.45
0.42	47.71	50.22	46.82	48.25	1.77
0.67	51.12	52.02	52.38	51.84	0.65
1.00	56.14	55.07	55.78	55.67	0.55
1.50	58.83	61.35	60.45	60.21	1.27
2.00	63.14	64.39	64.75	64.10	0.85
2.50	68.16	67.98	69.96	68.70	1.09
3.00	71.57	71.39	71.93	71.63	0.27
4.00	78.03	80.90	78.39	79.10	1.56
5.00	82.69	84.66	83.05	83.47	1.05
6.00	85.20	86.64	85.56	85.80	0.75
8.00	88.25	93.27	90.58	90.70	2.51
10.00	96.86	97.40	96.50	96.92	0.45
12.00	102.06	102.24	101.88	102.06	0.18

Table 143. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 18 mL/min in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	48.79	49.69	46.46	48.31	1.67
0.17	53.45	54.17	52.74	53.45	0.72
0.42	56.14	59.19	57.04	57.46	1.57
0.67	64.57	64.22	63.14	63.98	0.75
1.00	67.80	69.06	66.55	67.80	1.26
1.50	71.21	72.11	69.96	71.09	1.08
2.00	75.87	77.13	74.26	75.75	1.44
2.50	79.46	80.72	78.74	79.64	1.00
3.00	85.38	86.28	83.77	85.14	1.27
4.00	92.20	94.35	90.22	92.26	2.06
5.00	96.32	98.12	95.96	96.80	1.15
6.00	100.81	99.55	100.27	100.21	0.63
8.00	102.24	102.60	102.06	102.30	0.27
10.00	101.88	101.88	102.06	101.94	0.10
12.00	102.06	101.88	101.88	101.94	0.10

Table 144. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 24 mL/min in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.59	38.39	39.82	38.27	1.62
0.17	39.28	41.61	40.00	40.30	1.19
0.42	47.89	44.84	45.92	46.22	1.55
0.67	49.69	48.79	47.17	48.55	1.27
1.00	53.45	51.48	51.84	52.26	1.05
1.50	58.65	57.22	57.94	57.94	0.72
2.00	60.45	60.09	60.09	60.21	0.21
2.50	64.39	63.50	64.22	64.04	0.47
3.00	67.98	66.73	65.11	66.61	1.44
4.00	70.67	69.42	67.98	69.36	1.35
5.00	75.87	73.36	74.98	74.74	1.27
6.00	78.74	77.13	77.85	77.91	0.81
8.00	87.17	85.92	87.00	86.70	0.68
10.00	90.58	93.45	94.89	92.97	2.19
12.00	102.60	99.55	101.17	101.11	1.53

Table 145. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with feed rate 30 mL/min in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	39.28	36.77	37.85	37.97	1.26
0.17	40.90	38.39	39.64	39.64	1.26
0.42	43.95	42.87	43.59	43.47	0.55
0.67	48.61	45.92	47.53	47.35	1.35
1.00	52.02	51.30	52.38	51.90	0.55
1.50	56.32	56.50	56.68	56.50	0.18
2.00	59.37	59.55	58.83	59.25	0.37
2.50	60.63	60.45	59.73	60.27	0.47
3.00	64.93	64.57	64.39	64.63	0.27
4.00	66.55	66.37	65.47	66.13	0.58
5.00	69.06	68.88	70.49	69.48	0.88
6.00	73.00	72.65	72.83	72.83	0.18
8.00	76.41	76.05	76.23	76.23	0.18
10.00	84.13	86.46	85.74	85.44	1.19
12.00	87.89	92.38	90.58	90.28	2.26

