การพัฒนาระบบนำส่งยาที่ควบคุมการปลดปล่อยด้วยระบบออสโมซิสโดยใช้แคปซูลเจลาตินแข็งชนิดครอสลิงก์และไม่ครอสลิงก์

นางสาว นิจรัตน์ วิเชียรประสิทธิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาวิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2552

DEVELOPMENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM USING CROSSLINKED AND NON-CROSSLINKED HARD GELATIN CAPSULES

Miss Nijarat Wichianprasit

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Pharmacy Program in Industrial Pharmacy
Department of Pharmaceutics and Industrial Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 2009

Thesis Title	DEVELOPMENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM USING CROSSLINKED AND NON-CROSSLINKED HARD GELATIN CAPSULES
By	Miss Nijarat Wichianprasit
Field of Study	Industrial Pharmacy
Thesis Advisor	Associate Professor Poj Kulvanich, Ph.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

.....Dean of the Faculty of Pharmaceutical Sciences
(Associate Professor Pintip Pongpech, Ph.D.)

THESIS COMMITTEE

..... Chairman
(Associate Professor Kraisri Umprayn, Ph.D.)

..... Thesis Advisor
(Associate Professor Poj Kulvanich, Ph.D.)

..... Examiner
(Jittima Chatchawalsaisin, Ph.D.)

..... Examiner
(Phanphen Wattanaarsakit, Ph.D.)

..... External Examiner
(Associate Professor Sontaya Limmatvapirat, Ph.D.)

นิจรัตน์ วิเชียรประสิทธิ์ : การพัฒนาระบบนำส่งยาที่ควบคุมการปลดปล่อยด้วยระบบออสโมซิสโดยใช้แคปซูลเจลาตินแข็งชนิดครอสลิงก์และไม่ครอสลิงก์. (DEVELOPMENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM USING CROSSLINKED AND NON-CROSSLINKED HARD GELATIN CAPSULES) อ.ที่ปรึกษาวิทยานิพนธ์หลัก : รศ. ดร. พจน์ กุลวานิช, 172 หน้า.

วัตถุประสงค์ของงานวิจัยนี้เพื่อศึกษาลักษณะการปลดปล่อยยา จากระบบนำส่งยาที่ควบคุมการปลดปล่อยด้วยระบบออสโมซิสที่ใช้เปลือกแคปซูลเจลาตินแข็งชนิดครอสลิงก์ และไม่ครอสลิงก์ โดยใช้ยาดิลไทอะเซมไฮโดรคลอไรด์ซึ่งเป็นยาที่มีค่าการละลายน้ำสูง และยาละลายน้ำโพรพราโนลอลไฮโดรคลอไรด์ เป็นยาต้นแบบ สารก่อแรงดันออสโมติกใช้โซเดียมคลอไรด์ โดยมีแล็กโทสเป็นสารเพิ่มปริมาณ การเตรียมครอสลิงก์แคปซูลใช้การรมแคปซูลด้วยไอฟอร์มาลดีไฮด์ เตรียมระบบนำส่งยาโดยบรรจุผงผสมของตัวยาและสารช่วยลงในแคปซูล เบอร์1 ทำการเคลือบแคปซูลด้วยสารละลายไฮดรอกซีโพรพิลเมทิลเซลลูโลส และเคลือบทับด้วยสารละลายเซลลูโลสแอซิเตต จากนั้นจึงนำแคปซูลมาเจาะรูที่ส่วนหัว การปลดปล่อยยาทำการศึกษาในน้ำ สารละลายโซเดียมคลอไรด์ที่มีความเข้มข้นแตกต่างกัน และสารละลายที่มีความเป็นกรดเบสแตกต่างกัน แต่มีความแรงไอออนเท่ากัน เวลาเริ่มปลดปล่อยยาของระบบนำส่งยาที่ใช้แคปซูลชนิดครอสลิงก์ช้ากว่าระบบที่ใช้แคปซูลชนิดไม่ครอสลิงก์ สำหรับระบบนำส่งยาดิลไทอะเซมไฮโดรคลอไรด์ที่ใช้แคปซูลทั้งสองแบบสามารถปลดปล่อยยาได้นานประมาณ 9 ชั่วโมง และสามารถปลดปล่อยยาใกล้เคียงลำดับศูนย์ (zero-order) ได้ประมาณร้อยละ 80 ของปริมาณยาทั้งหมด (R^2>0.9) อัตราการปลดปล่อยยาจากระบบนำส่งยาที่ใช้แคปซูลทั้ง 2 แบบมีลักษณะคล้ายกัน ในส่วนของระบบนำส่งยาโพรพราโนลอลไฮโดรคลอไรด์ที่ใช้แคปซูลไม่ครอสลิงก์และครอสลิงก์สามารถปลดปล่อยยาได้นานประมาณ 9 ชั่วโมง และ 12 ชั่วโมงตามลำดับ และสามารถปลดปล่อยยาใกล้เคียงลำดับศูนย์ (zero-order) ได้ประมาณร้อยละ 90 ของปริมาณยาทั้งหมด (R^2>0.9) พบว่าระบบที่ใช้แคปซูลครอสลิงก์จะมีอัตราการปลดปล่อยยาโพรพราโนลอลใกล้เคียงลำดับศูนย์มากกว่า และความแปรปรวนของการปลดปล่อย ณ จุดเวลาต่างๆน้อยกว่า ในขณะที่อัตราการปลดปล่อยยาดิลไทอะเซมไฮโดรคลอไรด์ จากระบบที่ใช้แคปซูลทั้งสองแบบมีความคล้ายคลึงกัน อาจเนื่องมาจากค่าการละลายที่สูงกว่าของยาดิลไทอะเซมไฮโดรคลอไรด์ โดยความแรงไอออนในสารละลายมีผลต่อการปลดปล่อยยา แต่ความเป็นกรดเบสของสารละลายไม่มีผลต่อการปลดปล่อยยา

ภาควิชา วิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม ลายมือชื่อนิสิต นิจรัตน์

สาขาวิชา เภสัชอุตสาหกรรม ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก

ปีการศึกษา 2552

5076572633 : MAJOR INDUSTRIAL PHARMACY
KEYWORDS : OSMOTICALLY CONTROLLED DRUG DELIVER SYSTEM / HARD GELATIN CAPSULE/ FLUIDIZED BED / CROSSLINKED/ CELLOLUSE ACETATE

NIJARAT WICHIANPRASIT : DEVELOPMENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM USING CROSSLINKED AND NON-CROSSLINKED HARD GELATIN CAPSULES. THESIS ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 172 pp.

The aim of this study was to explore the release characteristics of an elementary osmotic pump capsule (OPC) by using a crosslinked and a non-crosslinked hard gelatin capsule shell. The influences of drug solubility, film thickness and orifice size on drug release from the system were examined. Diltiazem hydrochloride (freely water soluble drug) and propranolol hydrochloride (water soluble drug) were used as the model drugs. Sodium chloride was used as the osmotic agent. Crosslinked hard gelatin capsules were prepared by controlled exposure to formaldehyde vapours. The OPC was prepared by filling the capsule No. 1 with the mixture of the model drug (90 mg), lactose and sodium chloride. Core capsules were coated using hydroxypropyl methylcellulose as subcoating and cellulose acetate as the semipermeable membrane; then the coated capsule was drilled on the rounded end position. Drug release studies were conducted using water, different ionic strength and pH solutions with isotonicity as the dissolution media. Lag time of drug release from the OPC using the crosslinked capsule was longer than that the non-crosslinked capsule shell. Diltiazem hydrochloride OPC using the non-crosslinked and crosslinked capsules could prolong drug release about 9 hours and closed to zero-order drug release rate up to 80 % of drug release (R^2>0.9). Propranolol hydrochloride OPC using a non-crosslinked capsule and a crosslinked capsule could prolong drug release about 9 and 12 hours, respectively. About 90 % of the drug was released as zero-order rate for propranolol hydrochloride OPC (R^2 >0.9). It was found that propranolol hydrochloride OPC using the crosslinked capsule shell provided less fluctuations of release rate at various time intervals than using the non-crosslinked capsule. But the characteristics of release rate at various time points of diltiazem hydrochloride OPC prepared using different types of capsule shell was apparently similar. This might be attributed to the higher water soluble property of diltiazem hydrochloride. Ionic strength of dissolution media had effect on drug release of OPC. But drug release of OPC was independent of pH of dissolution media.

Department : Pharmaceutics and Industrial Pharmacy Student's Signature .....

Field of Study : Industrial Pharmacy Advisor's Signature .....

Academic Year : 2009

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Associate Professor Poj Kulvanich for his advice, guidance and encouragement. His kindness, patience and understanding are also deeply appreciated.

I also wish to express deep appreciation to all members of the thesis committee for spending their times to be on my thesis committee and for their suggestions and comments.

I would like to express my infinite thanks and deepest gratitude to my friends and staff members of the Department of Pharmaceutics and Industrial Pharmacy for their assistance and encouragement.

I would like to acknowledge the Thailand Research Fund and the Graduate School, Chulalongkorn University for financial support through the TRF Master Research Grants (Grant No. MRG-WII525S003) and the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund).

The other special thank to Siam Bheasach Co., Ltd for supplied the active ingredient, diltiazem hydrochloride and CAPSUGEL Co., Ltd for supplied the hard gelatin capsule to my study.

Finally, I would like to express my thanks to my family for their assistance, care cheerfulness and encouragement.

CONTENTS

LIST OF TABLES

Table Page

Table Page

Table Page

Table Page

Table Page

Table Page

Table Page

Table Page

Table Page

Table Page

LIST OF FIGURES

Figure Page

Figure Page

Figure Page

Figure Page

Figure Page

Figure Page

Figure Page

LIST OF ABBREVATIONS

%	percentage
ºC	degree Celsius (centrigrade)
CA	cellulose acetate
cm	centimeter (s)
CV	coefficient of variation
DI	deionized
et.al.	et alli, and others
g	gram(s)
HCl	hydrochlorid acid
hr	hour (s)
M	molarity
mcg	microgram (s)
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
mm	millimeter (s)
NaCl	sodium chloride
nm	nanometer (s)
OPC	osmotic pump capsule (s)
PBS	phosphate buffer solution
pH	the negative logarithm of hydrogen ion concentration
R^2	coefficient of determination
rpm	revolution (s) per minute
RSD	relative standard deviation
SD	standard deviation
SEM	scanning electron microscope

CHAPTER I
INTRODUCTION

Osmotic system is one of controlled release delivery systems that provide a uniform concentration of drug result for plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. Osmotic drug delivery tend to provide zero-order delivery and to deliver a greater percentage of the drug loading.

Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Osmosis is phenomena that solvent from lower concentration will move to higher concentration solution across semipermeable membrane, which is permeable to solvent only. The chemical potential of solution in two compartments will be equalized when pressure of the higher concentration solution compartment reaches the osmotic pressure of the solution (Wright and Stevenson, 1999) (Figure 1). Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system (Theeuwes et al., 1985). Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs. At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate.

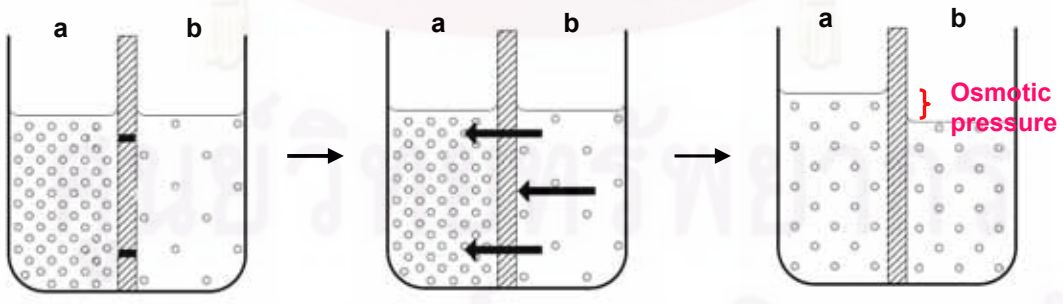


Figure 1 A schematic illustration of osmotic phenomena

Initial commercial oral dug delivery system was OROS^{TM} that use for deliver indomethacin (Theeuwes, 1983). After that several studies investigated about parameters that had effect on delivery of elementary osmotic pump such as

- osmotic agent
- semipermeable membrane polymer
- membrane plasticizer
- thickness of semipermeable membrane
- drug delivery orifice

There are a few studies about using hard gelatin capsules with elementary osmotic pump system. Most osmotic pump capsules (OPC) studies are asymmetric membrane system. This system is made from semipermeable membrane capsule that can form pore when contact with water. Previous studies reported the devolpment of asymmetric membrane OPC that using semipermeable capsules (Thombre *et al*., 1999). Asymmetric membrane capsule is produced by phase inversion technique. However, the process to produce this system is very complicated and expensive because special equipment use for production of semipermeable capsule. In previous investigation, non-crosslinked hard gelatin capsules had been used and was found the fluctuation of propranolol hydrochloride release (Siroratsakul, 2004). Drug release variation might be caused by disolved gelatin capsule forms a viscous mass inside OPC, therefore, drug release fluctuation should be reduced by crosslinked hard gelatin capsules which are insoluble. Drug solubility might effect on drug delivery from the system.

The purpose of this study was to examine drug release from elementary osmotic pump capsules using crosslinked and non-crosslinked hard gelatin capsules with various parameters such as film thickness and size of drug delivery orifice. In this study, different solubility model drugs were propranolol hydrochloride which is soluble drug in water and diltiazem hydrochloride which is freely soluble drug in water (O'Neil, 2006)

CHAPTER II
LITERATURE REVIEW

Controlled release systems can provide drug release prolongation, maintenance of drug levels in plasma in therapeutic range, side effect reduction and reduction of dosing frequency. Osmotically controlled drug delivery system is one of controlled release systems, which utilize osmotic pressure for drug delivery. The osmotic systems developments include contributions such as the Rose-Nelson pump, Higuchi-Leeper pump, Higuchi-Theeuwes pump and Theeuwes elementary osmotic pump.

Rose-Nelson pump

The Rose-Nelson was developed by Rose and Nelson that utilized the principles of osmotic pressure in drug delivery for the first time. This pump consists of three chambers : drug chamber , salt chamber and water chamber. The operation of this system will start when water from water chamber passes semipermeable membrane to salt chamber causes pressure in salt chamber increases then elastic diaphragm will expand and push drug solution out. Operation principle of this pump illustrates in Figure 2 (Rose and Nelson, 1955).

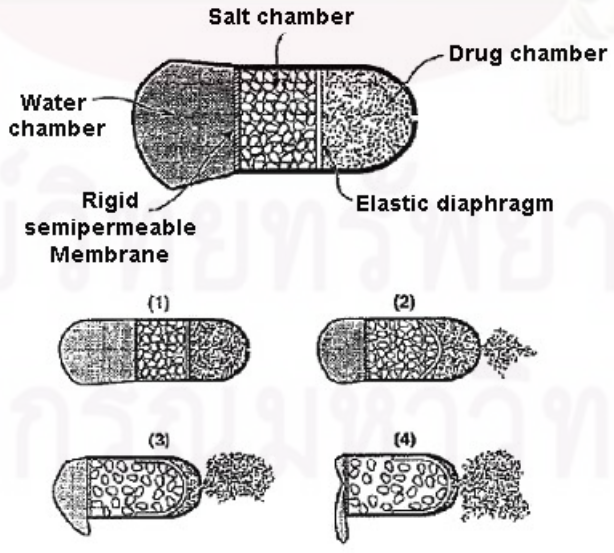


Figure 2 Operation principle of Rose-Nelson pump (Rose and Nelson, 1955).

Higuchi-Leeper pump

The Higuchi-Leeper pump was developed by Takeru Higuchi and Harold M Leeper. In this design, water chamber is removed. Because device, which has water chamber, is difficult to produce. So this system consists of two chambers only: Drug chamber and salt chamber (Figure 3). The operation of this system will start when water from environment passes semipermeable membrane to salt chamber causes pressure in salt chamber increases then movable separator will move and push drug solution out (Higuchi and Leeper, 1973).

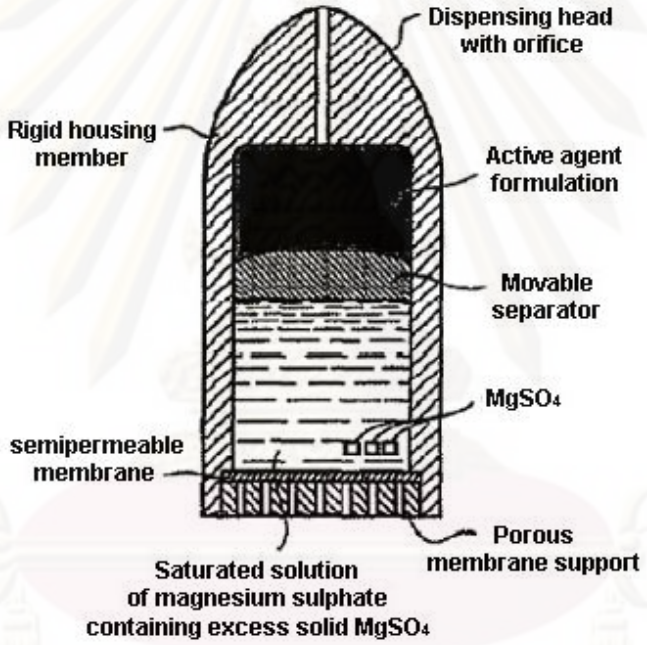


Figure 3 Basic components of a Higuchi-Leeper osmotic pump (Higuchi and Leeper, 1973).

Higuchi-Theeuwes pump

The Higuchi-Theeuwes pump was developed by Takeru Higuchi and Felix Theeuwes. This design and operation are similar to Higuchi-Leeper pump. But Higuchi-Theeeuwes pump can deliver semisolid substance (Figure 4) (Higuchi and Leeper, 1976).

Higuchi-Theeuwes mini pump is a model of Alzet® osmotic pumps which are well known miniature, implantable pumps used for research in laboratory animals (Figure 5 and 6) (Higuchi and Leeper, 1976 ; DURECT Corporation, 2008).

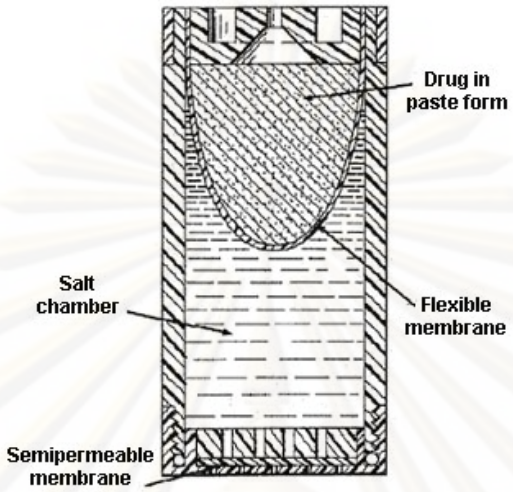


Figure 4 Higuchi-Theeuwes design utilising a flexible bag (Higuchi and Leeper, 1976)

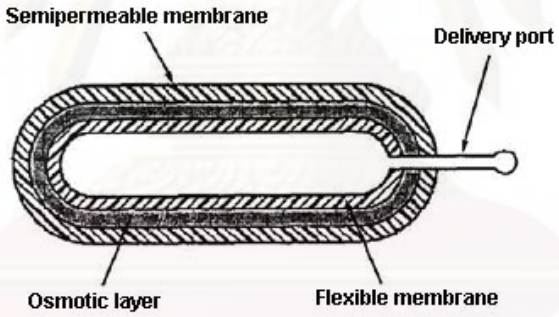


Figure 5 Components of the Higuchi-Theeuwes mini-pump (Higuchi and Leeper, 1976)

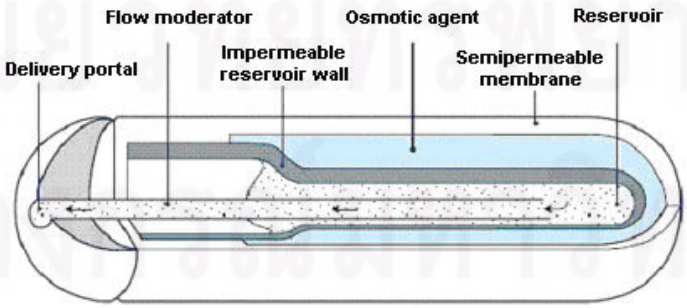


Figure 6 Schematic of Alzet ® osmotic pump (DURECT Corporation, 2008).

Theeuwes elementary osmotic pump

Theeuwes elementary osmotic pump is first oral osmotically drug delivery system which is very simple. In this elementary osmotic pump basic form, drug core is surrounded by semipermeable membrane with a drug delivery orifice (Figure 7). This pump is the most popular that used for oral drug delivery. This system is suitable for moderate to high solubility drugs. Elementary osmotic pump tablet working will start when surrounding water passes membrane and dissolves core containing agent. Then inside tablet pressure increases and drug solution passes through the delivery orifice to reduce pressure in system until pressure outside and inside tablet are equal.

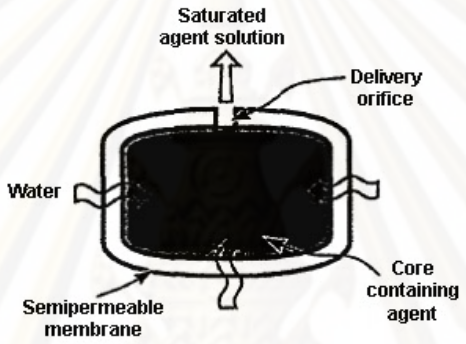


Figure 7 The basic concept of the Theeuwes elementary osmotic pump (Theeuwes and Higuchi, 1974)

Oral Osmotic Drug Delivery

Oral osmotic drug delivery give zero delivery rate and predictable drug release. Drug release of this system is not depending on pH, hydrodynamics of the external dissolution medium and outside agitation. Moreover, It has an excellent in vitro/in vivo correlation (Theeuwes, 1975). Osmotic drug delivery can use for drugs with a broad range of aqueous solubilities (Thombre et al., 2004).

Elementary osmotic pump

Elementary osmotic pump is simply design controlled drug delivery system. This pump can deliver 60–80% of its contents at a constant rate (Theeuwes, 1975) but it has short lag time of 30–60 min as the system hydrates before zero-order delivery

(Verma et al., 2000). It need a delivery port to deliver the drug at required rate (Theeuwes et al., 1983). Size of delivery orifice had no effect on drug delivery rate when use low agitation (Ramdan and Tawashi, , 1987). Optimum range of orifice size can control stable drug delivery (Ozdemir and Sahin, 1997 ; Mohammadi-Samani, 2000). Osmotic pump tablet with non-drilling orifice can be prepared by indent core tablet. This tablet had an orifice which is produced by punch with a needle (Liu and Che, 2006 ; Liu and Xu, 2008).

1. Simple elementary osmotic pump

Simple elementary osmotic pump is a homogeneous core which is surrounded by semipermeable membrane. It is suitable for moderate to high water soluble drug (Verma et al., 2002). The operation of this pump starts when contacts with water and agent inside osmotic pump draws water passes the semipermeable membrane (Figure 8). Volume in osmotic pump increased caused by the imbibition of water result for the development of pressure inside it. This pressure is relieved by flow of saturated solution out of the device via the delivery orifice. Delivery rate is still constant until the solid substance inside the device has been dissolved and only a solution-filled coating membrane is left. This residual dissolved substance continue to be delivered at decrease rate till osmotic pressure inside and outside the device are equal.

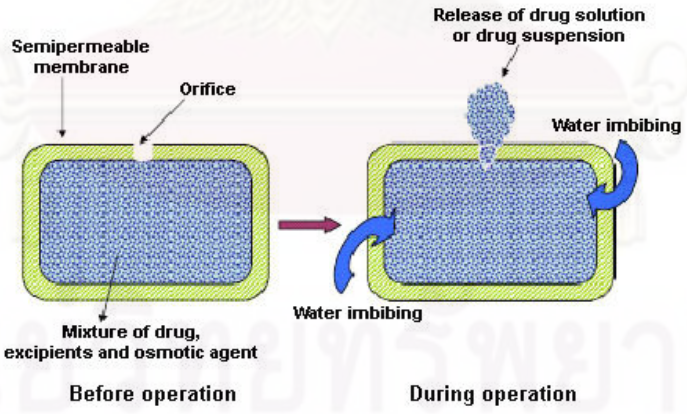


Figure 8 Operation of simple elementary osmotic pump (Shokri et al., 2007).

2 Modified elementary osmotic pump

Modified elementary osmotic pump is composed of multilayer core which is surrounded by semipermeable membrane. This system can be applied for poorly water

soluble drug to freely water soluble drug (Theeuwes et al., 1983). This pump has various designs. Modified elementary osmotic pump tablets is shown in Figure 9. The operation of this system is similar to simple elementary osmotic pump but it has swellable layer for assisting drug release (Figure 10). L-OROS^{TM} System was modified elementary osmotic system that produced in hard capsules and soft capsules dosage form for liquid or paste preparation delivery (Figure 11).

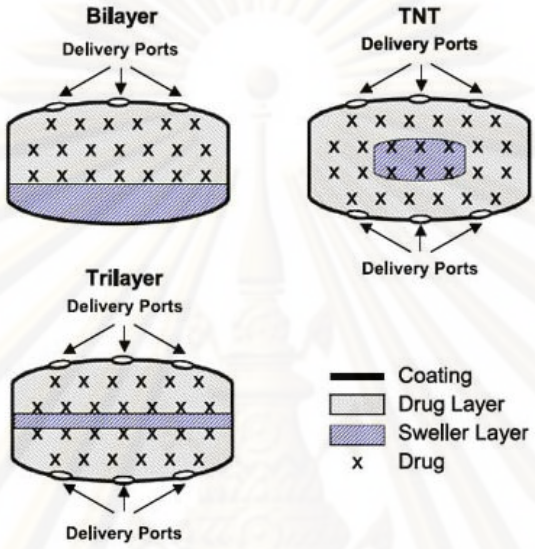


Figure 9 Schematic diagrams of three modified elementary osmotic pump : tablet-in-tablet (TNT), bilayer or push-pull, and trilayer or sandwiched (Thombre et al., 2004)

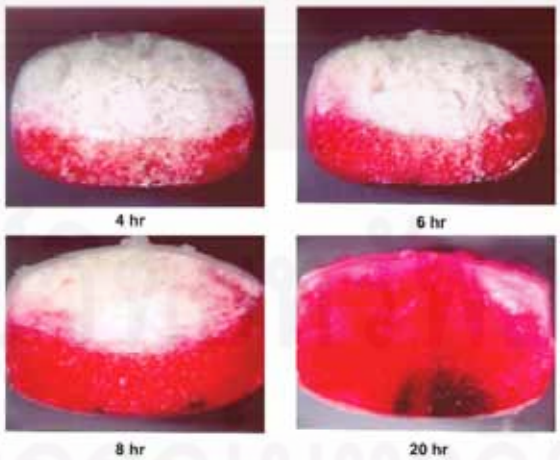


Figure 10 Cross-sectional photographs at various time from a bilayer SCT formulation. A red dye was included in the water swellable compositions (Thombre et al., 2004).

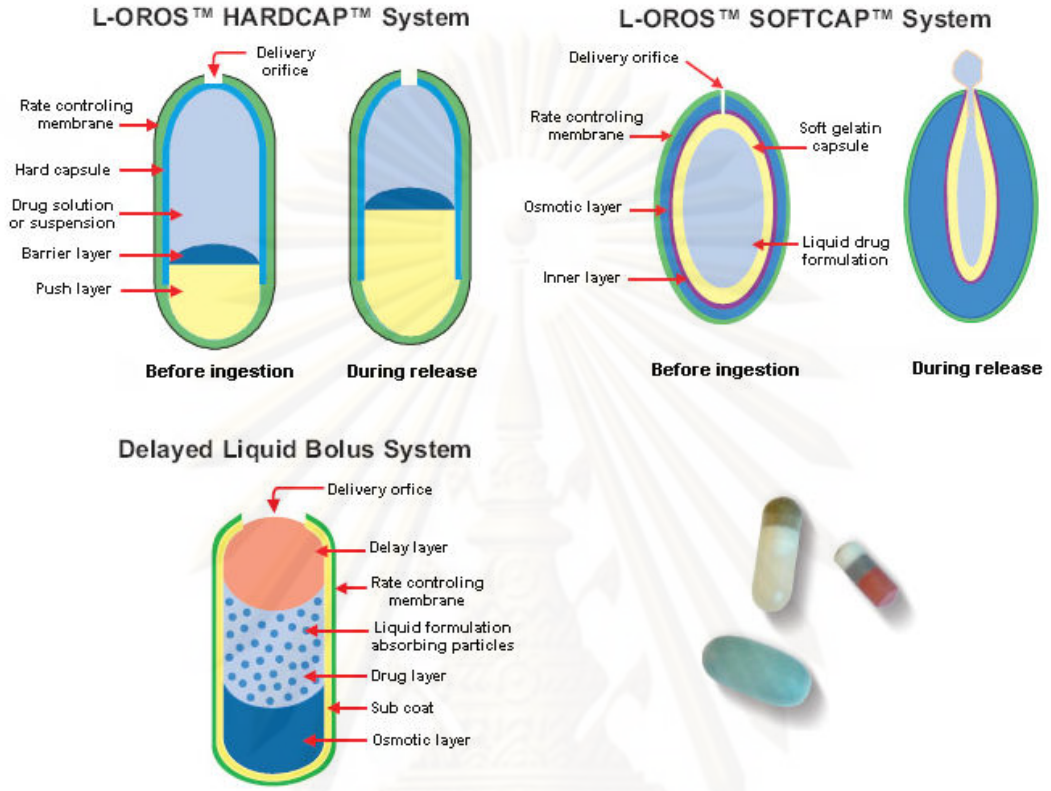


Figure 11 Schematic diagrams of L-OROS™ and delayed liquid bolus system (Wong, 2005).

Controlled porosity or asymmetric membrane osmotic pump

Asymmetric membrane is film that thin dense region relatively supported on a thicker porous region. This membrane is prepared by the phase inversion technique (Figure 12) (Thombre et al., 1999). Asymmetric membrane is *In situ* pore formation film (Figure 13 and 14). This system has higher rate of water influx due to the micro porous nature of membrane. It is suitable for poorly water soluble drug (Choudhury et al., 2007). For example, drug delivery of gilpizide was asymmetric membrane capsule with encapsulated excipients. This system was asymmetric membrane capsule filled with drug, additives, mini-tablets of osmogent/solubility modifier and coated mini-tablets of osmogent/solubility modifier that controlled glipizide delivery (Figure 15).

pH-controlling agent (meglumine) was used as osmotic agent and solubility modifier (Thombre et al., 1999). Coudhury et al. (2007) study effect of osmotic agent on flurbiprofen delivery from asymmetric membrane capsule. Asymmetric capsule sustained release of rifampicin and isoniazid can be provided by mixture of hydrophilic polymer and drug (Prabakaran et al., 2004).

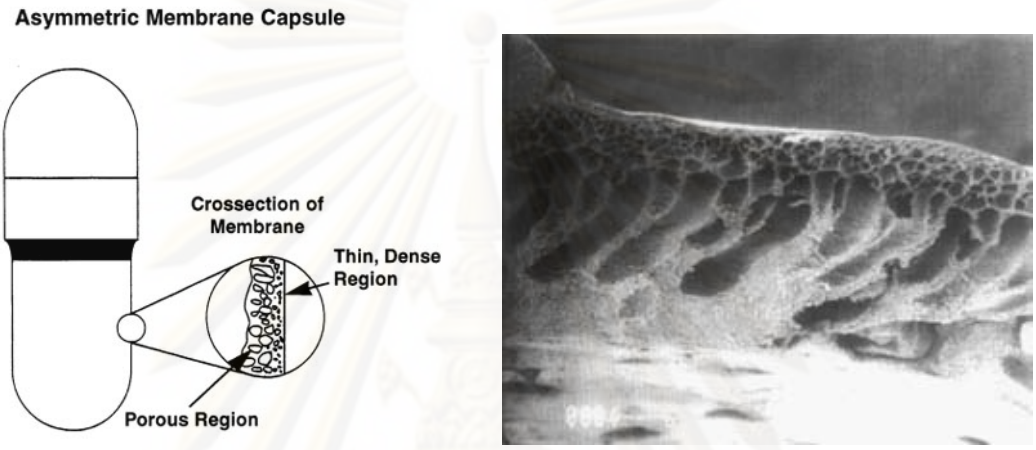


Figure 12 Asymmetric membrane wall cross-section (Thombre et al., 1999).

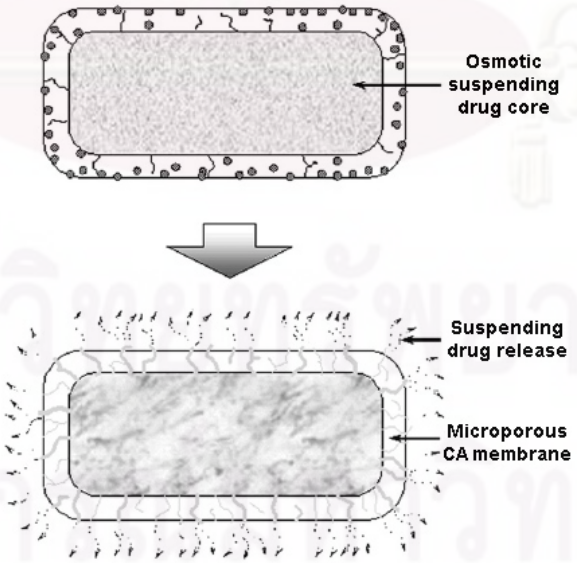


Figure 13 Operation of controlled porosity tablets (Liu et al., 2007).

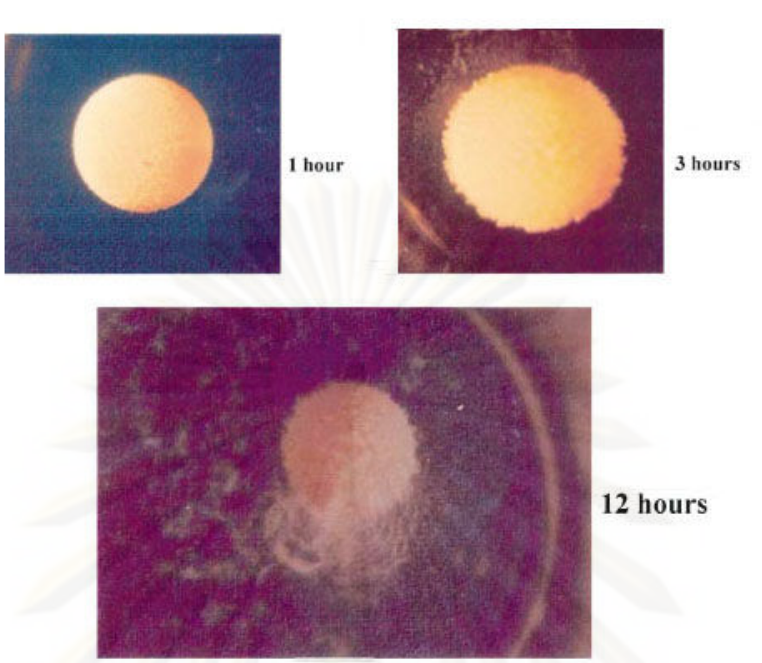


Figure 14 Controlled porosity bolus tablet kept in dissolution medium 1, 3 and 12 hrs (Makhija and Vavia, 2003)

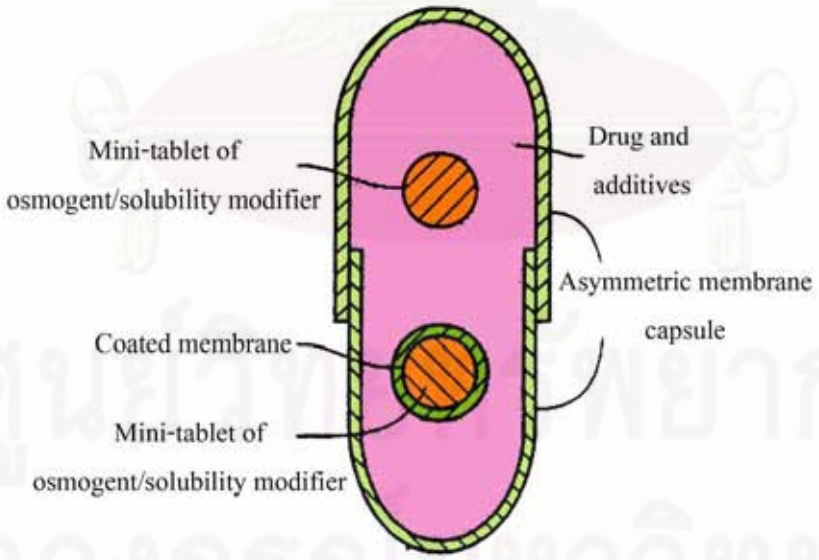


Figure 15 Asymmetric membrane capsule with encapsulated excipients (Thombre et al., 1999)

Delivery Rate

1. Delivery rate of simple elementary osmotic pump (Theeuwes, 1975)

The delivery of substance from the system is controlled by the water influx across the semipermeable membrane which carries the substance to the outside. Equation 1 (Eq. 1) describes the volume flux (dv/dt) across the semipermeable membrane

$$\frac{dV}{dt} = \frac{A}{h} L_p (\sigma \Delta\pi - \Delta P) \qquad \text{(Eq. 1)}$$

dV/dt = volume flux
A = membrane area
h = membrane thickness
L_p = mechanical permeability
σ = reflection coefficient
$\Delta\pi$ = osmotic pressure difference
ΔP = hydrostatic pressure difference

Equation 2 (Eq. 2) describes the solution delivery rate (*dm/dt*) obtained by pumping through the orifice.

$$\frac{dm}{dt} = \frac{dV}{dt} C \qquad \text{(Eq 2)}$$

dm/dt = solute delivery rate
C = concentration of compound in the dispensed fluid

Replacing Eq1 into Eq 2 results in Eq 3.

$$\frac{dm}{dt} = \frac{A}{h} L_p (\sigma \Delta\pi - \Delta P) C \qquad \text{(Eq 3)}$$

As expressed condition $\Delta\pi >> \Delta P$, hydrostatic pressure inside the system is minimized (Equation 4).

$$\frac{dm}{dt} = \frac{A}{h} L_p \sigma \Delta \pi C \qquad \text{(Eq 4)}$$

The osmotic pressure of formulation (π) can be replaced for $\Delta\pi$ when the osmotic pressure of formulation is large compared to the osmotic pressure of environment (Equation 5).

$$\frac{dm}{dt} = \frac{A}{h} L_p \sigma \pi C \qquad \text{(Eq 5)}$$

π = osmotic pressure of formulation

Because L_p and σ is constant value. Therefore constant P_w can be replaced for L_p and σ (Equation 6).

$$\frac{dm}{dt} = \frac{A}{h} P_w \pi C \qquad \text{(Eq 6)}$$

P_w = water permeability of the semipermeable membrane

For zero-order delivery rate, elementary osmotic pump release rate is zero-order from t =0 until a time t_z at which time that all of the solid in the core dissolved. Equation 7 describes zero-order delivery rate from the elementary osmotic pump

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h} P_w \pi_s S \qquad \text{(Eq 7)}$$

S = the component solubility

π_s = osmotic pressure at saturation

From time t =0 to t =t_z, the component solubility (S) can replace the concentration (C). Because the single compound rate of dissolution within the system is much larger than the rate of pumping as given by Equation 7.

2. Delivery rate of asymmetric membrane (Ende et al., 2000)

A model expresses drug release from an asymmetric membrane dosage form consists of osmotic and diffusional contributions. The diffusional contribution is derived from the fact that the asymmetric membrane is not perfectly semipermeable membrane, and therefore a portion of drug is released by diffusion, primary through pores in coating. The total mass of drug delivery per unit time, $(dm/dt)_t$, is modeled by Equation 8.

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_o + \left(\frac{dm}{dt}\right)_d \qquad \text{(Eq 8)}$$

$\left(\frac{dm}{dt}\right)_t$ = total drug mass of drug delivered per time

$\left(\frac{dm}{dt}\right)_o$ = mass released by osmotic pumping

$\left(\frac{dm}{dt}\right)_d$ = mass released due to diffusion

Equation 9 describes the osmotic drug release component. This equation is same as drug release equation of simple elementary osmotic pump.

$$\left(\frac{dm}{dt}\right)_o = \frac{A}{h} P_w \pi C \qquad \text{(Eq 9)}$$

A = membrane area

h = membrane thickness

P_w = water permeability of the semipermeable membrane

C = concentration of compound in the dispensed fluid

Equation 10 describes the diffusional release component.

$$\left(\frac{dm}{dt}\right)_d = \frac{P_d AC}{h} \qquad \text{(Eq 10)}$$

P_d = drug permeability in the membrane

Equation 11 describes the total drug release profile.

$$\left(\frac{dm}{dt}\right)_t = \frac{A}{h} P_w \pi C + \frac{P_d AC}{h} \qquad \text{(Eq 11)}$$

Method of Preparation

1. Elementary osmotic pump

Process to produce elementary osmotic pump tablets or capsules begins with tableting or capsule filling. Then tablets or capsules are coated by semipermeable membrane polymer. Final step, tablets or capsules are drilled by mechanical drilling or laser drilling (Deters et al., 1986).

2. Asymmetric membrane

Process to produce asymmetric membrane tablets are similar to elementary osmotic tablet that begin with tableting by dry or wet granulation or direct compression but tablets are coated by asymmetric membrane polymer.

Asymmetric membrane capsule shells are filled with powder or granule. Then connection area of capsules is sealed. For example, Asymmetric membrane capsule shell is prepared by phase inversion technique. First, a mold pin is dipped in the polymer solution and removed from solution. Polymer are shortly dried after that pin

is placed in Aqueous Quench bath to make membrane parcipitation and capsule shell are take off from pin. Dip-coating process is shown in Figure 16.

Difference of preparation method between elementary osmotic pump and asymmetric membrane were represented in Table 1.

Table 1 Method of preparation elementary osmotic pump and asymmetric membrane

Elementary osmotic pump		**Asymmetric membrane**	
Tablets	**Capsules**	**Tablets**	**Capsules**
Tableting by granulation or direct compression	Semipermeable membrane capsules preparing	Tableting by granulation or direct compression	Semipermeable membrane capsules preparing
Coating	Capsule filling	Coating	Capsule filling
Drilling	Capsule banding		Capsule banding
	Drilling		

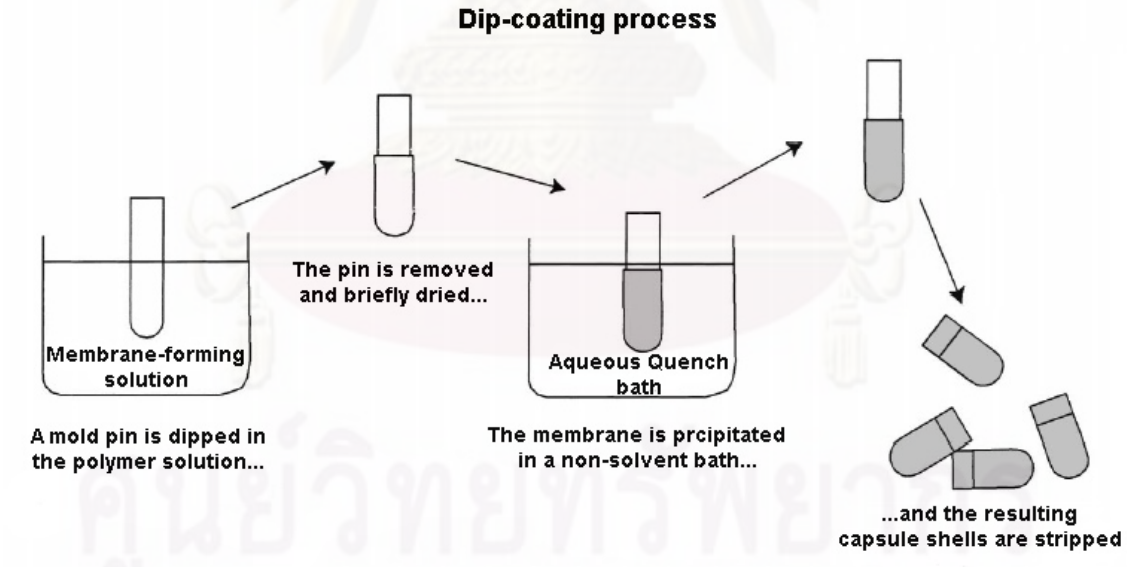


Figure 16 Phase inversion process for the manufacture of asymmetric membrane capsules (Thombre et al., 1999).