Table 146. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 5% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	53.81	53.99	54.17	53.99	0.18
0.17	56.86	58.30	60.81	58.65	2.00
0.42	63.14	64.57	63.32	63.68	0.78
0.67	65.65	70.31	69.60	68.52	2.51
1.00	71.21	73.90	72.47	72.53	1.35
1.50	78.21	80.36	80.00	79.52	1.15
2.00	84.48	85.92	85.20	85.20	0.72
2.50	87.89	89.51	88.61	88.67	0.81
3.00	90.76	92.38	91.30	91.48	0.82
4.00	94.35	95.78	96.68	95.61	1.18
5.00	96.86	98.12	97.22	97.40	0.65
6.00	99.55	99.19	100.27	99.67	0.55
8.00	102.42	102.60	102.42	102.48	0.10
10.00	101.88	102.42	102.60	102.30	0.37
12.00	101.52	102.24	102.06	101.94	0.37

Table 147. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 7% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.59	38.39	39.82	38.27	1.62
0.17	39.28	41.61	40.00	40.30	1.19
0.42	47.89	44.84	45.92	46.22	1.55
0.67	49.69	48.79	47.17	48.55	1.27
1.00	53.45	51.48	51.84	52.26	1.05
1.50	58.65	57.22	57.94	57.94	0.72
2.00	60.45	60.09	60.09	60.21	0.21
2.50	64.39	63.50	64.22	64.04	0.47
3.00	67.98	66.73	65.11	66.61	1.44
4.00	70.67	69.42	67.98	69.36	1.35
5.00	75.87	73.36	74.98	74.74	1.27
6.00	78.74	77.13	77.85	77.91	0.81
8.00	87.17	85.92	87.00	86.70	0.68
10.00	90.58	93.45	94.89	92.97	2.19
12.00	102.60	99.55	101.17	101.11	1.53

Table 148. The percent release of amoxycillin from amoxycillin microcapsules prepared by spray-drying technique with solid content 10% in simulated intestinal fluid without pancreatin pH 6.8.

Time	% released1	% released2	% released3	mean	S.D.
0.00	0.00	0.00	0.00	0.00	0.00
0.08	36.77	37.67	37.49	37.31	0.47
0.17	41.26	39.46	40.36	40.36	0.90
0.42	45.02	42.87	45.02	44.30	1.24
0.67	47.71	45.38	46.82	46.64	1.18
1.00	49.33	48.61	50.58	49.51	1.00
1.50	51.12	50.22	50.76	50.70	0.45
2.00	57.76	55.07	56.32	56.38	1.35
2.50	60.99	57.04	57.94	58.65	2.07
3.00	63.32	62.96	64.22	63.50	0.65
4.00	69.60	65.65	67.09	67.44	2.00
5.00	73.00	69.96	71.57	71.51	1.53
6.00	74.44	73.36	75.16	74.32	0.90
8.00	81.97	81.26	82.51	81.91	0.63
10.00	87.00	86.10	87.53	86.88	0.72
12.00	94.35	91.30	93.63	93.09	1.59

APPENDIX F

Data of the release rate constant of zero-order, first order and Higuchi model and the coefficient of determination of amoxycillin microcapsules

Table 149. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratio in pH 1.2.

Core : wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	10.6500	0.9401	0.1194	0.9217	18.7453	0.9801
1:2	12.7720	0.9689	0.2459	0.9556	21.9663	0.9753
1:3	11.4860	0.9637	0.2251	0.9665	19.7417	0.9770

Table 150. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratio in pH 1.2.

Core : wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	18.1500	0.9088	0.2359	0.8711	32.4283	0.9832
1:2	15.1950	0.9162	0.2263	0.8719	27.0460	0.9814

Table 151. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various core to wall ratio in pH 6.8.

Core : wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	10.7730	0.9643	0.1208	0.9523	18.5680	0.9741
1:2	6.1207	0.9253	0.0894	0.8558	21.8320	0.9909
1:3	5.1533	0.9393	0.0762	0.8718	20.0040	0.9921

Table 152. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various core to wall ratio in pH 6.8.