Osmotic Pump Excipients

1. Osmotic agent

Sodium chloride and potassium chloride are water soluble salt that widely use as osmotic agent in elementary osmotically drug delivery system (Lindstedt, et al. , 1989 ; Ozdemir and Sahin , 1997; Liu, et al. , 2000). Some studies used hydrophilic polymer or expanding agent as osmotic agent such as gum arabic , Polyethylene glycol 6000 (PEG 6000), Hydroxypropyl methylcellulose (HPMC), polyethylene oxide (PEO), polyvinyl pyrrolidine (PVP) and sodium carboxy methyl cellulose (NaCMC) (Liu, et al., 2000 ; Lu, et al., 2003; Prabakaran, et al., 2003). Table 2 shows example of osmotic pressure of saturated solutions.

2. Semipermeable membrane

Cellulose acetate is widely use semipermeable membrane polymer. A few studies selected ethylcellulose as semipermeable membrane (Lindstedt, et al. , 1989 ; Appel and Zetner , 1991). But ethylcellulose has lower water permeability than celluloase acetate (Bindschaedler, et al., 1986). Zhang, et al. (2003) study two layer osmotic pump tablet. HPMC was used as expanding layer (inner layer) and Eudragit® RS and RL was used as semipermeable membrane. Increasing membrane thickness causes drug delivery reduces when use same coating formulation (Mohammadi-Samani , 2000 ; Sinchaipanid, et al., 2003 ; Verma, et al. 2003 ; Verma, et al., 2004).

3. Plasticizer

Cellulose acetate film with plasticizer (PEG 400) 2 % had softer and less brittle characteristic than plain cellulose acetate film (Ozdemir and Sahin , 1997). Osmotic pump that was coated with semipermeable membrane with hydrophilic plasticizer (PEG 400) has higher delivery rate than osmotic pump that was coated semipermeable membrane using hydrophobic plasticizer (Triacetin) (Liu, et al., 2000). Drug delivery of osmotic pump increased when PEG 400 in film increased but membrane would fragile due to excess of plasticzer (Lu, et al., 2003). Poly(caprolactone triol) was use as plasticizer in system which used paracetamol as model drug.

Table 2 Examples of saturated solutions osmotic pressures (Zentner et al., 1990)

Compound or mixture	Osmotic pressure (atm)
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	335
Lactose-sucrose	250
Potassium chloride	245
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic · 12 H_2O	36
Sodium phosphate dibasic · 7 H_2O	31
Sodium phosphate dibasic · 12 H_2O	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic · H_2O	28

Table 3 Examples of osmotic pump excipients

Function	Material	Ref.
Osmotic agent	Sodium chloride	Makhija and Vavia (2003), Ende et al. (2000), Liu et al. (2000)
	Gum arabic	Zhang et al. (2003)
	Potassium chloride	Sinchaipanid et al. (2003), Lu et al. (2003)
	lactose	Choudhury et al. (2007)
	Xylitol	Theeuwes and Higuchi (1974)
	HPMC E5	Makhija and Vavia (2003)
	Gum arabic	Zhang et al. (2003)
	Polyethylene oxide	Lu et al. (2003), Liu et al. (2000)
	sodium starch glycolate	Theeuwes and Higuchi (1974)
	Croscarmellose sodium	Theeuwes and Higuchi (1974), Liu et al. (2003)
	Polyethylene oxide	Theeuwes and Higuchi (1974)
	Gum arabic	Zhang et al. (2003)
	Polyethylene oxide	Sinchaipanid et al. (2003), Lu et al. (2003), Theeuwes and Higuchi (1974)
	PVP K-90	Liu et al. (2003)
Semipermeable membrane	Eudragit RS-PO and RL-PO	Makhija and Vavia (2003)
	Cellulose acetate	Zhang et al. (2003), Choudhury et al. (2007), Sinchaipanid et al. (2003), Lu et al. (2003)
	Ethylcellulose	Liu et al. (2000)
Plasticizer	Triethyl citrate	Makhija and Vavia (2003), Sinchaipanid et al. (2003), Lu et al. (2003)
	PEG	Zhang et al. (2003), Choudhury et al. (2007), Sinchaipanid et al. (2003), Lu et al. (2003), Liu et al. (2003)
	Diethylphthalate	Choudhury et al. (2007)
	Dibutylphthalate	Choudhury et al. (2007)
	Dibutylsebacate	Choudhury et al. (2007)

Example of Marketed Products

1 CARDURA® XL (Available from : http://www.carduraxl.com)

This product is Doxazosin mesylate extended release tablet. It is used for treatment of benign postural hypotension (BPH). This product used push-pull osmotic pump for controlled drug release.

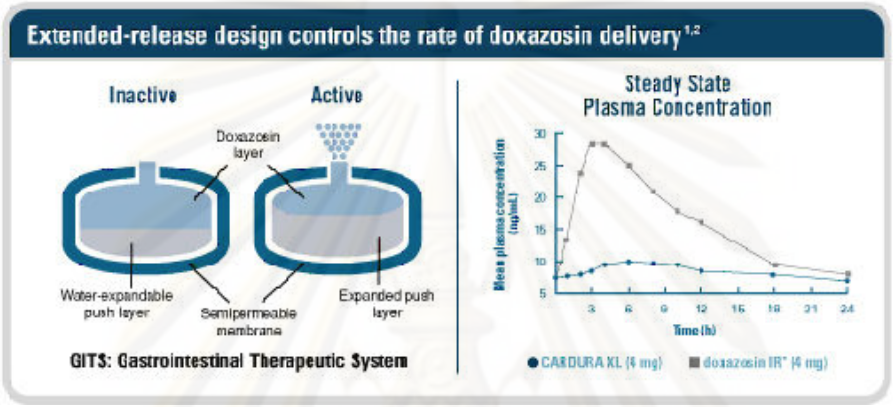


Figure 17 Operation of CARDURA® XL

2 CONCERTA® (Available from : http://www.concerta.net)

CONCERTA® is methylphenidate HCl once-daily tablet. Indication of this product is used for treatment of overactive bladder (OAB). Push-pull osmotic pump is utilized to controlled methylphenidate HCl release.

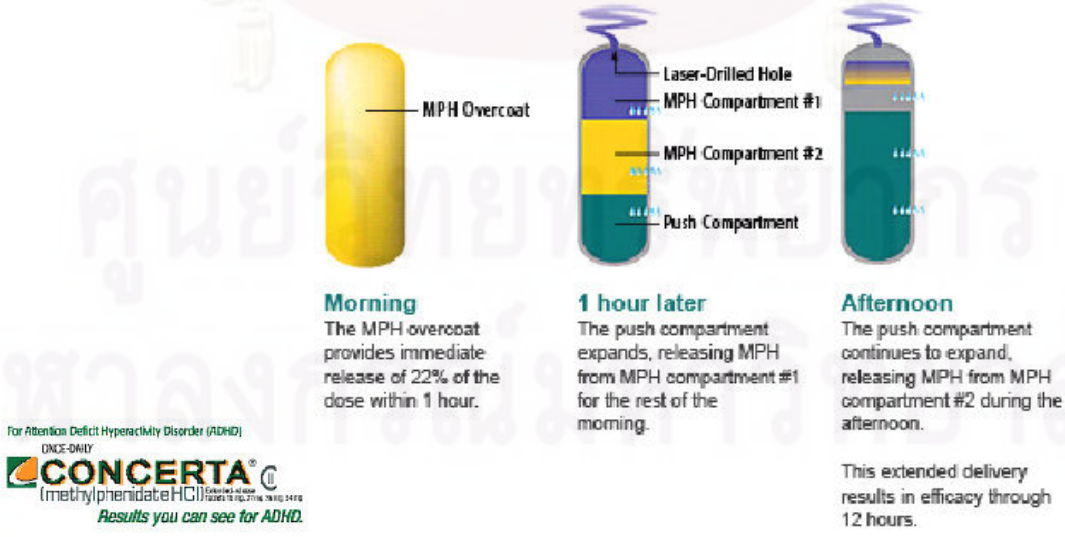


Figure 18 Operation of CONCERTA®

3 DITROPAN® XL (Available from : http://www.ditropanxl.com)

This product is oxybutynin cholride extended release tablet. This product used push-pull osmotic pump for controlled drug release. DITROPAN® XL is used for treatment of attention deficit hyperactivity disorder (ADHD).

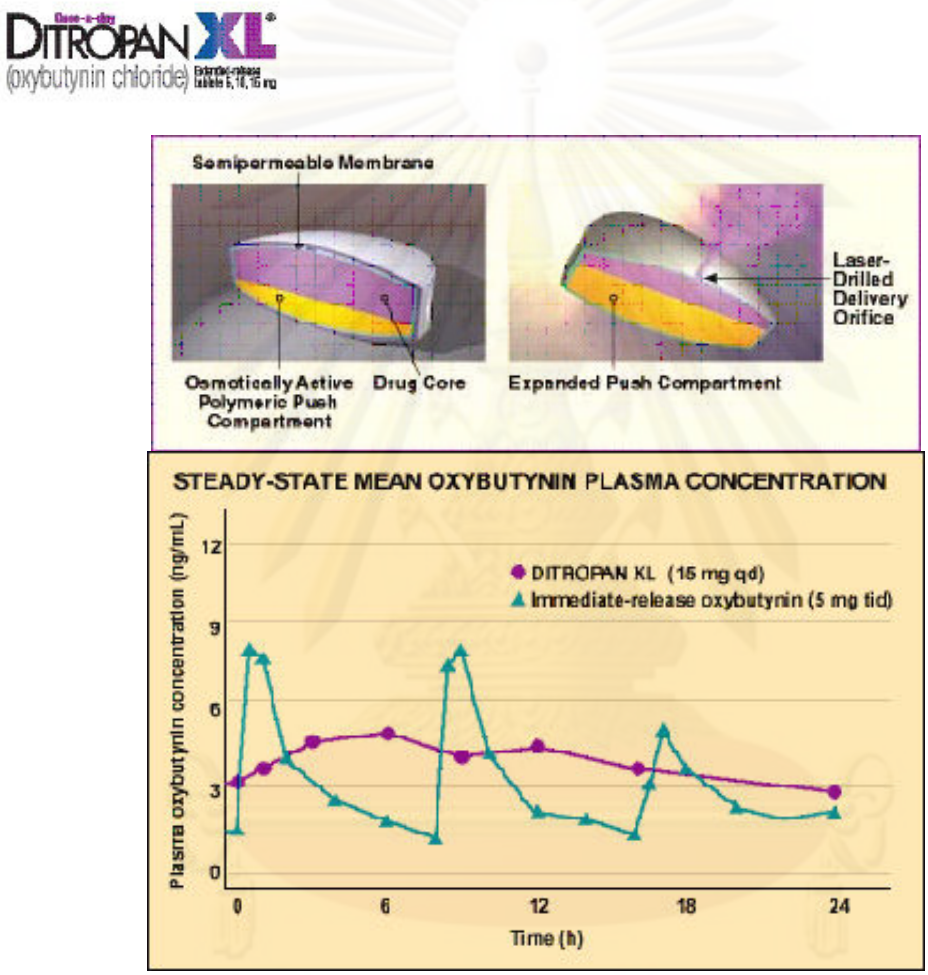


Figure 19 Operation of DITROPAN® XL

Diltiazem hydrochloride

Diltiazem hydrochloride is slow calcium channel blocker or calcium ion influx inhibitor (Reynolds, 1994).

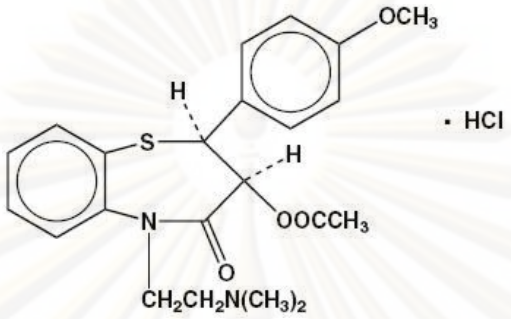


Figure 20 Chemical structure of diltiazem hydrochloride

Empirical name	$C_{22}H_{26}N_2O_4S \cdot HCl$
Chemical name	(2S,3S)-(+)-*cis*-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride
Chemical structure	Display in Figure 20
Molecular weight	450.98
Description	white to off white crystalline powder, odorless with a bitter taste
Melting point	207.5 to 212 ºC
Dissociation constant (pKa)	7.7
Solubility	Displayed in table 4
Stability	Diltiazem hydrochloride is very stable in solid state but UV light may be affected powder color changing. In aqueous system, diltiazem hydrochloride is stable over a pH range 3-6.

Table 4 Solubility of diltiazem hydrochloride in different media

Medium	Solubility (mg/ml)	Reference
Water	> 590	Zentner et al. (1991)
Simulated gastric fluid pH 1.2	636.63±3.41	Prabakaran et al. (2003)
Simulated intestinal fluid pH 6.8	606.38±1.68	Prabakaran et al. (2003)
0.25 M sodium chloride solution	545± 12	Zentner et al. (1991)
0.5 M sodium chloride solution	395± 29	Zentner et al. (1991)
0.75 M sodium chloride solution	278± 10	Zentner et al. (1991)
1 M sodium chloride solution	155±20	Zentner et al. (1991)

Propranolol hydrochloride

Propranolol hydrochloride is a non-selective β-adrenergic blocking agent (Reynolds, 1994).

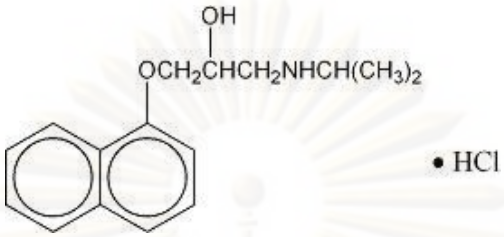


Figure 21 Chemical structure of propranolol hydrochloride

Empirical name	$C_{16}H_{21}NO_2 \cdot HCl$
Chemical name	(±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride
Chemical structure	Display in Figure 21
Molecular weight	295.8
Description	white to off white crystalline powder, odorless with a bitter taste
Melting point	163 to 166 ºC
Dissociation constant (pKa)	9.5
Solubility	Displayed in table 5
Stability	Propranolol hydrochloride solutions are most stable at pH of 3 and decompose rapidly under alkaline conditions. Light has effect on propranolol hydrochloride.

Table 5 Solubility of propranolol hydrochloride in different media

Medium	Solubility (mg/ml)	Reference
Water	50	Reynolds (1994)
Simulated gastric fluid pH 1.2	33.79 ± 0.09	Garg et al. (2007)
Simulated intestinal fluid pH 6.8	57.23 ± 1.08	Garg et al. (2007)

CHAPTER III

EXPERIMENTAL

Materials

The materials used and sourced of supply are as follows.

1. Model drugs:

   1.1 Diltiazem hydrochloride

   (Lot No. 08010814755, supplied by Siam Pharmaceutical Co., Ltd, Thailand),

   1.2 Propranolol hydrochloride

   (Lot No. M0808020, Changzhou Yabang Pharmaceutical Co., Ltd., China)

2. Capsule shell and crosslinked agent

   2.1 Hard gelatin capsule

   (Coni-Snap® Capsules, CAPSUGEL®, USA)

   2.2 Formaldehyde

   (CARLO ERBA, Italy)

3. Osmotic agents and filler

   3.1 Sodium chloride

   (Ajax Finechem, Australia)

   3.2 Lactose

   (Granulac ® 200, MEGGLE, Germany)

4. Film forming agents

4.1 Cellulose acetate (acetyl 39.8%)

(Lot No. AC-01467NF, CA-398-10NF/EP, Eastman Chemical Company, USA)

4.2 Hydroxypropyl methylcellulose

(Lot No. TD 23012406, METHOCEL™ E5 Premium, DOW® Chemical Company, USA)

4.3 Polyethylene glycol 6000

(Lot No. AF-401212, Ajax Finechem, Australia)

5. Solvents

5.1 Methylene chloride

(Mitsubishi Chemical, Japan)

5.2 Ethanol 95%

(Liquor Distillery Organization, Excise Department, Thailand)

6. Dissolution media

6.1 Deionized water

6.2 Hydrochloric acid 37%, AR grade

(J.T. Baker, USA)

6.3 Sodium hydroxide, AR grade

(Merck, Germany)

6.4 Tri-ortho sodium phosphate

(QRëC™, New Zealand)

Equipment

1. Semiautomatic filling capsule machine

   (Yiewheng , Thailand)

2. Fluidized bed coater

   (Model Strea1 , Niro-aeromatic , Germany)

3. Scanning electron microscope

   (Model JSM-5800LV , JEOL , Japan)

4. Dissolution apparatus

   (Model VK 7000 , VanKel , USA)

5. Ultraviolet/visible spectrophotometer

   (Model V-530 , Jasco , Japan)

6. Tablet friability tester

   (Model TA 3, Erweka, Germany)

7. Shaking incubator

   (Model Universal Shaking Incubator , DLabTech , India)

8. pH meter

   (Model 210A, Thermo Orion, USA)

9. Osmometer

   (Model Osmomat 030 , GONOTEC , Germany)

Methods

1. Crosslinked Capsule Shells

1.1 Investigate optimum time for preparation of crosslinked capsule shell

Cap and body of clear gelatin capsules were separated and lined on petri dish. Petri dish was placed in dessicator fill with formaldehyde at various length of time. Then capsules were taken to evaluate by visual characterization and determination of weight changed of capsule shell before and after stirred in various medium.

1.2 Preparation of crosslinked capsule shells

Crosslinked hard gelatin capsules were prepared by exposure of hard gelatin capsule shell to formaldehyde vapor for 6 hrs in dessicator filled with formaldehyde solution. Then crosslinked capsules were dried in hot air oven at 35ºC for 1 day. Crosslinked capsule shells were kept in dessicator filled with silica gel.

2. Preparation of Core Capsules

The model drug (diltiazem hydrochloride or propranolol hydrochloride), osmotic agent (sodium chloride) and filler (lactose) were passed through a 80 mesh screen and mixed together according to the formulation in Table 6 (Siroratsakul, 2004). Powder mixture was filled in crosslinked and non crosslinked capsule by semiautomatic capsule filling machine and core capsules were stored in dessicator before coating. Figure 22 shows photograph of core capsules.

Table 6 Powder mixture formulation for core capsules

Ingredients	Amount per capsule
Model drug	90 mg
Sodium chloride	80 mg
Lactose	160 mg
Total	330 mg

Core capsules were prepared into 4 groups

- Diltiazem hydrochloride crosslinked capsules
- Diltiazem hydrochloride non-crosslinked capsules
- Propranolol hydrochloride crosslinked capsules
- Propranolol hydrochloride non-crosslinked capsules

Figure 22 Photograph of core capsules

3. Preparation of Coating Solutions

Subcoating and coating solutions were adapted from previous study of Siroratkul (2004). Formulations of both solutions are given in Table 7 and 8.

Table 7 Subcoating solution formulation for 100 core capsules No 1

Ingredients	Amount per 100 caps
HPMC 5 cps	3 g
PEG 6000	3 g
Ethanol 95% : Water = 1:1 qs to	100 ml

Table 8 Coating solution formulation for 100 core capsules

Ingredients	Amount per 100 caps
Cellulose acetate (CA)	3.35 g
PEG 6000	2.35 g
Dichloromethane : Ethanol = 95:5 qs to	335 ml

HPMC coating solution was prepared as follow : ethanol 95% and water were placed in Erlenmeyer flask and stirred gently for 5 minutes. Then HPMC was added. Five minutes after addition HPMC, PEG 6000 was added. The solution was mixed overnight prior to use.

CA coating solution was prepared as follow : dichloromethane and ethanol 95% were placed in Erlenmeyer flask and stirred. After five minutes, CA was added, and ten minutes after addition of CA, PEG 6000 was added. The solution was mixed overnight prior to use.

4. Coating Core Capsules

A batch size of 60 core capsules and 40 lactose capsules (blank capsules) were placed in chamber of bottom spray fluidized bed coater. Before spray coating solutions, core capsules were heated for five minutes. Then core capsules were coated with HPMC solution and dried in fluidized bed coater for 10 minutes. After completion of subcoating, capsules were coated with CA solution and dried in fluidized bed coater for 5 minutes. The coating conditions are presented in the Table 9 and 10. Coated capsules were kept in dessicator at room temperature. Photograph of coated capsules are presented in Figure 23.

Table 9 Coating parameters for subcoating layer

Parameter	Value
Inlet air temperature	: 55°C
Atomizing air pressure	: 1.6-1.8 bar
Pump speed	: 7 rpm
Spray rate	: 3 ml/min
Air brower	: level 10
Drying time	: 10 min

Table 10 Coating parameters for semipermeable membrane (CA) layer

Parameter	Value
Inlet air temperature	: 55°C
Atomizing air pressure	: 1.6-1.8 bar
Pump speed	: 8 rpm
Spray rate	: 4 ml/min
Air brower	: level 10
Drying time	: 5 min

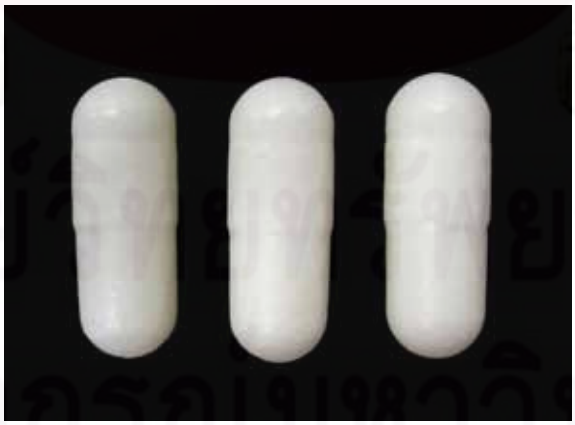


Figure 23 Photograph of coated capsules

5. Drilling of The Orifice

Coated capsules were drilled by hypodermic needle of 0.4, 0.6 and 0.8 mm before use. Photograph of coated capsules with the orifice and schematic diagram of coated capsules are displayed in Figure 24 and 25, respectively.

Figure 24 Photograph of coated capsules with the orifice

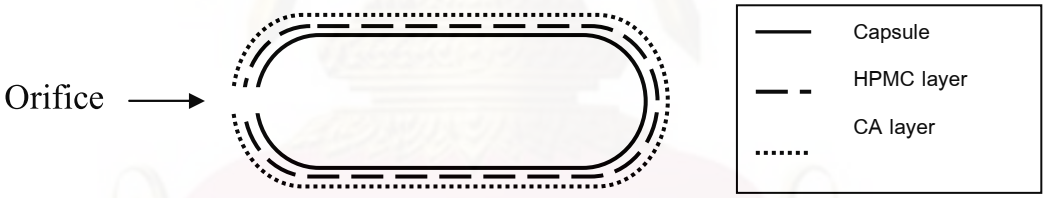


Figure 25 Schematic diagram of coated capsule

6. Evaluation of Coated Capsules

6.1 Capsules weight gain, coated layer weight and coated layer weight per surface area

6.1.1 Capsules weight gain and coated layer weight

$$\text{Average weight of core capsules } (a) = \frac{\text{Weight of 60 core capsules}}{60}$$

$$\text{Average weight of subcoating capsules } (b) = \frac{\text{Weight of 60 subcoating capsules}}{60}$$

$$\text{Average weight of semipermeable coating capsules } (c) = \frac{\text{Weight of 60 membrane coating capsules}}{60}$$

subcoating weight gain per cap (e) = b-a

semipermeable membrane weight gain per cap (f) = c-b

6.1.2 Coated layer weight per surface area

Capsule No. 1 length (h) = 1.9126 cm

Capsule No. 1 diameter (d) = 0.6789 cm

Surface area of the capsule = ¶dh

Surface area of capsule no.1 = 4.0808 cm^2

Amount of subcoating per surface area = e/4.0808 g/cm^2

Amount of semipermeable membrane per surface area = f/4.0808 g/cm^2

6.2 Theoretical capsule weight gain and percentage of actual coated layer weight per theoretical coated layer weight

Theoretical weight of subcoating material per cap = w g

Theoretical weight of semipermeable membrane material per cap = y g

Percentage of actual subcoating weight per theoretical subcoating weight = e/w x 100

Percentage of actual semipermeable weight per theoretical semipermeable weight = f/y x 100

6.3 Coated film characterization

Before dissolution test, surface and cross section of coated film were examined using scanning electron microscope.

6.4 Coated film thickness

Coated film thickness in different areas of OPC were measured using SEM.

6.5 Size of the orifice

Morphology and size of the orifice of OPC were examined using SEM photomicrography. Three groups of six capsules were drilled in different size using 0.4, 0.6 and 0.8 mm hypodermic needle at the top end of capsule.

6.6 Powder loss from orifice of coated capsule

Each ten capsules were drilled into 0.4, 0.6 and 0.8 mm orifice size. After that the capsules with different orifice sizes were weighted and tested by tablet friability tester (25 rpm, 4mins). Then capsules were weighted after tested and calculated percentage of powder loss.

$$\% \text{ powder loss} = \frac{(\text{weight before testing} - \text{weight after testing})}{\text{weight before testing}} \times 100$$

6.7 Determination of model drugs content in OPC

The OPC (no orifice) were cut and accurate weight of powder was placed in 100 ml volumetric flask. The mixture was dissolved and adjusted to volume with deionized water. Then an aliquot was filtered and diluted to suitable concentration. Then solution was assayed for diltiazem hydrochloride or propranolol hydrochloride by spectrophotometer at wavelength of 237 nm for diltiazem hydrochloride and 287 nm for propranolol hydrochloride.

6.8 Solubility study

Solubility of propranolol hydrochloride was examined in different ionic strength media as follows: 0.154 (0.9 %, isotonic), 0.5 and 1 M sodium chloride solutions. An excess amount of propranolol hydrochloride was added to each medium in amber glass bottles. The bottles were closed and placed in a shaker maintained at 25 ºC and rotated at 100 rpm for 30 hrs. Ten milliliters of sample were collected at 24, 27 and 30 hrs. Samples were filtered and prepared to suitable concentration and analyzed for amount of propranolol hydrochloride by spectrophotometer at wavelength 287 nm. Solubility of propranolol hydrochloride in each media was analyzed in triplicate.

6.9 Dissolution study

6.9.1 Calibration curve of model drugs

Twenty milligrams of diltiazem hydrochloride were weighted into a 100 ml volumetric flask. The powder was dissolved and adjusted with each medium. The solution was used as a stock solution. Stock solution of diltiazem hydrochloride 1, 2, 3, 4, 5, 3 and 4 ml were pipetted into 100, 100, 100, 100, 100, 50 and 50 ml volumetric flask, respectively. Then solutions were adjusted to volume with each medium. The final concentrations of each solution were 2, 4, 6, 8, 10, 12 and 16 mcg/ml. The absorbance was measured by spectrophotometer at wavelength 237 nm.

Propranolol hydrochloride 80 mg were weighted into a 100 ml volumetric flask. The powder was dissolved and adjusted with each medium. The solution was used as stock solution. Stock solution of propranolol hydrochloride 1, 2, 3, 4, 5 and 3 ml were pipetted into 100, 100, 100, 100, 100 and 50 ml volumetric flask, respectively. Then solutions were adjusted to volume with each medium. The final concentrations of each solution were 8, 16, 24, 32, 40 and 48 mcg/ml. The absorbance was measured by spectrophotometer at wavelength 287 nm.

Calibration curves of both model drugs were performed in following media

- deionized water
- 0.154 (isotonic), 0.5 and 1 M sodium chloride solution
- 0.1 M hydrochloric acid pH 1.2 adjusted to be isotonic with sodium chloride
- Phosphate buffer pH 6.8 adjusted to be isotonic with sodium chloride

6.9.2 Evaluation of drug release in various media

The diltiazem hydrochloride capsule and propranolol hydrochloride capsule release studies were modified form diltiazem hydrochloride extended-release capsules and propranolol hydrochloride extended release capsule monograph of USP 29. Drug release studies were performed using USP dissolution test apparatus II (paddle method, model VK7000, VanKel,) and operated at 100 rpm in 37±0.5°C dissolution medium. Ten milliliters sample was withdrawn through filter. After sampling, the same volume of medium was replaced immediately to keep constant volume in vessel through out the experiment. The dissolution parameters were shown in Table 11 to 14.

Table 11 Dissolution parameters of diltiazem hydrochloride OPC

Parameter	value
Paddle speed	100 rpm
Temperature	37±0.5°C
Operating time	9 hrs
Medium volume	900 ml
Sampling volume	10 ml
Sampling time (hours)	0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9

Table 12 Dissolution parameters of diltiazem hydrochloride OPC for pH-change method

Parameter	value
Paddle speed	100 rpm
Temperature	37±0.5°C
Operating time	9 hrs
Medium volume	750 ml HCl pH1.2 after 2 hr adjusted to 1000 ml PBS pH 6.8 with 250 ml 0.20 M tribasic sodium phosphate
Sampling volume	10 ml
Sampling time (hour)	0.5, 1, 1.5, 2, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9

Table 13 Dissolution parameters of propranolol hydrochloride OPC

Parameter	value
Paddle speed	100 rpm
Temperature	37±0.5°C
Operating time	12 hrs
Medium volume	900 ml
Sampling volume	10 ml
Sampling time (hour)	0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12

Table 14 Dissolution parameters of propranolol hydrochloride OPC for pH-change method

Parameter	value
Paddle speed	100 rpm
Temperature	37±0.5°C
Operating time	12 hrs
Medium volume	750 ml HCl pH1.2 after 2 hr adjusted to 1000 ml PBS pH 6.8 with 250 ml 0.20 M tribasic sodium phosphate
Sampling volume	10 ml
Sampling time (hour)	0.5, 1, 1.5, 2, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12

Effect of ionic strength and pH on drug release from OPC coating with 335 ml CA solution and 0.6 mm orifice were investigated in various dissolution media as follows :

- 900 ml deionized water
- 900 ml 0.154 (0.9 %, isotonic), 0.5 and 1 M sodium chloride solution
- 900 ml 0.1M hydrochloric acid adjusted ionic strength to isotonic with sodium chloride
- 900 ml Phosphate buffer pH 6.8 adjusted to be isotonic with sodium chloride
- 750 ml 0.1M hydrochloric acid adjusted to be isotonic with sodium chloride after 2 hrs changed to phosphate buffer pH 6.8 adjusted to be isotonic with sodium chloride by adding 0.20 M tribasic sodium phosphate 250 ml

Effect of various parameters on drug release from select OPC were investigated using deionized water as dissolution medium

- amount of coating materials
- orifice size

The sample was prepared to suitable concentration and assayed for the content of diltiazem hydrochloride and propranolol hydrochloride at wavelength of 237 nm and 287 nm, respectively. The amount of model drugs were calculated from equation of standard solution calibration curve of each dissolution medium. A cumulative correction was done for the previously removed sample to determine the total of drug release.

6.9.3 Mathematical treatments

An ideal osmotic system should be able to release as zero-order kinetic. Release data of dissolution study were analyzed by different mathematical parameters. Different parameters were used to evaluate results of dissolution study as follows :

- percentage of drug release at various time points
- release rate of drug release at middle time point of 2 adjacent time points

$$\text{release rate at middle time point} = \frac{Qobs_{tn} - Qobs_{t(n-1)}}{t_n - t_{(n-1)}}$$

$Qobs_{tn}$ = percentage of drug release at sampling time point

$Qobs_{t(n-1)}$ = percentage of drug release at previous sampling time point

t_n = sampling time point

$t_{(n-1)}$ = previous sampling time point

- calculated zero-order equation from percentage of drug release at various time points
- R square of release data fitted to zero-order equation (R^2)

CHAPTER IV

RESULTS AND DISCUSSION

2. Study of Optimum Time for Preparation of Crosslinked Capsule Shells

Gelatin capsules that exposed with formaldehyde vapor for 1, 2, 4, 6, 8 and 24 hrs were subjected to integrity test by immersion with stirring in deionized (DI) water, 0.1 N hydrochloric acid (HCl) pH 1.2 and phosphate buffer (PBS) pH 6.8. Photograph of crosslinked and non-crosslinked hard gelatin capsules are displayed in Figure 26. It was shown that crosslinked and non-crosslinked hard gelatin capsules gave no difference of physical characteristics. The results of crosslinked capsule characteristic are presented in Table 15. It was found that capsules were insoluble in all media when capsules were exposed to formaldehyde vapors for over 6 hrs. Based on the results, 6 hrs was adopted as the least and optimum time for exposure of hard gelatin capsules to formaldehyde vapors. Capsule shell characteristics are displayed in Figure 27.

Table 15 Summary of crosslinked capsule characteristics

Medium	Time (hrs)	Shell characteristics	Weight
DI water	1	partially insoluble	-
	2	partially insoluble	-
	4	insoluble	not changing*
	6	insoluble	not changing*
	8	insoluble	not changing*
	24	insoluble	not changing*
0.1 N HCl pH 1.2	4	partially insoluble	-
	6	insoluble	not changing*
PBS pH 6.8	6	insoluble	not changing*

*Not changing = ± not more than 5 % of initial capsule shell weight

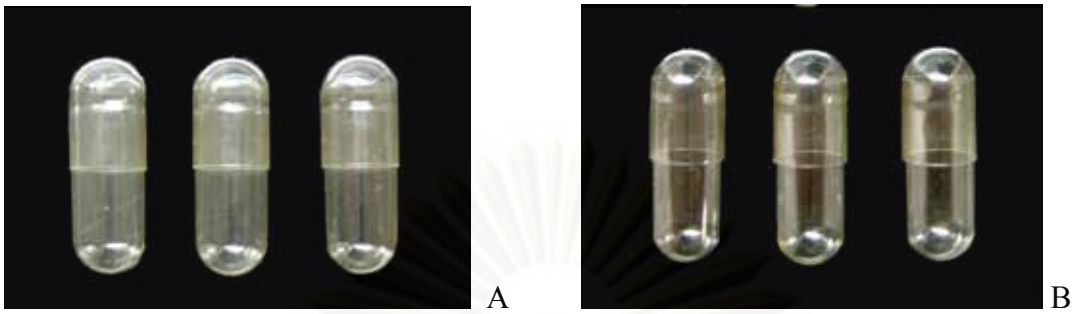


Figure 26 Photograph of crosslinked hard gelatin capsules(A) and non-crosslinked hard gelatin capsules (B)

Figure 27 Photograph of partially insoluble hard capsules (A) and insoluble hard capsules (B) when immersed in media

7. Evaluation of Coated Capsules

7.1 Capsule weight gain, coated membrane weight, theoretical coated membrane weight and coated membrane weight per surface area

As presented in Table 16 and 17, average weight of capsule shell and average weight of mixture powder of diltiazem hydrochloride OPC and propranolol hydrochloride OPC with all levels of coating solution were similar. The results

showed that HPMC layer average weights were varies among different OPC groups. Table 16 and 18 show that the average weight of CA layer of diltiazem hydrochloride OPC increased as the amount of coating solution increased, resulting in increment of coated membrane weight per surface area. Nevertheless, there was clear evidence from Table 17 and 19 that the average weight of CA layer of propranolol hydrochloride OPC was independent of the level of CA solution led to an equivalent of coated membrane weight per surface area. In case of propranolol hydrochloride OPC, the preparing procedures were inaccurate because of some deviant coating conditions and coating machine.

Table 16 Average weight of capsule shell, containing powder and coated membrane weight of diltiazem hydrochloride OPC coating with various amounts of CA solution

Amount of coating solution	Capsule type	Average weight per cap (mg)*			
		Capsule shell	Powder	HPMC layer	CA layer
250 ml	Crosslinked	75.50	334.18	39.26	25.04
	Non-crosslinked	75.83	333.64	38.86	28.37
290 ml	Crosslinked	75.83	336.61	41.11	32.61
	Non-crosslinked	75.78	337.17	41.39	32.22
335 ml	Crosslinked	75.61	336.37	38.99	39.79
	Non-crosslinked	75.61	336.69	36.00	35.98

*Average weight per cap = (total weight of 60 capsules/60)

Table 17 Average weight of capsule shell, containing powder and coated membrane weight of propranolol hydrochloride OPC coating with various amounts of CA solution

Amount of coating solution	Capsule type	Average weight per cap (mg)*			
		Capsule shell	Powder	HPMC layer	CA layer
290 ml	Crosslinked	76.00	336.33	42.39	33.67
	Non-crosslinked	75.55	336.33	43.83	34.83
335 ml	Crosslinked	75.50	337.52	35.64	33.01
	Non-crosslinked	75.75	337.80	34.74	34.50

*Average weight per cap = (total weight of 60 capsules/60)

Table 18 Coated membrane weight per surface area of diltiazem hydrochloride OPC coating with various amounts of CA solution

Amount of coating solution	Capsule type	Coated membrane weight per surface area (mg/cm^2)	
		Subcoating (HPMC layer)	Semipermeable membrane (CA layer)
250 ml	Crosslinked	9.62	6.14
	Non-crosslinked	9.52	6.95
290 ml	Crosslinked	10.07	7.99
	Non-crosslinked	10.14	7.90
335 ml	Crosslinked	9.55	9.75
	Non-crosslinked	8.82	8.82

Table 19 Coated membrane weight per surface area of propranolol hydrochloride OPC coating with various amounts of CA solution

Amount of coating solution	Capsule type	Coated membrane weight per surface area (mg/cm^2)	
		Subcoating (HPMC layer)	Semipermeable membrane (CA layer)
290 ml	Crosslinked	10.39	8.25
	Non-crosslinked	10.74	8.54
335 ml	Crosslinked	8.73	8.09
	Non-crosslinked	8.51	8.45

Theoretical coated membrane weights are presented in Table 20. It was found that actual average weight of coated layers of diltiazem hydrochloride OPC and propranolol hydrochloride OPC were approximately 60-70 % of theoretical coated layers weight (Table 21 and 22).

Table 20 Theoretical average weight of coated layers per capsule

Amount of coating solution	Theoretical weight per cap (mg)	
	Subcoating (HPMC layer)	semipermeable membrane (CA layer)
250 ml	60	43
290 ml	60	49
335 ml	60	57

Table 21 Percentage of actual coated layers weight per theoretical coated layers weight of diltiazem hydrochloride OPC

Amount of coating solution	Capsule type	Actual weight per theoretical weight (%)	
		Subcoating (HPMC layer)	Semipermeable membrane (CA layer)
250 ml	Crosslinked	65.435	58.223
	Non-crosslinked	64.772	65.974
290 ml	Crosslinked	68.518	66.553
	Non-crosslinked	68.982	65.759
335 ml	Crosslinked	64.977	69.809
	Non-crosslinked	60.002	63.121

Table 22 Percentage of actual coated layers weight per theoretical coated layers weight of propranolol hydrochloride OPC

Amount of coating solution	Capsule type	Actual weight per theoretical weight (%)	
		Subcoating (HPMC layer)	Semipermeable membrane (CA layer)
290 ml	Crosslinked	70.648	68.708
	Non-crosslinked	73.055	71.088
335 ml	Crosslinked	59.402	57.904
	Non-crosslinked	57.898	60.526

7.2 Coated film characterization

Coated layers of diltiazem hydrochloride OPC and propranolol hydrochloride OPC were characterized using scanning electron microscope as diplayed in Figure 28-29 and 30-31, respectively.

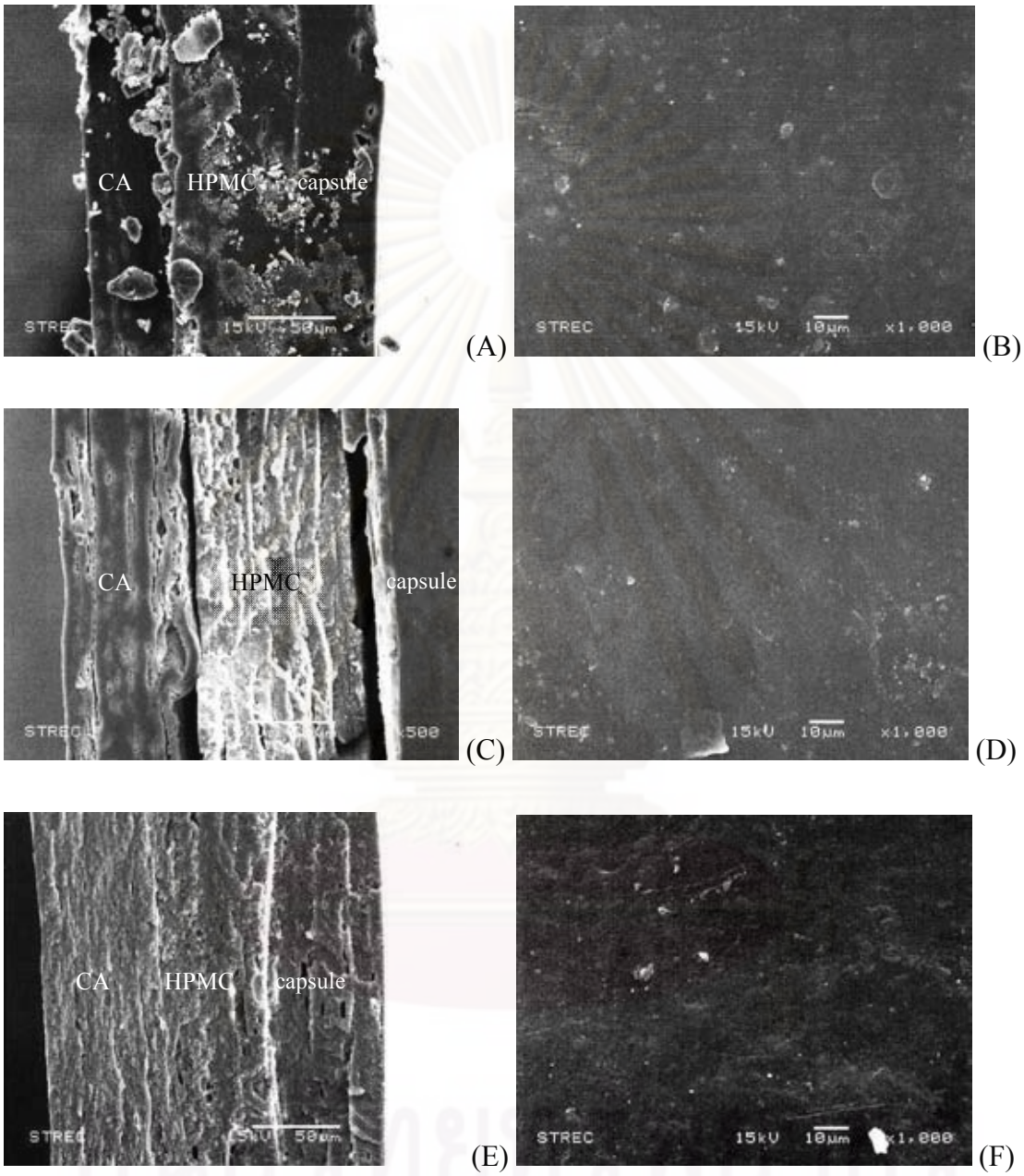


Figure 28 The photomicrograph (SEM) of cross-section view (x500) and surface view (x1000) of diltiazem hydrochloride crosslinked OPC coated with 250 ml [cross-section (A) and surface (B)], 290 ml [cross-section (C) and surface (D)] and 335 ml [cross-section (E) and surface (F)] CA coating solution

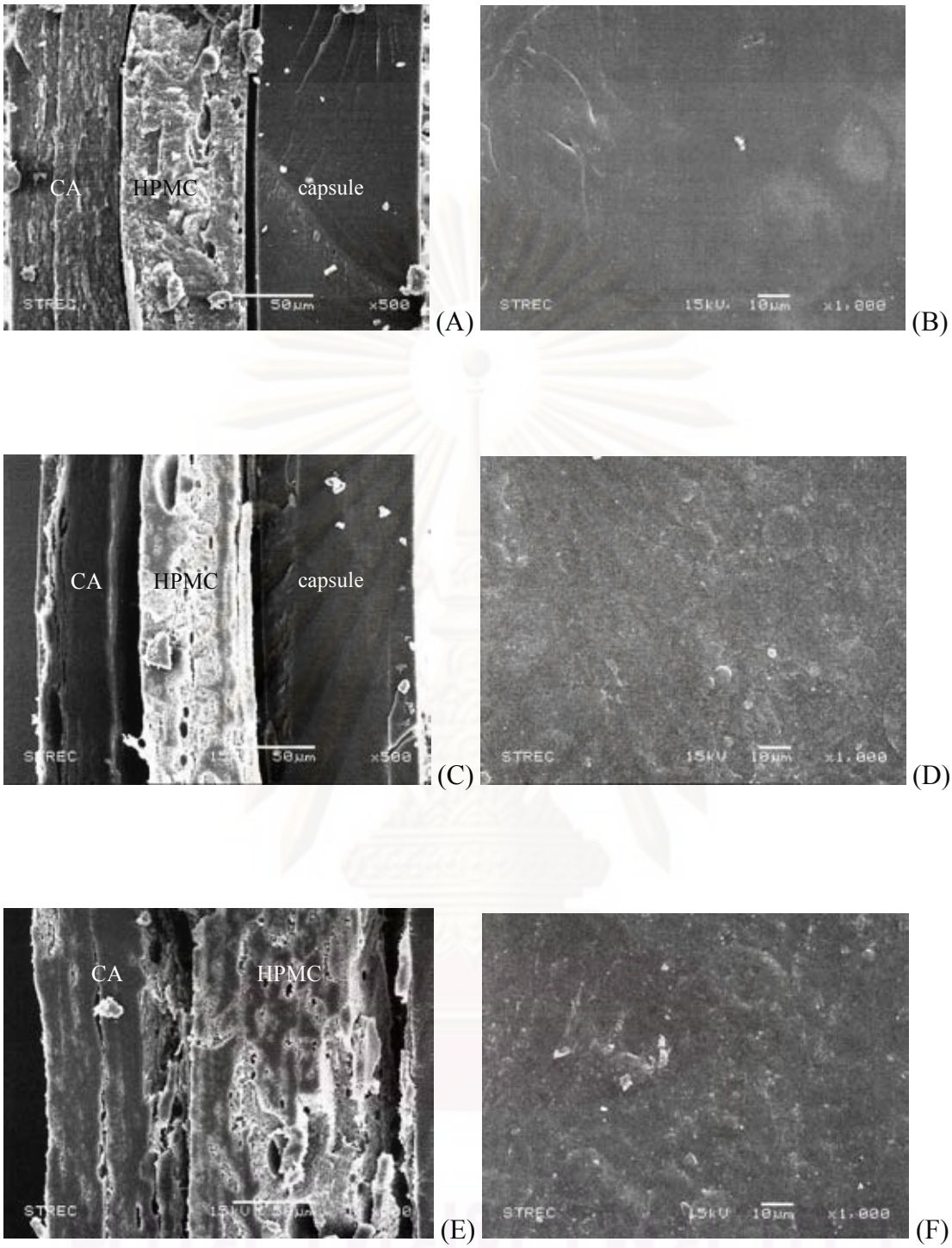


Figure 29 The photomicrograph (SEM) of cross-section view (x500) and surface view (x1000) of diltiazem hydrochloride non-crosslinked OPC coated with 250 ml [cross-section (A) and surface (B)], 290 ml [cross-section (C) and surface (D)] and 335 ml [cross-section (E) and surface (F)] CA coating solution

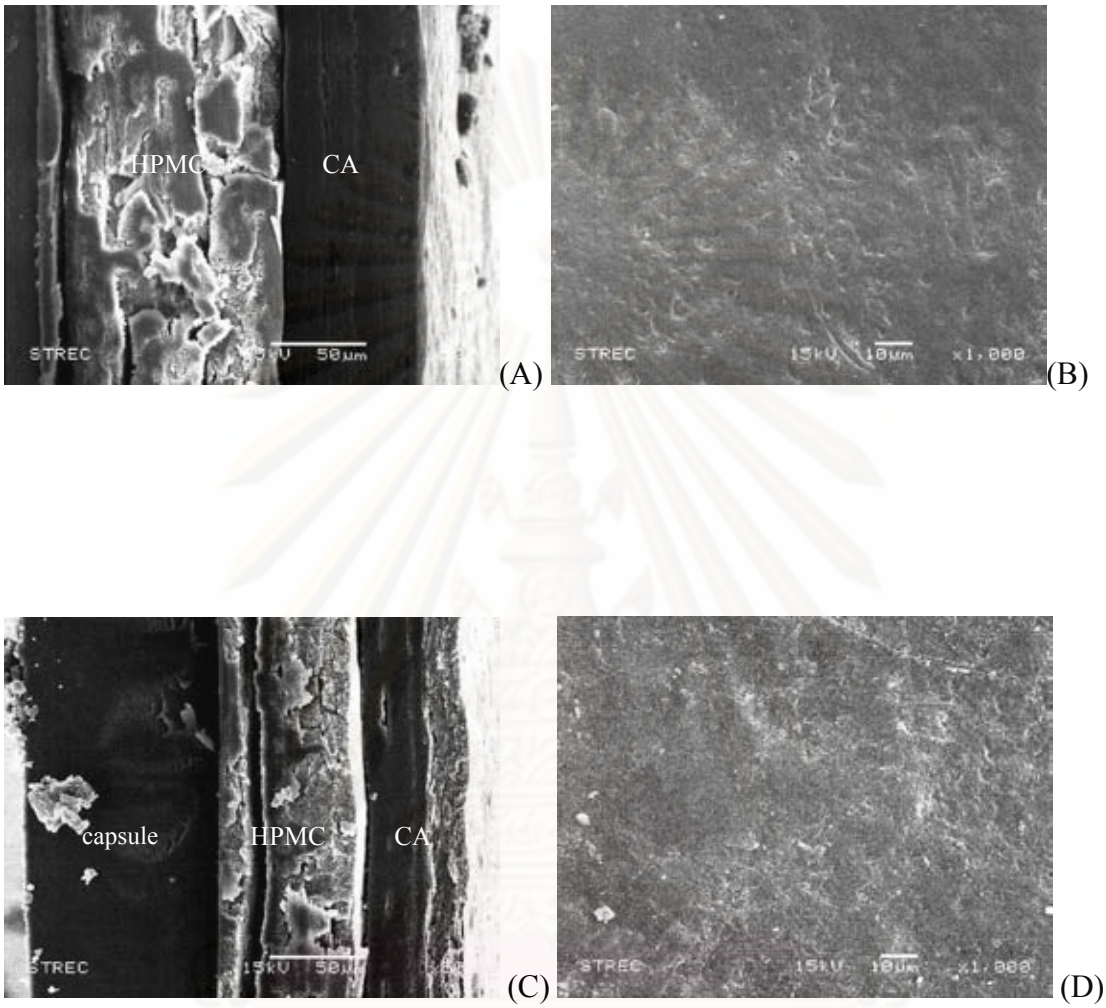


Figure 30 The photomicrograph (SEM) of cross-section view (x500) and surface view (x1000) of propranolol hydrochloride crosslinked OPC coated with 290 ml [cross-section (A) and surface (B)] and 335 ml [cross-section (C) and surface (D)] CA coating solution

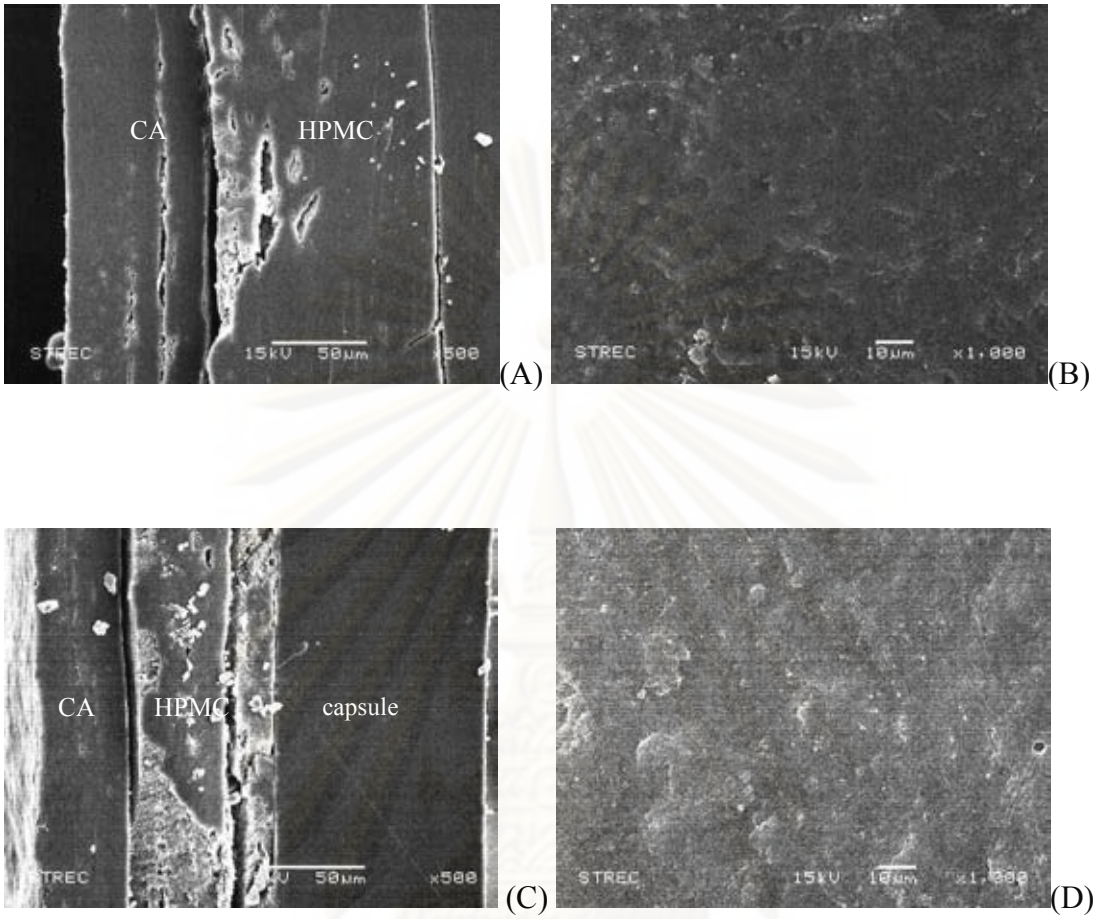
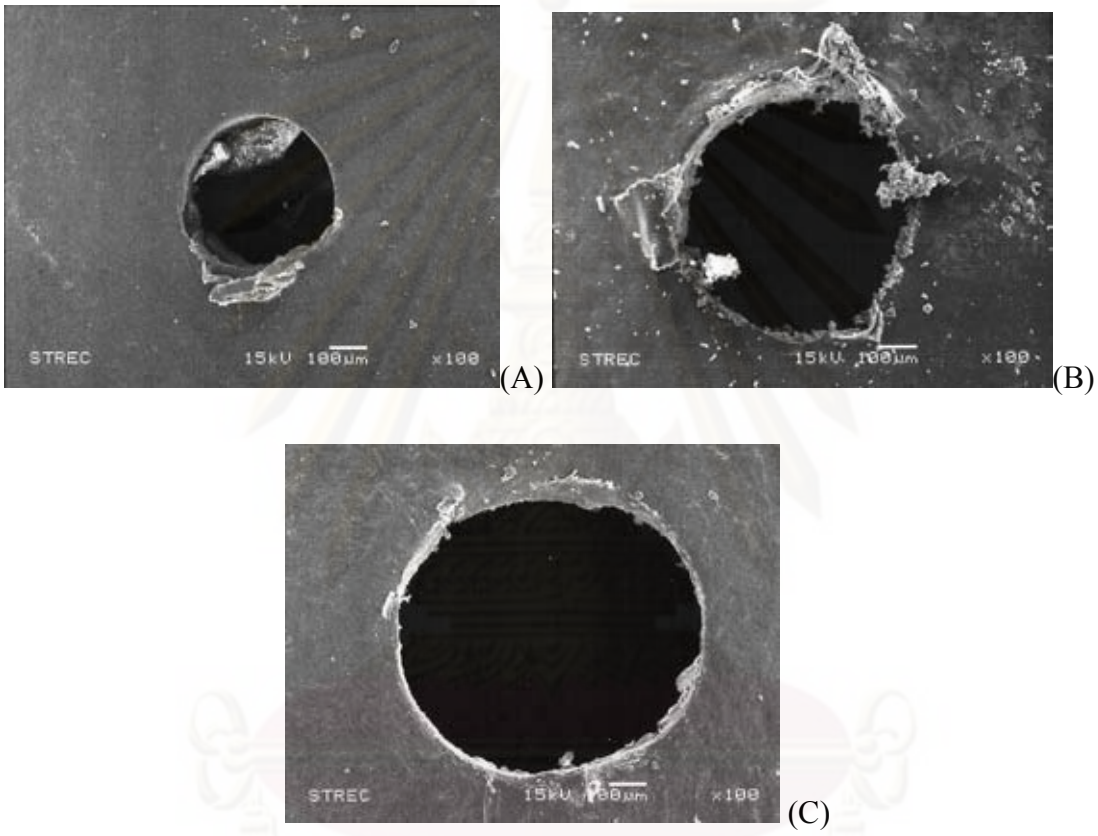


Figure 31 The photomicrograph (SEM) of cross-section view (x500) and surface view (x1000) of propranolol hydrochloride non-crosslinked OPC coated with 290 ml [cross-section (A) and surface (B)] and 335 ml [cross-section (C) and surface (D)] CA coating solution

. Cross-section view of OPC clearly show three separated layers; capsule shell layer, HPMC layer and CA layer. As shown in figures, surface of all groups of OPC were smooth and homogeneous. It was found that film thickness can not be measured correctly because coating layers were distorted during specimen preparation. Nevertheless, it was indicated that HPMC layer was thicker than CA layer due to high HPMC layer weight gain.

7.3 Orifice characterization

The photomicrograph of the orifices are displayed in Figure 32. It was found that the orifice, which drilled using hypodermic needle, had rounded shape and smooth edge. Needles with 0.4, 0.6 and 0.8 mm diameter gave roughly 0.4, 06, and 0.8 orifice sizes, respectively.



(A) (B) (C)

Figure 32 The photomicrograph (SEM) of various sizes of the orifice that drilled with 0.4 mm (A) ,0.6mm (B) and 0.8 mm (C) needle

7.4 Effect of orifice size of OPC on powder loss

To study the effect of orifice size of OPC on powder loss, OPC were drilled using 0.4, 0.6 and 0.8 mm needle. Powder losses and area of the orifice were shown in Table 23. It was clearly evident that loss of powder increase with an increase in diameter and area of the orifice. In an attempt to reduce powder loss

before dissolution testing, OPC were drilled prior to use. Figure 33 shows correlation between % powder loss and area of the orifice.

Table 23 Percentage of powder loss from various orifice sizes OPC

Size of the orifice (mm)	Area of the orifice (mm^2)	% loss of powder
0.4	0.126	0.782
0.6	0.283	1.546
0.8	0.503	2.998

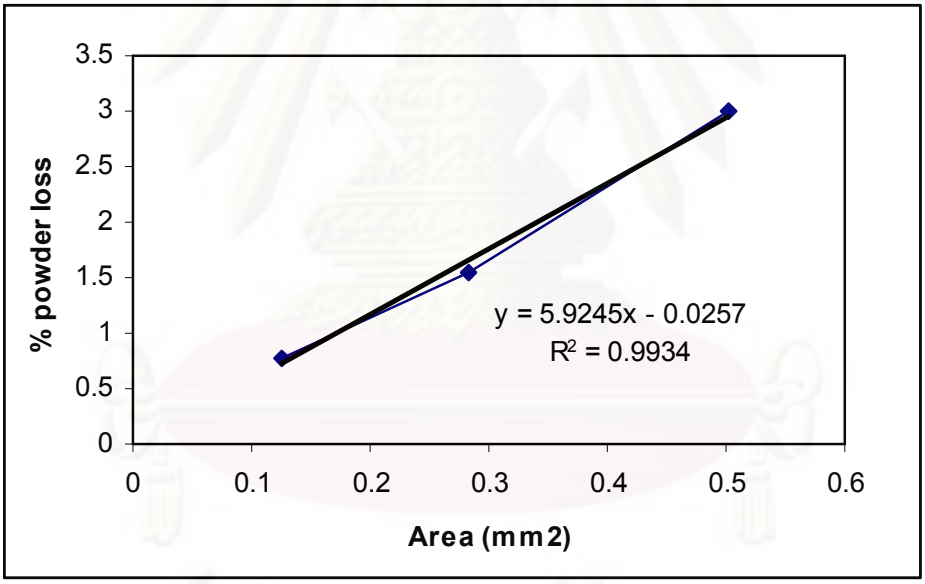


Figure 33 Correlation between % powder loss and area of the orifice

7.5 Content of model drug in OPC

Content of diltiazem hydrochloride and propranolol hydrochloride in OPC were about 100 %. Table 24 and 25 displayed content of diltiazem hydrochloride and propranolol hydrochloride in OPC, respectively.

Table 24 Content of diltiazem hydrochloride coating with various amounts of CA solution (n=3)

Amount of coating solution	Content of diltiazem hydrochloride	
	Crosslinked capsule	Non-crosslinked capsule
250 ml	90.23 ± 1.30 mg (100.26 ± 1.45 %)	89.59 ± 3.21 mg (99.54 ± 3.57 %)
290 ml	89.98 ± 2.25 mg (99.98 ± 2.50 %)	94.71 ± 1.46 mg (105.24 ± 1.62 %)
335 ml	90.72 ± 2.19 mg (100.80 ± 2.34 %)	89.33 ± 3.64 mg (99.25 ± 4.05 %)

Table 25 Content of propranolol hydrochloride coating with various amounts of CA solution (n=3)

Amount of coating solution	Content of propranolol hydrochloride	
	Crosslinked capsule	Non-crosslinked capsule
290 ml	93.60 ± 2.81 mg (104.00 ± 3.12 %)	92.77 ± 1.02 mg (103.09 ± 1.13 %)
335 ml	94.45 ± 0.90 mg (104.94 ± 1.00 %)	96.03 ± 2.44 mg (106.70 ± 2.71 %)

7.6 Dissolution study

7.6.1 Evaluation of various parameters affecting on drug release profile

2.6.1.1 Amount of cellulose acetate coating solutions

Influence of coating solution level on drug release from OPC was investigated using deionized water as dissolution medium. All OPC were drilled using 0.6 mm needle. OPC in this experiment were divided into four groups as follows:

- diltiazem HCl crosslinked OPC coating with 250, 290 and 335 ml CA solution
- diltiazem HCl non-crosslinked OPC coating with 250, 290 and 335 ml CA solution
- propranolol HCl crosslinked OPC coating with 290 and 335 ml CA solution
- propranolol HCl non-crosslinked OPC coating with 290 and 335 ml CA solution

The influences of cellulose acetate solution level on drug release profiles of diltiazem hydrochloride crosslinked and non-crosslinked OPC are shown in Figure 34 and 35. Diltiazem hydrochloride crosslinked OPC coating with 250, 290 and 335 ml had 1, 1.5 and 2.5 hrs lag time, respectively. Lag time of diltiazem hydrochloride non-crosslinked OPC coating with 250, 290 and 335 ml were 0.5, 1 and 1 hrs, respectively. As shown in Figure 34, level of coating solution could affect lag time of diltiazem hydrochloride crosslinked OPC. Diltiazem hydrochloride crosslinked and non-crosslinked OPC could sustain release profile about 9 hrs and between 10%-80% of cumulative drug release profiles closed to zero-order of drug content (R^2 are shown in Table 26 and 27).

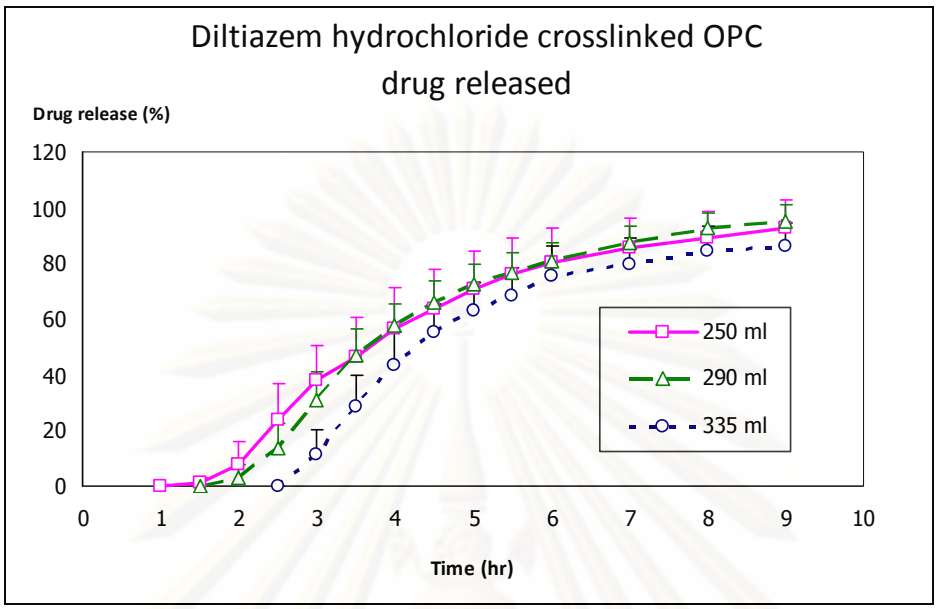


Figure 34 The release profiles of diltiazem hydrochloride from crosslinked OPC (n=18) coating with various amounts of CA solution (250, 290 and 335 ml) in deionized water.

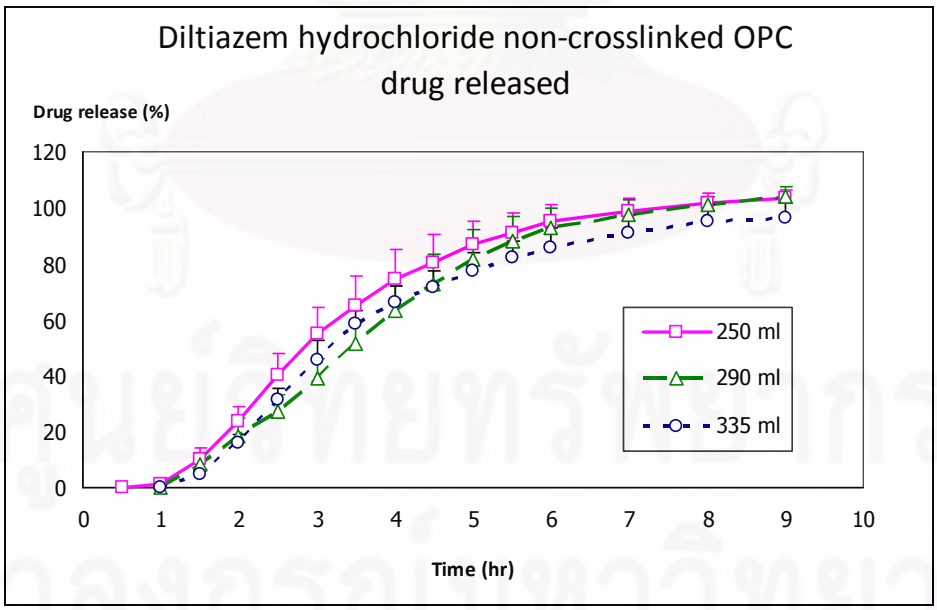


Figure 35 The release profiles of diltiazem hydrochloride from non-crosslinked OPC (n=18) coating with various amounts of CA solution (250, 290 and 335 ml) in deionized water.

Table 26 The comparative parameters of diltiazem hydrochloride crosslinked OPC with various CA solution levels including calculated release rate and R^2

diltiazem hydrochloride crosslinked OPC			
coating solution level	Qobs* (%)	calculated release rate (%/hr)	R^2
250 ml	7.92-80.25	17.661	0.962
290 ml	13.92-80.77	18.581	0.9322
335 ml	11.54-79.55	16.943	0.9055

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Table 27 The comparative parameters of diltiazem hydrochloride non-crosslinked OPC with various CA solution levels including calculated release rate and R^2

diltiazem hydrochloride non-crosslinked OPC			
coating solution level	Qobs* (%)	calculated release rate (%/hr)	R^2
250 ml	9.92-94.9	18.824	0.9463
290 ml	8.17-92.66	19.793	0.989
335 ml	4.58-91.1	16.15	0.9182

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Release rate of diltiazem hydrochloride crosslinked and non-crosslinked OPC are shown in Figure 36 and 37. For the initial period release rate were increasing after that release rate were decreasing. In last 3 hrs, release rate were steady. Release rate of diltiazem hydrochloride crosslinked OPC coating with 335 ml CA solution was the slowest release rate but release rate from OPC coating with 250 and 290 ml CA solution were similar. Release rate from diltiazem hydrochloride non-crosslinked OPC coating with 250, 290 and 335 ml CA solution were similar. From Table 26 and 27, diltiazem hydrochloride crosslinked and non-crosslinked OPC coating with various CA solution levels gave no clear different calculated release rate.

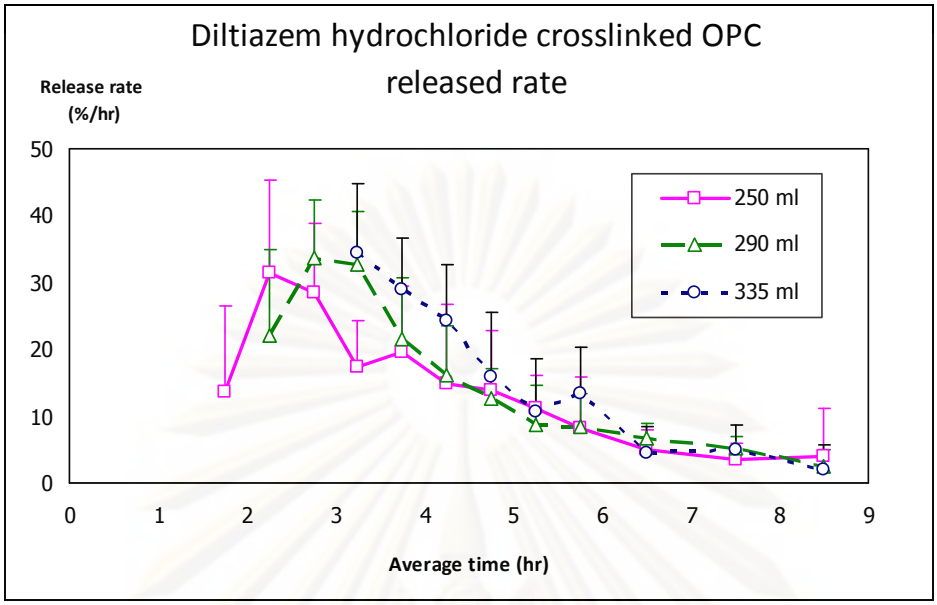


Figure 36 The release rate profiles of diltiazem hydrochloride from crosslinked OPC (n=18) coating with various amounts of CA solution (250, 290 and 335 ml) in deionized water.

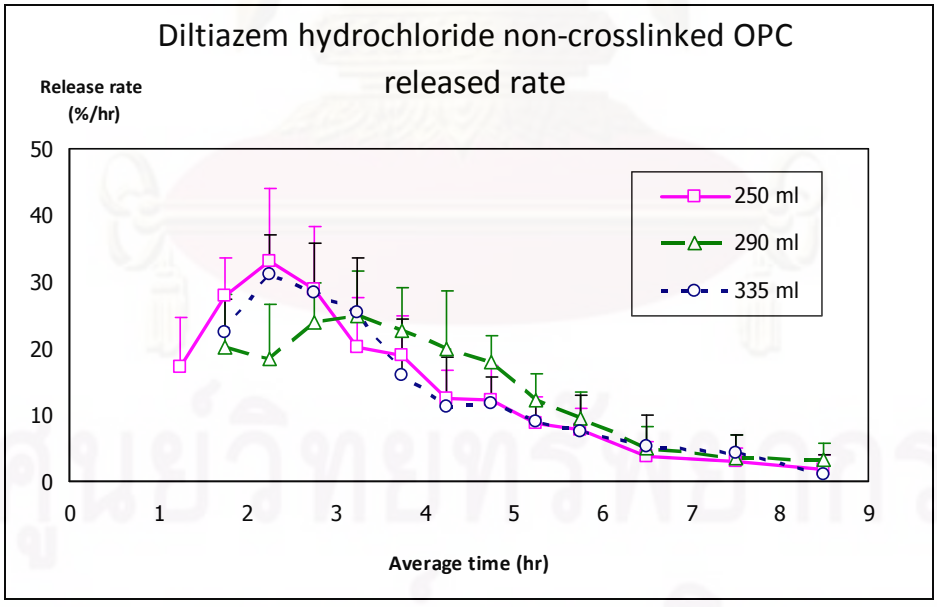


Figure 37 The release rate profiles of diltiazem hydrochloride from non-crosslinked OPC (n=18) coating with various amounts of CA solution (250, 290 and 335 ml) in deionized water.

The release profiles of propranolol from each group of OPC are shown in Figure 38 and 39.

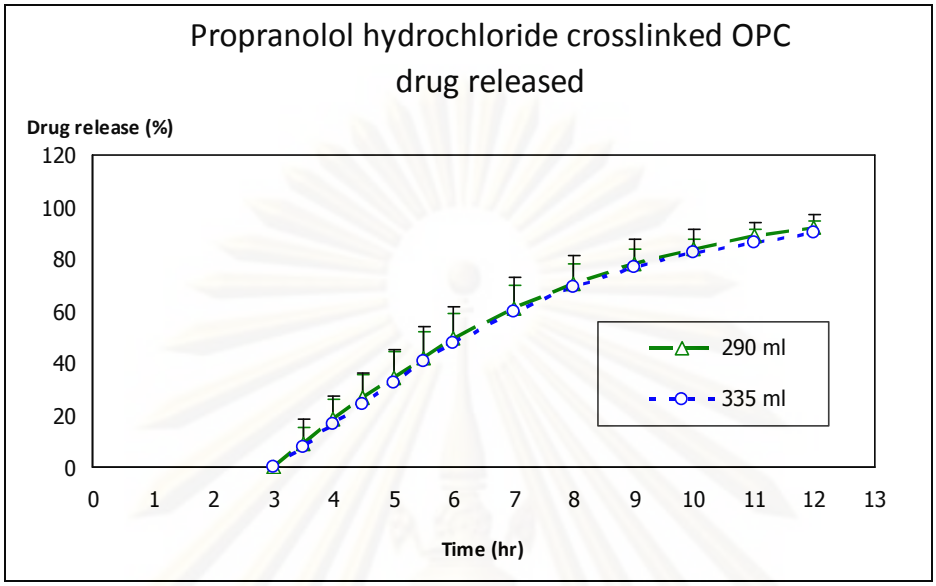


Figure 38 The release profiles of propranolol hydrochloride from crosslinked OPC (n=18) coating with various amounts of CA solution (290 and 335 ml) in deionized water.

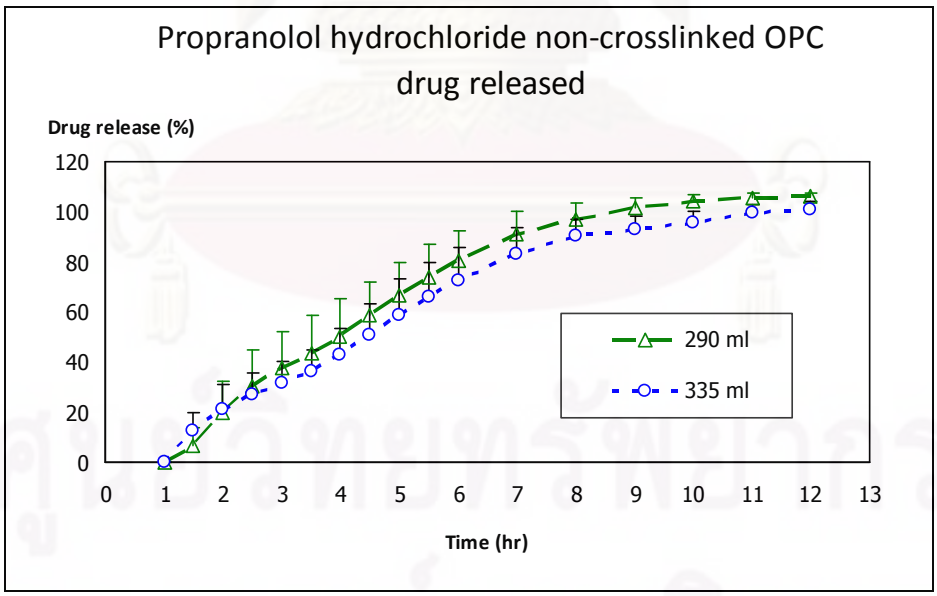


Figure 39 The release profiles of propranolol hydrochloride from non-crosslinked OPC (n=18) coating with various amounts of CA solution (290 and 335 ml) in deionized water.

Lag time of propranolol hydrochloride crosslinked and non-crosslinked OPC coating with both CA solution levels were 3 and 1 hrs, respectively. For propranolol hydrocloride OPC, up to 90% of drug release was closed zere-order relase (R^2 are shown in Table 28 and 29).

Table 28 The comparative parameters of propranolol hydrochloride crosslinked OPC coating with various CA solution levels including calculated release rate and R^2

propranolol hydrochloride crosslinked OPC			
coating solution level	Qobs* (%)	calculated release rate (%/hr)	R^2
290 ml	9.02-92.04	9.8159	0.9478
335 ml	7.58-90.40	9.8013	0.9502

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Table 29 The comparative parameters of propranolol hydrochloride non-crosslinked OPC with various CA solution levels including calculated release rate and R^2

propranolol hydrochloride non-crosslinked OPC			
coating solution level	Qobs* (%)	calculated release rate (%/hr)	R^2
290 ml	6.74-90.78	15.023	0.9897
335 ml	12.50-90.11	12.386	0.9928

*Qobs=percentage of drug release interval used for calculation of zero-order equation

As shown in Figure 40 and 41, it was no diferrence between release rate profiles of propranolol hydrochloride OPC coating with 290 and 335 ml CA solution (calculated release rates are presented in Table 28 and 29). Release rate of propranolol hydrochloride crosslinked OPC had more linear pattern and less variation of release rate than release rate of propranolol hydrochloride non-crosslinked OPC.

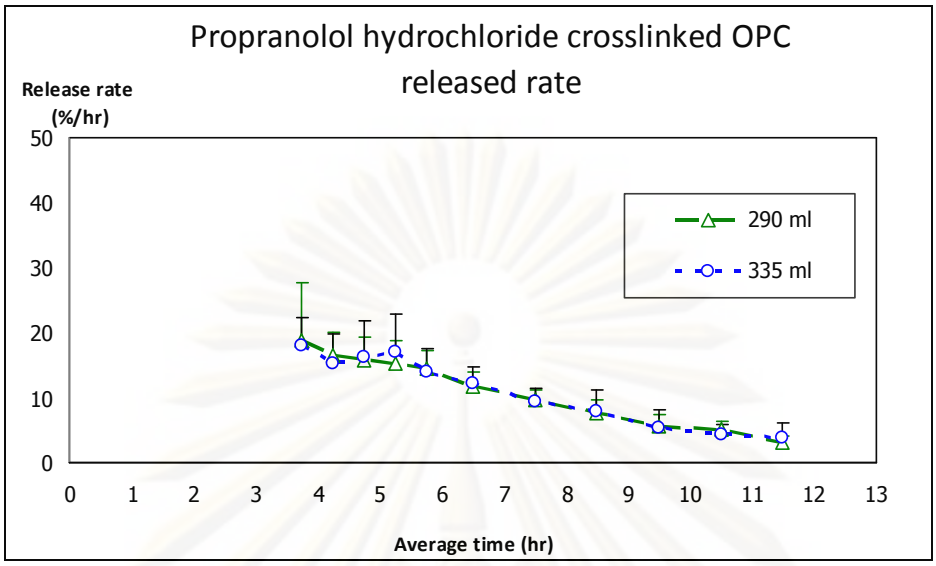


Figure 40 The release rate profiles of propranolol hydrochloride from crosslinked OPC (n=18) coating with various amounts of CA solution (290 and 335 ml) in deionized water.

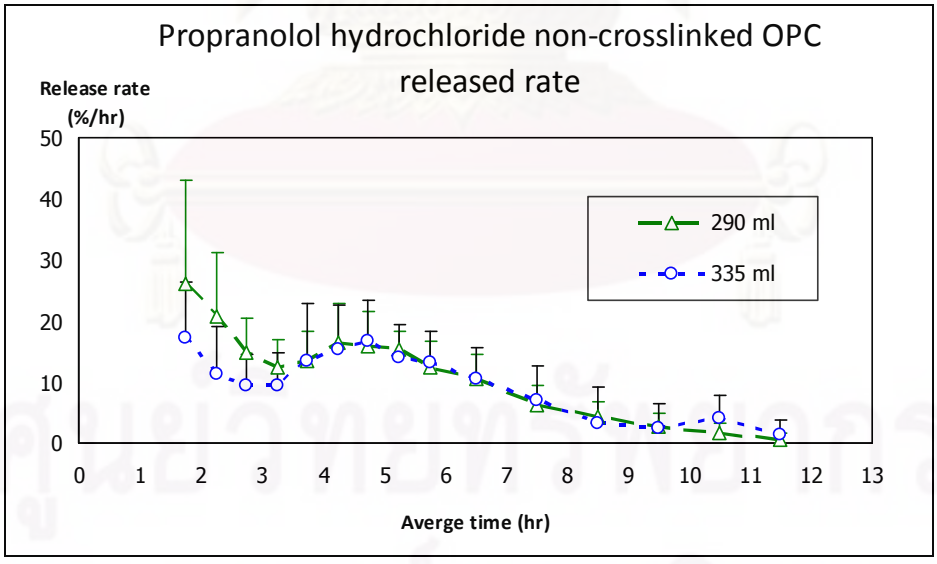


Figure 41 The release rate profiles of propranolol hydrochloride from non-crosslinked OPC (n=18) coating with various amounts of CA solution (290 and 335 ml) in deionized water.

According to equation 4, the increment in membrane thickness (*h*) led to a reduction of solute delivery rate (*dm/dt*).

$$\frac{dm}{dt} = \frac{A}{h} L_p \sigma \Delta \pi C \qquad \text{(Eq. 4)}$$

dm/dt = solute delivery rate

A = membrane area

h = membrane thickness

L_p = mechanical permeability

σ = reflection coefficient

$\Delta\pi$ = osmotic pressure difference

C = concentration of compound in the dispensed fluid

It seem reasonable to assume that thickness of film depended on semipermeable membrane weight. Average weight of CA layer of diltiazem hydrochloride crosslinked OPC coating with 250, 290 and 335 ml were found to be 25.04, 32.61 and 39.79 mg/cap, respectively (Table 16). As shown in Figure 34, level of CA solution increase led to an increase of semipermeable film thickness, resulting in the lag time of diltiazem hydrochloride crosslinked OPC increase. However, Figure 35 shows that diltiazem hydrochloride non-croslinked OPC showed not much diference of lag time which might be caused by slight difference of average weight of CA layer. Average weight of CA layer of diltiazem hydrochloride non-crosslinked OPC coating with 250, 290 and 335 ml were found to be 28.37, 32.22 and 35.98 mg/cap, respectively (Table 16). The reason is that membrane resistance to water penetration increased as the membrane thickness increased resulting in an increase of lag time and a reduction of release rate (Liu and Xu, 2008) During dissolution test, coating film of diltiazem hydrochloride OPC coating with 250 ml CA solutions were broken (Figure 42), therefore 250 ml coating solution was not use for propranolol hydrochloride OPC study. As shown in Table 17, semipermeable membrane weight of porpranolol hydrochloride OPC coating with 290 and 335 ml are similar led to no difference of lag time of propranolol hydrochloride OPC coating with various amounts of CA solution. For both model drugs, lag time of crosslinked OPC were

longer than lag time of non-crosslinked OPC. Since crosslinked capsule was a hydrophobic shell, it was dfficult for water to penetrate into OPC.

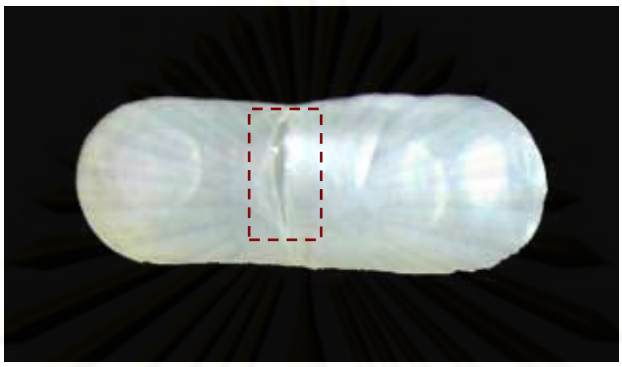
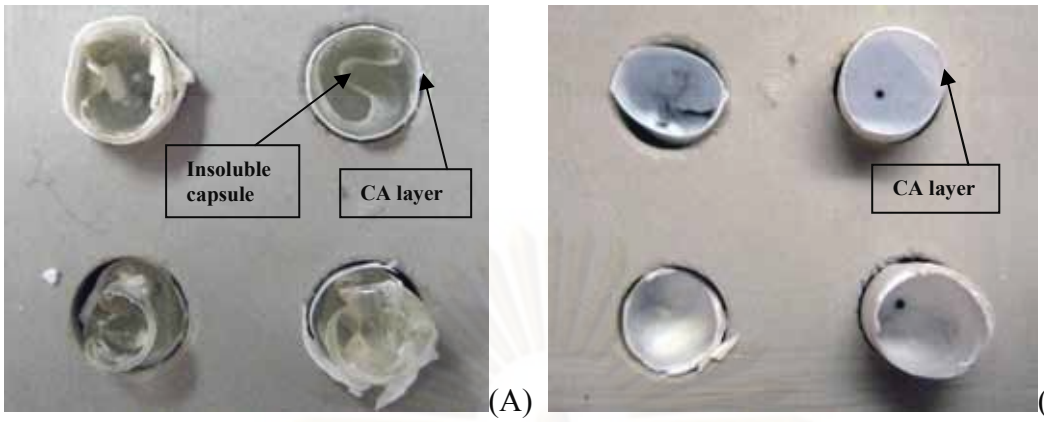


Figure 42 Photograph of broken OPC

Release rate of diltiazem hydrochloride crosslinked and non-crosslinked coating with various amounts of CA solution had no clear diversity (Figure 36 and 37). Amount of coating solutions did not affect release rate of propranolol hydrochloride crosslinked and non crosslinked due to similarity of CA layer weight. However, capsule type had effect on propranolol hydrochloride release rate. It can indicated that propranolol hydrochloride crosslinked OPC gave more linear release rate profile and less variation of release rate at various sampling time points than non-crosslinked OPC (Figure 40 and 41). Propranolol hydrochloride OPC release rate had less fluctuation than diltiazem hydrochloride OPC release rate. Propranolol hydrochloride OPC could extended zero-order release rate longer than diltiazem hydrochloride OPC due to difference of drugs solubility hence affecting OPC water influx and OPC delivery rate.