Core : wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	12.6390	0.8593	0.1580	0.8105	27.4487	0.9619
1:2	13.8090	0.9583	0.1915	0.9134	28.8120	0.9893

Table 153. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various pH in pH 1.2.

pH	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
3.5	12.7720	0.9689	0.2459	0.9556	21.9663	0.9753
3.75	14.7900	0.9625	0.2499	0.9352	25.7497	0.9859
4.0	14.2720	0.9805	0.2641	0.9581	24.6683	0.9909

Table 154. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various pH in pH 1.2.

pH	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
3.5	15.1950	0.9162	0.2263	0.8719	27.0460	0.9814
3.75	15.7990	0.9550	0.2791	0.9198	27.5940	0.9851
4.0	17.4000	0.8902	0.2704	0.8414	31.2997	0.9727

Table 155. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various pH in pH 6.8.

pH	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
3.5	6.1207	0.9253	0.0894	0.8558	21.8320	0.9909
3.75	8.8510	0.9293	0.1253	0.8744	25.3107	0.9920
4.0	9.8677	0.9655	0.1471	0.9159	27.6600	0.9901

Table 156. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC with various pH in pH 6.8.

pH	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
3.5	13.8090	0.9583	0.1915	0.9134	28.8120	0.9893
3.75	9.7669	0.9436	0.1420	0.8907	27.6720	0.9891
4.0	14.1950	0.9552	0.2050	0.9108	29.7610	0.9960

Table 157. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in pH 1.2.

Conc. of wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1%	15.9750	0.9360	0.2008	0.9014	28.2363	0.9891
1.5%	12.7720	0.9689	0.2459	0.9556	21.9663	0.9753
2%	8.5129	0.9037	0.1717	0.8693	16.0757	0.9697

Table 158. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in pH 1.2.

Conc. of wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1%	16.5130	0.8756	0.1965	0.8419	29.8393	0.9693
1.5%	15.7990	0.9550	0.2791	0.9198	27.5940	0.9851
2%	15.2450	0.9305	0.2673	0.9000	26.9367	0.9834

Table 159. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various concentration of wall in pH 6.8.

Conc. of wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1%	13.9380	0.9098	0.1725	0.8643	27.4183	0.9776
1.5%	6.1207	0.9253	0.0894	0.8558	21.8320	0.9909
2%	5.1926	0.9250	0.0757	0.8570	20.2200	0.9849

Table 160. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various concentration of wall in pH 6.8.

Conc. of wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1%	20.8920	0.9206	0.2589	0.8900	32.8237	0.9862
1.5%	9.7669	0.9436	0.1420	0.8907	27.6720	0.9891
2%	10.2650	0.9538	0.1535	0.8973	26.5833	0.9951

Table 161. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rate in pH 1.2.

Stirring rate	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
500	10.9040	0.9667	0.2178	0.9441	18.9820	0.9969
700	8.5129	0.9037	0.1717	0.8693	15.1757	0.9697
900	18.1410	0.9307	0.2222	0.9005	32.0853	0.9863

Table 162. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rate in pH 1.2.

Stirring rate	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
500	14.1460	0.9411	0.2185	0.9039	24.1820	0.9894
700	15.7990	0.9550	0.2791	0.9198	27.5940	0.9851
900	15.9560	0.9458	0.1951	0.9265	27.9633	0.9841

Table 163. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-acacia coacervation with various stirring rate in pH 6.8.

Stirring rate	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
500	7.1967	0.9737	0.1180	0.9199	22.5070	0.9891
700	5.1926	0.9250	0.0757	0.8570	20.2200	0.9849
900	17.7440	0.9191	0.2164	0.8883	31.5393	0.9825

Table 164. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by gelatin-SCMC coacervation with various stirring rate in pH 6.8.

Stirring rate	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
500	10.7750	0.9800	0.1463	0.9561	24.7327	0.9843
700	9.7669	0.9436	0.1420	0.8907	27.6720	0.9891
900	15.0290	0.9380	0.1868	0.9169	26.3400	0.9743

Table 165. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various core to wall ratio in pH 1.2.

Core:wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	17.9930	0.9561	0.2616	0.9192	31.4523	0.9915
1:2	13.3600	0.9683	0.2567	0.9343	23.1283	0.9821
1:3	12.2920	0.9686	0.2407	0.9720	20.9437	0.9734

Table 166. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various core to wall ratio in pH 6.8.

Core:wall	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
1:1	20.9060	0.9535	0.2962	0.9231	36.5930	0.9888
1:2	5.7859	0.9300	0.0952	0.8595	18.5610	0.9935
1:3	4.9703	0.9176	0.0800	0.8462	17.8390	0.9922

Table 167. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various inlet air temperature in pH 1.2.

Inlet air temperature	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
110°C	13.3510	0.9632	0.2511	0.9323	23.2967	0.9900
120°C	13.3600	0.9683	0.2567	0.9343	23.1283	0.9821
130°C	13.8590	0.9459	0.2567	0.9007	24.3840	0.9855

Table 168. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various inlet air temperature in pH 6.8.

Inlet air temperature	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
110°C	5.2425	0.9345	0.0835	0.8270	19.5257	0.9927
120°C	5.7859	0.9300	0.0952	0.8595	18.5610	0.9935
130°C	5.6181	0.8954	0.0837	0.8152	20.4437	0.9897

Table 169. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various feed rate in pH 1.2.

Feed rate	Zero- order		First- order		Higuchi's model	
(mL/min)	k_0	R^2	k	R^2	k_H	R^2
18	14.0450	0.9700	0.2211	0.9511	24.2990	0.9725
24	13.3600	0.9683	0.2567	0.9343	23.1283	0.9821
30	12.1970	0.9747	0.2426	0.9689	20.9173	0.9734

Table 170. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various feed rate in pH 6.8.

Feed rate	Zero- order		First- order		Higuchi's model	
(mL/min)	k_0	R^2	k	R^2	k_H	R^2
18	10.4610	0.9543	0.1504	0.9085	24.4180	0.9919
24	5.7859	0.9300	0.0952	0.8595	18.5610	0.9935
30	4.3624	0.8960	0.0728	0.8179	15.7747	0.9851

Table 171. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various solid content in pH 1.2.

Solid content	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
5%	16.1340	0.9151	0.2316	0.8754	28.8618	0.9831
7%	13.3600	0.9683	0.2567	0.9343	23.1283	0.9821
10%	15.5810	0.9623	0.2964	0.9690	26.4933	0.9702

Table 172. The release rate constants of zero-order(k_0), first-order (k) and Higuchi model (k_H) and the coefficient of determination (R^2) of amoxycillin microcapsules prepared by spray-drying with various solid content in pH 6.8.

Solid content	Zero- order		First- order		Higuchi's model	
	k_0	R^2	k	R^2	k_H	R^2
5%	10.5670	0.9251	0.1408	0.8746	25.0503	0.9904
7%	5.7859	0.9300	0.0952	0.8595	18.5610	0.9935
10%	4.8945	0.9449	0.0804	0.8822	17.3433	0.9939

APPENDIX G

Data of statistics for comparison of time of 50% released of amoxycillin microcapsules

Table 173. Test of statistics on the effect of core to wall ratio on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated gastric fluid without pepsin pH 1.2 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	1.602[b]	5	.320	76.781	.000	383.904	1.000
Intercept	.884	1	.884	211.824	.000	211.824	1.000
POLYMER	.798	1	.798	191.116	.000	191.116	1.000
RATIOS	.415	2	.207	49.683	.000	99.367	1.000
POLYMER * RATIOS	.390	2	.195	46.711	.000	93.422	1.000
Error	5.008E-02	12	4.173E-03				
Total	2.536	18					
Corrected Total	1.652	17					

a. Computed using alpha = .05

b. R Squared = .970 (Adjusted R Squared = .957)

Post Hoc Tests
RATIOS
Homogeneous Subsets

T50

Duncan[a,b]

RATIOS	N	Subset 1	Subset 2
11	6	7.32E-03	
12	6		.318000
13	6		.339517
Sig.		1.000	.575