After dissolution testing, there were insoluble capsule inside crosslinked OPC but non-crosslinked OPC had nothing inside. Figure 43 exhibits cross-section views of crosslinked and non-crosslinked OPC.



(A) (B)

Figure 43 Photograph of cross-section views of crosslinked (A) and non-crosslinked (B) OPC after dissolution testing

2.6.1.2 Orifice size

In order to study the influence of orifice size on drug release profile of diltiazem hydrochloride crosslinked and non-crosslinked OPC and propranolol hydrochloride crosslinked and non-crosslinked OPC coating with 335 ml CA solution, the release characteristics of OPC were investigated using deionized water as dissolution medium. OPC study in this experiment divided into four subgroups as follows

- diltiazem HCl crosslinked OPC with 0.4, 0.6 and 0.8 mm orifice size.
- diltiazem HCl non-crosslinked OPC with 0.4, 0.6 and 0.8 mm orifice size.
- propranolol HCl crosslinked OPC with 0.4, 0.6 and 0.8 mm orifice size.
- propranolol HCl non-crosslinked OPC with 0.4, 0.6 and 0.8 mm orifice size.

Figure 44 and 45 show the release profiles of diltiazem hydrochloride from crosslinked and non-crosslinked OPC with various orifice sizes. Lag time of diltiazem hydrochloride crosslinked OPC with orifice size 0.4, 0.6 and 0.8 mm were found to be 2, 2.5 and 1.5 hrs, respectively. Lag time of diltiazem hydrochloride non-crosslinked OPC with orifice size 0.4, 0.6 and 0.8 mm were obtained to be 1.5, 1 and 1 hrs,

respectively. It indicated that orifice size might not have effect on lag time of diltiazem hydrochloride OPC. Diltiazem hydrochloride OPC could prolong drug release about 9 hours and about 80 % of drug content released close to zero-order model (R^2 are presented in Table 30 and 31) with similar variations of drug release at various sampling time points.

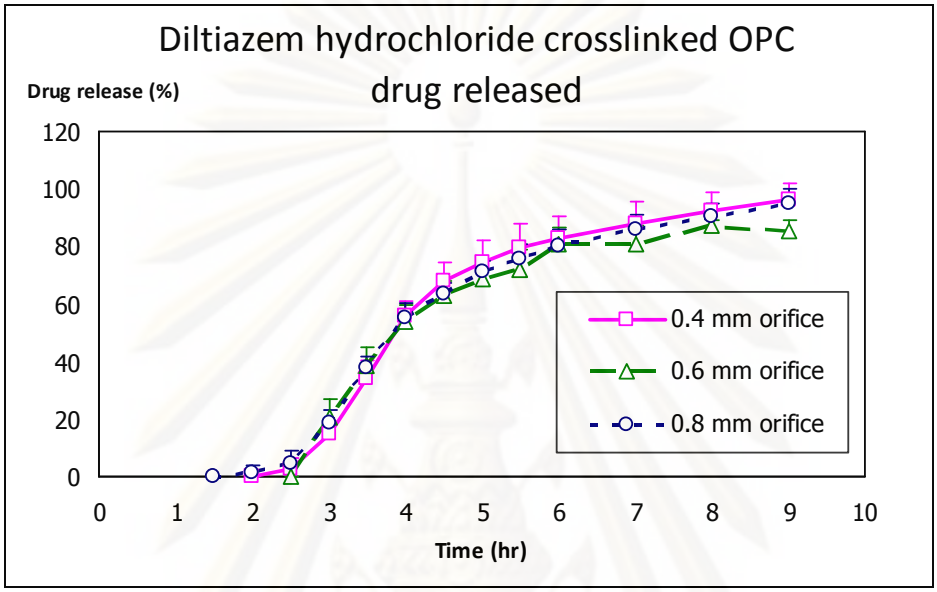


Figure 44 The release profiles of diltiazem hydrochloride from crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

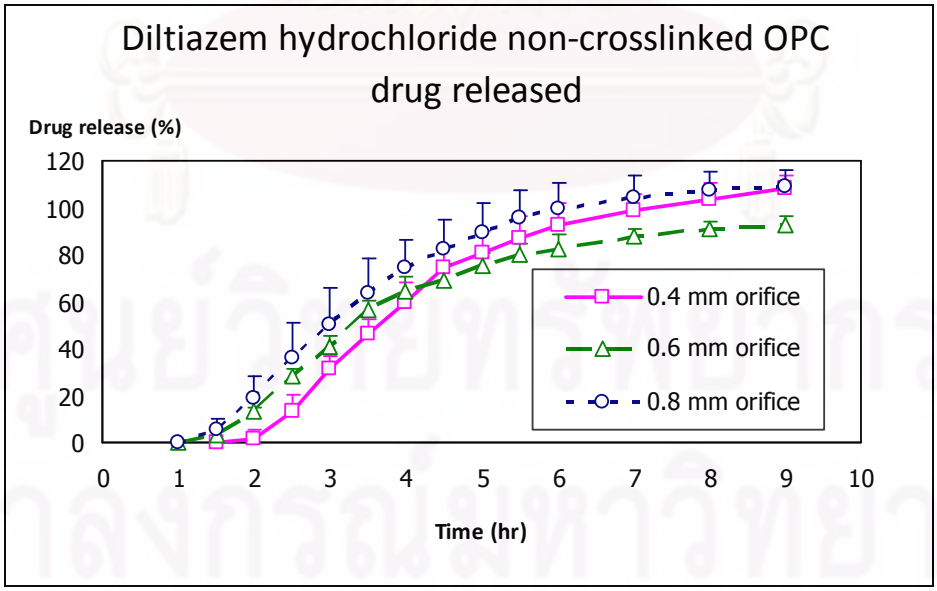


Figure 45 The release profiles of diltiazem hydrochloride from non-crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

Table 30 The comparative parameters of diltiazem hydrochloride crosslinked OPC with various orifice sizes including calculated release rate and R^2

diltiazem hydrochloride crosslinked OPC			
orifice size	Qobs* (%)	calculated release rate (%/hr)	R^2
0.4 mm	14.94-82.53	22.337	0.9015
0.6 mm	20.51-80.94	18.722	0.9283
0.8 mm	4.59-80.25	21.985	0.9351

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Table 31 The comparative parameters of diltiazem hydrochloride non-crosslinked OPC with various orifice sizes including calculated release rate and R^2

diltiazem hydrochloride non-crosslinked OPC			
orifice size	Qobs* (%)	calculated release rate (%/hr)	R^2
0.4 mm	13.66-80.7	27.325	0.9853
0.6 mm	13.12-79.92	18.836	0.9496
0.8 mm	5.48-82.35	26.377	0.9902

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Release rate profiles of diltiazem hydrochloride from crosslinked and non-crossliniked OPC with various orifice sizes are displayed in Figure 46 and 47. Orifice size had slight effect on release rate of diltazem hydrochloride crosslinked and non-crosslinked OPC. But the results showed that there were different release rate profiles between diltiazem hydrochloride crosslinked OPC and diltiazem hydrochloride non-crosslinked OPC. Release rate of diltiazem hydrochloride crosslinked OPC immediately decreased from 3 hrs to 5 hrs when past 6 hrs release rate was steady. But release rate of diltiazem hydrochloride non-crosslinked OPC slowly decreased

from 2 to 6 hrs. As shown in Table 30 and 31, diltizem hydrochloride crosslinked and non-crosslinked OPC with 0.6 mm orifice size gave lower calculated release rate.

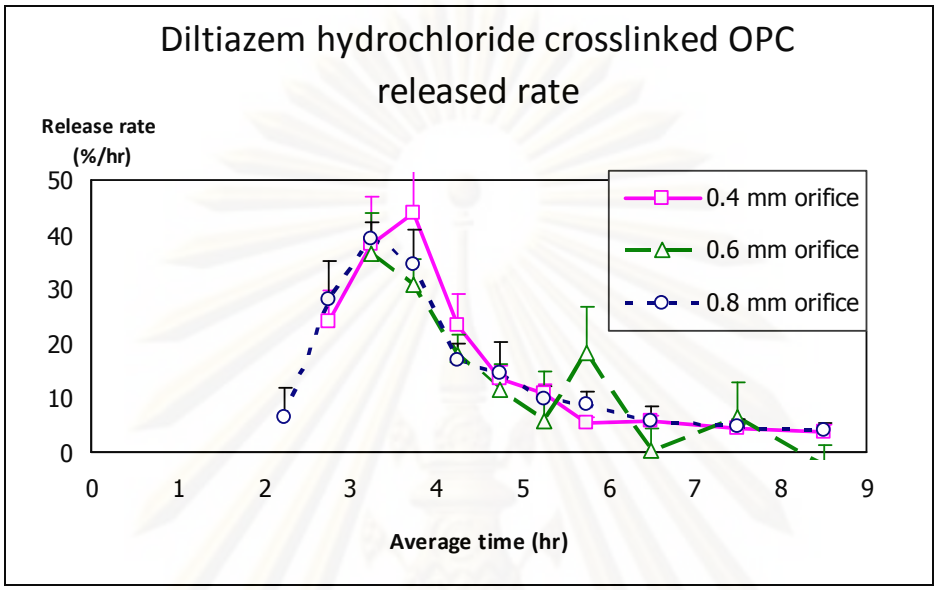


Figure 46 The release rate profiles of diltiazem hydrochloride from crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

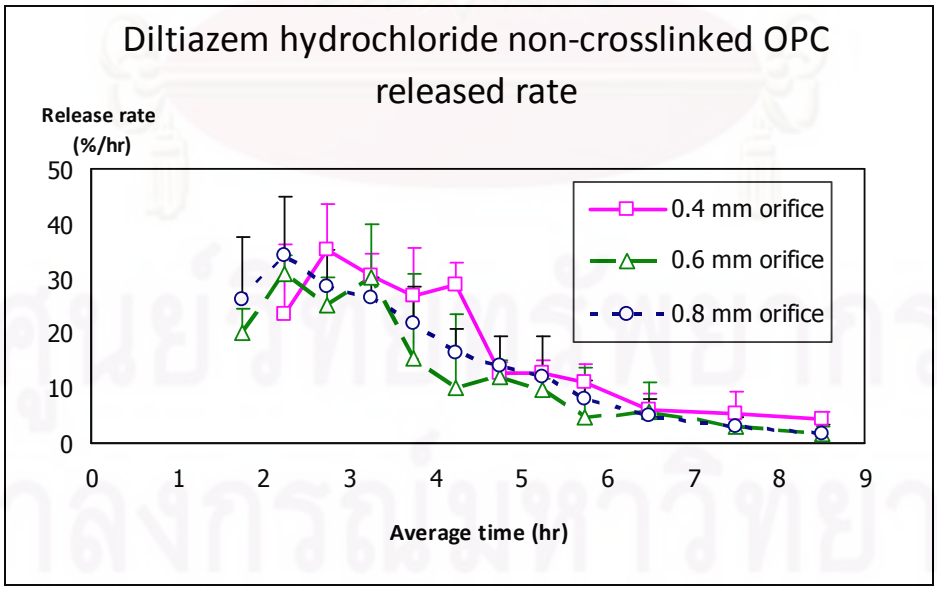


Figure 47 The release rate profiles of diltiazem hydrochloride from non-crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

As shown in Figure 48, lag time of propranolol hydrochloride crosslinked OPC with orifice size 0.4, 0.6 and 0.8 mm were 3.5, 3 and 3 hrs, respectively. Figure 49 showed that lag time of propranolol hydrochloride non-crosslinked OPC with 0.4, 0.6 and 0.8 mm orifice sizes were 1 hr.

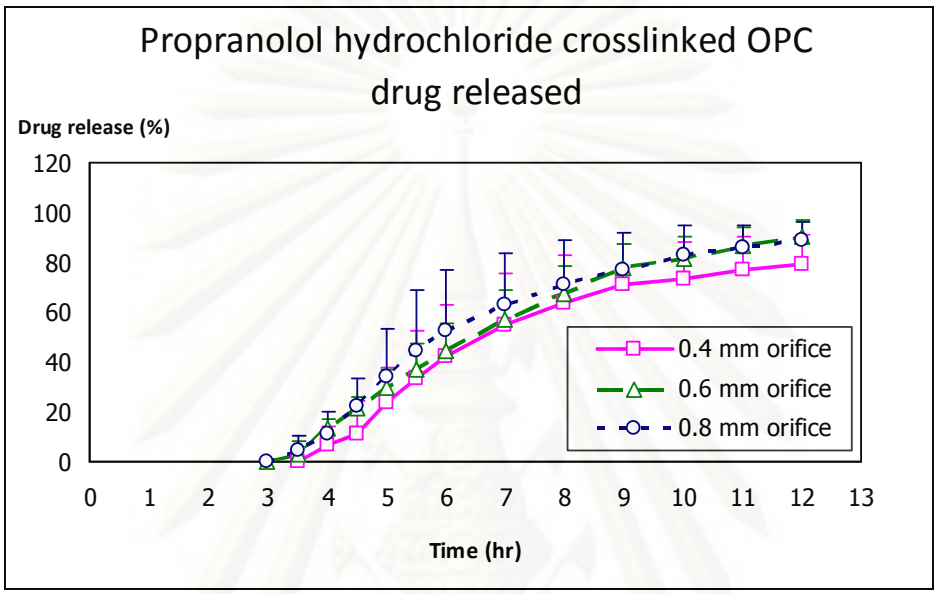


Figure 48 The release profiles of propranolol hydrochloride from crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

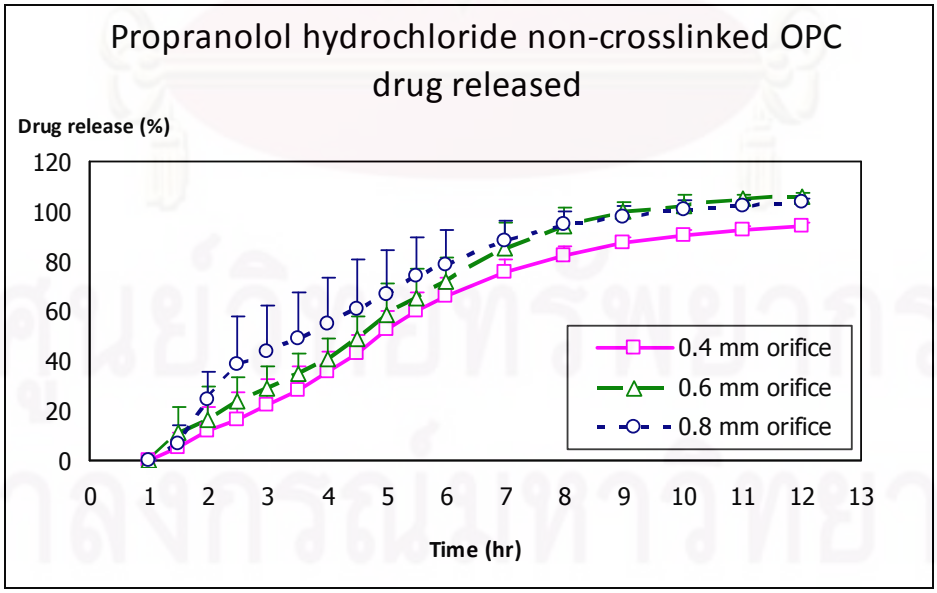


Figure 49 The release profiles of propranolol hydrochloride from non-crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

Propranolol hydrochloride crosslinked and non-crosslinked OPC could prolong release for 12 and 9 hrs, respectively. About 90 % of drug release were closed to zero-order kinetics (R^2 are shown in Table 32 and 33). Propranolol hydrochloride crosslinked OPC with 0.6 mm orifice size had lower drug release variation at various sampling time points and non-crosslinked OPC with 0.8 mm orifice size had the most drug release variation at various sampling time points (Figure 48 and 49).

Table 32 The comparative parameters of propranolol hydrochloride crosslinked OPC with various orifice sizes including calculated release rate and R^2

propranolol hydrochloride crosslinked OPC			
orifice size	Qobs* (%)	calculated release rate (%/hr)	R^2
0.4 mm	11.28-79.5	8.6714	0.8946
0.6 mm	13.59-90.18	9.7697	0.9535
0.8 mm	11.21-89.24	9.3077	0.9053

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Table 33 The comparative parameters of propranolol hydrochloride non-crosslinked OPC with various orifice sizes including calculated release rate and R^2

propranolol hydrochloride non-crosslinked OPC			
orifice size	Qobs* (%)	calculated release rate (%/hr)	R^2
0.4 mm	11.68-90.52	10.735	0.9593
0.6 mm	10.79-94.35	13.478	0.9958
0.8 mm	6.77-94.66	12.581	0.9529

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Figure 50 and 51 show release rate profiles of propranolol hydrochloride crosslinked and non-crosslinked OPC that had low fluctuation except for release rate profile of propranolol hydrochloride non-crosslinked OPC with 0.8 mm orifice size.

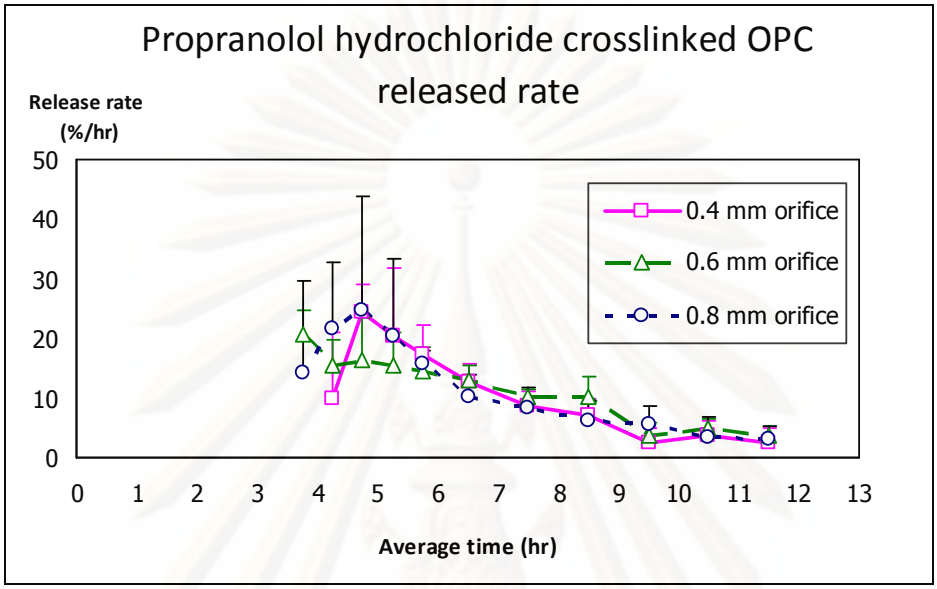


Figure 50 The release rate profiles of propranolol hydrochloride from crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

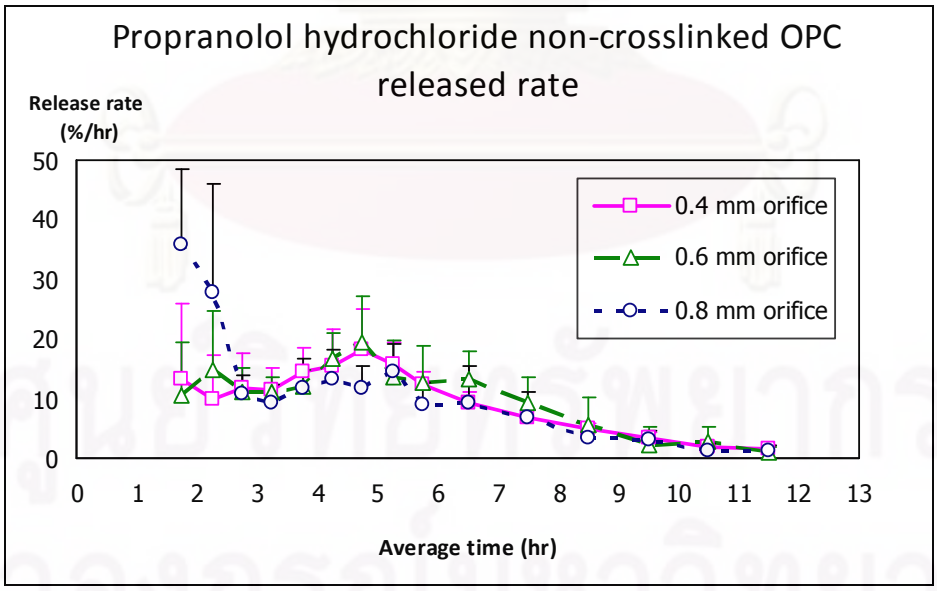


Figure 51 The release rate profiles of propranolol hydrochloride from non-crosslinked OPC with various orifice sizes 0.4, 0.6 and 0.8 mm (n=6) in deionized water.

It was found that no clear difference existed in the release profiles of all groups OPC among 0.4, 0.6 and 0.8 mm in orifice diameter (Figure 44, 45, 48 and 49). However for all orifice sizes, crosslinked OPC seemed to have more similar drug release than non-crosslinked OPC. The results showed that the orifice size affected variation of drug release at various sampling time points. As presented in Figure 45 and 49, diltiazem hydrochloride and propranolol hydrochloride non-crosslinked OPC with 0.8 mm orifice size were observed high variation of drug release at various sampling time points. Drug release variation at various sampling time points of propranolol hydrochloride crosslinked OPC with 0.6 mm was the lowest (Figure 48). Diltiazem hydrochloride crosslinked OPC with various orifice sizes gave slight different variation of drug release at various sampling time points (Figure 44). Diameter of orifice increased led to an increas of variation at various sampling time points except for propranolol hydrochloride crosslinked OPC with 0.4 mm orifice which gave high variation due to broken membrane of OPC. High variation of release rate at various time points of OPC with 0.8 orifice size may be due to high water influx through the larger orifice (Liu et al., 2000).

Mohammadi-Samani et al. (2000) reported that propranolol hydrochloride osmotic pump tablets with 0.2 mm to 0.8 mm orifice size gave release mechanism followed zero-order model. But release rate of propranolol hydrochloride osmotic pump tablets with 1.0 mm orifice size became abnormal. It can be indicated that the delivery rate of osmotic pump is independent of orifice size within predictable limits (Theeuwes, 1975). Hence lag time and delivery rate of OPC might be affected by orifice size which was out of optimum range. The minimum area of the optimum orifice size can be calculated from Poiseuille's law (Lakshminarayanaiah, 1969).

$$\text{Minimum area of the orifice} = 5\left(l \frac{dV}{dt} \frac{\eta}{\Delta P_{\max}} \right)^{\frac{1}{2}}$$

dV/dt = volume flux

l = length of the orifice

η = viscosity of the delivery fluid

ΔP_{max} = maximum hydrostatic pressure of the device

The maximum area of the optimum orifice size is established to reduce the diffusion contribution to the delivery rate. These area can be calculated from following equation that was developed by Theeuwes (1974).

$$\text{Maximum area of the orifice} = \frac{l}{F}\left(\frac{dm}{dt}\right)_z \frac{1}{DS}$$

$(dm/dt)_z$ = fluid delivery rate from t=0 to t=z

F = the ratio of total delivery rate to diffusive rate

(If $F \geq 40$, diffusive contribution to delivery rate is insignificant)

D = diffusion coefficient of drug in dissolution medium

S = the component solubility

From Figure 34 to 41 and 44 to 51, diltiazem hydrochloride OPC gave short time of drug release and high release rate. As presented in Table 24 to 31, calculated release rate of propranolol hydrochloride OPC was less than calculated release rate of diltiazem hydrochloride. According to Equation 7, the soluble component increase resulting in increment of delivery rate. The soluble component of diltiazem hydrochloride OPC was higher than the component solubility of propranolol hydrochloride OPC.

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h} P_w \pi_s S \qquad \text{(Eq. 7)}$$

Based on the aboved results, OPC prepared using 335 ml CA solution with orifice size of 0.6 mm were selected for investigating the effect of release media having different ionic strenghts and pHs on drug release from the system.

7.6.2 Evaluation of drug release in various media

2.6.2.1 Different ionic strength media

Drug release of diltiazem hydrochloride crosslinked and non-crosslinked OPC and propranolol hydrochloride crosslinked and non-crosslinked OPC were studied using various ionic strength solutions as follows

- 0.154 M or 0.9 % sodium chloride (NaCl) solution (isotonic)
- 0.5 M NaCl solution
- 1 M NaCl solution

Figure 52 and 53 display drug release profiles and release rate profiles of diltiazem hydrochloride crosslinked OPC. Lag time of diltiazem hydrochloride crosslinked OPC in deionized water, 0.9 %, 0.5 M and 1 M NaCl solutions were 2.5, 2.5, 3.5 and 5.5 hrs, respectively. The results showed that increasing ionic strength of medium could increase lag time and decreased drug release of diltiazem hydrochloride crosslinked OPC (Calculated release rates are presented in Table 34).

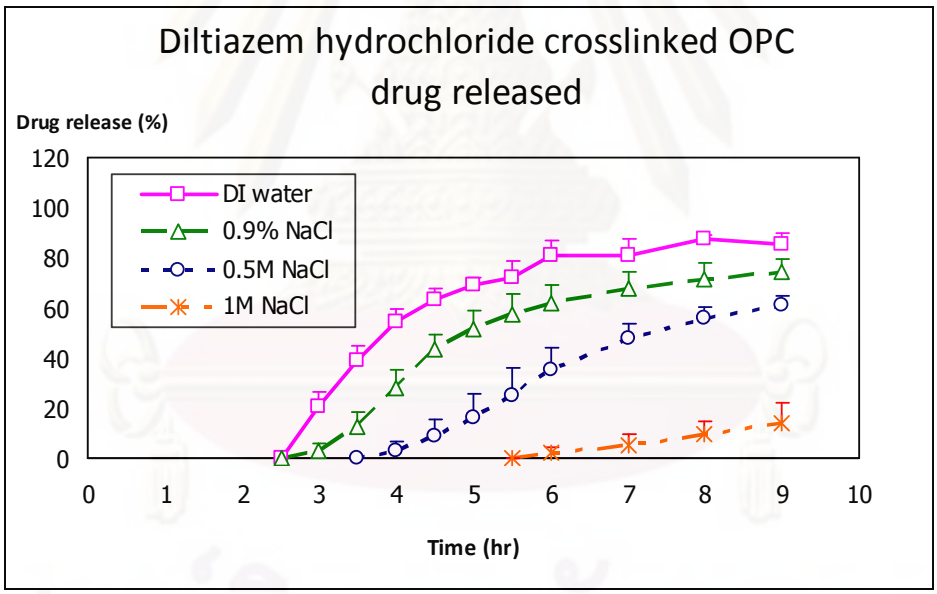


Figure 52 The release profiles of diltiazem hydrochloride from crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

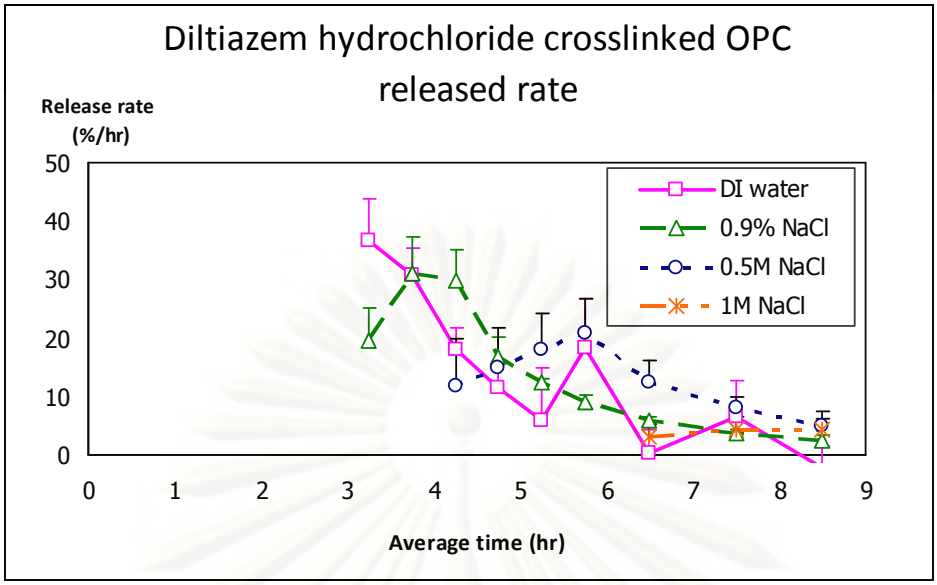


Figure 53 The release rate profiles of diltiazem hydrochloride from crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

Table 34 The comparative parameters of diltiazem hydrochloride crosslinked OPC in deionized water and various concentration NaCl solutions including calculated release rate and R^2

diltiazem hydrochloride crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
DI water	20.51-63.12	28.63	0.9787
0.9 % NaCl	12.69-62.16	19.662	0.9438
0.5 M NaCl	8.79-60.98	11.931	0.9553
1 M NaCl	3.90-7.37	4.4371	1.000

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Drug release profiles and release rate profiles of diltiazem hydrochloride non-crosslinked OPC were displayed in Figure 54 and 55, respectively. Diltiazem hydrochloride crosslinked OPC lag time in deionized water, 0.9 %, 0.5 M and 1 M NaCl solution were 1, 1.5, 1.5 and 2 hrs, respectively. The increase in ionic strength

of dissolution medium led to reduction of diltiazem hydrochloride release from non-crosslinked OPC (Calculated release rates are presented in Table 35).

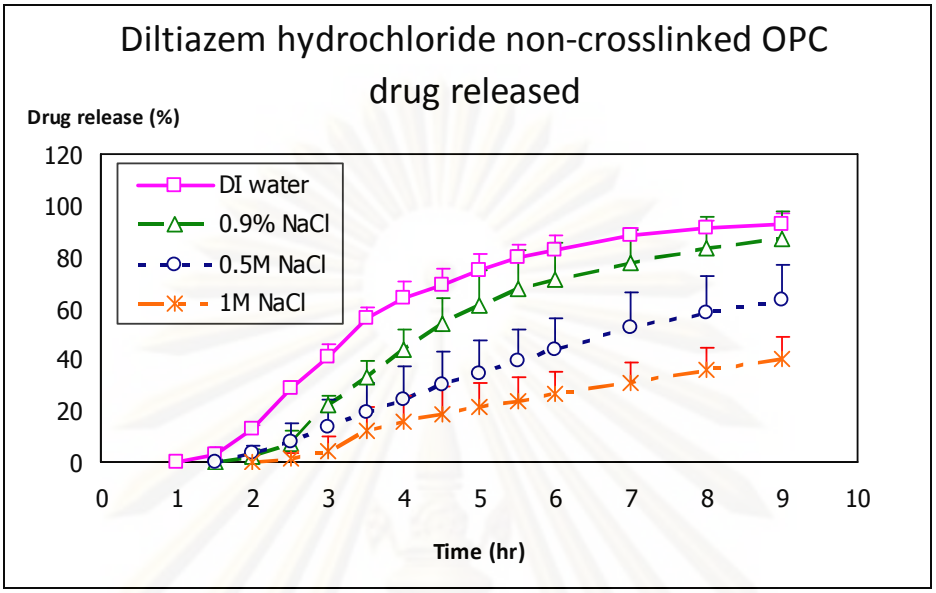


Figure 54 The release profiles of diltiazem hydrochloride from non-crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

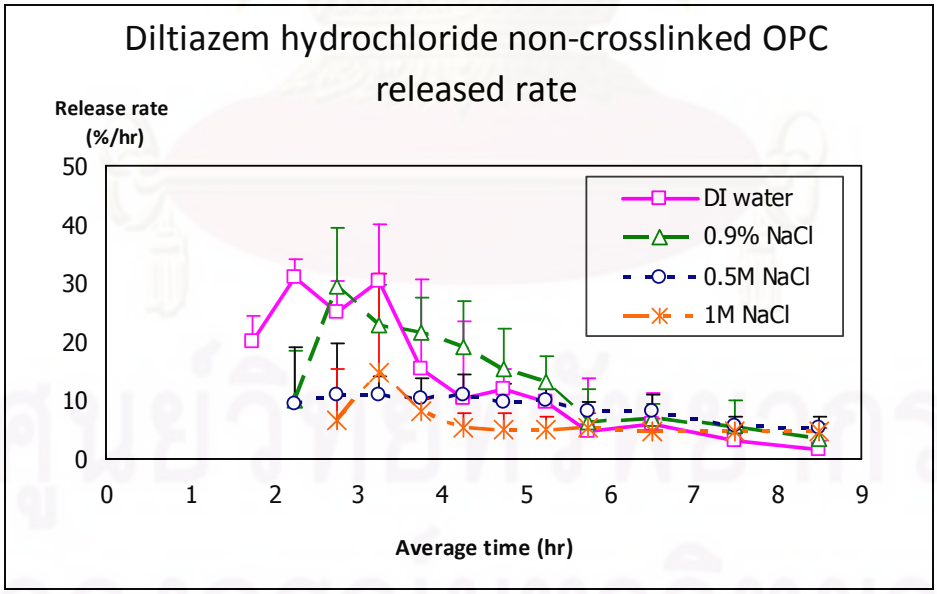


Figure 55 The release rate profiles of diltiazem hydrochloride from non-crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

Table 35 The comparative parameters of diltiazem hydrochloride non-crosslinked OPC in deionized water and various concentration NaCl solutions including calculated release rate and R^2

diltiazem hydrochloride non-crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
DI water	13.12-63.95	25.868	0.9895
0.9 % NaCl	7.25-61.36	21.513	0.9891
0.5 M NaCl	8.21-63.14	8.6339	0.9831
1 M NaCl	12.00-40.18	4.9743	0.9955

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Figure 56 and 57 exhibit drug release profiles and release rate profiles of propranolol hydrochloride crosslinked OPC. Lag time of propranolol hydrochloride crosslinked OPC in deionized water, 0.9 %, 0.5 M and 1 M NaCl solution were found to be 3, 5.5, 5.5 and 5 hrs, respectively. Increasing ionic strength of medium extremely decreased in drug release and release rate of propranolol hydrochloride crosslinked OPC (Calculated release rates are shown in Table 36). As shown in Figure 56 and 57, propranolol hydrochloride barely released in 0.5 M and 1 M NaCl solutions.

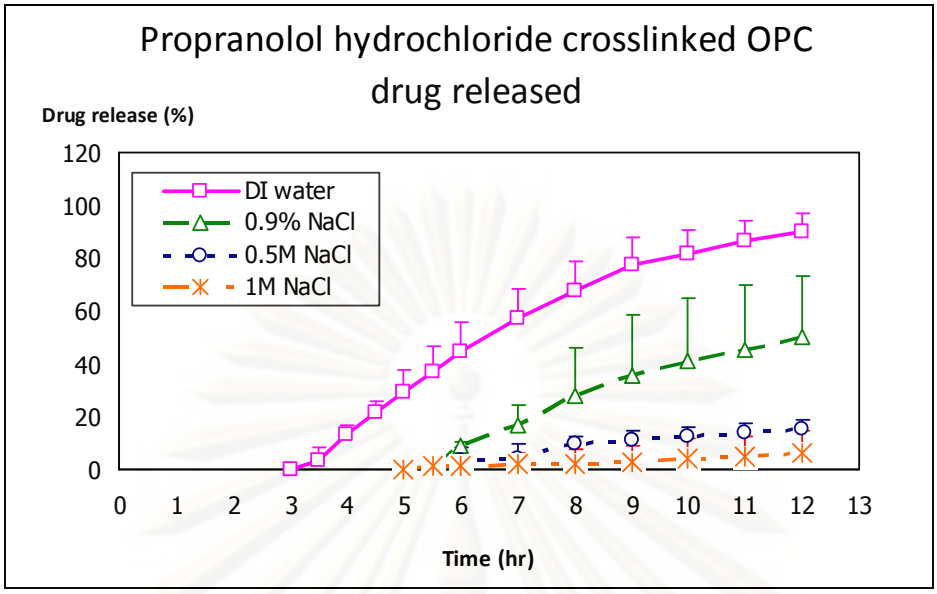


Figure 56 The release profiles of propranolol hydrochloride from crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

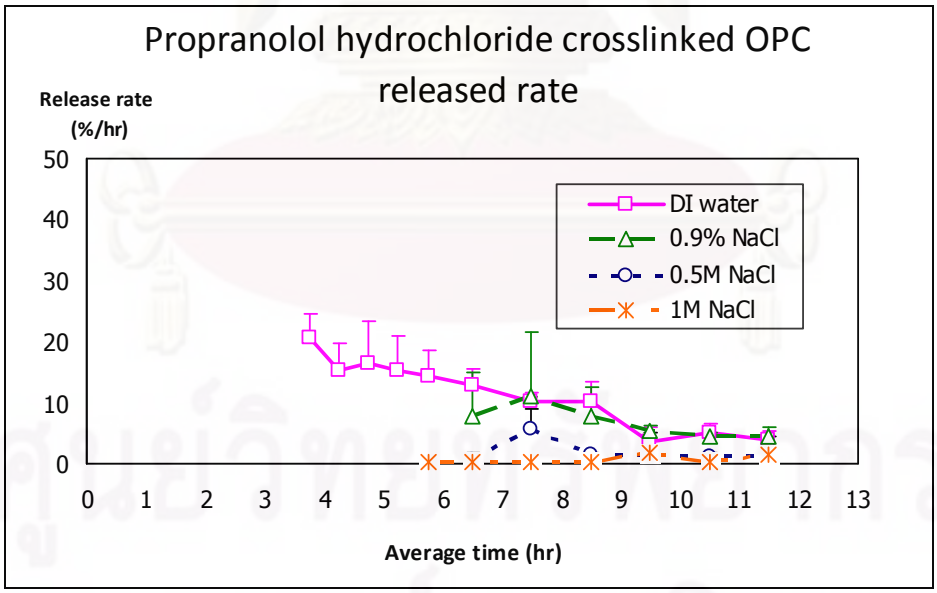


Figure 57 The release rate profiles of propranolol hydrochloride from crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

Table 36 The comparative parameters of propranolol hydrochloride crosslinked OPC in deionized water and various concentration NaCl solutions including calculated release rate and R^2

propranolol hydrochloride crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
DI water	13.59-57.32	14.67	0.9976
0.9 % NaCl	8.94-50.14	6.95	0.9717
0.5 M NaCl	9.75-15.25	1.38	0.9991
1 M NaCl	4.33-6.40	1.04	0.9005

*Qobs=percentage of drug release interval used for calculation of zero-order equation

As shown in Figure 58 and 59, there was no clear difference in lag time of propranolol hydrochloride crosslinked OPC in various ionic strength media. Drug release of propranolol hydrochloride non-crosslinked OPC during 1 to 4 hrs were similar (Calculated drug release are presented in Table 37). But after 4 hrs of propranolol hydrochloride release, the effect of ionic strength was clearly observed and propranolol hydrochloride release about 40 % of drug content in 1M NaCl solution.

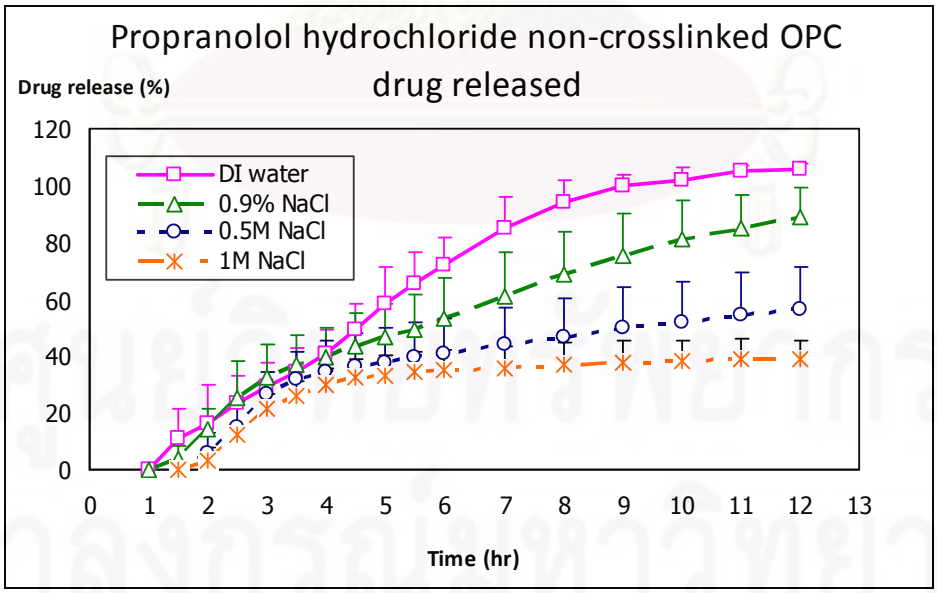


Figure 58 The release profiles of propranolol hydrochloride from non-crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

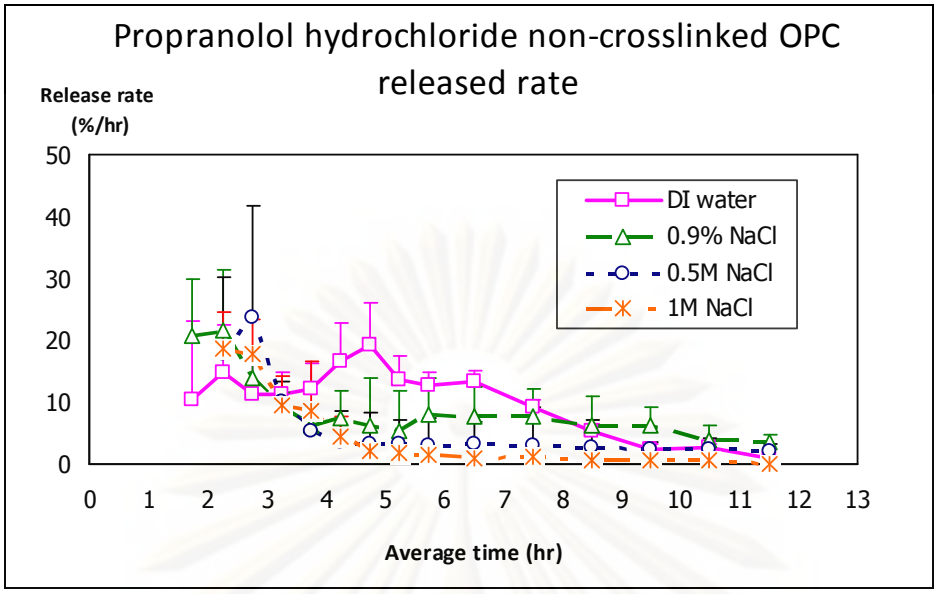


Figure 59 The release rate profiles of propranolol hydrochloride from non-crosslinked OPC (n=6) in deionized water and various concentration NaCl solutions (0.9%, 0.5 M and 1 M).