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 4.173E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 174. Test of statistics on the effect of pH on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated gastric fluid without pepsin pH 1.2 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	.726[b]	5	.145	59.302	.000	296.511	1.000
Intercept	1.644	1	1.644	671.719	.000	671.719	1.000
POLYMER	.345	1	.345	141.146	.000	141.146	1.000
PH	2.299E-03	2	1.149E-03	.470	.636	.939	.110
POLYMER * PH	.378	2	.189	77.213	.000	154.425	1.000
Error	2.936E-02	12	2.447E-03				
Total	2.399	18					
Corrected Total	.755	17					

a. Computed using alpha = .05

b. R Squared = .961 (Adjusted R Squared = .945)

Post Hoc Tests
PH
Homogeneous Subsets

T50

Duncan[a,b]

PH	N	Subset 1
4.00	6	.292267
3.75	6	.296300
3.50	6	.318000
Sig.		.408

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 2.447E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 175. Test of statistics on the effect of concentration of wall on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated gastric fluid without pepsin pH 1.2 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	.887[b]	5	.177	22.720	.000	113.602	1.000
Intercept	2.190	1	2.190	280.389	.000	280.389	1.000
POLYMER	.134	1	.134	17.120	.001	17.120	.966
WALLCONC	.612	2	.306	39.152	.000	78.305	1.000
POLYMER * WALLCONC	.142	2	7.100E-02	9.088	.004	18.177	.927
Error	9.375E-02	12	7.812E-03				
Total	3.172	18					
Corrected Total	.981	17					

a. Computed using alpha = .05

b. R Squared = .904 (Adjusted R Squared = .865)

Post Hoc Tests
WALLCONC
Homogeneous Subsets

T50

Duncan[a,b]

WALLCONC	N	Subset 1	Subset 2
1.0	6	8.81E-02	
1.5	6		.478700
2.0	6		.479700
Sig.		1.000	.985

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 7.812E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 176. Test of statistics on the effect of stirring rate on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated gastric fluid without pepsin pH 1.2 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	1.401[b]	5	.280	68.899	.000	344.494	1.000
Intercept	1.719	1	1.719	422.753	.000	422.753	1.000
POLYMER	.395	1	.395	97.061	.000	97.061	1.000
STIRRING	.690	2	.345	84.882	.000	169.764	1.000
POLYMER * STIRRING	.316	2	.158	38.835	.000	77.669	1.000
Error	4.881E-02	12	4.067E-03				
Total	3.169	18					
Corrected Total	1.450	17					

a. Computed using alpha = .05

b. R Squared = .966 (Adjusted R Squared = .952)

Post Hoc Tests
STIRRING
Homogeneous Subsets

T50

Duncan[a,b]

STIRRING	N	Subset 1	Subset 2	Subset 3
900	6	5.72E-02		
500	6		.335167	
700	6			.534833
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 4.067E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 177. Test of statistics on the effect of core to wall ratio on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated intestinal fluid without pancreatin pH 6.8 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	1.849[b]	5	.370	157.447	.000	787.234	1.000
Intercept	1.115	1	1.115	474.864	.000	474.864	1.000
POLYMER	.870	1	.870	370.479	.000	370.479	1.000
RATIOS	.466	2	.233	99.119	.000	198.238	1.000
POLYMER * RATIOS	.513	2	.257	109.259	.000	218.517	1.000
Error	2.819E-02	12	2.349E-03				
Total	2.993	18					
Corrected Total	1.877	17					

a. Computed using alpha = .05

b. R Squared = .985 (Adjusted R Squared = .979)

Post Hoc Tests
RATIOS
Homogeneous Subsets

T50

Duncan[a,b]