Table 37 The comparative parameters of propranolol hydrochloride non-crosslinked OPC in deionized water and various concentration NaCl solutions including calculated release rate and R^2

propranolol hydrochloride non-crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
DI water	10.79-49.02	12.52	0.9967
0.9 % NaCl	14.42-49.34	9.26	0.9377
0.5 M NaCl	14.80-49.65	4.36	0.8520
1 M NaCl	12.36-37.57	3.12	0.7018

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Solubility of diltiazem hydrochloride and propranolol hydrochloride are reported in Table 4 and 5 in different media to confirm that sink conditions were maintained during dissolution studies. And solubility of propranolol hydrochloride in different ionic strength media are displayed in Table 38. The solubility of both model drugs in high ionic strength medium are reduced due to common ion effects (Florence and Attwood, 2006). According to equation 4, ionic strength of dissolution medium increases led to decrease of osmotic pressure difference ($\Delta\pi$) resulting in reduction of drug delivery rate (*dm/dt*). The lag time values of OPC were affected by the ionic strength of dissolution medium. For both model drugs, ionic strength of dissolution medium had more effect on lag time and release rate of crosslinked OPC than lag time and release rate of non-crosslinked OPC. Propranolol hydrochloride OPC was found to be highly dependent on ionic strength of dissolution media more than diltiazem hydrochloride OPC. Based on the results of this study, the increase of ionic strength of dissolution medium led to a reduction of drug release rate of diltiazem hydrochloride and propranolol hydrochloride OPC. Previous studies reported that ionic strength of dissolution media increased resulting in reduction of drug release (Okimoto et al., 1999; Verma et al., 2003). It can be concluded that osmotic pumping is the main mechanism of drug release from the OPC (Liu et al., 1984; Appel and Zentner, 1991)

Table 38 Solubility of propranolol hydrochloride in different ionic strength media

Medium	Solubility (mg/ml)
0.154 M NaCl solution	25.32 ± 0.95
0.5 M NaCl solution	6.36 ± 0.27
1 M NaCl solution	2.74 ± 0.09

Osmolarity (ξ_c) of delivery solutions can be calculated by molar concentration (USP 29/NF24, 2006)

$$\xi_c = \Sigma i C_i$$

i = van ‘t Hoff factor (accounts for the number of individual particles of a compund dissolved in solution)

C_i = molar concentration of the solute in solution

From above equation, omolarity of diltiazem hydrochloride and propranolol hydrochloride formulation solutions were 7.198 and 6.748 Osmol/L, respectively. And osmolarity of 0.9%, 0.5 and 1 M NaCl solution were 0.308, 1 and 2 Osmol/L, respectively. The increment of concentration of NaCl solution led to reduction of osmolarity difference between inside and outside OPC.

The estimation of osmotic pressure (π) of each ingredient saturated solution can be calculated by Morse equation (Amiji and Sandmann, 2003)

$$\pi = iMRT$$

M = molarity of solution
R = gas constant (0.08206 L · atm · mol^{-1} · K^{-1})
T = Temeperature (ºK)

Table 39 are presented osmotic pressure of saturated solution of diltiazem hydrochloride, propranolol hydrochloride and lactose. Osmotic pressure of NaCl saturated solution is shown in Tale 2.

Table 39 Osmotic pressure of saturated solution of formulation ingredients

Ingrdient	Osmotic pressure (atm)
Diltiazem hydrochloride	67
Propranolol hydrochloride	9
Lactose	24

These results also seemed to confirm that ionic strength had effect on drug release and diltiazem hydrochloride formulation had higher osmotic pressure resulting in more drug release rate.

2.6.2.2 Different pH media

To study the effect of pH of dissolution medium, release studies of diltiazem hydrochloride or propranolol hydrochloride crosslinked and non-crosslinked OPC were conducted in isotonic media of different pH as follows

- Isotonic 0.1 M hydrochloric acid pH 1.2
- Isotonic phosphate buffer pH 6.8
- 0.1 M hydrochloric acid pH 1.2 for 2 hrs and changed to isotonic phosphate buffer pH 6.8

Drug release profiles and release rate profiles of diltiazem hydrochloride crosslinked OPC in various pH media were displayed in Figure 60 and 61. It was shown that lag time of diltiazem hydrochloride crosslinked OPC in isotonic, isotonic HCl pH 1.2, isotonic PBS pH 6.8 and pH-change medium were 2.5, 3, 3 and 3 hrs, respectively. It indicated that no clear differences existed in drug release rate of diltiazem hydrochloride crosslinked OPC in different pH isotonic media (Calculated release rates are presented in Table 40).

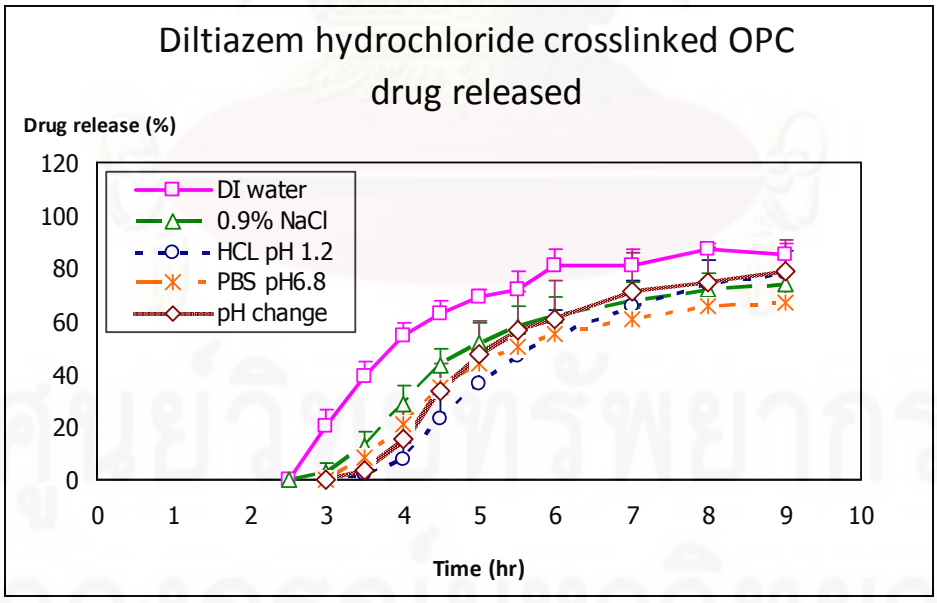


Figure 60 The release profiles of diltiazem hydrochloride from crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonicity (HCl pH1.2, PBS pH6.8 and pH-change method).

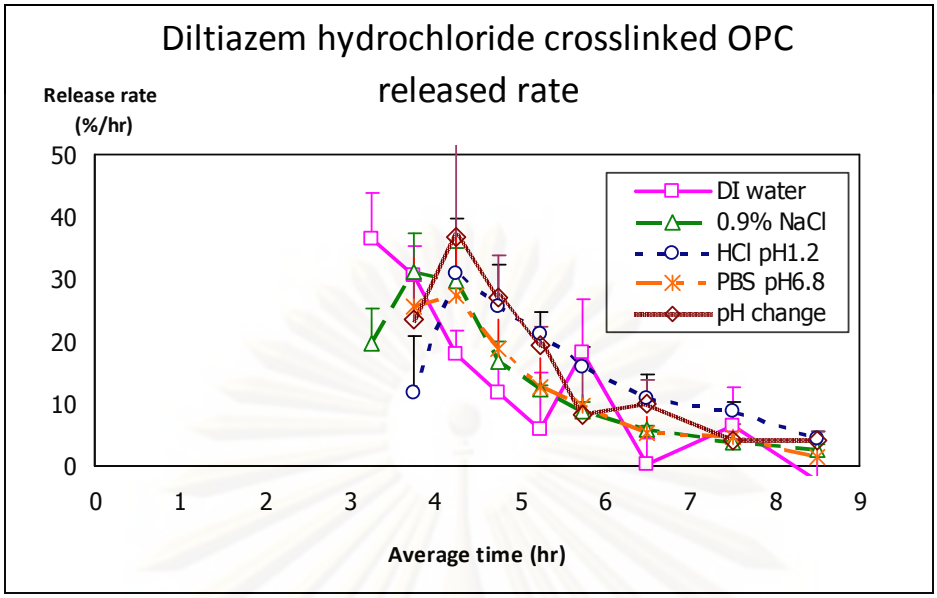


Figure 61 The release rate profiles of diltiazem hydrochloride from crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonic (HCl pH1.2, PBS pH6.8 and pH-change method).

Table 40 The comparative parameters of diltiazem hydrochloride crosslinked OPC in different pH media with isotonic including calculated release rate and R^2

diltiazem hydrochloride crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
HCl	7.82-74.07	16.05	0.9372
PBS	8.23-65.30	12.24	0.8740
pH-change	15.24-70.82	17.84	0.9085

*Qobs=percentage of drug release interval used for calculation of zero-order equation

As shown in Figure 62, lag time of diltiazem hydrochloride non-crosslinked OPC in isotonic, isotonic HCl pH 1.2, isotonic PBS pH 6.8 and pH-change medium were found to be 1.5, 1.5, 1 and 1.5 hrs, respectively. Figure 63 show that drug release rate profile of diltiazem hydrochloride non-crosslinked OPC are apparently similar in all different pH media with isotonic (Calculated release rates are presented in Table 41).

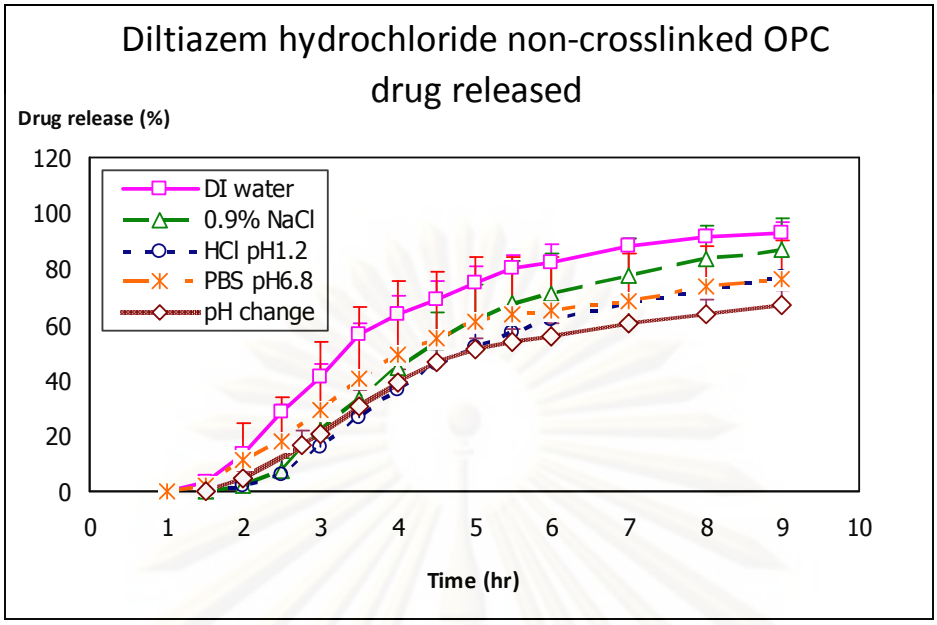


Figure 62 The release profiles of diltiazem hydrochloride from non-crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonic (HCl pH1.2, PBS pH6.8 and pH-change method).

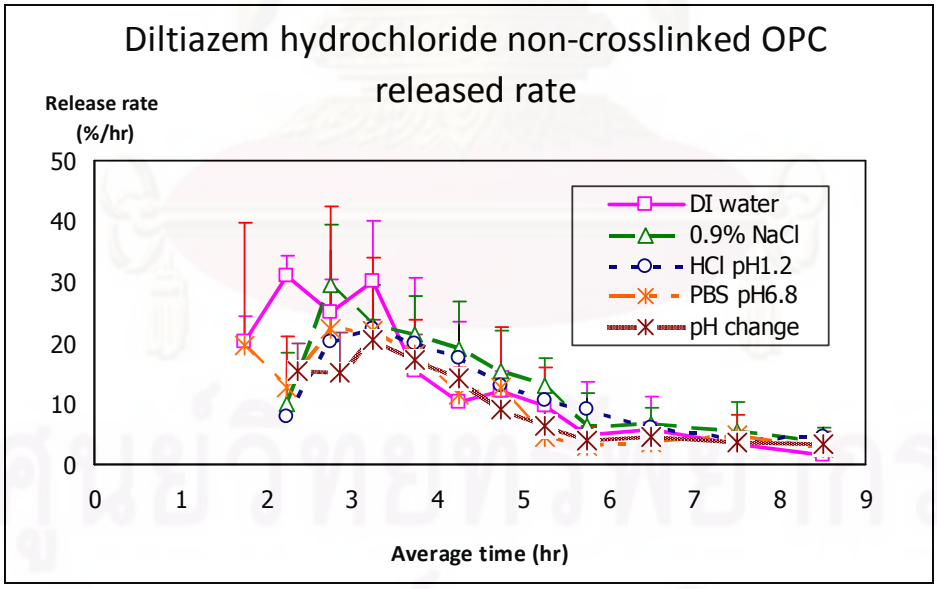


Figure 63 The release rate profiles of diltiazem hydrochloride from non-crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonic (HCl pH1.2, PBS pH6.8 and pH-change method).

Table 41 The comparative parameters of diltiazem hydrochloride non-crosslinked OPC in different pH media with isotonic including calculated release rate and R^2

diltiazem hydrochloride non-crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
HCl	5.64-72.01	12.23	0.9200
PBS	11.56-68.53	12.21	0.9082
pH-change	4.89-67.27	8.76	0.8774

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Figure 64 and 65 display the release profiles and release rate profiles of propranolol hydrochloride from crosslinked OPC. As can be seen from the figure, lag time of propranolol hydrochloride crosslinked OPC in isotonic, isotonic HCl pH 1.2, isotonic PBS pH 6.8 and pH-change medium were found to be 5.5, 3, 4 and 3.5 hrs, respectively. Drug release profiles and release rate profiles of propranolol hydrochloride crosslinked OPC are similar all different pH media with isotonic (Calculated release rates are shown in Table 42).

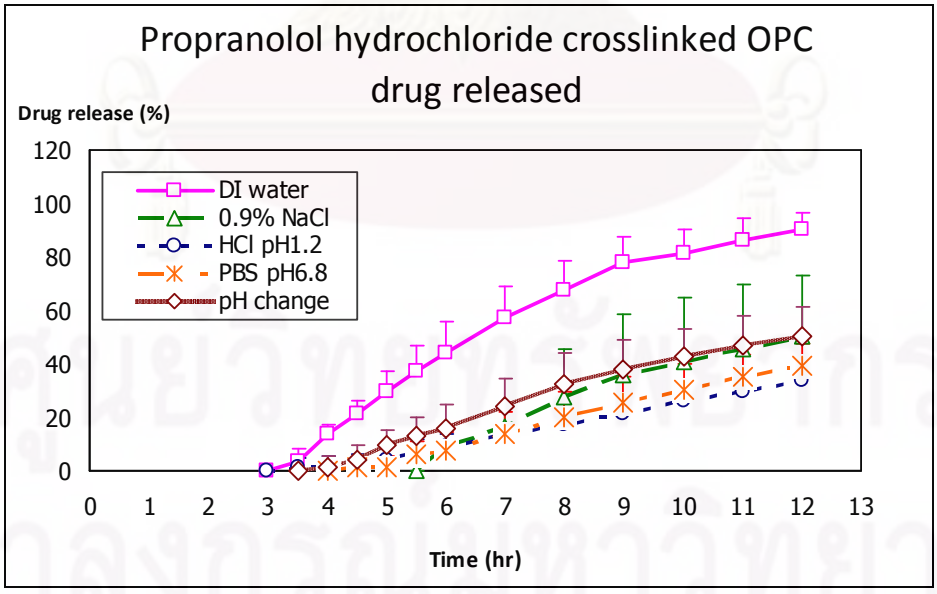


Figure 64 The release profiles of propranolol hydrochloride from crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonic (HCl pH1.2, PBS pH6.8 and pH-change method).

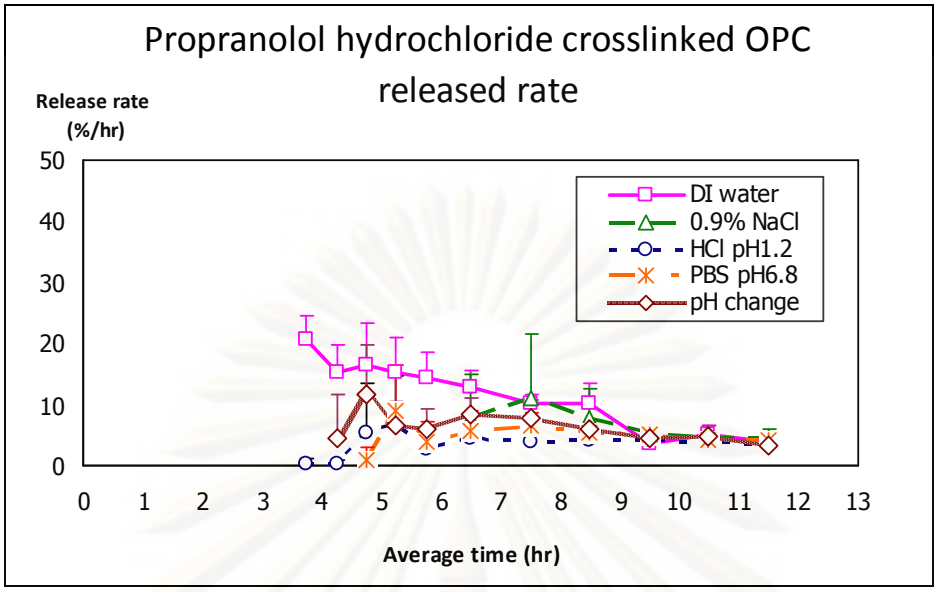


Figure 65 The release rate profiles of propranolol hydrochloride from crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonicity (HCl pH1.2, PBS pH6.8 and pH-change method).

Table 42 The comparative parameters of propranolol hydrochloride crosslinked OPC in different pH media with isotonicity including calculated release rate and R^2

propranolol hydrochloride crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
HCl	9.09-33.50	4.08	0.9994
PBS	7.93-39.15	5.26	0.9942
pH-change	9.56-38.02	7.34	0.9971

*Qobs=percentage of drug release interval used for calculation of zero-order equation

The release profiles and release rate profiles of propranolol hydrochloride from non-crosslinked OPC are exhibited in Figure 66 and 67. Lag time of propranolol hydrochloride non-crosslinked OPC in isotonic, isotonic HCl pH 1.2, isotonic PBS pH 6.8 and pH-change medium were obtained to be 1, 1.5, 1 and 1.5 hrs, respectively. About 40% of drug release of propranolol hydrochloride non-crosslinked OPC in various medium were similar and after that drug release in all different pH

media with isotonicity were different from drug release in deionized water (Calculated release rates are presented in Table 43).

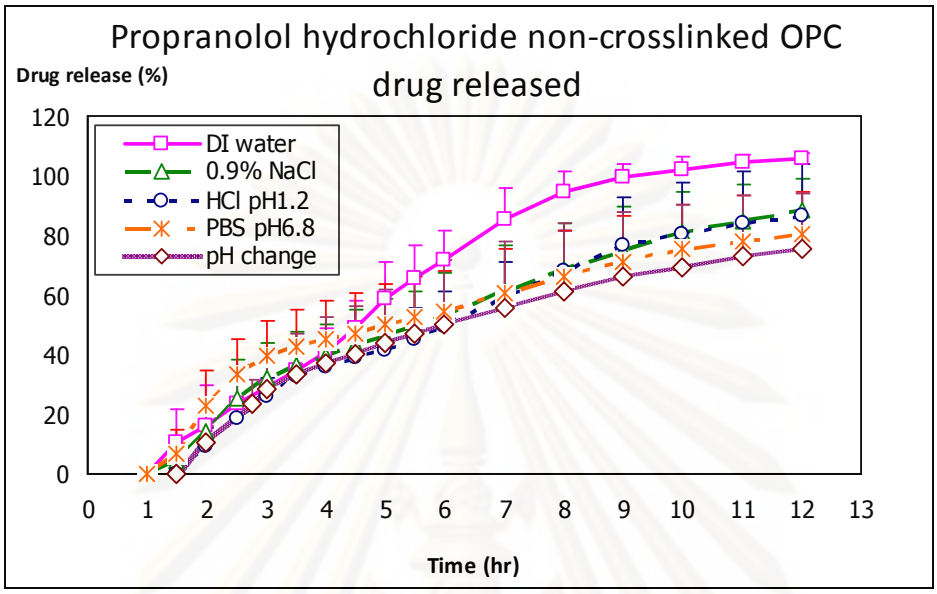


Figure 66 The release profiles of propranolol hydrochloride from non-crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonicity (HCl pH1.2, PBS pH6.8 and pH-change method).

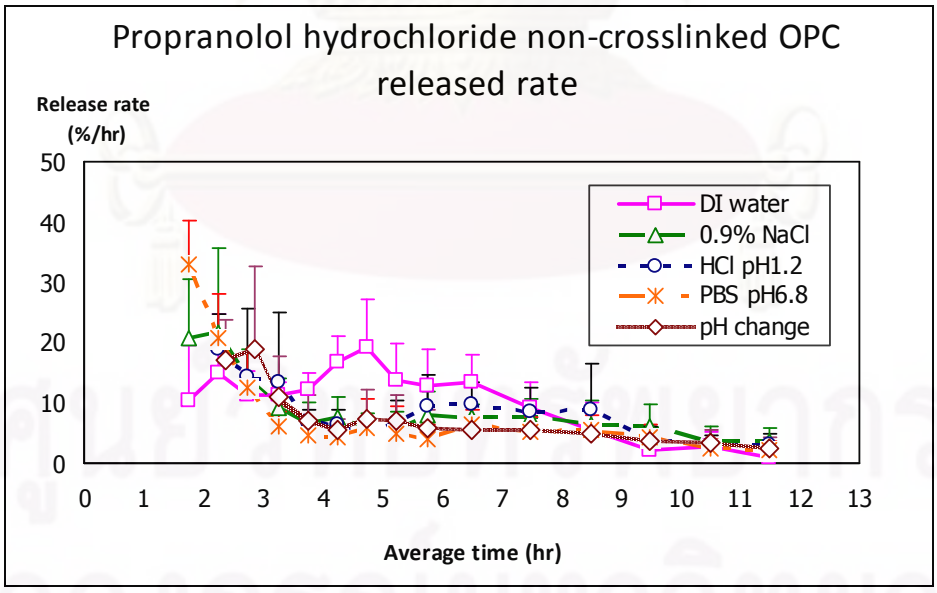


Figure 67 The release rate profiles of propranolol hydrochloride from non-crosslinked OPC (n=6) in deionized water, 0.9 % NaCl solution and different pH media with isotonicity (HCl pH1.2, PBS pH6.8 and pH-change method).

Table 43 The comparative parameters of propranolol hydrochloride non-crosslinked OPC in different pH media with isotonicity including calculated release rate and R^2

propranolol hydrochloride non-crosslinked OPC			
dissolution medium	Qobs* (%)	calculated release rate (%/hr)	R^2
HCl	9.16-76.67	8.89	0.9833
PBS	6.58-75.5	6.70	0.8977
pH-change	10.61-75.41	5.93	0.9436

*Qobs=percentage of drug release interval used for calculation of zero-order equation

Based on this study, drug release of diltiazem hydrochloride and propranolol hydrochloride are independent of pH of dissolution media, even though drug solubility were difference in different pH media (Table 4 and 5). In previous studies, there was no difference in drug release with changing the media pH (Theeuwes, 1975; Zentner et al., 1991; Verma et al., 2003; Garg et al., 2007) It can be predicted that the environment of gastrointestinal tract scarcely affect the drug release from OPC.

From the above results, the release profiles of OPC might not completely fit to zero-order delivery due to another delivery mechanism such as drug diffusion through the semipermable membrane pores and swellable of subcoating polymer. Semipermable membrane pores were induced by high level of hydrophilic plasticizer in semipermeable membrane led to drug diffusion through membrane pores. In further study, amount of hydrophilic polymer in CA coating solution should be decreased to reduce drug diffusion mechanism of OPC. In case of subcoating polymer, HPMC E5 should be changed to less hydrophilic swellable polymer such as HPC and/or concentration of subcoating solution should be reduced.

CHAPTER V
CONCLUSIONS

Osmotically controlled drug delivery system using crosslinked and non-crosslinked hard gelatin capsules could be successfully prepared by fluidized bed coating method. Diltiazem hydrochloride and propranolol hydrochloride using crosslinked capsules and non-crosslinked capsules nearly achieved zero-order model. Physical characteristics of crosslinked and non-crosslinked hard gelatin capsules were similar. But capsules which were exposed to formaldehyde vapors for over 6 hrs are insoluble in all dissolution media.

Thickness of semipermeable membrane had effect on drug release of OPC. An increase of semipermeable film thickness, resulting in an increase of OPC lag time and a reduction of OPC release rate. In this study, suitable level of CA coating solution was 335 ml which equivalent to CA of 9.75 mg/cm^2.

For both model drugs, lag time and drug release of OPC slightly affected by orifice size. Nevertheless, larger orifice size OPC seemed to have high varion of drug release at various sampling time points. OPC with 0.6 mm orifice size were selected in this study.

OPC using crosslinked capsule had longer lag time than OPC using non-crosslink capsules. For diltiazem hydrochloride OPC, there was no difference between release rate of crosslinked OPC and release rate of non-crosslinked OPC. However, release rate of crosslinked OPC was more linear release rate profile and less variation of release rate at various sampling time points in case of propranolol hydrochloride OPC.

Diltiazem hydrochloride OPC had shorter drug release period and higher drug release rate than propranolol hydrochloride OPC. But, propranolol hydrochloride OPC could provided approximated zero-order release longer than diltiazem hydrochloride OPC.

Ionic strength of dissolution media had highly effect on drug release for both model drugs especially for propranolol hydrochloride. It was found that ionic strength

of dissolution medium increased led to decrease of osmotic pressure difference ($\Delta\pi$) resulting in drug delivery rate (dm/dt) decreased. It can be predicted that osmotic pumping is the main mechanism of drug release from the OPC. Based on the result, drug release of OPC are independent of pH of dissolution media.

Both crosslinked and non-crosslinked hard gelatin capsules could be applied in development OPC system of high water soluble drug. However, crosslinked hard gelatin capsules might be more promising in development OPC system of water soluble drug.

REFERENCES

Appel, L. E. and Zentner, G. M. Use of modified ethylcellulose lattices for microporous coating of osmotic tablets. Pharmaceutical Research 8 (1991): 600-604.

Bindschaedler, C., Gurnya, R. and Doelkera, E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. Journal of Controlled Release 4 (1986): 203-212

Choudhury, P. K., Ranawat, M. S., Pillai, M. K. and Chauhan, C. S. Asymmetric membrane capsule for osmotic delivery of flurbiprofen. Acta Pharmaceutica 57 (2007): 343-350.

Deters, J. C., Theeuwes, F., Mullins, K. J. and Eckenhoff, J. B., inventors; ALZA Corporaion, assignee. Osmotic capsule. US patent 4,627,850. 1986.

DURECT Corporation. ALZET® Technical Information Manual. 2008.

Ende, M. T. a., Herbig, S. M. and Korsmeyer, R. W. Osmotic Drug Delivery from Asymmetric Membrane Film-Coated Dosage Forms. in Wise, D. L. (Eds), Handbook of Pharmaceutical Controlled Release Technology, page 751-785. New York: Marcel Dekker 2000.

Florence, A. T. and Attwood, D. The solubility of drugs. Physicochemical principles of pharmacy, pp 139-176. London: Pharmaceutical Press, 2006.

Garg, A., Gupta, M. and Bhargava, H. N. Effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets. European Journal of Pharmaceutics and Biopharmaceutics 67 (2007): 725-731.

Higuchi, T. and Leeper, H. M., inventors; ALZA Coporation, assignee. Improved osmotic dispenser employing magnesium sulphate and magnesium chloride. US patent 3,760,804. 1973.

Higuchi, T. and Leeper, H. M., inventors; ALZA Corporation, assignee. Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient. US patent 3,995,631. 1976.

Lakshminarayanaiah, N. Transport Phenomena in Membrane. New York: Academic Press, 1969.

Lindstedt, B., Ragnarsson, G. and Hjärtstam, J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Indian Journal of Pharmaceutical Sciences 56 (1989): 261-268.

Liu, H., et al. Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in vitro investigation. International Journal of Pharmaceutics 332 (2007): 115-124.

Liu, J.C., Farber, M. and Chien, Y. W. Comparative release of phenylpropranolamine HCl from long-acting appetite suppressant products: accutrim vs dexatrim. Drug Development and Industrial Pharmacy 10 (1984): 1639-1661.

Liu, L. and Che, B. Preparation of monolithic osmotic pump system by coating the indented core tablet. European Journal of Pharmaceutics and Biopharmaceutics 64 (2006): 180-184.

Liu, L., Khang, G., Rhee, J. M. and Lee, H. B. Monolithic osmotic tablet system for nifedipine delivery. Journal of Controlled Release 67 (2000): 309-322.

Liu, L., et al. Nifedipine controlled delivery by sandwiched osmotic tablet system. Journal of Controlled Release 68 (2000): 145-156.

Liu, L. and Xu, X. Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. International Journal of Pharmaceutics 352 (2008): 225-230.

Lu, E.-X., Jiang, Z.-Q., Zhang, Q.-Z. and Jiang, X.-G. A water-insoluble drug monolithic osmotic tablet system utilizing gum arabic as an osmotic, suspending and expanding agent. Journal of Controlled Release 92 (2003): 375-382.

Makhija, S. N. and Vavia, P. R. Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine I. Cellulose acetate as a semipermeable membrane. Journal of Controlled Release 89 (2003): 5-18.

Meier, M. M., Kanis, L. A. and Soldi, V. Characterization and drug-permeation profiles of microporous and dense cellulose acetate membranes: influence of plasticizer and pore forming agent. International Journal of Pharmaceutics 278 (2004): 99-110.

Mohammadi-Samani, S., Adrangui, M., Siahi-Shadbad, M. R. and Nokhodchi, A. An approach to controlled-release dosage form of propranolol hydrochloride. Drug Development and Industrial Pharmacy 26 (2000): 91-94.

O'Neil, M.J., ed. The Merk Index : an acyclopedia of chemicals, drugs, and biological. 14th ed. NJ, USA: MERCK & Co.,Inc. 2006.

Okimoto, K., Rajewski, R. A. and Stella, V. J. Release of testosterone from an osmotic pump tablet utilizing $(SBE)_{7m}$ -b-cyclodextrin as both a solubilizing and an osmotic pump agent. Journal of Controlled Release 58 (1999): 29-38.

Prabakaran, D., Singh, P., Kanaujia, P. and Vyas, S. P. Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps. International Journal of Pharmaceutics 259 (2003): 173-179.

Reynolds, J.E.F., ed. Martindale: The extra pharmacopoeia 30th ed. London, UK: The pharmaceutical press. 1994.

Rose, S. and Nelson, J. F. A continuous long-term injector. Australian Journal of Experimental Biology and Medical Science 33 (1955): 415-419.

Shokri, J., et al. Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics 68 (2008): 289-297.

Sinchaipanid, N., Pongwai, S., Limsuwan, P. and Mitrevej, A. Design of salbutamol EOP tablets from pharmacokinetics parameters. Pharmaceutical Development and Technology 8 (2003): 135-142.

Siroratsakul, N. Development of osmotically controlled drug delivery capsules. Bangkok: Chulalongkorn University; 2004.

Theeuwes, F. Elementary osmotic pump. Journal of Pharmaceutical Sciences 64 (1975): 1987-1991.

Theeuwes, F. and Higuchi, T., inventors; ALZA Corporation, assignee. Osmatic dispensing device for releasing beneficial agent. US patent 3,845,770. 1974.

Theeuwes, F., et al. Elementary osmotic pump for indomethacin. Journal of Pharmaceutical Sciences 72 (1983): 253-258.

Theeuwes, F., Swanson, D. R., Guittard, G., Ayer, A. and Khanna, S. Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: design and evaluation of systems for once-daily administration. British Journal of Clinical Pharmacology 19 (1985): 69S-76S.

The United Stated Pharmacopoeia Convention. The United States Pharmacopoeia 29/The National Formulary 24. Asian edition. Toronto: Web Cam, 2006.

Thombre, A. G., Cardinal, J. R., DeNoto, A. R., Herbig, S. M. and Smith, K. L. Asymmetric membrane capsules for osmotic drug delivery I. Development of a manufacturing process. Journal of Controlled Release 57 (1999): 55-64.

Thombre, A. G., DeNoto, A. R. and Gibbes, D. C. Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. Journal of Controlled Release 60 (1999): 333-341.

Thombre, A. G., et al. Osmotic drug delivery using swellable-core technology. Journal of Controlled Release 94 (2004): 75-89.

Verma, R. K., Kaushal, A. M. and Garg, S. Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology. International Journal of Pharmaceutics 263 (2003): 9-24.

Verma, R. K., Krishna, D. M. and Garg, S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. Journal of Controlled Release 79 (2002): 7-27.

Verma, R. K., Mishra, B. and Garg, S. Osmotically controlled oral drug delivery. Drug Development and Industrial Pharmacy 26 (2000): 695-708.

Wong, P. L-OROS™ technology advancing new therapies through ALZA's liquid drug formulation. Delivery Times 2 (2005): 1-4.

Wright, J. C. and Stevenson, C. L. PUMPS/OSMOTIC. In Mathiowitz, E. (eds), ENCYCLOPEDIA OF CONTROLED DRUG DELIVERY, pp 896-900. A Wiley-lnterscience Publication, 1999.

Zentner, G. M., McClelland, G. A. and Sutton, S. C. Controlled porosity solubility- and resin-modulated osmotic drug delivery systems for release of diltiazem hydrochloride. Journal of Controlled Release 16 (1991): 237-244

Zentner, G. M., Rork, G. S. and K. J. Himmelstein, inventors; Merck & Co., Inc., assignee. Controlled porosity osmotic pump. US patent 4,968,507. 1990.

Zhang, Y., Zhang, Z. and Wu, F. A novel pulsed-release system based on swelling and osmotic pumping mechanism. Journal of Controlled Release 89 (2003): 47-55.

APPENDICES

APPENDIX A

Calibration curve

The amounts of diltiazem hydrochloride and propranolol hydrochloride were determined by the spectrophotometer. The absorbance of model drugs are presented in Tabl 1(A) and 2(A). The calibration curve and the linear relationship with the correlation of determination in each medium of diltiazem hydrochloride and propranolol hydrochloride were displayed in Figure 1(A) -6(A) and Figure 7(A) - 12(A), respectively.

Table 1(A) The absorbance of diltiazem hydrochloride in different media at wavelength 237 nm

concentration (mcg/ml)	Absorbance					
	DI water	0.9 % NaCl	0.5 M NaCl	1 M NaCl	HCl pH 1.2 with isotonicity	PBS pH 6.8 with isotonicity
2	0.1090	0.1110	0.1063	0.1093	0.1087	0.1057
4	0.2030	0.2106	0.2125	0.2124	0.2110	0.2186
6	0.3079	0.3141	0.3180	0.3181	0.3188	0.3168
8	0.4164	0.4224	0.4222	0.4270	0.4268	0.4214
10	0.5186	0.5268	0.5250	0.5332	0.5225	0.5172
12	0.6195	0.6261	0.6266	0.6311	0.6362	0.6215
16	0.8450	0.8462	0.8389	0.8567	0.8531	0.8390

Table 2(A) The absorbance of propranolol hydrochloride in different media at wavelength 287 nm

concentration (mcg/ml)	Absorbance					
	DI water	0.9 % NaCl	0.5 M NaCl	1 M NaCl	HCl pH 1.2 with isotonicity	PBS pH 6.8 with isotonicity
8	0.1543	0.1529	0.1543	0.1513	0.1522	0.1537
16	0.3016	0.3034	0.3016	0.3101	0.3030	0.3053
24	0.4530	0.4547	0.4530	0.4633	0.4550	0.4625
32	0.6129	0.6086	0.6129	0.6235	0.6153	0.6166
40	0.7521	0.7591	0.7521	0.7746	0.7643	0.7582
48	0.8980	0.9073	0.8980	0.9363	0.9203	0.9073

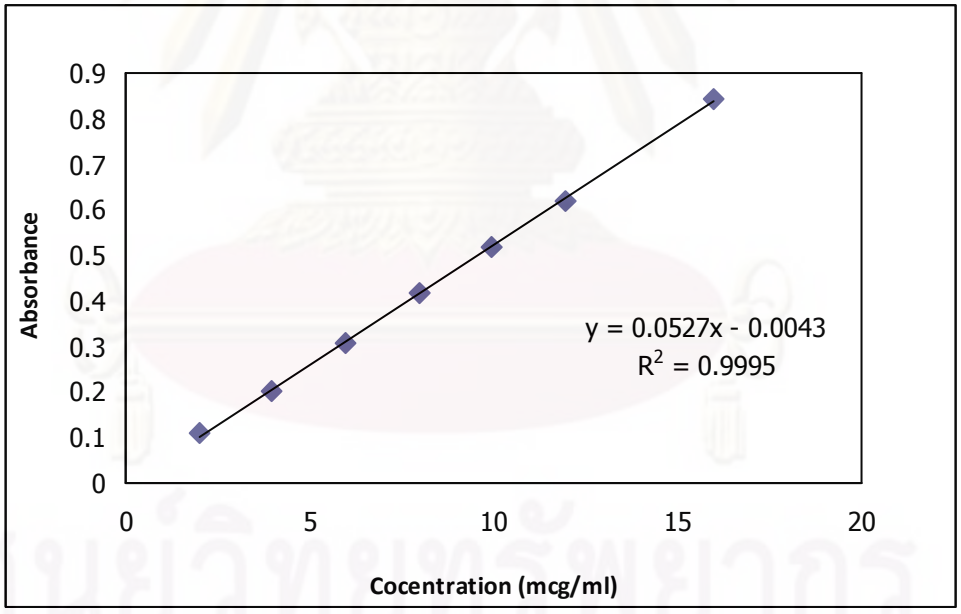


Figure 1(A) Calibration curve of diltiazem hydrochloride in deionized water at 237 nm.

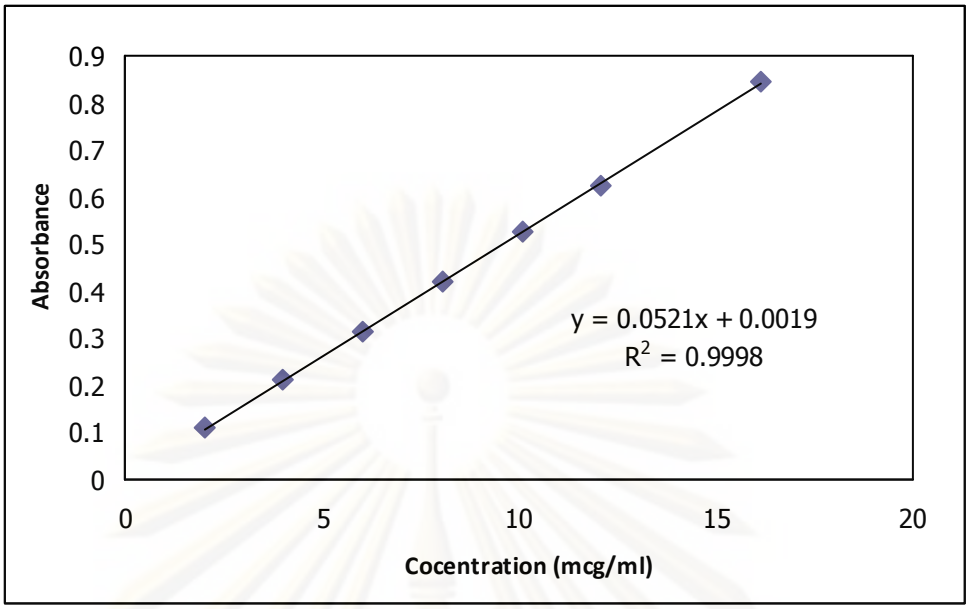


Figure 2(A) Calibration curve of diltiazem hydrochloride in 0.9 % NaCl solution at 237 nm.

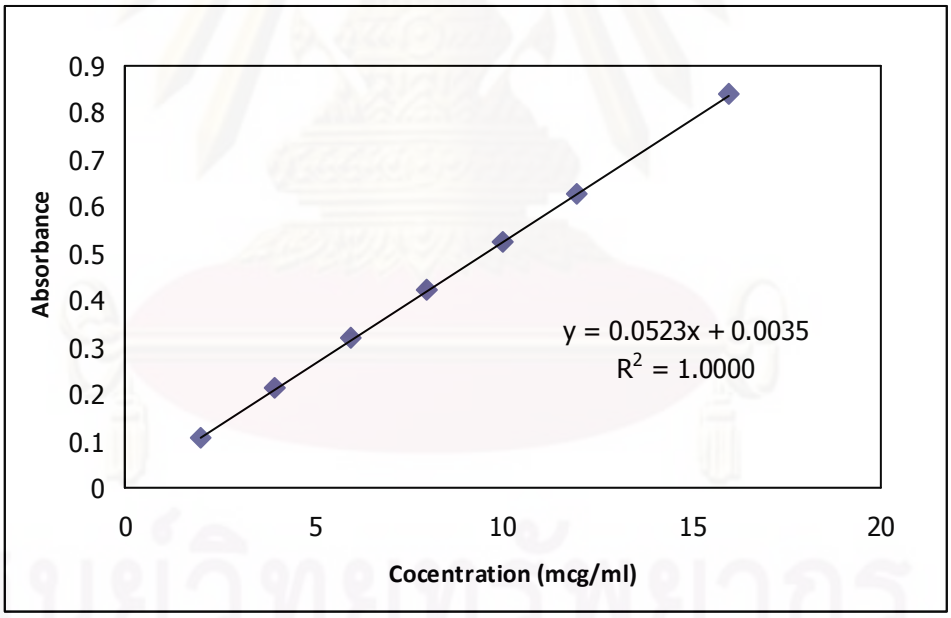


Figure 3(A) Calibration curve of diltiazem hydrochloride in 0.5 M NaCl solution at 237 nm.

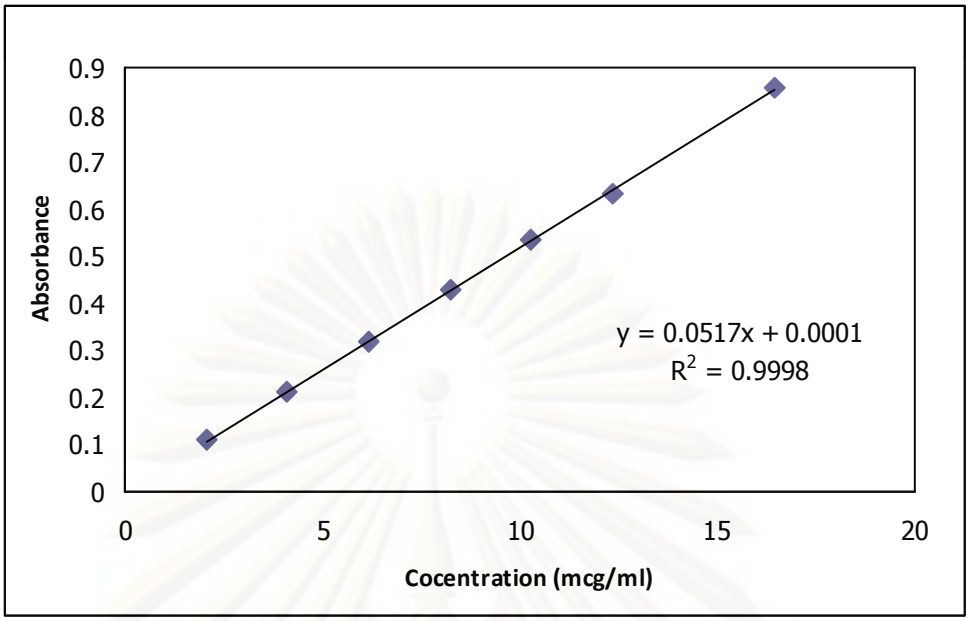


Figure 4(A) Calibration curve of diltiazem hydrochloride in 1 M NaCl solution at 237 nm.

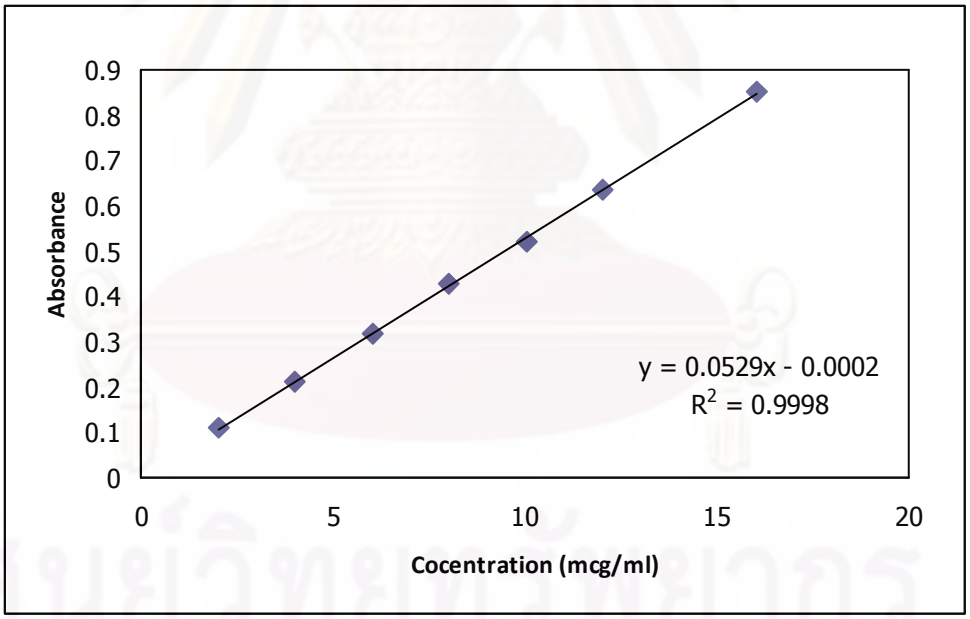


Figure 5(A) Calibration curve of diltiazem hydrochloride in 0.1 M HCl pH 1.2 at 237 nm.

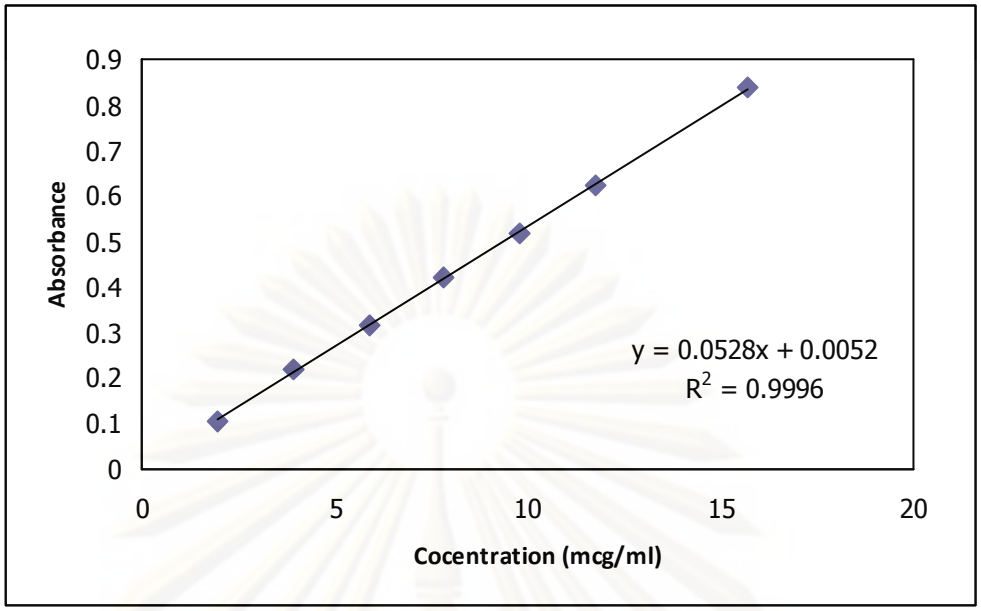


Figure 6(A) Calibration curve of diltiazem hydrochloride in PBS pH 6.8 at 237 nm.

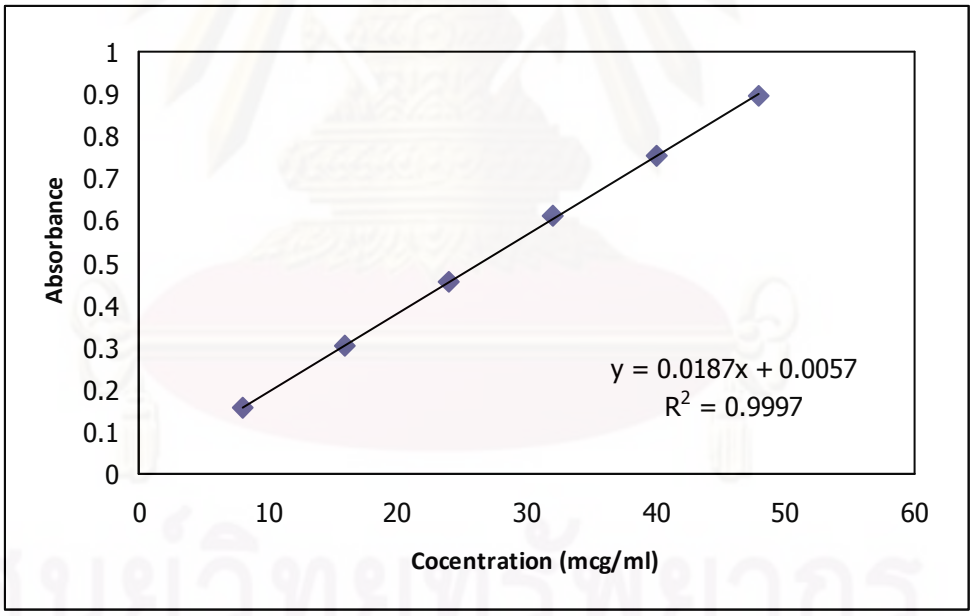


Figure 7(A) Calibration curve of propranolol hydrochloride in water at 287 nm

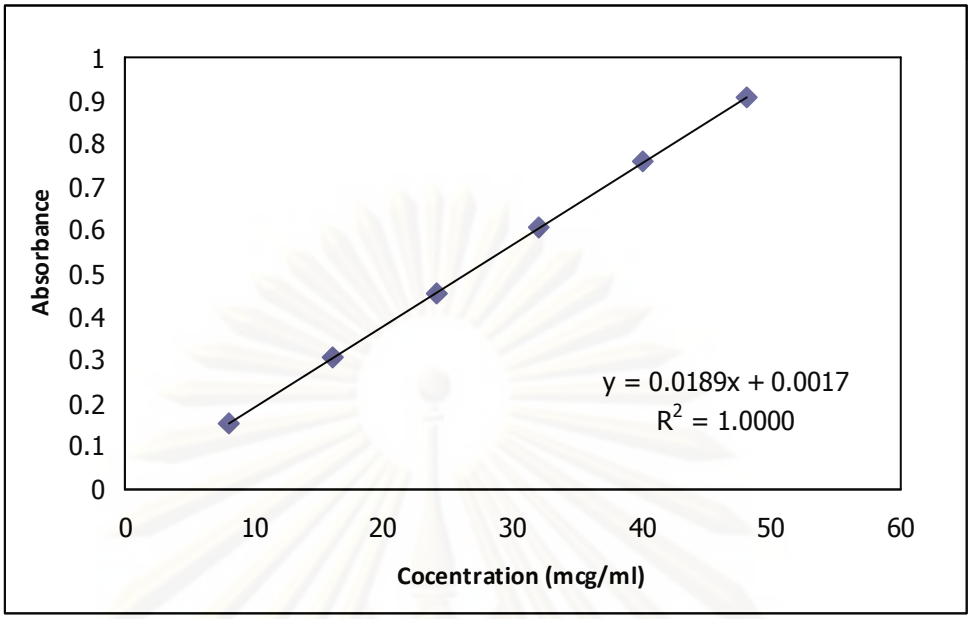


Figure 8(A) Calibration curve of propranolol hydrochloride in 0.9 % NaCl solution at 287 nm

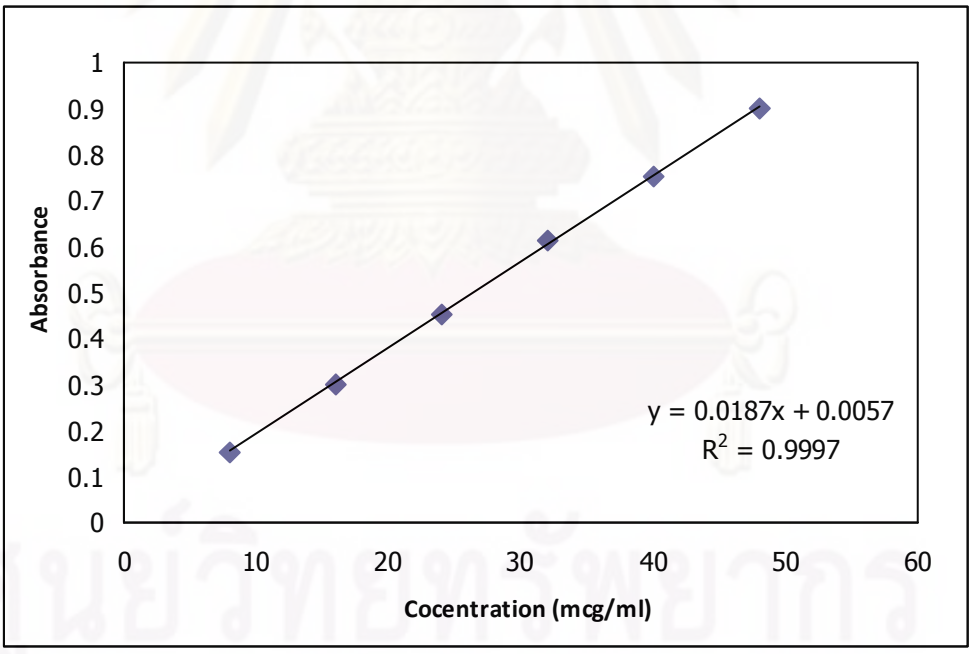


Figure 9(A) Calibration curve of propranolol hydrochloride in 0.5 M NaCl solution at 287 nm

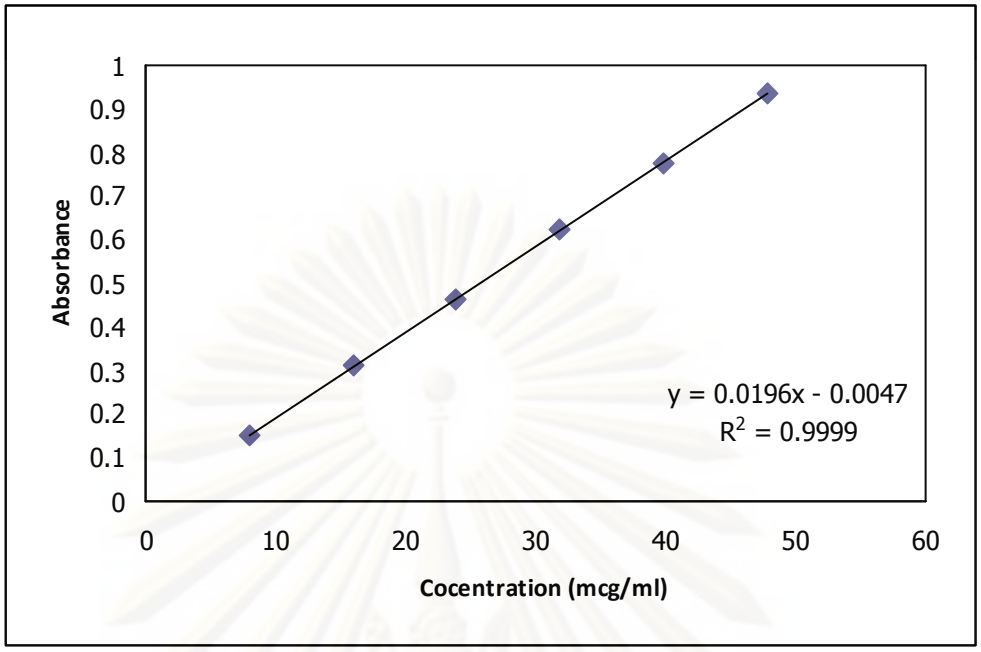


Figure 10(A) Calibration curve of propranolol hydrochloride in 1 M NaCl solution at 287 nm

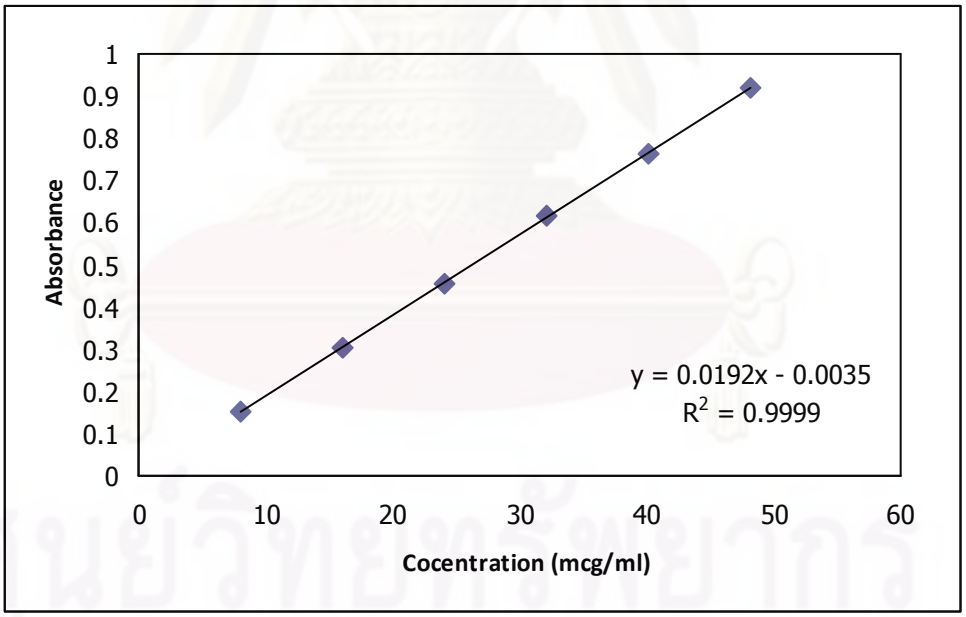


Figure 11(A) Calibration curve of propranolol hydrochloride in 0.1 M HCl pH 1.2 at 287 nm

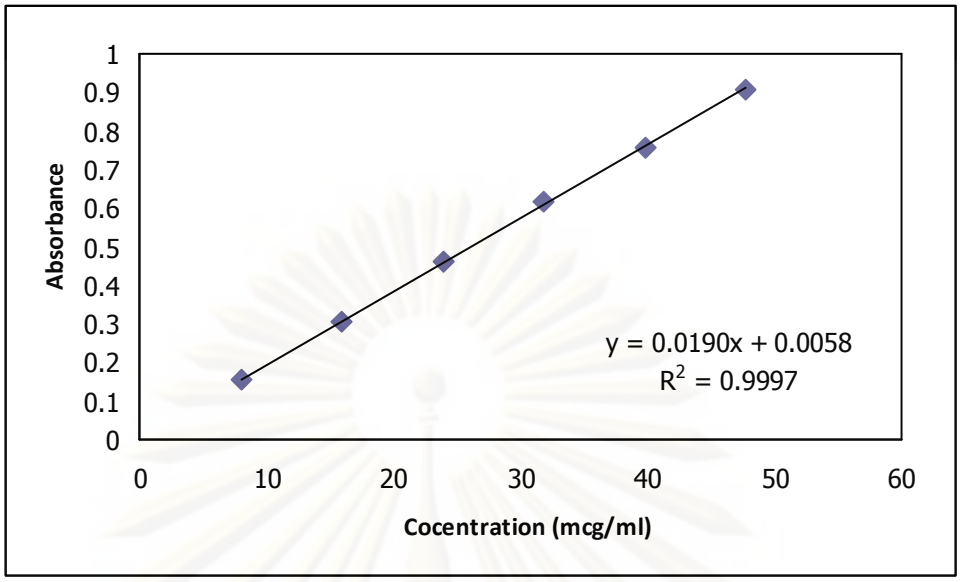


Figure 12(A) Calibration curve of propranolol hydrochloride in PBS pH 6.8 at 287 nm

APPENDIX B

Validation of UV-VIS spectrophotometer

The parameters were assessed to ensure the acceptability of the selected analytical method performance. The parameters are accuracy, precision, specificity and linearity.

1. Accuracy

The accuracy was performed by measuring placebos spiked with knowing amounts of diltiazem hydrochloride and propranolol hydrochloride and evaluated as the percentage of recovery. Each sample was analyzed from triplicate. Accuracy data of diltiazem hydrochloride and propranolol hydrochloride are presented in Table 1(B) and 2(B), respectively.

Table 1(B) Accuracy data of percentage of analytical recovery of diltiazem hydrochloride

Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)		
	n1	n2	n3	n1	n2	n3
1.994	0.1053	0.1054	0.1053	2.0797	2.0816	2.0797
3.988	0.2031	0.203	0.203	3.9355	3.9336	3.9336
5.982	0.3081	0.308	0.3077	5.9279	5.9260	5.9203
7.976	0.417	0.4172	0.4172	7.9943	7.9981	7.9981
9.970	0.5194	0.5194	0.5194	9.9374	9.9374	9.9374
11.964	0.6197	0.62	0.6201	11.8406	11.8463	11.8482
15.952	0.846	0.8461	0.8457	16.1347	16.1366	16.1290

Actual concentration (mcg/ml)	% Recovery					
	n1	n2	n3	Mean	SD	% CV
1.994	104.30	104.39	104.30	104.33	0.0549	0.0527
3.988	98.68	98.64	98.64	98.65	0.0275	0.0278
5.982	99.10	99.06	98.97	99.04	0.0660	0.0667
7.976	100.23	100.28	100.28	100.26	0.0275	0.0274
9.970	99.67	99.67	99.67	99.67	0.0000	0.0000
11.964	98.97	99.02	99.03	99.01	0.0330	0.0333
15.952	101.15	101.16	101.11	101.14	0.0248	0.0245

Table 2(B) Accuracy data of percentage of analytical recovery of propranolol hydrochloride

Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)		
	n1	n2	n3	n1	n2	n3
7.999	0.1551	0.1554	0.1552	7.9893	8.0053	7.9947
15.998	0.3018	0.3019	0.3018	15.8342	15.8396	15.8342
23.997	0.4527	0.4527	0.4526	23.9037	23.9037	23.8984
31.996	0.6131	0.6128	0.6128	32.4813	32.4652	32.4652
39.995	0.7522	0.7521	0.7522	39.9198	39.9144	39.9198
47.994	0.8981	0.898	0.898	47.7219	47.7166	47.7166

Actual concentration (mcg/ml)	% Recovery					
	n1	n2	n3	Mean	SD	% CV
7.999	99.88	100.08	99.95	99.97	0.1021	0.1022
15.998	98.98	99.01	98.98	98.99	0.0193	0.0195
23.997	99.61	99.61	99.59	99.60	0.0129	0.0129
31.996	101.52	101.47	101.47	101.48	0.0289	0.0285
39.995	99.81	99.80	99.81	99.81	0.0077	0.0077
47.994	99.43	99.42	99.42	99.43	0.0064	0.0065

2. Precision

2.1 Within run precision

The within run precision was evaluated by analyzing the calibration curve in the same day. The percentage of coefficient of variation (% CV) of diltiazem hydrochloride concentration and propranolol hydrochloride concentration was determined. Each sample was analyzed from six replicated. Within run precision data of diltiazem hydrochloride and propranolol hydrochloride are displayed in Table 3(B) and 4(B), respectively.

Table 3(B) Within run precision data of diltiazem hydrochloride

Actual concentration (mcg/ml)	Absorbance					
	n1	n2	n3	n4	n5	n6
2.012	0.1041	0.1039	0.1039	0.1040	0.1038	0.1039
4.024	0.2082	0.2081	0.2082	0.2082	0.2083	0.2083
6.036	0.3134	0.3134	0.3133	0.3133	0.3133	0.3134
8.048	0.4270	0.4270	0.4270	0.4271	0.4269	0.4270
10.06	0.5295	0.5294	0.5293	0.5293	0.5295	0.5296
12.072	0.6445	0.6445	0.6444	0.6443	0.6443	0.6445
16.096	0.8820	0.8820	0.8819	0.8820	0.8818	0.8818

Actual concentration (mcg/ml)	Analytical concentration (mcg/ml)								
	n1	n2	n3	n4	n5	n6	Mean	SD	% CV
2.012	2.1264	2.1227	2.1227	2.1245	2.1209	2.1227	2.1233	0.0019	0.0891
4.024	4.0330	4.0311	4.0330	4.0330	4.0348	4.0348	4.0333	0.0014	0.0342
6.036	5.9597	5.9597	5.9579	5.9579	5.9579	5.9597	5.9588	0.0010	0.0168
8.048	8.0403	8.0403	8.0403	8.0421	8.0385	8.0403	8.0403	0.0012	0.0144
10.06	9.9176	9.9158	9.9139	9.9139	9.9176	9.9194	9.9164	0.0022	0.0224
12.072	12.0238	12.0238	12.0220	12.0201	12.0201	12.0238	12.0223	0.0018	0.0150
16.096	16.3736	16.3736	16.3718	16.3736	16.3700	16.3700	16.3721	0.0018	0.0110

Table 4(B) Within run precision data of propranolol hydrochloride

Actual concentration (mcg/ml)	Absorbance					
	n1	n2	n3	n4	n5	n6
8.049	0.1596	0.1595	0.1594	0.1596	0.1594	0.1595
16.098	0.3163	0.3165	0.3164	0.3164	0.3163	0.3163
24.147	0.4718	0.4717	0.4717	0.4719	0.4717	0.4717
32.196	0.6376	0.6376	0.6376	0.6377	0.6378	0.6377
40.245	0.7758	0.7759	0.7758	0.7758	0.7758	0.7759
48.294	0.9527	0.9528	0.9526	0.9528	0.9529	0.9529

Actual concentration (mcg/ml)	Analytical concentration (mcg/ml)								
	n1	n2	n3	n4	n5	n6	Mean	SD	% CV
8.049	8.1276	8.1224	8.1173	8.1276	8.1173	8.1224	8.1224	0.0046	0.0562
16.098	16.1224	16.1327	16.1276	16.1276	16.1224	16.1224	16.1259	0.0042	0.0258
24.147	24.0561	24.0510	24.0510	24.0612	24.0510	24.0510	24.0536	0.0043	0.0177
32.196	32.5153	32.5153	32.5153	32.5204	32.5255	32.5204	32.5187	0.0042	0.0128
40.245	39.5663	39.5714	39.5663	39.5663	39.5663	39.5714	39.5680	0.0026	0.0067
48.294	48.5918	48.5969	48.5867	48.5969	48.6020	48.6020	48.5961	0.0060	0.0123

2.2 Between run precision

The between run precision was evaluated by comparing each concentration of calibration curves prepared and analyzed on different day for three days. The percentage of coefficient of variation of concentration of diltiazem hydrochloride and propranolol hydrochloride from three sets of calibration curve were determined. Between run precision data of diltiazem hydrochloride and propranolol hydrochloride are displayed in Table 5(B) and 6(B), respectively.

Table 5(B) Between run precision data of diltiazem hydrochloride

Day 1									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
2.004	0.1024	0.1024	0.1023	2.0451	2.0451	2.0432	102.05	102.05	101.96
4.008	0.2049	0.2048	0.2047	3.9718	3.9699	3.9680	99.10	99.05	99.00
6.012	0.3073	0.3073	0.3072	5.8966	5.8966	5.8947	98.08	98.08	98.05
8.016	0.4219	0.422	0.422	8.0508	8.0526	8.0526	100.43	100.46	100.46
10.02	0.5202	0.5202	0.5201	9.8985	9.8985	9.8966	98.79	98.79	98.77
12.024	0.6266	0.6268	0.6269	11.8985	11.9023	11.9041	98.96	98.99	99.00
16.032	0.8537	0.8539	0.8539	16.1673	16.1711	16.1711	100.84	100.87	100.87

Day 2									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
2.010	0.1035	0.1034	0.1031	2.1200	2.1181	2.1124	105.47	105.38	105.09
4.020	0.2003	0.2003	0.2002	3.9638	3.9638	3.9619	98.60	98.60	98.55
6.030	0.3019	0.3019	0.3019	5.8990	5.8990	5.8990	97.83	97.83	97.83
8.040	0.412	0.4119	0.4117	7.9962	7.9943	7.9905	99.46	99.43	99.38
10.050	0.5133	0.5133	0.5131	9.9257	9.9257	9.9219	98.76	98.76	98.73
12.060	0.6209	0.6209	0.6212	11.9752	11.9752	11.9810	99.30	99.30	99.34
16.080	0.8459	0.8458	0.8457	16.2610	16.2590	16.2571	101.13	101.11	101.10

Day 3									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
1.994	0.1053	0.1054	0.1053	2.0797	2.0816	2.0797	104.30	104.39	104.30
3.988	0.2031	0.203	0.203	3.9355	3.9336	3.9336	98.68	98.64	98.64
5.982	0.3081	0.308	0.3077	5.9279	5.9260	5.9203	99.10	99.06	98.97
7.976	0.417	0.4172	0.4172	7.9943	7.9981	7.9981	100.23	100.28	100.28
9.970	0.5194	0.5194	0.5194	9.9374	9.9374	9.9374	99.67	99.67	99.67
11.964	0.6197	0.62	0.6201	11.8406	11.8463	11.8482	98.97	99.02	99.03
15.952	0.846	0.8461	0.8457	16.1347	16.1366	16.1290	101.15	101.16	101.11

Table 5(B) Between run precision data of diltiazem hydrochloride (continue)

Approximate concentration (mcg/ml)	% Recovery		
	Mean	SD	% CV
2	103.89	1.4683	1.4134
4	98.76	0.2196	0.2224
6	98.31	0.5584	0.5680
8	100.04	0.4735	0.4733
10	99.07	0.4533	0.4576
12	99.10	0.1616	0.1630
16	101.04	0.1347	0.1334

Table 6(B) Between run precision data of propranolol hydrochloride

Day 1									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
8.035	0.1566	0.1566	0.1567	8.0206	8.0206	8.0258	99.82	99.82	99.89
16.070	0.3115	0.3115	0.3112	16.0052	16.0052	15.9897	99.60	99.60	99.50
24.105	0.4676	0.4675	0.4677	24.0515	24.0464	24.0567	99.78	99.76	99.80
32.140	0.6315	0.6313	0.6313	32.5000	32.4897	32.4897	101.12	101.09	101.09
40.175	0.7755	0.7756	0.7754	39.9227	39.9278	39.9175	99.37	99.38	99.36
48.210	0.9360	0.9356	0.9360	48.1959	48.1753	48.1959	99.97	99.93	99.97

Day 2									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
8.003	0.1542	0.1543	0.1541	8.1212	8.1263	8.1162	101.48	101.54	101.41
16.006	0.3092	0.3092	0.3093	15.9495	15.9495	15.9545	99.65	99.65	99.68
24.009	0.4660	0.4663	0.4662	23.8687	23.8838	23.8788	99.42	99.48	99.46
32.012	0.6320	0.6321	0.6322	32.2525	32.2576	32.2626	100.75	100.77	100.78
40.015	0.7828	0.7828	0.7826	39.8687	39.8687	39.8586	99.63	99.63	99.61
48.018	0.9473	0.9472	0.9471	48.1768	48.1717	48.1667	100.33	100.32	100.31

Table 6(B) Between run precision data of propranolol hydrochloride (continue)

Day 3									
Actual concentration (mcg/ml)	Absorbance			Analytical concentration (mcg/ml)			% Recovery		
	n1	n2	n3	n1	n2	n3	n1	n2	n3
7.999	0.1551	0.1554	0.1552	7.9893	8.0053	7.9947	99.88	100.08	99.95
15.998	0.3018	0.3019	0.3018	15.8342	15.8396	15.8342	98.98	99.01	98.98
23.997	0.4527	0.4527	0.4526	23.9037	23.9037	23.8984	99.61	99.61	99.59
31.996	0.6131	0.6128	0.6128	32.4813	32.4652	32.4652	101.52	101.47	101.47
39.995	0.7522	0.7521	0.7522	39.9198	39.9144	39.9198	99.81	99.80	99.81
47.994	0.8981	0.898	0.898	47.7219	47.7166	47.7166	99.43	99.42	99.42

Approximate concentration (mcg/ml)	% Recovery		
	Mean	SD	% CV
8	100.43	0.7907	0.7873
16	99.40	0.3155	0.3174
24	99.61	0.1427	0.1432
32	101.12	0.3117	0.3082
40	99.60	0.1894	0.1902
48	99.90	0.3902	0.3906

3. Specificity

The method specificity was evaluated by comparing the chromatograms from UV/Vis spectrophotometer between model drugs (diltiazem hydrochloride or propranolol hydrochloride) and non-active ingredients. The specificity is established by showing that chromatograms of non-active ingredients should not interfere with chromatograms of active ingredients. This validation was performed by comparing the peak scan between the dissolution medium taken from placebo system and drug containing system of the similar compositions. The absorbance of the dissolution medium taken from non-drug containing at wavelength 237 nm and 287 nm were presented in Table 7(B) and 8(B).

Table 7(B) The absorbance of hard gelatin capsules shell in deionized water

Wavelength (nm)	Concentration (mcg/ml)	Time (hr)	Absorbance			Mean	SD	% CV
237	44	1	0.0295	0.0295	0.0295	0.0295	0.0000	0.0000
		12	0.0348	0.0347	0.0349	0.0348	0.0001	0.2874
	92	1	0.0614	0.0614	0.0616	0.0615	0.0001	0.1879
		12	0.0687	0.0689	0.0687	0.0688	0.0001	0.1679
287	44	1	0.0019	0.0019	0.0018	0.0019	0.0001	3.0929
		12	0.0045	0.0047	0.0048	0.0047	0.0002	3.2733
	92	1	0.0044	0.0043	0.0043	0.0043	0.0001	1.3323
		12	0.0051	0.0051	0.0053	0.0052	0.0001	2.2349

Table 8(B) The absorbance of non-active ingredients (Sodium chloride and lactose) in deionized water

Wavelength (nm)	Concentration (mcg/ml)	Time (hr)	Absorbance			Mean	SD	% CV
237	NaCl 399 + Lactose 796	1	0.0053	0.0051	0.0051	0.0052	0.0001	2.2349
		12	0.0069	0.0068	0.0068	0.0068	0.0001	0.8449
	NaCl 803 + Lactose 1618	1	0.0029	0.0029	0.0029	0.0029	0.0000	0.0000
		12	0.0050	0.0049	0.0047	0.0049	0.0002	3.1388
287	NaCl 399 + Lactose 796	1	0.0028	0.0027	0.0026	0.0027	0.0001	3.7037
		12	0.0040	0.0039	0.0039	0.0039	0.0001	1.4678
	NaCl 803 + Lactose 1618	1	0.0038	0.0037	0.0038	0.0038	0.0001	1.5328
		12	0.0043	0.0043	0.0041	0.0042	0.0001	2.7276

4. Linearity

Triplicate of solutions containing model drugs (diltiazem hydrochloride or propranolol hydrochloride) in various concentrations were prepared and analyzed. The linear equations of the curve obtained by plotting absorbance versus the concentrations were calculated.

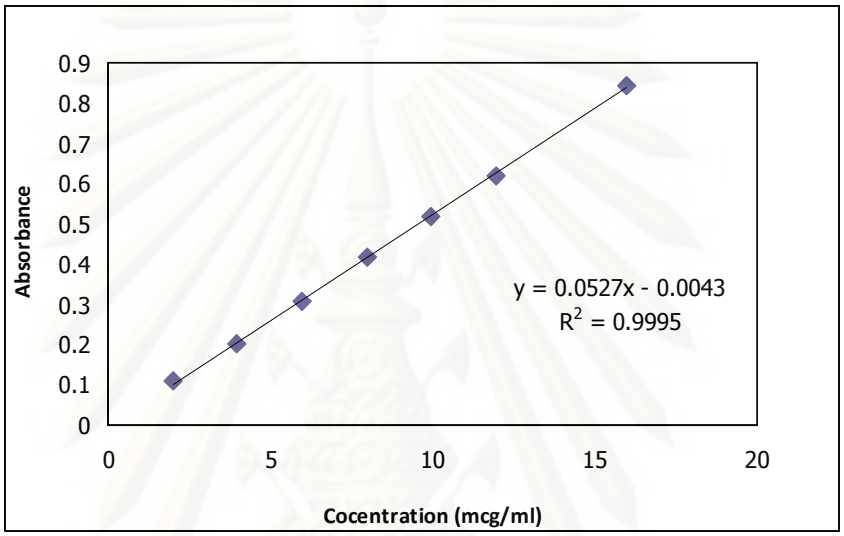


Figure 1(B) Calibration curve of diltiazem hydrochloride in deionized water at wavelength 237 nm

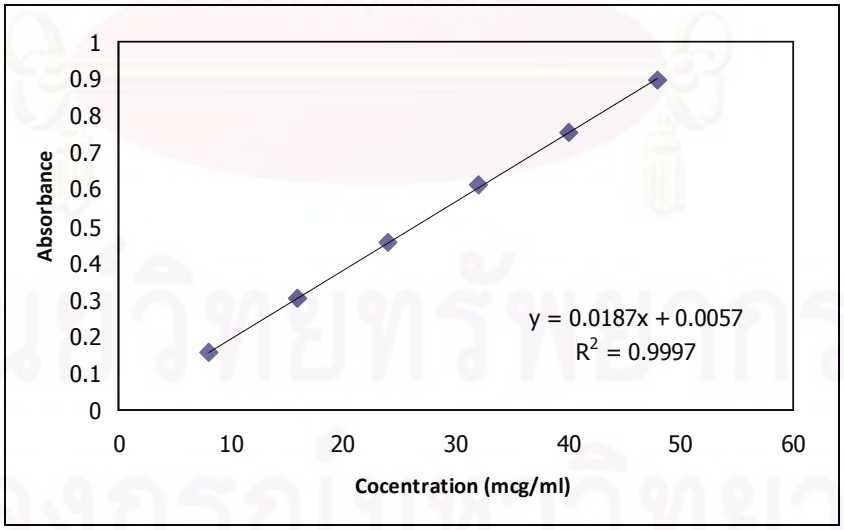


Figure 2(B) Calibration curve of propranolol hydrochloride in water at wavelength 287 nm

Result values of validation parameters of UV/Vis spectrophotometer for diltiazem hydrochloride and propranolol hydrochloride were presented in Table 9(B).

Table 9(B) Limited of acceptability and result values of analytical method validation parameters of UV/Vis spectrophotometer for diltiazem hydrochloride and propranolol hydrochloride

Parameter	Limited of acceptability	Result value of diltiazem hydrochloride	Result value of propranolol hydrochloride
1. Accuracy			
• % recovery	95.0-105.0 %	98.65-104.33 %	98.99-101.48 %
• SD		0.0000-0.0549	0.0064-0.1021
2. Precision (% CV)			
• Within run precision	not more than 2	0.0110-0.0891	0.0067-0.0562
• Between run precision		0.1334-1.4134	0.1902-0.7873
3. Specificity	No other peak interfere drug peak	No other peak interfere drug peak	No other peak interfere drug peak
4. Linearity			
• Correlation coefficient (R^2)	more than 0.999	0.9995	0.9997

APPENDIX C

Solubility of drug

The solubility of propranolol hydrochloride was determined by continuous shaking of excess amount of drug for 30 hrs in 0.1588, 0.5 and 1 M NaCl solutions at 25 ºC.

Table 1(C) Solubility of propranolol hydrochloride in 0.1588 M (0.9 %) NaCl solution

time (hr)	solubility (mg/ml)			Mean	SD	% CV
	n1	n2	n3			
24	23.83	24.99	25.17	24.66	0.73	2.96
27	23.84	25.42	25.41	24.89	0.91	3.66
30	24.25	25.64	26.08	25.32	0.95	3.76

Table 2(C) Solubility of propranolol hydrochloride in 0.5 M NaCl solution

time (hr)	solubility (mg/ml)			Mean	SD	% CV
	n1	n2	n3			
24	5.81	6.21	6.44	6.15	0.32	5.26
27	5.98	6.26	6.41	6.22	0.22	3.55
30	6.05	6.45	6.57	6.36	0.27	4.24

Table 3(C) Solubility of propranolol hydrochloride in 1 M NaCl solution

time (hr)	solubility (mg/ml)			Mean	SD	% CV
	n1	n2	n3			
24	2.55	2.78	2.67	2.67	0.12	4.34
27	2.60	2.76	2.74	2.70	0.09	3.30
30	2.65	2.83	2.74	2.74	0.09	3.12

APPENDIX D

Data of in vitro dissolution study

Table 1(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 250 ml CA solution in deionized water

Time (hr)	diltiazem hydrochloride release (%)										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	4.01	0.00	0.00	0.00	0.00	0.00	0.00	5.72	4.42	3.35	0.00
2	19.57	11.79	0.00	0.00	0.00	0.00	4.73	21.00	21.22	16.53	10.59
2.5	33.38	31.72	15.21	8.66	14.88	10.33	18.31	32.54	42.19	43.97	33.90
3	48.18	53.63	30.54	28.65	22.19	27.17	24.96	48.98	54.15	52.81	39.80
3.5	61.25	61.15	33.77	38.09	24.15	40.77	32.07	58.86	64.60	60.08	50.87
4	71.99	78.58	37.42	45.92	35.99	66.09	39.08	65.77	72.36	66.87	60.43
4.5	76.99	71.64	38.00	64.03	48.95	83.47	54.64	70.59	78.16	73.26	67.61
5	83.54	77.53	48.59	86.72	56.09	90.11	63.51	77.51	81.93	77.47	72.99
5.5	88.01	80.80	58.85	91.19	65.38	99.43	70.79	81.41	84.82	82.40	78.31
6	91.44	82.54	69.28	103.76	70.46	97.28	80.11	84.43	86.99	85.22	75.30
7	96.13	88.57	73.92	99.50	77.28	100.82	83.41	90.81	91.61	90.98	86.37
8	98.62	91.19	82.49	99.32	82.34	100.35	87.87	94.95	93.45	95.51	90.55
9	98.32	92.93	84.79	100.16	114.33	103.16	92.27	96.58	95.51	97.99	91.03

Time (hr)	diltiazem hydrochloride release (%)							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
1.5	0.00	3.60	0.00	0.00	0.00	0.00	0.00	1.17	2.00	170.35
2	0.00	16.26	7.10	3.10	10.64	0.00	0.00	7.92	8.15	102.96
2.5	23.27	37.98	24.06	11.53	32.97	10.38	0.00	23.63	12.96	54.84
3	34.50	57.20	36.73	20.27	50.62	29.69	21.21	37.85	12.92	34.14
3.5	42.56	68.07	43.79	24.15	57.56	40.11	35.41	46.52	14.07	30.24
4	51.96	76.61	51.98	36.26	65.85	44.44	46.49	56.34	14.69	26.07
4.5	57.97	84.75	60.04	40.42	71.99	49.51	55.40	63.74	13.98	21.94
5	65.15	86.83	65.58	44.08	79.01	52.34	62.75	70.65	13.97	19.77
5.5	70.07	87.91	70.45	49.21	84.85	56.47	71.05	76.19	13.16	17.27
6	73.84	90.74	75.89	54.22	88.08	58.62	76.25	80.25	12.59	15.69
7	80.20	94.41	81.64	60.86	93.11	63.99	82.15	85.32	11.16	13.08
8	85.54	95.23	85.85	67.49	95.06	67.29	86.56	88.87	9.57	10.77
9	88.83	96.18	89.24	72.22	96.42	70.68	91.03	92.87	10.12	10.89

Table 2(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 290 ml CA solution in deionized water

Time (hr)	diltiazem hydrochloride release (%)										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	10.75	0.00	0.00	15.55	0.00	0.00	0.00	0.00	0.00	0.00
2.5	11.96	25.32	20.91	17.65	31.72	21.61	5.74	7.49	11.67	0.00	8.48
3	32.87	33.08	38.63	31.99	46.64	45.64	12.99	26.68	28.66	17.63	21.27
3.5	50.36	43.22	57.95	50.81	56.55	60.32	29.99	47.88	47.90	34.17	40.78
4	62.77	49.11	66.52	56.81	64.11	67.06	52.92	56.41	58.49	50.04	53.79
4.5	76.39	58.43	73.44	65.65	70.38	74.03	51.15	63.19	63.80	62.96	59.70
5	82.38	62.86	75.78	71.25	70.46	82.56	59.15	70.94	71.41	68.70	65.79
5.5	87.51	72.75	78.58	66.93	73.23	82.04	63.68	74.14	75.41	74.28	70.19
6	88.91	74.69	79.41	75.79	79.80	90.54	66.89	78.89	80.15	81.35	75.56
7	95.09	84.94	87.48	78.81	83.49	92.94	72.19	87.25	87.19	91.91	83.43
8	97.78	90.74	92.75	88.59	90.66	97.57	76.27	92.32	91.80	97.38	89.03
9	99.96	88.83	92.03	85.57	94.09	99.46	79.89	97.97	97.00	101.75	93.31

Time (hr)	diltiazem hydrochloride release (%)							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	3.20	0.00	0.00	8.32	0.00	3.37	10.39	2.87	4.90	171.02
2.5	9.42	0.00	9.69	27.35	10.60	15.39	15.59	13.92	8.87	63.72
3	25.99	15.78	28.46	48.86	30.59	33.43	34.27	30.75	10.13	32.96
3.5	39.55	37.58	37.82	62.85	50.14	46.61	53.13	47.09	9.24	19.61
4	48.44	54.76	49.20	71.47	59.46	53.37	67.29	57.89	7.18	12.40
4.5	55.25	67.72	58.94	75.79	67.88	64.43	78.36	65.97	7.71	11.68
5	63.24	76.43	67.30	80.84	75.13	71.08	85.26	72.25	7.35	10.17
5.5	69.48	82.07	74.94	84.92	80.56	76.83	89.98	76.53	7.03	9.19
6	74.96	84.95	78.86	86.82	82.46	82.04	91.78	80.77	6.27	7.76
7	83.35	90.10	86.71	93.14	89.20	88.91	96.39	87.36	5.92	6.78
8	90.22	94.75	91.90	96.60	95.18	94.12	99.37	92.61	5.20	5.61
9	94.58	98.40	95.64	99.53	97.17	95.67	101.16	95.11	5.67	5.96