RATIOS	N	Subset 1	Subset 2	Subset 3
11	6	2.56E-02		
12	6		.323067	
13	6			.398083
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 2.349E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 178. Test of statistics on the effect of pH on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated intestinal fluid without pancreatin pH 6.8 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	.714[b]	5	.143	39.413	.000	197.063	1.000
Intercept	1.818	1	1.818	501.831	.000	501.831	1.000
POLYMER	.298	1	.298	82.397	.000	82.397	1.000
PH	2.712E-04	2	1.356E-04	.037	.963	.075	.054
POLYMER * PH	.415	2	.208	57.296	.000	114.592	1.000
Error	4.347E-02	12	3.622E-03				
Total	2.575	18					
Corrected Total	.757	17					

a. Computed using alpha = .05

b. R Squared = .943 (Adjusted R Squared = .919)

Post Hoc Tests
PH
Homogeneous Subsets

T50

Duncan[a,b]

PH	N	Subset 1
4.00	6	.313833
3.75	6	.316483
3.50	6	.323067
Sig.		.805

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 3.622E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 179. Test of statistics on the effect of concentration of wall on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated intestinal fluid without pancreatin pH 6.8 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	1.102[b]	5	.220	72.287	.000	361.433	1.000
Intercept	2.303	1	2.303	755.044	.000	755.044	1.000
POLYMER	.170	1	.170	55.785	.000	55.785	1.000
WALLCONC	.833	2	.416	136.550	.000	273.099	1.000
POLYMER * WALLCONC	9.927E-02	2	4.963E-02	16.274	.000	32.549	.996
Error	3.660E-02	12	3.050E-03				
Total	3.442	18					
Corrected Total	1.139	17					

a. Computed using alpha = .05

b. R Squared = .968 (Adjusted R Squared = .954)

Post Hoc Tests
WALLCONC
Homogeneous Subsets

T50

Duncan[a,b]

WALLCONC	N	Subset 1	Subset 2
1.0	6	5.39E-02	
1.5	6		.495167
2.0	6		.523950
Sig.		1.000	.384

Means for groups in homogeneous subsets are displayed.

Based on Type III Sum of Squares

The error term is Mean Square(Error) = 3.050E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 180. Test of statistics on the effect of stirring rate on the time of 50% released from the amoxycillin microcapsules prepared by complex coacervation technique in simulated intestinal fluid without pancreatin pH 6.8 by TWO-WAY ANOVA.

Tests of Between-Subjects Effects

Dependent Variable: T50

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Noncent. Parameter	Observed Power[a]
Corrected Model	1.156[b]	5	.231	83.983	.000	419.914	1.000
Intercept	2.087	1	2.087	758.318	.000	758.318	1.000
POLYMER	.230	1	.230	83.386	.000	83.386	1.000
STIRRING	.729	2	.364	132.388	.000	264.776	1.000
POLYMER * STIRRING	.198	2	9.875E-02	35.876	.000	71.752	1.000
Error	3.303E-02	12	2.753E-03				
Total	3.276	18					
Corrected Total	1.189	17					

a. Computed using alpha = .05

b. R Squared = .972 (Adjusted R Squared = .961)

Post Hoc Tests
STIRRING
Homogeneous Subsets

T50

Duncan[a,b]

STIRRING	N	Subset 1	Subset 2	Subset 3
900	6	7.17E-02		
500	6		.394233	
700	6			.555700
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.
Based on Type III Sum of Squares
The error term is Mean Square(Error) = 2.753E-03.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha = .05.

Table 181. Test of statistics on the effect of core to wall ratio on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated gastric fluid without pepsin pH 1.2 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	.702	2	.351	106.403	.000
	Within Groups	1.979E-02	6	3.298E-03		
	Total	.722	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

RATIO	N	Subset for alpha = .05	
		1	2
11	3	5.59E-02	
12	3		.586300
13	3		.695167
Sig.		1.000	.059

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 182. Test of statistics on the effect of inlet air temperature on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated gastric fluid without pepsin pH 1.2 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	6.864E-02	2	3.432E-02	13.634	.006
	Within Groups	1.510E-02	6	2.517E-03		
	Total	8.375E-02	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

		Subset for alpha = .05	
INLETAIR	N	1	2
130	3	.373133	
110	3		.495233
120	3		.586300
Sig.		1.000	.068

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 183. Test of statistics on the effect of feed rate on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated gastric fluid without pepsin pH 1.2 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	.679	2	.340	191.454	.000
	Within Groups	1.064E-02	6	1.773E-03		
	Total	.690	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

		Subset for alpha = .05		
FEEDRATE	N	1	2	3
18	3	9.26E-02		
24	3		.586300	
30	3			.735300
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 184. Test of statistics on the effect of solid content on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated gastric fluid without pepsin pH 1.2 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	.675	2	.338	96.121	.000
	Within Groups	2.107E-02	6	3.512E-03		
	Total	.696	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

CONTENT	N	Subset for alpha = .05	
		1	2
5	3	1.64E-02	
7	3		.586300
10	3		.607967
Sig.		1.000	.670

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 185. Test of statistics on the effect of core to wall ratio on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated intestinal fluid without pancreatin pH 6.8 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	1.105	2	.553	474.357	.000
	Within Groups	6.991E-03	6	1.165E-03		
	Total	1.112	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

		Subset for alpha = .05		
RATIO	N	1	2	3
11	3	7.12E-02		
12	3		.777600	
13	3			.846833
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 186. Test of statistics on the effect of inlet air temperature on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated intestinal fluid without pancreatin pH 6.8 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	9.572E-02	2	4.786E-02	46.991	.000
	Within Groups	6.111E-03	6	1.018E-03		
	Total	.102	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

		Subset for alpha = .05		
INLET	N	1	2	3
130	3	.525667		
110	3		.667667	
120	3			.777600
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 187. Test of statistics on the effect of feed rate on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated intestinal fluid without pancreatin pH 6.8 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	1.166	2	.583	235.596	.000
	Within Groups	1.485E-02	6	2.475E-03		
	Total	1.181	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

FEEDRATE	N	Subset for alpha = .05		
		1	2	3
18	3	9.94E-02		
24	3		.777600	
30	3			.926500
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 188. Test of statistics on the effect of solid content on the time of 50% released from the amoxycillin microcapsules prepared by spray-drying technique in simulated intestinal fluid without pancreatin pH 6.8 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	1.746	2	.873	248.064	.000
	Within Groups	2.112E-02	6	3.519E-03		
	Total	1.767	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

CONTENT	N	Subset for alpha = .05		
		1	2	3
5	3	8.03E-03		
7	3		.777600	
10	3			1.047700
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

Table 189. Test of statistics on the effect of polymer on the time of 50% released from the amoxycillin microcapsules in simulated gastric fluid without pepsin pH 1.2 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	.207	2	.103	10.713	.010
	Within Groups	5.786E-02	6	9.643E-03		
	Total	.264	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

POLYMER	N	Subset for alpha = .05	
		1	2
2	3	.354133	
3	3		.607967
1	3		.715533
Sig.		1.000	.228

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

1 = gelatin-acacia

2 = gelatin-SCMC

3 = polyvinylacetate

Table 190. Test of statistics on the effect of polymer on the time of 50% released from the amoxycillin microcapsules in simulated intestinal fluid without pancreatin pH 6.8 by ONE-WAY ANOVA.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T50	Between Groups	.632	2	.316	51.505	.000
	Within Groups	3.680E-02	6	6.133E-03		
	Total	.669	8			

Post Hoc Tests
Homogeneous Subsets

T50

Duncan[a]

		Subset for alpha = .05		
POLYMER	N	1	2	3
2	3	.398833		
1	3		.712567	
3	3			1.047700
Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3.000

1 = gelatin-acacia

2 = gelatin-SCMC

3 = polyvinylacetate

VITA

Miss Atchara Maimansomsook was born on Febuary 26, 1976 in Saraburi, Thailand. She received the Bachelor degree of Pharmacy from the Faculty of Pharmacy, Huachiew Chalermprakieat University, Samutr-prakarn in 1998. She entered the Master's Degree Program in Pharmacy at Chulalongkorn University in 1998.