Table 3(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
2.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	12.12	9.56	13.68	13.70	11.72	7.35	23.05	19.01	13.19	30.86	15.19
3.5	31.34	33.14	28.77	42.03	27.92	27.01	43.99	35.29	36.64	46.02	29.60
4	46.16	50.94	39.06	62.40	36.10	43.54	61.28	51.63	52.59	56.70	46.12
4.5	51.35	61.58	51.75	73.37	46.52	61.09	66.77	60.44	62.70	65.85	55.32
5	57.92	70.08	74.64	76.97	54.48	73.24	69.35	67.44	69.04	69.82	64.21
5.5	68.67	74.32	85.25	79.96	59.65	80.81	77.37	63.05	73.59	72.70	64.09
6	79.97	81.69	93.14	84.07	64.60	87.46	80.64	77.81	78.64	83.69	73.73
7	86.10	88.35	97.86	87.33	71.29	93.43	84.36	72.12	84.49	81.52	75.12
8	90.93	92.62	98.82	88.61	75.23	97.27	90.31	86.75	89.02	85.45	87.51
9	96.11	96.72	101.14	91.30	79.07	100.75	88.12	88.59	86.87	85.65	85.55

Time (hr)	% diltiazem hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
2.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3	21.78	7.18	0.00	0.00	0.00	9.39	0.00	11.54	8.64	74.88
3.5	41.32	12.63	11.09	11.35	18.65	25.05	14.89	28.71	11.33	39.47
4	56.53	29.89	27.66	27.60	26.65	33.27	30.03	43.23	12.29	28.43
4.5	67.65	42.78	41.97	46.71	46.10	45.74	48.60	55.35	9.73	17.59
5	73.78	50.12	49.24	50.39	53.15	51.08	63.58	63.25	9.69	15.32
5.5	80.20	53.96	56.90	56.25	61.31	61.28	64.03	68.52	9.71	14.18
6	91.11	59.12	60.62	60.31	63.90	66.27	66.69	75.19	11.05	14.70
7	89.10	66.33	67.05	66.72	70.92	76.59	73.30	79.56	9.74	12.24
8	86.25	71.78	72.34	71.02	75.50	83.20	77.18	84.43	8.67	10.27
9	77.25	76.20	75.97	77.26	80.04	85.83	81.19	86.31	8.26	9.57

Table 4(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 250 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	0.00	0.00	0.00	0.00	3.49	0.00	5.52	3.22	3.03	0.00	0.00
2	11.40	12.18	4.34	6.34	10.99	11.89	23.28	10.12	10.62	9.87	8.39
2.5	22.12	29.36	15.85	13.85	25.04	26.41	34.61	23.17	31.48	25.86	20.61
3	42.35	44.80	32.75	32.01	47.82	45.33	45.66	35.02	65.02	39.59	31.70
3.5	60.12	67.53	44.58	55.34	64.24	53.65	57.46	48.09	82.64	56.69	42.47
4	71.86	74.41	49.72	68.27	71.22	57.15	74.29	63.85	95.76	67.38	50.87
4.5	77.84	80.77	56.08	75.73	77.18	63.57	86.42	76.42	101.25	78.79	63.65
5	81.72	86.62	63.01	80.60	83.22	69.93	92.52	85.63	102.56	86.17	71.83
5.5	85.26	89.35	69.44	88.10	87.43	75.97	98.37	91.24	102.84	91.87	78.75
6	90.86	90.66	77.80	92.78	90.82	80.89	101.20	95.06	103.09	96.50	85.05
7	94.50	96.40	84.17	95.90	93.19	83.27	104.16	99.93	104.59	99.86	92.39
8	98.12	99.62	91.34	99.80	97.26	90.16	104.18	102.37	104.11	102.44	97.73
9	99.75	101.13	95.71	101.32	98.41	93.21	106.41	103.54	104.69	104.97	101.42

Time (hr)	% diltiazem hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
1.5	3.82	0.00	0.00	0.00	0.00	4.41	0.00	1.30	1.96	150.51
2	11.12	14.98	5.62	6.84	5.86	8.74	6.01	9.92	4.38	44.12
2.5	25.79	29.78	20.45	20.54	23.15	22.00	19.05	23.84	5.33	22.35
3	38.26	39.03	36.65	36.61	39.22	39.05	35.38	40.35	7.80	19.33
3.5	55.79	48.25	46.85	53.99	48.27	49.09	51.97	54.84	9.58	17.46
4	70.91	59.54	54.60	64.86	54.83	57.41	60.62	64.86	11.04	17.02
4.5	85.47	73.67	64.22	74.70	63.62	68.32	69.89	74.31	10.63	14.30
5	95.18	79.57	70.19	81.18	69.90	76.80	73.06	80.54	10.10	12.54
5.5	99.11	88.41	78.41	87.68	77.17	88.06	82.06	86.64	8.65	9.99
6	101.46	93.02	83.72	91.37	83.72	92.96	87.15	91.01	7.07	7.77
7	103.30	97.25	88.08	95.69	88.00	97.99	89.50	94.90	6.43	6.77
8	104.35	101.80	94.39	100.49	93.80	102.05	92.88	98.72	4.55	4.61
9	104.85	104.96	98.67	103.32	99.76	107.08	100.80	101.67	3.71	3.65

Table 5(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 290 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	7.21	10.83	12.60	10.29	10.08	16.77	9.26	6.05	8.63	4.47	5.81
2	13.43	20.68	21.73	21.81	19.13	28.99	27.52	26.35	15.88	13.88	9.98
2.5	29.00	23.68	25.75	26.07	26.06	33.10	37.10	39.51	25.82	29.24	20.56
3	41.58	35.61	38.74	39.21	39.21	49.83	46.16	46.64	36.24	42.58	31.30
3.5	56.66	52.62	53.47	55.14	54.42	66.63	54.52	54.23	45.99	53.52	40.67
4	66.29	66.66	67.35	65.96	68.67	79.69	61.75	60.76	53.62	63.79	49.32
4.5	77.46	78.66	80.29	75.57	73.16	89.81	70.68	66.22	60.94	72.16	57.97
5	83.39	88.44	87.98	83.66	85.58	93.91	82.18	76.62	70.77	79.99	66.65
5.5	88.08	94.55	92.91	89.49	90.10	97.70	91.65	84.82	78.53	84.95	75.03
6	91.87	98.49	97.13	94.15	94.21	100.83	97.95	90.96	84.73	89.63	80.93
7	95.90	102.51	100.89	99.66	99.67	103.65	102.10	96.14	90.48	95.40	89.09
8	99.84	103.62	102.40	102.12	101.31	103.69	96.92	101.47	99.00	100.18	95.40
9	102.69	104.66	104.48	103.22	103.28	104.34	105.80	103.67	102.56	102.85	100.07

Time (hr)	% diltiazem hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	3.55	0.00	0.00	0.00	0.00	0.00	-
1.5	0.00	4.05	3.34	16.79	5.71	7.57	7.55	8.17	4.36	53.38
2	6.15	16.36	11.65	25.74	17.07	15.18	16.42	18.22	6.32	34.68
2.5	15.54	29.13	22.86	31.60	31.99	24.30	21.58	27.38	5.92	21.61
3	25.90	40.48	33.14	40.50	51.64	33.05	35.16	39.28	6.61	16.84
3.5	34.14	50.91	47.60	50.50	67.45	41.00	50.27	51.65	8.17	15.81
4	45.46	57.30	58.71	64.04	82.77	59.17	62.09	62.97	9.11	14.47
4.5	51.82	64.51	65.94	81.95	92.30	81.49	71.88	72.93	10.61	14.55
5	59.56	72.76	75.38	92.47	99.73	93.36	80.64	81.84	10.34	12.64
5.5	68.56	78.93	81.36	97.45	101.53	99.66	87.50	87.93	8.98	10.21
6	75.75	85.34	90.26	100.86	102.41	100.88	91.43	92.66	7.45	8.04
7	86.02	92.97	97.63	104.22	104.31	95.48	99.51	97.54	5.35	5.48
8	92.80	98.98	102.20	104.76	104.16	105.29	102.35	100.92	3.33	3.30
9	97.73	101.95	104.71	105.05	114.68	106.14	104.65	104.03	3.34	3.21

Table 6(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	7.10	4.67	5.30	4.46	3.96	4.39	4.66	5.17	5.05	0.00	3.68
2	20.09	13.26	16.75	18.37	18.24	16.20	15.57	13.31	11.72	11.43	14.16
2.5	35.62	28.77	37.31	35.49	29.56	32.89	33.81	28.99	25.30	26.94	28.33
3	51.32	40.29	62.53	47.62	39.91	47.10	49.11	38.77	35.85	40.51	38.82
3.5	63.24	50.79	69.71	62.29	52.91	57.96	56.69	57.56	51.96	61.81	50.60
4	67.92	59.85	76.73	70.21	60.17	66.34	64.92	69.51	53.74	58.62	69.53
4.5	72.98	65.33	81.78	75.65	66.49	70.53	71.88	75.69	58.32	72.85	63.25
5	77.67	68.92	85.31	80.97	69.19	74.77	79.06	79.03	65.24	77.50	70.10
5.5	83.55	74.20	89.85	84.00	73.36	76.55	84.24	82.64	71.48	82.53	75.72
6	89.15	80.37	93.03	90.49	76.15	80.45	92.48	85.51	75.70	77.10	78.50
7	96.27	94.46	98.30	99.32	80.95	85.74	91.54	90.10	84.67	90.72	85.78
8	101.39	99.30	102.43	104.48	85.95	92.40	95.44	91.29	86.08	93.63	90.56
9	103.24	101.82	102.80	103.99	89.53	94.32	98.13	94.60	87.82	95.72	90.71

Time (hr)	% diltiazem hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
1.5	0.00	5.62	4.77	7.31	6.31	3.64	6.43	4.58	1.98	43.14
2	12.54	17.02	18.24	15.76	20.04	11.68	20.58	15.83	3.06	19.32
2.5	28.28	32.32	26.69	37.12	37.07	25.79	34.43	31.37	4.19	13.36
3	43.88	51.36	40.26	53.89	49.10	41.79	48.36	45.58	6.77	14.86
3.5	59.12	64.98	53.37	60.81	57.97	59.37	57.97	58.28	5.14	8.81
4	67.40	74.55	62.47	68.94	67.24	67.00	66.49	66.20	5.62	8.49
4.5	72.29	77.77	69.76	78.14	73.87	73.19	72.48	71.79	5.66	7.89
5	79.36	87.80	75.35	86.36	80.68	80.32	80.17	77.65	6.19	7.96
5.5	82.91	93.13	79.22	91.23	86.26	83.30	84.50	82.15	6.10	7.43
6	84.51	97.21	83.78	95.88	91.30	85.04	88.30	85.83	6.81	7.93
7	85.84	99.62	78.57	99.63	95.87	90.04	92.38	91.10	6.49	7.12
8	90.70	100.94	92.02	101.48	98.33	94.59	94.54	95.31	5.54	5.82
9	90.32	103.66	87.41	92.61	100.98	96.44	97.60	96.20	5.66	5.89

Table 7(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 290 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3.5	0.00	0.00	0.00	0.00	9.36	8.15	12.08	11.83	13.38	0.00	19.07
4	11.24	11.39	12.61	11.16	15.14	13.93	20.20	21.37	21.73	13.48	42.10
4.5	17.52	17.53	19.03	19.09	23.45	20.76	29.41	32.67	30.31	19.45	52.95
5	25.60	24.52	26.36	24.10	30.18	29.90	37.20	45.65	38.73	25.30	60.98
5.5	34.55	31.24	34.10	30.54	36.28	40.42	46.12	54.83	47.23	31.02	67.15
6	43.62	38.98	42.33	37.71	41.47	49.74	54.51	61.87	55.12	37.34	72.42
7	58.34	49.51	56.45	51.32	51.41	62.97	65.76	71.31	66.59	50.74	80.00
8	69.23	59.58	67.29	62.38	61.19	72.03	74.81	78.06	75.61	61.57	86.18
9	77.29	70.17	75.52	71.67	70.82	78.91	82.26	84.17	82.29	71.52	89.67
10	84.16	79.47	80.50	78.60	78.20	84.96	87.17	88.11	86.38	79.09	90.31
11	89.09	86.61	87.46	84.78	85.54	89.38	91.24	91.27	90.24	84.77	94.86
12	92.72	91.73	91.63	89.11	88.97	92.21	93.74	93.59	93.59	89.89	97.69

Time (hr)	% propranolol hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
3	0.00	0.00	0.00	0.00	0.00	0.00	7.83	0.00	0.00	
3.5	8.35	9.09	14.92	10.90	11.22	17.44	16.61	9.02	6.49	71.99
4	13.88	16.16	24.49	16.72	14.73	27.54	23.71	18.42	7.73	41.97
4.5	19.93	22.21	34.83	24.56	24.84	37.44	33.00	26.61	9.15	34.39
5	26.06	28.53	43.80	32.21	35.22	45.39	41.15	34.49	9.97	28.91
5.5	32.66	34.51	50.52	39.40	47.45	52.16	48.87	42.17	10.19	24.16
6	39.58	40.43	56.76	47.02	57.21	58.16	54.92	49.40	9.96	20.16
7	55.32	52.35	65.75	59.66	68.76	68.38	65.20	61.10	8.54	13.97
8	67.29	63.49	73.86	70.17	77.60	78.58	74.20	70.73	7.33	10.36
9	76.65	73.23	80.68	77.55	82.87	83.57	80.75	78.31	5.45	6.96
10	82.42	79.54	85.75	83.48	87.24	88.38	85.91	83.87	3.85	4.59
11	87.46	85.38	90.30	88.12	90.49	92.81	90.27	88.89	2.85	3.21
12	90.67	88.63	91.99	90.56	92.85	94.93	92.17	92.04	2.27	2.47

Table 8(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
3	0.00	0.00	0.00	8.68	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3.5	0.00	0.00	0.00	13.78	0.00	46.95	0.00	0.00	8.55	0.00	10.74
4	13.15	8.50	9.37	20.06	8.22	58.18	11.73	10.86	15.76	11.30	19.52
4.5	24.10	13.49	18.39	26.85	12.72	67.85	18.31	17.95	27.69	18.28	27.36
5	34.15	19.01	32.55	34.16	17.60	74.68	26.51	23.09	42.51	24.85	35.87
5.5	44.37	25.54	45.51	40.99	23.30	81.28	38.02	27.81	52.61	29.79	44.77
6	50.83	31.88	54.30	46.54	28.94	86.15	48.62	32.91	60.21	36.34	53.00
7	60.49	44.34	66.59	56.80	39.94	93.05	65.62	44.90	71.16	51.29	65.16
8	70.15	54.26	76.34	65.16	49.86	96.50	77.34	54.79	78.63	62.47	75.66
9	77.24	63.17	82.90	68.99	61.18	97.30	90.94	67.71	83.56	73.90	84.25
10	84.59	73.01	90.88	80.02	67.46	98.55	91.13	69.70	88.43	78.13	88.69
11	88.60	79.18	94.05	84.27	74.70	100.26	96.29	76.52	91.37	83.60	91.92
12	90.84	85.24	96.65	87.61	79.45	100.49	97.52	81.42	94.41	88.43	95.67

Time (hr)	% propranolol hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3.5	0.00	8.94	9.22	11.16	8.08	9.13	9.93	7.58	11.07	146.04
4	12.37	16.69	15.92	18.89	15.75	16.71	15.92	16.61	11.01	66.29
4.5	18.09	22.48	26.44	24.88	23.11	26.76	21.67	24.25	11.84	48.83
5	23.98	29.29	35.25	34.33	29.83	35.21	30.45	32.41	12.36	38.13
5.5	29.72	35.14	50.86	43.64	38.14	42.95	41.32	40.88	13.15	32.18
6	34.86	40.36	61.75	52.68	44.41	49.17	47.73	47.82	13.55	28.34
7	45.81	50.30	78.32	65.18	59.56	58.71	60.64	59.88	13.15	21.96
8	55.43	59.91	87.40	73.20	71.50	69.08	70.48	69.34	12.10	17.45
9	65.81	68.40	91.95	79.66	79.99	74.68	76.59	77.12	10.24	13.28
10	72.32	73.75	93.92	84.05	86.21	80.39	82.18	82.41	8.80	10.68
11	78.51	78.89	95.66	86.89	90.04	83.93	85.25	86.66	7.40	8.54
12	83.65	83.91	97.13	90.15	100.61	86.57	87.40	90.40	6.58	7.27

Table 9(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 290 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	14.50	0.00	0.00	9.58	18.06	0.00	0.00	7.79	18.85	14.54	0.00
2	34.01	0.00	12.51	16.38	38.07	16.16	18.03	10.68	35.07	36.83	20.52
2.5	45.15	0.00	24.29	27.37	43.94	21.86	25.61	16.83	46.14	52.80	45.83
3	49.58	11.30	33.92	33.25	48.13	26.76	30.27	23.05	52.68	62.22	60.39
3.5	52.31	18.75	40.99	38.31	52.42	33.45	35.15	29.20	58.63	71.33	71.51
4	55.43	29.04	53.20	43.17	58.17	37.40	40.52	37.27	68.26	78.79	79.00
4.5	57.77	40.71	62.88	48.79	66.56	52.54	48.67	50.15	76.25	83.87	83.53
5	63.29	51.08	78.29	55.04	75.40	61.46	56.20	59.96	82.92	88.72	88.79
5.5	70.08	59.83	87.87	61.71	83.90	70.04	64.37	69.23	90.18	93.31	94.74
6	76.08	66.81	95.74	69.13	91.43	80.09	71.30	75.52	94.06	95.23	96.65
7	87.56	78.09	103.07	81.84	99.89	102.20	84.66	86.72	100.39	99.19	101.76
8	96.82	85.28	104.93	90.30	103.24	103.37	93.79	92.15	103.31	100.33	103.84
9	101.19	92.86	107.03	98.03	106.20	106.18	99.96	98.58	104.74	104.09	104.79
10	106.09	96.28	106.45	101.45	106.36	106.23	104.69	102.03	106.45	106.41	107.05
11	108.20	102.31	109.83	103.53	105.90	106.93	105.71	103.91	107.39	106.79	105.95
12	107.89	104.79	108.28	106.08	107.18	107.95	107.12	104.00	106.55	105.90	105.65

Time (hr)	% propranolol hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
1.5	0.00	8.84	0.00	0.00	14.78	14.33	0.00	6.74	7.44	110.41
2	20.08	11.38	0.00	0.00	28.90	33.91	22.28	19.71	12.74	64.63
2.5	26.67	22.28	11.97	11.18	40.44	41.59	36.97	30.05	14.74	49.06
3	30.56	29.28	20.61	20.29	46.10	49.52	45.46	37.41	14.75	39.42
3.5	33.99	34.15	29.28	28.72	49.51	56.06	52.05	43.66	15.01	34.39
4	37.47	40.52	37.70	35.23	53.15	62.72	59.44	50.36	15.11	30.00
4.5	42.38	49.26	49.90	44.26	61.08	69.39	65.39	58.52	13.45	22.99
5	47.32	55.73	59.93	51.77	73.15	75.66	71.82	66.47	13.13	19.76
5.5	53.54	62.88	69.28	59.97	83.53	81.72	78.42	74.14	12.80	17.26
6	59.09	69.81	76.33	67.83	91.53	86.63	83.57	80.38	11.83	14.71
7	71.31	82.71	88.47	81.13	99.65	93.21	92.26	90.78	9.65	10.63
8	82.95	93.28	96.64	91.00	103.95	99.55	98.87	96.87	6.69	6.91
9	91.60	98.85	101.23	97.20	105.06	103.01	102.27	101.27	4.46	4.41
10	99.30	102.52	104.38	101.30	106.36	105.14	104.90	104.08	2.99	2.87
11	102.48	103.64	105.85	104.35	107.57	106.80	106.51	105.76	2.03	1.92
12	103.40	105.07	106.84	105.19	107.36	107.32	106.74	106.29	1.39	1.30

Table 10(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release										
	n1	n2	n3	n4	n5	n6	n7	n8	n9	n10	n11
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	16.59	17.23	20.10	10.77	16.65	14.03	18.62	9.14	0.00	7.84	25.05
2	31.47	27.65	32.91	19.51	25.52	22.96	28.25	16.53	0.00	16.33	28.88
2.5	33.88	29.82	35.68	23.66	35.20	28.57	31.35	20.03	15.05	23.90	32.45
3	39.04	33.22	40.09	28.42	40.72	31.83	35.80	24.13	23.62	29.80	35.64
3.5	40.31	36.55	43.13	32.35	43.45	35.69	40.87	28.72	29.47	33.45	40.95
4	44.32	45.70	46.73	36.67	49.41	40.15	46.01	34.09	35.23	37.37	48.54
4.5	49.93	55.67	50.17	42.53	58.80	45.98	52.18	43.98	43.59	42.78	58.70
5	54.85	68.30	54.74	48.06	70.93	52.13	60.12	53.16	50.05	50.08	74.90
5.5	61.21	78.47	59.59	56.52	80.73	60.54	68.45	63.06	54.54	57.94	76.75
6	68.13	85.30	64.89	64.48	87.86	67.40	74.11	71.03	63.54	64.26	77.60
7	80.29	93.71	74.09	76.69	95.18	83.27	86.08	76.30	74.17	79.17	95.17
8	91.16	99.40	83.21	89.69	100.03	93.37	92.64	89.89	82.65	88.75	96.86
9	95.33	101.15	89.76	96.23	99.96	96.98	91.11	95.95	89.03	94.37	98.95
10	97.91	101.39	94.71	98.58	101.72	99.58	97.06	97.53	87.84	95.69	99.13
11	99.91	102.54	97.55	101.35	102.56	100.83	98.66	99.02	94.53	97.12	99.39
12	102.34	104.28	99.69	102.81	103.43	100.76	98.57	100.45	96.17	96.16	99.67

Time (hr)	% propranolol hydrochloride release							Mean	SD	% CV
	n12	n13	n14	n15	n16	n17	n18			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
1.5	0.00	18.65	8.58	0.00	10.30	21.38	10.09	12.50	7.51	60.08
2	0.00	26.42	20.56	7.53	19.04	28.34	28.29	21.12	9.95	47.10
2.5	9.06	30.34	24.08	9.40	32.49	32.43	35.05	26.80	8.53	31.82
3	14.18	32.52	26.48	13.04	45.19	35.95	38.41	31.56	8.76	27.76
3.5	21.04	35.33	29.09	21.39	58.53	39.85	41.86	36.22	8.85	24.43
4	27.44	38.39	31.19	32.94	69.97	62.39	46.30	42.94	10.69	24.89
4.5	34.09	42.53	33.72	45.66	80.85	78.91	49.81	50.55	12.76	25.23
5	41.14	47.51	38.73	58.94	89.93	88.15	57.89	58.87	14.45	24.54
5.5	46.92	53.42	43.19	69.78	93.55	92.58	67.77	65.83	14.16	21.51
6	52.81	62.50	48.92	80.64	97.26	96.04	77.89	72.48	13.40	18.49
7	67.02	78.55	62.14	91.53	95.46	96.94	88.53	83.02	10.43	12.56
8	78.01	88.49	76.66	84.29	96.16	97.30	93.38	90.11	6.93	7.69
9	89.41	92.64	82.96	97.04	84.78	89.20	93.06	93.22	5.05	5.42
10	93.76	95.93	85.88	89.08	95.15	97.13	94.71	95.71	4.37	4.56
11	97.51	98.10	95.14	104.78	100.94	105.43	98.38	99.65	2.97	2.98
12	99.09	97.07	105.11	105.60	101.99	106.80	100.06	101.11	3.17	3.13

Table 11(D) The diltiazem hydrochloride release from 0.4 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.5	7.11	0.00	0.00	0.00	4.87	5.24	2.87	3.24	112.69
3	19.32	10.08	9.49	17.15	15.27	18.35	14.94	4.22	28.26
3.5	32.80	26.89	26.88	43.20	34.97	39.74	34.08	6.65	19.52
4	49.58	54.46	51.77	63.40	57.83	59.53	56.09	5.14	9.16
4.5	55.92	69.35	64.14	75.65	69.63	71.90	67.77	6.91	10.20
5	60.78	77.24	71.33	81.76	75.90	79.77	74.46	7.59	10.19
5.5	64.81	83.18	76.60	86.86	81.67	86.13	79.87	8.24	10.32
6	67.57	86.66	79.51	88.86	84.21	88.38	82.53	8.09	9.80
7	73.81	91.67	87.18	93.47	90.14	93.09	88.23	7.42	8.41
8	80.50	96.06	92.51	97.00	93.94	95.32	92.55	6.11	6.60
9	84.92	98.60	98.61	99.44	96.70	99.27	96.26	5.64	5.86

Table 12(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
2.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	23.05	19.01	13.19	30.86	15.19	21.78	20.51	6.32	30.79
3.5	43.99	35.29	36.64	46.02	29.60	41.32	38.81	6.12	15.76
4	61.28	51.63	52.59	56.70	46.12	56.53	54.14	5.22	9.64
4.5	66.77	60.44	62.70	65.85	55.32	67.65	63.12	4.68	7.42
5	69.35	67.44	69.04	69.82	64.21	73.78	68.94	3.13	4.54
5.5	77.37	63.05	73.59	72.70	64.09	80.20	71.83	6.95	9.68
6	80.64	77.81	78.64	83.69	73.73	91.11	80.94	5.97	7.38
7	84.36	72.12	84.49	81.52	75.12	89.10	81.12	6.37	7.85
8	90.31	86.75	89.02	85.45	87.51	86.25	87.55	1.82	2.08
9	88.12	88.59	86.87	85.65	85.55	77.25	85.34	4.15	4.87

Table 13(D) The diltiazem hydrochloride release from 0.8 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	5.55	0.00	3.10	0.00	0.00	0.00	1.44	2.36	164.01
2.5	10.71	0.00	6.50	0.00	3.23	7.09	4.59	4.27	93.17
3	23.04	20.88	19.06	10.89	15.60	21.85	18.55	4.56	24.60
3.5	42.29	40.21	37.39	32.34	36.84	39.38	38.07	3.43	9.01
4	63.05	58.52	51.83	52.58	49.35	56.47	55.30	5.03	9.10
4.5	70.07	65.01	60.57	62.74	59.53	64.20	63.69	3.76	5.90
5	78.89	69.17	67.30	68.30	71.49	70.99	71.02	4.17	5.87
5.5	85.61	74.84	72.21	72.01	75.00	75.44	75.85	5.00	6.60
6	91.59	78.89	76.66	75.45	80.65	78.23	80.25	5.84	7.28
7	95.71	84.32	81.72	86.50	84.04	83.32	85.93	5.03	5.86
8	98.28	89.14	86.07	92.81	88.74	88.65	90.62	4.33	4.78
9	102.81	95.22	88.72	98.20	91.62	91.99	94.76	5.12	5.40

Table 14(D) The diltiazem hydrochloride release from 0.4 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	8.02	0.00	3.52	1.92	3.30	171.69
2.5	13.14	20.12	9.21	21.67	13.43	4.39	13.66	6.51	47.67
3	30.06	38.86	24.01	37.95	26.62	29.83	31.22	6.00	19.22
3.5	49.26	53.07	39.87	51.84	40.05	44.72	46.47	5.80	12.47
4	71.04	66.10	50.82	61.80	51.29	58.70	59.96	8.05	13.43
4.5	87.96	79.00	63.17	77.97	64.01	74.23	74.39	9.51	12.78
5	93.85	83.79	69.59	84.06	70.67	82.22	80.70	9.16	11.36
5.5	100.02	89.09	75.98	92.75	77.02	87.54	87.07	9.26	10.63
6	104.66	92.95	81.58	101.15	83.40	91.91	92.61	9.22	9.96
7	109.85	97.51	88.60	103.65	94.85	97.26	98.62	7.34	7.44
8	111.79	101.25	93.48	106.84	108.64	101.31	103.89	6.57	6.32
9	113.54	104.99	99.31	112.03	113.66	105.61	108.19	5.82	5.38

Table 15(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	4.66	5.17	5.05	0.00	3.68	0.00	3.09	2.45	79.29
2	15.57	13.31	11.72	11.43	14.16	12.54	13.12	1.57	11.94
2.5	33.81	28.99	25.30	26.94	28.33	28.28	28.61	2.87	10.02
3	49.11	38.77	35.85	40.51	38.82	43.88	41.16	4.70	11.42
3.5	56.69	57.56	51.96	61.81	50.60	59.12	56.29	4.28	7.60
4	64.92	69.51	53.74	58.62	69.53	67.40	63.95	6.44	10.07
4.5	71.88	75.69	58.32	72.85	63.25	72.29	69.05	6.72	9.73
5	79.06	79.03	65.24	77.50	70.10	79.36	75.05	5.95	7.93
5.5	84.24	82.64	71.48	82.53	75.72	82.91	79.92	5.11	6.40
6	92.48	85.51	75.70	77.10	78.50	84.51	82.30	6.39	7.76
7	91.54	90.10	84.67	90.72	85.78	85.84	88.11	3.00	3.40
8	95.44	91.29	86.08	93.63	90.56	90.70	91.28	3.18	3.49
9	98.13	94.60	87.82	95.72	90.71	90.32	92.88	3.89	4.18

Table 16(D) The diltiazem hydrochloride release from 0.8 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	0.00	0.00	9.90	9.11	4.65	9.25	5.48	4.64	84.61
2	6.04	10.25	31.93	26.11	16.00	21.32	18.61	9.76	52.42
2.5	15.84	22.21	56.11	45.20	32.83	41.96	35.69	15.04	42.13
3	32.74	36.84	73.97	57.25	41.94	57.33	50.01	15.60	31.20
3.5	46.57	49.05	84.05	71.13	55.81	72.95	63.26	14.99	23.70
4	61.99	63.48	92.09	82.13	65.27	80.06	74.17	12.34	16.63
4.5	69.69	73.15	100.08	93.75	71.34	86.06	82.35	12.84	15.59
5	75.23	84.91	104.61	102.43	76.58	92.17	89.32	12.60	14.11
5.5	80.20	97.66	107.02	106.44	81.83	99.19	95.39	11.76	12.33
6	83.48	104.23	109.27	109.43	87.17	102.94	99.42	11.28	11.35
7	89.91	110.75	112.41	109.94	95.48	108.91	104.57	9.43	9.02
8	95.31	112.18	112.78	112.09	100.41	111.86	107.44	7.60	7.07
9	98.99	112.48	115.39	111.42	103.26	114.13	109.28	6.60	6.04

Table 17(D) The propranolol hydrochloride release from 0.4 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4	0.00	0.00	9.04	19.12	0.00	9.69	6.31	7.78	123.28
4.5	0.00	0.00	17.91	29.58	0.00	20.20	11.28	12.96	114.90
5	15.00	9.21	29.56	43.26	9.50	34.08	23.44	14.22	60.70
5.5	22.35	18.05	37.44	64.15	14.06	45.62	33.61	19.20	57.12
6	30.09	28.11	44.92	72.94	19.59	58.25	42.32	20.33	48.04
7	40.67	43.90	54.53	83.30	31.59	75.44	54.91	20.47	37.28
8	49.02	56.95	62.07	89.05	41.05	83.59	63.62	19.05	29.95
9	58.16	67.26	67.76	93.20	49.92	88.38	70.78	16.90	23.88
10	60.24	72.64	69.79	92.54	55.29	88.99	73.25	14.99	20.47
11	64.57	79.33	73.12	92.97	61.07	90.30	76.89	13.12	17.06
12	68.07	84.56	75.83	92.94	65.77	89.81	79.50	11.36	14.29

Table 18(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propanolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3.5	0.00	0.00	8.55	0.00	10.74	0.00	3.22	5.03	156.40
4	11.73	10.86	15.76	11.30	19.52	12.37	13.59	3.39	24.95
4.5	18.31	17.95	27.69	18.28	27.36	18.09	21.28	4.84	22.76
5	26.51	23.09	42.51	24.85	35.87	23.98	29.47	7.90	26.81
5.5	38.02	27.81	52.61	29.79	44.77	29.72	37.12	9.94	26.79
6	48.62	32.91	60.21	36.34	53.00	34.86	44.33	11.22	25.32
7	65.62	44.90	71.16	51.29	65.16	45.81	57.32	11.36	19.81
8	77.34	54.79	78.63	62.47	75.66	55.43	67.39	11.14	16.52
9	90.94	67.71	83.56	73.90	84.25	65.81	77.69	10.08	12.97
10	91.13	69.70	88.43	78.13	88.69	72.32	81.40	9.24	11.36
11	96.29	76.52	91.37	83.60	91.92	78.51	86.37	8.01	9.27
12	97.52	81.42	94.41	88.43	95.67	83.65	90.18	6.70	7.43

Table 19(D) The propranolol hydrochloride release from 0.8 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3.5	0.00	9.97	0.00	0.00	14.64	0.00	4.10	6.52	159.05
4	0.00	16.99	20.01	11.54	18.73	0.00	11.21	9.15	81.63
4.5	12.26	25.79	40.79	16.63	24.94	11.48	21.98	11.05	50.26
5	19.70	52.82	62.46	21.14	33.70	16.01	34.31	19.27	56.18
5.5	27.54	75.71	72.40	27.16	43.01	21.31	44.52	24.00	53.91
6	35.84	84.75	79.48	33.27	51.82	28.83	52.33	24.40	46.62
7	49.48	91.43	87.08	44.82	59.63	43.54	62.66	21.40	34.15
8	59.82	95.53	91.19	55.63	68.55	55.19	70.99	18.04	25.41
9	68.20	97.30	93.67	64.84	74.80	64.29	77.18	14.70	19.05
10	74.30	99.74	95.46	71.58	80.92	74.66	82.78	11.96	14.45
11	78.91	98.06	95.52	76.73	85.06	82.48	86.13	8.78	10.19
12	82.43	98.67	96.69	80.68	87.92	89.04	89.24	7.29	8.17

Table 20(D) The propranolol hydrochloride release from 0.4 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	8.61	12.86	8.70	0.00	0.00	0.00	5.03	5.72	113.73
2	18.84	23.03	12.67	0.00	15.55	0.00	11.68	9.68	82.89
2.5	21.46	31.40	15.02	0.00	22.68	9.07	16.61	11.08	66.75
3	24.06	38.46	18.40	10.74	27.36	15.61	22.44	9.83	43.82
3.5	28.39	44.55	23.13	17.09	31.39	24.41	28.16	9.39	33.35
4	34.90	50.93	30.77	26.48	35.31	33.82	35.37	8.31	23.49
4.5	41.36	57.23	42.73	35.85	38.58	43.14	43.15	7.43	17.21
5	49.02	64.25	52.70	47.13	43.17	57.30	52.26	7.60	14.54
5.5	58.70	70.68	61.05	57.14	48.35	64.64	60.09	7.51	12.50
6	65.46	75.23	67.16	64.54	55.01	70.35	66.29	6.76	10.19
7	74.31	81.91	77.37	74.87	66.97	78.52	75.66	5.06	6.69
8	80.95	87.00	83.10	82.57	75.64	84.61	82.31	3.85	4.68
9	86.33	90.61	88.03	87.46	82.00	88.23	87.11	2.87	3.30
10	89.49	92.62	91.42	91.05	86.91	91.63	90.52	2.04	2.25
11	91.28	94.00	92.98	92.85	89.57	93.55	92.37	1.65	1.79
12	93.14	95.22	94.98	94.69	91.11	94.29	93.91	1.55	1.65

Table 21(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	19.86	9.75	0.00	8.37	26.73	0.00	10.79	10.74	99.53
2	30.14	17.63	0.00	17.43	30.82	0.00	16.00	13.68	85.51
2.5	33.46	21.37	16.06	25.51	34.64	9.67	23.45	9.78	41.71
3	38.22	25.75	25.20	31.80	38.05	15.13	29.03	8.86	30.51
3.5	43.64	30.65	31.45	35.71	43.73	22.45	34.61	8.24	23.81
4	49.15	36.40	37.61	39.90	51.85	29.29	40.70	8.42	20.69
4.5	55.75	46.98	46.54	45.69	62.73	36.39	49.02	9.10	18.57
5	64.26	56.80	53.46	53.50	80.08	43.93	58.67	12.36	21.07
5.5	73.21	67.40	58.27	61.91	82.11	50.11	65.50	11.32	17.28
6	79.30	75.96	67.93	68.67	83.06	56.43	71.89	9.61	13.36
7	92.17	81.63	79.33	84.62	101.93	71.65	85.22	10.58	12.41
8	99.26	96.24	88.44	94.92	103.83	83.44	94.35	7.37	7.81
9	97.69	102.80	95.33	101.00	106.14	95.68	99.77	4.29	4.30
10	104.15	104.56	94.13	102.48	106.42	100.41	102.03	4.37	4.28
11	105.95	106.25	101.37	104.10	106.79	104.50	104.83	1.98	1.89
12	105.94	107.87	103.21	103.15	107.18	106.28	105.61	2.00	1.89

Table 22(D) The propranolol hydrochloride release from 0.8 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	12.05	14.50	0.00	14.08	0.00	0.00	6.77	7.46	110.23
2	26.80	27.46	16.44	43.48	20.43	13.62	24.71	10.71	43.36
2.5	36.94	37.11	29.70	74.26	35.55	18.31	38.65	18.85	48.77
3	44.68	40.96	36.33	77.50	40.51	23.90	43.98	17.93	40.76
3.5	47.90	44.40	40.38	83.98	47.39	27.57	48.60	18.87	38.83
4	55.18	48.16	45.35	88.59	57.67	32.01	54.49	18.99	34.84
4.5	64.80	52.90	49.27	93.93	67.44	38.04	61.06	19.34	31.67
5	69.92	58.54	54.64	97.07	74.35	46.68	66.87	17.91	26.78
5.5	78.06	66.08	62.75	100.16	81.46	56.60	74.18	15.80	21.30
6	81.77	72.20	68.53	101.98	84.81	63.05	78.72	13.99	17.78
7	88.22	81.37	81.25	103.23	90.75	82.63	87.91	8.46	9.62
8	93.80	89.39	90.51	103.79	94.78	95.67	94.66	5.10	5.39
9	97.09	93.67	93.65	105.03	97.85	100.29	97.93	4.32	4.41
10	99.71	97.05	99.89	106.44	100.01	102.96	101.01	3.25	3.22
11	101.04	99.88	101.79	106.16	101.19	103.29	102.23	2.23	2.18
12	102.50	101.50	102.76	106.02	103.09	105.33	103.53	1.76	1.70

Table 23(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
2.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	23.05	19.01	13.19	30.86	15.19	21.78	20.51	6.32	30.79
3.5	43.99	35.29	36.64	46.02	29.60	41.32	38.81	6.12	15.76
4	61.28	51.63	52.59	56.70	46.12	56.53	54.14	5.22	9.64
4.5	66.77	60.44	62.70	65.85	55.32	67.65	63.12	4.68	7.42
5	69.35	67.44	69.04	69.82	64.21	73.78	68.94	3.13	4.54
5.5	77.37	63.05	73.59	72.70	64.09	80.20	71.83	6.95	9.68
6	80.64	77.81	78.64	83.69	73.73	91.11	80.94	5.97	7.38
7	84.36	72.12	84.49	81.52	75.12	89.10	81.12	6.37	7.85
8	90.31	86.75	89.02	85.45	87.51	86.25	87.55	1.82	2.08
9	88.12	88.59	86.87	85.65	85.55	77.25	85.34	4.15	4.87

Table 24(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.9 % NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
2.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3	8.24	0.00	0.00	0.00	4.70	4.07	2.84	3.42	120.47
3.5	20.47	4.57	11.82	9.47	14.65	15.15	12.69	5.43	42.81
4	34.39	15.77	29.31	24.42	34.86	30.91	28.28	7.21	25.51
4.5	45.28	31.08	43.16	43.23	49.51	46.82	43.18	6.39	14.80
5	52.41	37.28	52.20	53.87	59.14	54.61	51.58	7.45	14.43
5.5	58.81	42.99	58.97	60.04	65.01	60.48	57.72	7.56	13.10
6	63.82	48.15	63.77	64.35	68.63	64.22	62.16	7.11	11.43
7	70.18	54.83	69.37	69.30	73.79	69.95	67.91	6.62	9.75
8	73.43	59.18	73.39	73.34	76.92	73.24	71.58	6.24	8.72
9	75.15	63.43	75.39	76.04	79.55	75.39	74.16	5.51	7.43

Table 25(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.5 M NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
4	3.10	0.00	0.00	0.00	4.02	10.09	2.87	3.96	137.88
4.5	6.76	10.60	4.06	0.00	11.53	19.77	8.79	6.86	78.07
5	11.63	24.25	9.85	4.63	17.84	29.08	16.21	9.26	57.11
5.5	15.62	36.51	19.85	12.83	29.46	37.28	25.26	10.63	42.10
6	27.08	44.69	34.72	24.73	38.82	43.54	35.60	8.34	23.43
7	39.66	53.63	51.37	41.76	49.94	51.41	47.96	5.78	12.05
8	49.01	60.95	58.54	52.81	55.89	59.04	56.04	4.45	7.95
9	54.79	64.70	63.09	59.93	59.77	63.59	60.98	3.63	5.96

Table 26(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 1 M NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
5.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
6	3.73	5.74	0.00	0.00	0.00	3.82	2.22	2.53	114.23
7	5.36	10.69	3.11	4.65	0.00	9.03	5.47	3.90	71.31
8	5.99	16.34	7.28	11.45	3.94	14.52	9.92	4.96	49.96
9	6.61	23.31	13.32	18.47	4.97	19.41	14.35	7.37	51.39

Table 27(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.5	4.66	5.17	5.05	0.00	3.68	0.00	3.09	2.45	79.29
2	15.57	13.31	11.72	11.43	14.16	12.54	13.12	1.57	11.94
2.5	33.81	28.99	25.30	26.94	28.33	28.28	28.61	2.87	10.02
3	49.11	38.77	35.85	40.51	38.82	43.88	41.16	4.70	11.42
3.5	56.69	57.56	51.96	61.81	50.60	59.12	56.29	4.28	7.60
4	64.92	69.51	53.74	58.62	69.53	67.40	63.95	6.44	10.07
4.5	71.88	75.69	58.32	72.85	63.25	72.29	69.05	6.72	9.73
5	79.06	79.03	65.24	77.50	70.10	79.36	75.05	5.95	7.93
5.5	84.24	82.64	71.48	82.53	75.72	82.91	79.92	5.11	6.40
6	92.48	85.51	75.70	77.10	78.50	84.51	82.30	6.39	7.76
7	91.54	90.10	84.67	90.72	85.78	85.84	88.11	3.00	3.40
8	95.44	91.29	86.08	93.63	90.56	90.70	91.28	3.18	3.49
9	98.13	94.60	87.82	95.72	90.71	90.32	92.88	3.89	4.18

Table 28(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.9 % NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	5.43	3.27	5.17	0.00	0.00	0.00	2.31	2.64	114.21
2.5	10.94	11.65	6.80	3.05	0.00	11.07	7.25	4.86	66.98
3	19.05	28.82	24.24	17.62	21.35	20.58	21.95	4.05	18.43
3.5	26.13	42.25	33.75	27.12	37.44	33.72	33.40	6.12	18.32
4	33.56	51.53	42.59	37.59	53.40	46.14	44.14	7.76	17.59
4.5	40.47	58.30	50.05	47.11	70.52	55.65	53.68	10.39	19.35
5	45.86	63.23	56.40	55.19	84.67	62.79	61.36	13.05	21.27
5.5	51.58	68.36	62.45	62.18	95.38	67.41	67.90	14.73	21.69
6	56.58	70.79	67.82	67.29	98.23	65.41	71.02	14.17	19.96
7	61.92	75.58	77.93	74.20	101.72	75.14	77.75	13.03	16.76
8	68.14	78.83	92.25	78.12	102.55	79.49	83.23	12.18	14.63
9	71.73	84.22	98.49	81.89	101.57	82.91	86.80	11.21	12.91

Table 29(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.5 M NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	3.33	0.00	8.11	3.52	0.00	5.89	3.47	3.21	92.35
2.5	6.21	4.45	22.29	5.78	4.06	6.49	8.21	6.96	84.80
3	8.84	10.66	34.78	8.47	11.95	7.32	13.67	10.47	76.60
3.5	14.62	16.44	42.05	11.88	18.98	11.31	19.21	11.55	60.10
4	21.29	20.75	49.62	14.61	24.07	16.08	24.40	12.84	52.62
4.5	28.74	25.31	55.25	17.36	29.81	23.01	29.91	13.19	44.09
5	35.70	30.77	58.15	21.16	34.12	29.04	34.82	12.51	35.92
5.5	40.76	37.40	62.20	25.46	39.04	34.40	39.88	12.20	30.59
6	45.80	42.21	65.48	28.48	43.32	38.23	43.92	12.19	27.74
7	51.68	49.16	78.09	35.01	50.05	48.91	52.15	14.08	26.99
8	55.16	55.66	84.86	40.62	55.37	55.86	57.92	14.48	25.00
9	59.65	62.28	89.36	46.99	57.56	62.99	63.14	14.09	22.31

Table 30(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 1 M NaCl solution

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2.5	0.00	0.00	3.67	4.33	0.00	0.00	1.33	2.08	155.70
3	0.00	10.39	6.15	11.09	0.00	0.00	4.61	5.32	115.52
3.5	22.62	16.28	14.99	18.13	0.00	0.00	12.00	9.65	80.40
4	25.84	21.95	20.25	21.79	2.93	3.85	16.10	10.02	62.25
4.5	27.47	25.42	21.83	26.53	5.50	5.65	18.74	10.37	55.34
5	27.80	29.07	23.80	28.48	9.44	9.02	21.27	9.51	44.69
5.5	28.77	33.37	25.50	30.12	12.77	11.69	23.70	9.25	39.01
6	29.78	36.87	27.52	32.33	17.45	14.20	26.36	8.79	33.36
7	32.42	41.56	31.54	35.85	26.36	17.95	30.95	8.11	26.22
8	36.35	46.41	35.63	41.44	32.80	21.11	35.62	8.60	24.13
9	40.46	50.39	40.25	47.37	37.35	25.27	40.18	8.79	21.88

Table 31(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
3.5	0.00	0.00	8.55	0.00	10.74	0.00	3.22	5.03	156.40
4	11.73	10.86	15.76	11.30	19.52	12.37	13.59	3.39	24.95
4.5	18.31	17.95	27.69	18.28	27.36	18.09	21.28	4.84	22.76
5	26.51	23.09	42.51	24.85	35.87	23.98	29.47	7.90	26.81
5.5	38.02	27.81	52.61	29.79	44.77	29.72	37.12	9.94	26.79
6	48.62	32.91	60.21	36.34	53.00	34.86	44.33	11.22	25.32
7	65.62	44.90	71.16	51.29	65.16	45.81	57.32	11.36	19.81
8	77.34	54.79	78.63	62.47	75.66	55.43	67.39	11.14	16.52
9	90.94	67.71	83.56	73.90	84.25	65.81	77.69	10.08	12.97
10	91.13	69.70	88.43	78.13	88.69	72.32	81.40	9.24	11.36
11	96.29	76.52	91.37	83.60	91.92	78.51	86.37	8.01	9.27
12	97.52	81.42	94.41	88.43	95.67	83.65	90.18	6.70	7.43

Table 32(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.9 % NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
5.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
6	10.36	10.96	7.98	9.05	7.63	7.68	8.94	1.44	16.06
7	16.13	16.25	13.47	31.69	12.05	10.51	16.68	7.69	46.08
8	28.82	22.63	20.57	63.15	17.47	14.33	27.83	17.99	64.65
9	36.65	28.65	26.70	80.62	22.58	19.04	35.71	22.80	63.85
10	42.93	34.00	31.29	87.46	27.01	23.22	40.98	23.74	57.92
11	47.31	39.25	36.07	92.33	31.19	27.35	45.58	23.91	52.46
12	51.35	44.16	40.82	94.85	37.95	31.69	50.14	22.86	45.59

Table 33(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.5 M NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
5.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
6	0.00	0.00	0.00	7.74	11.72	0.00	3.24	5.18	159.71
7	0.00	0.00	0.00	10.05	13.42	0.00	3.91	6.15	157.29
8	7.94	8.21	7.79	12.36	14.76	7.42	9.75	3.06	31.42
9	9.50	9.12	9.42	14.55	16.02	8.75	11.23	3.19	28.42
10	10.89	9.93	11.01	16.69	17.29	10.02	12.64	3.40	26.93
11	12.18	10.78	12.49	18.74	18.44	11.22	13.97	3.63	25.97
12	13.42	11.68	13.89	20.64	19.50	12.39	15.25	3.83	25.10

Table 34(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 1 M NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
5.5	0.00	0.00	0.00	0.00	7.53	0.00	1.25	3.07	244.95
6	0.00	0.00	0.00	0.00	8.77	0.00	1.46	3.58	244.95
7	0.00	0.00	0.00	0.00	11.30	0.00	1.88	4.61	244.95
8	0.00	0.00	0.00	0.00	13.68	0.00	2.28	5.58	244.95
9	0.00	0.00	0.00	0.00	15.87	0.00	2.64	6.48	244.95
10	8.22	0.00	0.00	0.00	17.78	0.00	4.33	7.36	169.88
11	9.12	0.00	0.00	0.00	19.52	0.00	4.77	8.09	169.57
12	9.98	0.00	7.35	0.00	21.09	0.00	6.40	8.40	131.09

Table 35(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
1.5	19.86	9.75	0.00	8.37	26.73	0.00	10.79	10.74	99.53
2	30.14	17.63	0.00	17.43	30.82	0.00	16.00	13.68	85.51
2.5	33.46	21.37	16.06	25.51	34.64	9.67	23.45	9.78	41.71
3	38.22	25.75	25.20	31.80	38.05	15.13	29.03	8.86	30.51
3.5	43.64	30.65	31.45	35.71	43.73	22.45	34.61	8.24	23.81
4	49.15	36.40	37.61	39.90	51.85	29.29	40.70	8.42	20.69
4.5	55.75	46.98	46.54	45.69	62.73	36.39	49.02	9.10	18.57
5	64.26	56.80	53.46	53.50	80.08	43.93	58.67	12.36	21.07
5.5	73.21	67.40	58.27	61.91	82.11	50.11	65.50	11.32	17.28
6	79.30	75.96	67.93	68.67	83.06	56.43	71.89	9.61	13.36
7	92.17	81.63	79.33	84.62	101.93	71.65	85.22	10.58	12.41
8	99.26	96.24	88.44	94.92	103.83	83.44	94.35	7.37	7.81
9	97.69	102.80	95.33	101.00	106.14	95.68	99.77	4.29	4.30
10	104.15	104.56	94.13	102.48	106.42	100.41	102.03	4.37	4.28
11	105.95	106.25	101.37	104.10	106.79	104.50	104.83	1.98	1.89
12	105.94	107.87	103.21	103.15	107.18	106.28	105.61	2.00	1.89

Table 36(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.9 % NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
1.5	9.23	7.68	0.00	7.33	0.00	0.00	4.04	4.47	110.68
2	21.43	25.43	10.53	10.27	11.01	7.84	14.42	7.18	49.78
2.5	43.55	39.04	23.31	12.05	19.89	13.29	25.19	13.23	52.52
3	50.11	42.40	32.42	19.53	24.91	23.50	32.14	11.95	37.18
3.5	53.79	45.56	36.26	29.12	28.47	26.92	36.69	10.88	29.65
4	54.84	48.46	38.96	35.94	31.68	29.04	39.82	9.99	25.08
4.5	61.39	51.47	41.92	41.30	34.51	30.82	43.57	11.25	25.81
5	65.64	54.21	44.04	45.73	37.50	32.53	46.61	11.90	25.54
5.5	67.31	57.07	46.29	51.61	39.61	34.16	49.34	12.02	24.35
6	74.60	60.72	50.13	56.55	42.03	35.80	53.31	13.88	26.03
7	85.17	67.35	58.42	65.03	49.57	40.85	61.07	15.39	25.21
8	92.39	73.23	69.08	70.27	61.49	45.76	68.70	15.25	22.20
9	95.26	75.81	82.82	76.45	69.32	50.72	75.06	14.80	19.72
10	94.36	85.02	89.97	83.56	77.84	56.72	81.24	13.27	16.34
11	96.22	89.42	89.54	89.06	83.62	61.87	84.96	12.00	14.12
12	96.28	91.87	94.87	92.12	89.03	67.64	88.63	10.59	11.95

Table 37(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.5 M NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	15.33	10.24	0.00	10.16	0.00	0.00	5.96	6.79	113.97
2.5	22.65	17.16	7.94	21.40	0.00	19.65	14.80	8.95	60.46
3	33.03	18.33	19.10	28.71	23.64	36.76	26.60	7.52	28.26
3.5	37.19	18.98	24.30	29.45	33.63	46.08	31.61	9.62	30.42
4	40.11	19.64	26.86	30.26	38.06	50.77	34.28	11.01	32.10
4.5	42.18	20.21	28.58	31.14	41.59	53.04	36.12	11.73	32.46
5	43.70	20.78	29.89	32.06	44.51	55.25	37.70	12.41	32.91
5.5	44.99	23.16	31.05	33.25	46.55	57.27	39.38	12.43	31.58
6	46.35	24.64	32.19	34.51	49.62	57.86	40.86	12.45	30.46
7	47.93	27.41	34.37	37.65	56.85	60.25	44.08	13.06	29.63
8	49.91	29.76	36.37	41.11	62.78	61.60	46.92	13.53	28.84
9	52.02	31.73	38.16	44.74	68.89	62.35	49.65	14.24	28.69
10	53.71	33.79	39.94	47.90	72.44	63.69	51.91	14.50	27.93
11	55.63	35.78	41.56	51.72	76.30	64.87	54.31	14.89	27.43
12	57.46	37.64	43.12	55.81	78.09	65.87	56.33	14.76	26.21

Table 38(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 1 M NaCl solution

Time (hr)	% propranolol hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	0.00	9.57	8.32	0.00	0.00	0.00	2.98	4.64	155.49
2.5	9.33	15.28	14.95	13.86	11.09	9.66	12.36	2.67	21.57
3	15.24	23.68	27.82	24.13	21.37	15.15	21.23	5.11	24.07
3.5	18.26	28.66	33.52	24.84	28.25	21.89	25.90	5.42	20.93
4	20.16	30.21	34.89	35.52	30.36	29.78	30.15	5.50	18.24
4.5	21.20	31.35	35.44	40.69	32.15	33.06	32.32	6.41	19.82
5	21.73	32.37	35.78	42.87	32.94	34.13	33.30	6.83	20.50
5.5	22.18	33.27	36.08	44.60	33.48	35.18	34.13	7.19	21.07
6	22.62	34.08	36.43	46.16	33.98	36.00	34.88	7.52	21.56
7	23.58	35.38	37.04	46.65	34.83	37.31	35.80	7.38	20.61
8	24.47	36.38	37.66	48.62	35.55	38.37	36.84	7.70	20.91
9	25.27	37.22	38.19	49.60	36.12	39.07	37.58	7.76	20.64
10	25.88	37.79	38.63	49.74	36.65	39.72	38.07	7.61	20.00
11	26.47	38.42	39.14	50.10	37.15	40.31	38.60	7.55	19.55
12	27.00	38.90	39.60	48.07	37.54	40.78	38.65	6.80	17.59

Table 39(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.1 M HCl pH 1.2

Time (hr)	% diltiazem hydrochloride release						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3.5	0.00	2.93	0.00	0.00	4.80	4.19	1.99	2.26	113.67
4	8.76	10.16	0.00	0.00	15.26	12.75	7.82	6.46	82.52
4.5	22.47	29.08	11.25	13.92	38.05	25.09	23.31	9.88	42.38
5	38.50	43.98	25.96	25.72	50.50	31.84	36.08	10.04	27.82
5.5	51.47	55.37	37.70	35.81	59.06	40.44	46.64	9.89	21.21
6	57.99	64.11	48.10	44.15	66.59	46.46	54.57	9.63	17.64
7	70.08	76.57	63.06	57.16	74.33	51.05	65.37	10.06	15.39
8	77.87	84.71	73.20	66.98	80.50	61.18	74.07	8.79	11.87
9	83.04	87.91	78.65	72.47	82.61	65.58	78.38	8.12	10.36

Table 40(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in PBS pH 6.8

Time (hr)	diltiazem hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3.5	3.91	15.85	9.45	5.22	8.17	6.76	8.23	4.23	51.40
4	11.52	30.38	18.01	20.08	20.56	25.18	20.96	6.41	30.57
4.5	24.72	39.87	40.49	33.22	29.20	40.64	34.69	6.75	19.45
5	38.42	47.47	48.53	41.26	38.48	50.68	44.14	5.41	12.25
5.5	48.48	51.97	52.75	46.58	46.73	56.14	50.44	3.81	7.56
6	53.56	55.82	56.90	52.13	52.85	60.44	55.28	3.11	5.63
7	60.82	60.62	57.58	59.02	59.53	66.40	60.66	3.05	5.02
8	66.00	64.07	63.72	63.13	64.22	70.64	65.30	2.79	4.27
9	70.03	66.35	58.29	67.27	67.16	72.00	66.85	4.70	7.03

Table 41(D) The diltiazem hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in pH-change method

Time (hr)	diltiazem hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
3.5	0.00	3.98	4.43	3.32	5.02	4.33	3.51	1.81	51.52
4	7.91	14.52	17.24	14.44	22.16	15.16	15.24	4.62	30.32
4.5	49.45	20.00	36.07	29.37	37.96	28.75	33.60	10.03	29.84
5	69.25	30.15	49.44	43.62	50.59	39.62	47.11	13.14	27.90
5.5	81.44	38.17	58.73	52.42	59.90	50.13	56.80	14.36	25.28
6	79.95	37.47	65.97	57.54	66.91	57.52	60.89	14.12	23.19
7	96.01	50.70	73.70	64.33	74.79	65.39	70.82	15.07	21.27
8	97.67	58.82	75.22	68.04	78.03	71.65	74.91	13.00	17.35
9	99.19	62.85	81.49	73.21	81.56	75.54	78.97	12.06	15.27

Table 42(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.1 M HCl pH 1.2

Time (hr)	diltiazem hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	0.00	2.94	4.18	0.00	0.00	3.63	1.79	2.00	111.71
2.5	0.00	10.41	5.28	9.50	0.00	8.64	5.64	4.70	83.34
3	13.53	24.92	5.80	20.21	19.68	10.00	15.69	7.16	45.64
3.5	20.28	37.93	17.61	33.31	30.80	20.69	26.77	8.33	31.10
4	31.29	48.65	26.30	41.51	40.23	32.20	36.70	8.20	22.35
4.5	41.79	55.93	38.82	48.72	45.56	42.11	45.49	6.15	13.52
5	49.44	59.87	48.43	53.45	51.08	49.55	51.97	4.25	8.17
5.5	55.13	63.48	56.29	57.50	56.43	54.96	57.30	3.17	5.53
6	59.66	67.37	62.30	62.13	59.52	59.75	61.79	3.01	4.88
7	67.19	71.25	69.59	68.37	65.18	65.26	67.81	2.41	3.56
8	70.70	74.22	74.07	74.02	69.49	69.56	72.01	2.33	3.24
9	74.90	77.51	78.43	81.74	73.28	73.74	76.60	3.25	4.24

Table 43(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in PBS pH 6.8

Time (hr)	diltiazem hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
1.5	7.82	0.00	0.00	2.92	0.00	0.00	1.79	3.18	177.49
2	37.82	4.83	9.78	7.63	6.07	3.24	11.56	13.06	112.97
2.5	49.74	12.18	19.66	8.19	9.20	8.32	17.88	16.19	90.56
3	78.94	20.46	22.70	21.33	10.27	20.78	29.08	24.83	85.40
3.5	93.14	26.51	26.15	30.67	30.23	34.12	40.14	26.13	65.11
4	101.13	34.32	31.11	40.25	41.26	47.26	49.22	26.05	52.92
4.5	102.47	41.30	36.28	46.65	47.73	54.92	54.89	24.14	43.99
5	103.41	48.12	41.24	51.41	52.44	70.63	61.21	22.86	37.35
5.5	104.32	53.90	47.20	56.03	57.44	62.01	63.48	20.58	32.43
6	102.62	56.74	50.20	56.81	60.05	63.10	64.92	18.96	29.21
7	102.65	60.10	53.89	63.16	64.42	66.97	68.53	17.31	25.26
8	103.27	69.74	61.48	66.29	68.29	71.87	73.49	15.01	20.42
9	102.30	73.54	63.88	68.86	69.73	78.94	76.21	13.74	18.03

Table 44(D) The diltiazem hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in pH-change method

Time (hr)	diltiazem hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	4.87	4.71	5.37	7.55	0.00	6.83	4.89	2.65	54.14
2.5	13.83	14.34	21.00	23.47	9.24	17.24	16.52	5.18	31.33
3	15.97	16.38	27.46	27.21	13.97	20.62	20.27	5.89	29.05
3.5	23.83	26.94	37.44	36.57	25.94	32.61	30.55	5.78	18.93
4	33.73	34.85	42.48	44.78	36.70	42.69	39.20	4.67	11.92
4.5	39.39	44.94	49.53	50.44	42.24	51.06	46.26	4.82	10.42
5	45.06	50.81	52.86	55.22	45.96	54.71	50.77	4.37	8.61
5.5	49.88	54.14	55.55	58.61	46.79	58.29	53.88	4.71	8.74
6	53.08	56.41	57.88	60.13	47.88	60.06	55.91	4.73	8.45
7	58.02	61.68	62.13	64.17	51.83	65.01	60.47	4.88	8.07
8	61.63	66.97	65.42	67.78	54.40	67.55	63.96	5.20	8.14
9	64.22	72.50	67.59	70.59	58.22	70.48	67.27	5.29	7.87

Table 45(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in 0.1 M HCl pH 1.2

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
3.5	0.00	0.00	8.55	0.00	0.00	0.00	1.42	3.49	244.95
4	0.00	0.00	9.60	0.00	0.00	0.00	1.60	3.92	244.95
4.5	0.00	0.00	10.27	0.00	0.00	0.00	1.71	4.19	244.95
5	0.00	8.16	10.82	7.47	0.00	0.00	4.41	4.96	112.45
5.5	9.04	8.88	11.47	9.79	0.00	7.72	7.82	4.02	51.48
6	11.17	9.79	12.40	11.92	0.00	9.27	9.09	4.61	50.75
7	15.61	11.81	14.58	16.04	9.13	13.98	13.53	2.62	19.35
8	20.27	14.06	20.54	20.12	11.17	18.89	17.51	3.94	22.50
9	24.97	17.33	26.66	24.00	13.48	23.70	21.69	5.12	23.62
10	29.71	22.12	31.99	27.86	15.97	27.74	25.90	5.86	22.63
11	34.35	25.62	36.88	31.58	18.71	32.04	29.86	6.63	22.19
12	38.67	29.00	40.64	35.32	21.45	35.94	33.50	7.11	21.21

Table 46(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in PBS pH 6.8

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
4.5	0.00	0.00	0.00	0.00	7.11	0.00	1.18	2.90	244.95
5	0.00	0.00	0.00	0.00	9.66	0.00	1.61	3.94	244.95
5.5	7.82	0.00	7.50	0.00	13.28	7.60	6.03	5.16	85.52
6	10.27	0.00	9.94	0.00	17.59	9.76	7.93	6.81	85.93
7	15.59	9.06	15.52	0.00	26.84	13.94	13.49	8.81	65.33
8	20.94	13.35	23.84	8.28	35.55	18.29	20.04	9.40	46.92
9	25.38	17.98	30.75	13.78	41.90	23.13	25.48	9.96	39.09
10	29.77	23.22	36.42	20.89	45.91	27.67	30.65	9.23	30.13
11	34.22	27.61	39.82	26.53	49.81	31.86	34.97	8.71	24.90
12	38.13	31.40	42.89	33.13	53.52	35.85	39.15	8.11	20.70

Table 47(D) The propranolol hydrochloride release from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in pH-change method

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
3.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
4	9.62	0.00	0.00	0.00	0.00	0.00	1.60	3.93	244.95
4.5	14.19	0.00	8.61	0.00	0.00	0.00	3.80	6.15	161.71
5	18.22	9.94	11.44	9.62	8.17	0.00	9.56	5.86	61.31
5.5	22.69	13.31	14.16	15.19	11.73	0.00	12.85	7.36	57.27
6	26.85	17.43	17.04	19.02	14.94	0.00	15.88	8.80	55.40
7	38.94	23.20	24.63	29.70	20.64	8.48	24.26	10.08	41.56
8	52.40	29.52	32.43	35.67	27.36	15.62	32.17	12.05	37.45
9	56.68	35.90	39.21	40.75	33.23	22.34	38.02	11.23	29.53
10	60.21	41.64	44.78	42.57	38.16	27.19	42.43	10.70	25.23
11	63.53	46.20	49.19	50.69	42.77	30.14	47.08	10.90	23.15
12	65.42	50.17	53.07	54.81	46.37	33.10	50.49	10.66	21.11

Table 48(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in 0.1 M HCl pH 1.2

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	12.95	0.00	8.44	17.30	12.05	4.21	9.16	6.29	68.69
2.5	22.85	14.65	15.67	24.99	22.47	11.17	18.63	5.54	29.71
3	25.70	31.91	17.56	33.45	26.32	19.80	25.79	6.33	24.54
3.5	27.40	41.23	20.32	41.65	28.34	36.24	32.53	8.55	26.29
4	29.20	45.30	24.16	46.31	30.67	39.48	35.85	9.16	25.56
4.5	30.83	50.05	28.56	49.30	32.44	43.00	39.03	9.62	24.65
5	32.51	53.15	32.04	52.03	34.31	45.50	41.59	9.85	23.67
5.5	34.09	55.22	36.30	55.91	36.45	52.00	44.99	10.40	23.11
6	35.99	58.41	42.26	65.36	39.92	56.01	49.66	11.83	23.83
7	40.82	64.24	55.69	75.78	53.81	65.70	59.34	12.01	20.25
8	43.03	74.51	69.55	84.25	64.09	71.78	67.87	13.87	20.44
9	45.15	81.30	82.11	88.86	86.71	75.86	76.66	16.09	20.99
10	47.98	85.99	89.82	92.27	90.61	77.15	80.64	16.89	20.94
11	49.70	90.30	94.29	95.23	91.74	81.74	83.84	17.40	20.75
12	53.72	93.37	96.00	96.05	97.52	84.65	86.88	16.90	19.45

Table 49(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in PBS pH 6.8

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
1.5	0.00	0.00	10.72	19.83	8.95	0.00	6.58	8.10	123.06
2	14.27	16.74	29.23	42.26	23.50	12.66	23.11	11.25	48.67
2.5	22.39	33.34	34.95	54.12	32.62	23.05	33.41	11.50	34.41
3	27.46	43.27	36.83	60.91	37.70	31.74	39.65	11.73	29.58
3.5	29.67	46.20	38.28	65.89	40.07	35.70	42.64	12.61	29.58
4	31.31	48.69	39.81	68.88	42.45	38.54	44.95	13.01	28.94
4.5	32.80	51.87	41.06	71.74	43.31	41.59	47.06	13.53	28.75
5	34.46	54.55	42.29	73.65	45.57	49.41	49.99	13.42	26.85
5.5	35.87	57.64	42.35	75.39	47.38	55.95	52.43	13.92	26.54
6	38.07	60.70	42.97	76.17	50.87	57.74	54.42	13.67	25.12
7	44.23	67.27	46.08	83.15	61.11	62.80	60.77	14.40	23.69
8	46.98	71.08	49.49	89.29	69.92	69.00	65.96	15.67	23.75
9	53.09	75.24	52.75	91.81	76.39	78.57	71.31	15.43	21.64
10	58.12	78.77	55.80	92.88	83.49	83.94	75.50	15.08	19.98
11	59.32	81.89	58.47	92.73	86.99	88.32	77.95	15.17	19.45
12	63.37	83.30	61.65	93.16	89.23	90.71	80.24	14.12	17.60

Table 50(D) The propranolol hydrochloride release from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in pH-change method

Time (hr)	propranolol hydrochloride release (%)						Mean	SD	% CV
	n1	n2	n3	n4	n5	n6			
1.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-
2	0.00	12.09	10.40	11.40	13.64	16.09	10.60	5.56	52.46
2.5	10.89	31.44	19.52	22.82	32.28	23.91	23.48	7.95	33.85
3	13.75	39.02	20.68	29.23	41.48	24.97	28.19	10.68	37.88
3.5	18.50	48.37	21.74	36.08	49.94	27.31	33.66	13.41	39.86
4	20.56	55.07	22.94	40.57	54.88	29.20	37.20	15.41	41.43
4.5	22.58	58.60	24.51	44.65	58.00	31.48	39.97	16.17	40.46
5	24.76	63.82	25.82	48.35	65.71	33.65	43.69	18.39	42.09
5.5	27.15	68.32	27.36	52.92	72.46	35.38	47.27	20.26	42.86
6	29.56	71.23	28.95	56.41	78.10	37.13	50.23	21.48	42.77
7	35.87	75.98	32.57	63.22	85.53	41.13	55.72	22.36	40.12
8	41.38	80.47	37.47	70.91	91.45	45.62	61.22	22.71	37.10
9	47.96	84.87	42.31	78.26	93.17	49.34	65.98	21.95	33.26
10	52.76	87.49	46.25	83.95	93.86	53.10	69.57	21.05	30.26
11	56.93	89.61	49.75	89.90	94.14	57.40	72.95	20.25	27.76
12	60.07	91.02	53.74	92.54	93.39	61.68	75.41	18.73	24.84

Table 51(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution (n=18)

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	amount of CA solution								
		250 ml			290 ml			335 ml		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	13.49	13.01	96.43	-	-	-	-	-	-
2.25	0.5	31.42	13.83	44.02	22.11	12.91	58.37	-	-	-
2.75	0.5	28.44	10.48	36.86	33.65	8.64	25.68	-	-	-
3.25	0.5	17.34	6.90	39.78	32.68	7.82	23.93	34.33	10.53	30.66
3.75	0.5	19.64	9.93	50.54	21.60	9.00	41.65	29.05	7.46	25.69
4.25	0.5	14.81	11.91	80.38	16.16	7.41	45.83	24.24	8.56	35.31
4.75	0.5	13.81	8.94	64.74	12.56	4.51	35.87	15.80	9.58	60.64
5.25	0.5	11.07	4.90	44.25	8.55	6.08	71.17	10.54	7.99	75.82
5.75	0.5	8.12	7.70	94.88	8.48	4.90	57.80	13.34	7.05	52.88
6.5	1	5.07	2.90	57.09	6.59	2.27	34.47	4.36	4.04	92.67
7.5	1	3.55	2.29	64.37	5.25	1.63	31.07	4.88	3.83	78.46
8.5	1	4.00	7.13	178.13	2.50	2.36	94.57	1.88	3.70	196.80

Table 52(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution (n=18)

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	amount of CA solution								
		250 ml			290 ml			335 ml		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
1.25	0.5	17.23	7.39	42.89	-	-	-	-	-	-
1.75	0.5	27.84	5.86	21.05	20.11	8.01	39.82	22.50	4.79	21.29
2.25	0.5	33.01	10.97	33.23	18.33	8.33	45.43	31.08	5.97	19.19
2.75	0.5	28.98	9.24	31.88	23.79	5.97	25.11	28.42	7.49	26.36
3.25	0.5	20.06	7.50	37.39	24.75	6.88	27.81	25.40	8.14	32.06
3.75	0.5	18.89	6.04	31.96	22.63	6.56	28.98	15.84	8.66	54.65
4.25	0.5	12.46	4.15	33.28	19.93	8.69	43.60	11.18	7.60	67.95
4.75	0.5	12.21	5.13	42.01	17.81	4.17	23.42	11.73	3.97	33.84
5.25	0.5	8.73	3.84	43.98	12.19	3.91	32.07	8.99	2.36	26.21
5.75	0.5	7.78	3.19	40.95	9.44	4.02	42.53	7.36	5.66	76.90
6.5	1	3.82	2.16	56.58	4.88	3.35	68.57	5.27	4.59	87.11
7.5	1	2.95	1.99	67.27	3.38	3.60	106.40	4.21	2.82	66.95
8.5	1	1.69	2.18	129.53	3.11	2.72	87.44	0.90	3.12	347.65

Table 53(D) The propranolol hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution (n=18)

propranolol hydrochloride release rate (%/hr)							
time point (hr)	time interval (hr)	amount of CA solution					
		290 ml			335 ml		
		Mean	SD	% CV	Mean	SD	% CV
3.75	0.5	18.80	8.75	46.57	18.05	4.41	24.45
4.25	0.5	16.38	3.68	22.47	15.28	4.41	28.83
4.75	0.5	15.77	3.63	22.99	16.32	5.48	33.55
5.25	0.5	15.35	3.50	22.77	16.94	5.97	35.26
5.75	0.5	14.46	2.74	18.96	13.88	3.71	26.70
6.5	1	11.70	2.16	18.49	12.06	2.59	21.46
7.5	1	9.63	1.54	15.96	9.46	1.89	19.94
8.5	1	7.58	1.94	25.65	7.78	3.34	42.94
9.5	1	5.56	1.85	33.21	5.29	2.83	53.44
10.5	1	5.02	1.25	24.93	4.25	1.66	39.05
11.5	1	3.14	1.02	32.51	3.73	2.32	62.00

Table 54(D) The propranolol hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution (n=18)

propranolol hydrochloride release rate (%/hr)							
time point (hr)	time interval (hr)	amount of CA solution					
		290 ml			335 ml		
		Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	25.95	16.93	65.24	17.24	8.97	52.04
2.25	0.5	20.68	10.61	51.31	11.36	7.75	68.18
2.75	0.5	14.71	5.62	38.18	9.52	4.95	51.98
3.25	0.5	12.50	4.41	35.26	9.33	5.47	58.67
3.75	0.5	13.41	4.96	36.99	13.43	9.50	70.79
4.25	0.5	16.32	6.58	40.29	15.23	7.31	48.03
4.75	0.5	15.91	5.58	35.05	16.64	6.66	40.03
5.25	0.5	15.34	3.07	20.02	13.93	5.34	38.29
5.75	0.5	12.47	4.19	33.58	13.29	4.90	36.83
6.5	1	10.41	4.18	40.14	10.53	5.12	48.59
7.5	1	6.08	3.43	56.38	7.09	5.55	78.29
8.5	1	4.40	2.36	53.68	3.11	5.97	192.00
9.5	1	2.81	1.97	70.28	2.49	3.84	154.17
10.5	1	1.68	1.59	94.66	3.94	3.93	99.60
11.5	1	0.54	1.11	207.74	1.46	2.34	160.24

Table 55(D) The diltiazem hydrochloride release rate from various orifice sizes crosslinked OPC coating with 335 ml CA solution (n=6)

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	orifice size								
		0.4 mm			0.6 mm			0.8 mm		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
2.25	0.5	-	-	-	-	-	-	6.29	5.62	89.30
2.75	0.5	24.14	5.68	23.54	-	-	-	27.93	7.21	25.82
3.25	0.5	38.28	8.66	22.62	36.60	7.16	19.57	39.04	3.12	8.00
3.75	0.5	44.03	7.77	17.64	30.66	4.76	15.52	34.45	6.50	18.86
4.25	0.5	23.34	5.67	24.28	17.96	3.81	21.19	16.78	3.15	18.76
4.75	0.5	13.40	2.36	17.60	11.64	4.49	38.54	14.67	5.48	37.34
5.25	0.5	10.82	1.64	15.12	5.79	9.10	157.25	9.65	2.43	25.21
5.75	0.5	5.31	1.05	19.68	18.21	8.47	46.51	8.79	2.48	28.20
6.5	1	5.70	1.17	20.59	0.18	4.27	2364.27	5.69	2.73	48.03
7.5	1	4.33	1.54	35.63	6.43	6.31	98.09	4.68	1.24	26.46
8.5	1	3.70	1.43	38.50	-2.21	3.70	-167.50	4.14	1.41	33.98

Table 56(D) The diltiazem hydrochloride release rate from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution (n=6)

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	amount of CA solution								
		250 ml			290 ml			335 ml		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	-	-	-	20.06	4.40	21.93	26.25	11.21	42.71
2.25	0.5	23.47	12.76	54.34	30.97	3.23	10.42	34.16	10.82	31.66
2.75	0.5	35.12	8.59	24.47	25.10	5.21	20.74	28.64	6.50	22.68
3.25	0.5	30.49	4.23	13.86	30.27	9.82	32.46	26.50	3.79	14.30
3.75	0.5	26.98	8.63	31.99	15.32	15.45	100.81	21.82	6.79	31.09
4.25	0.5	28.86	4.00	13.87	10.19	13.20	129.48	16.35	4.34	26.52
4.75	0.5	12.61	2.10	16.66	12.00	3.23	26.91	13.95	5.49	39.34
5.25	0.5	12.74	2.48	19.46	9.74	2.16	22.19	12.14	7.21	59.42
5.75	0.5	11.09	3.33	30.07	4.76	8.93	187.72	8.06	3.23	40.11
6.5	1	6.01	3.04	50.56	5.81	5.30	91.19	5.15	2.82	54.76
7.5	1	5.27	4.29	81.45	3.18	1.62	50.89	2.87	1.97	68.74
8.5	1	4.31	1.44	33.57	1.60	1.44	90.20	1.84	1.67	90.66

Table 57(D) The propranolol hydrochloride release rate from various orifice sizes crosslinked OPC coating with 335 ml CA solution (n=6)

propranolol hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	orifice size								
		0.4 mm			0.6 mm			0.8 mm		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
3.75	0.5	-	-	-	20.75	3.95	19.03	14.22	15.40	108.30
4.25	0.5	9.95	10.96	110.18	15.38	4.38	28.50	21.54	11.30	52.47
4.75	0.5	24.30	4.85	19.95	16.37	7.00	42.76	24.65	19.23	78.02
5.25	0.5	20.35	11.42	56.13	15.31	5.80	37.87	20.43	12.92	63.25
5.75	0.5	17.41	4.88	28.02	14.41	4.18	29.01	15.62	2.23	14.31
6.5	1	12.59	3.15	25.02	13.00	2.45	18.83	10.33	3.43	33.21
7.5	1	8.72	2.45	28.06	10.06	1.49	14.80	8.33	3.38	40.61
8.5	1	7.16	2.59	36.25	10.31	3.19	30.92	6.20	3.34	53.93
9.5	1	2.47	2.47	99.91	3.71	2.25	60.71	5.60	3.13	55.93
10.5	1	3.64	2.46	67.49	4.97	1.57	31.64	3.35	3.51	104.75
11.5	1	2.60	2.39	91.89	3.82	1.50	39.36	3.11	2.14	68.70

Table 58(D) The propranolol hydrochloride release rate from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution (n=6)

propranolol hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	orifice size								
		0.4 mm			0.4 mm			0.4 mm		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	13.31	12.65	95.05	10.44	9.09	87.07	35.87	12.44	34.67
2.25	0.5	9.85	7.49	76.06	14.89	9.94	66.76	27.88	17.98	64.48
2.75	0.5	11.67	5.92	50.77	11.15	4.00	35.90	10.66	3.37	31.64
3.25	0.5	11.44	3.55	31.00	11.16	2.33	20.84	9.25	3.25	35.09
3.75	0.5	14.41	4.18	28.97	12.19	2.64	21.68	11.78	4.92	41.80
4.25	0.5	15.56	6.12	39.31	16.63	4.27	25.70	13.13	5.04	38.35
4.75	0.5	18.23	6.80	37.31	19.31	7.79	40.35	11.61	3.69	31.80
5.25	0.5	15.67	3.75	23.96	13.66	6.24	45.71	14.64	4.56	31.18
5.75	0.5	12.39	1.99	16.05	12.78	6.01	47.03	9.08	3.70	40.81
6.5	1	9.37	1.86	19.86	13.33	4.55	34.16	9.19	6.35	69.11
7.5	1	6.65	1.33	19.92	9.13	4.36	47.70	6.75	4.35	64.44
8.5	1	4.80	1.06	21.99	5.42	4.67	86.12	3.28	1.18	36.14
9.5	1	3.41	0.93	27.29	2.25	2.85	126.37	3.08	1.68	54.61
10.5	1	1.85	0.44	23.78	2.80	2.49	88.89	1.21	1.10	90.96
11.5	1	1.53	0.48	31.33	0.78	1.15	147.69	1.31	0.80	61.33

Table 59(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions (n=6)

diltiazem hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	deionized water		
		Mean	SD	% CV
3.25	0.5	36.60	7.16	19.57
3.75	0.5	30.66	4.76	15.52
4.25	0.5	17.96	3.81	21.19
4.75	0.5	11.64	4.49	38.54
5.25	0.5	5.79	9.10	157.25
5.75	0.5	18.21	8.47	46.51
6.5	1	0.18	4.27	2364.27
7.5	1	6.43	6.31	98.09
8.5	1	-2.21	3.70	-167.50

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	concentration of NaCl solution								
		0.1588 M (0.9 %)			0.5 M			1 M		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
3.25	0.5	19.70	5.59	28.39	-	-	-	-	-	-
3.75	0.5	31.18	6.16	19.76	-	-	-	-	-	-
4.25	0.5	29.81	5.20	17.43	11.83	8.11	68.52	-	-	-
4.75	0.5	16.81	3.32	19.77	14.85	6.97	46.91	-	-	-
5.25	0.5	12.27	0.79	6.47	18.09	5.99	33.11	-	-	-
5.75	0.5	8.88	1.31	14.78	20.68	6.10	29.48	-	-	-
6.5	1	5.75	0.67	11.67	12.36	3.84	31.06	3.26	2.09	64.29
7.5	1	3.68	0.52	14.12	8.08	1.82	22.56	4.45	2.14	48.17
8.5	1	2.57	0.90	35.05	4.94	1.29	26.07	4.43	2.90	65.54

Table 60(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions (n=6)

diltiazem hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	deionized water		
		Mean	SD	% CV
1.75	0.5	20.06	4.40	21.93
2.25	0.5	30.97	3.23	10.42
2.75	0.5	25.10	5.21	20.74
3.25	0.5	30.27	9.82	32.46
3.75	0.5	15.32	15.45	100.81
4.25	0.5	10.19	13.20	129.48
4.75	0.5	12.00	3.23	26.91
5.25	0.5	9.74	2.16	22.19
5.75	0.5	4.76	8.93	187.72
6.5	1	5.81	5.30	91.19
7.5	1	3.18	1.62	50.89
8.5	1	1.60	1.44	90.20

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	concentration of NaCl solution								
		0.1588 M (0.9 %)			0.5 M			1 M		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
2.25	0.5	9.88	8.42	85.25	9.47	9.65	101.83	-	-	-
2.75	0.5	29.39	10.13	34.46	10.92	8.63	79.02	6.55	8.75	133.61
3.25	0.5	22.91	6.64	28.97	11.08	3.13	28.28	14.79	16.63	112.41
3.75	0.5	21.47	6.12	28.48	10.38	3.46	33.28	8.19	2.23	27.25
4.25	0.5	19.09	7.82	40.94	11.02	3.38	30.70	5.27	2.52	47.86
4.75	0.5	15.35	6.75	43.99	9.82	3.02	30.79	5.07	2.75	54.19
5.25	0.5	13.07	4.40	33.64	10.11	1.83	18.08	4.87	2.47	50.84
5.75	0.5	6.25	5.61	89.73	8.09	1.63	20.12	5.31	2.55	48.10
6.5	1	6.73	2.71	40.24	8.23	2.74	33.27	4.59	2.22	48.42
7.5	1	5.48	4.67	85.14	5.77	1.30	22.47	4.68	1.20	25.61
8.5	1	3.57	2.50	69.95	5.22	1.85	35.52	4.56	0.72	15.80

Table 61(D) The propranolol hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions (n=6)

propranolol hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	deionized water		
		Mean	SD	% CV
3.75	0.5	20.75	3.95	19.03
4.25	0.5	15.38	4.38	28.50
4.75	0.5	16.37	7.00	42.76
5.25	0.5	15.31	5.80	37.87
5.75	0.5	14.41	4.18	29.01
6.5	1	13.00	2.45	18.83
7.5	1	10.06	1.49	14.80
8.5	1	10.31	3.19	30.92
9.5	1	3.71	2.25	60.71
10.5	1	4.97	1.57	31.64
11.5	1	3.82	1.50	39.36

propranolol hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	concentration of NaCl solution								
		0.1588 M (0.9 %)			0.5 M			1 M		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
5.75	0.5	-	-	-	-	-	-	0.41	1.01	244.95
6.5	1	7.74	7.37	95.26	0.67	1.06	157.63	0.42	1.04	244.95
7.5	1	11.14	10.40	93.33	5.84	3.13	53.64	0.40	0.97	244.95
8.5	1	7.88	4.82	61.16	1.48	0.43	29.17	0.36	0.89	244.95
9.5	1	5.28	1.08	20.47	1.41	0.44	30.88	1.69	3.29	194.84
10.5	1	4.60	0.45	9.70	1.33	0.41	30.49	0.44	0.73	166.64
11.5	1	4.56	1.37	30.17	1.28	0.35	27.44	1.63	2.88	176.27

Table 62(D) The propranolol hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solution (n=6)

propranolol hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	deionized water		
		Mean	SD	% CV
1.75	0.5	10.44	9.09	87.07
2.25	0.5	14.89	9.94	66.76
2.75	0.5	11.15	4.00	35.90
3.25	0.5	11.16	2.33	20.84
3.75	0.5	12.19	2.64	21.68
4.25	0.5	16.63	4.27	25.70
4.75	0.5	19.31	7.79	40.35
5.25	0.5	13.66	6.24	45.71
5.75	0.5	12.78	6.01	47.03
6.5	1	13.33	4.55	34.16
7.5	1	9.13	4.36	47.70
8.5	1	5.42	4.67	86.12
9.5	1	2.25	2.85	126.37
10.5	1	2.80	2.49	88.89
11.5	1	0.78	1.15	147.69

propranolol hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	concentration of NaCl solution								
		0.1588 M (0.9 %)			0.5 M			1 M		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	20.76	9.79	47.14	-	-	-	-	-	-
2.25	0.5	21.54	14.25	66.16	17.69	12.88	72.85	18.76	5.94	31.65
2.75	0.5	13.91	5.09	36.55	23.59	15.60	66.11	17.74	5.68	32.01
3.25	0.5	9.09	4.97	54.68	10.02	8.06	80.47	9.34	4.79	51.31
3.75	0.5	6.27	3.92	62.55	5.35	3.43	64.15	8.50	8.01	94.31
4.25	0.5	7.49	3.61	48.14	3.68	2.12	57.71	4.33	3.51	81.08
4.75	0.5	6.08	2.21	36.40	3.16	1.73	54.76	1.98	1.29	65.32
5.25	0.5	5.47	3.21	58.77	3.35	1.05	31.41	1.66	1.05	63.63
5.75	0.5	7.93	3.99	50.36	2.97	1.68	56.56	1.49	0.88	59.34
6.5	1	7.76	1.87	24.05	3.22	2.03	63.23	0.92	0.34	37.11
7.5	1	7.64	2.97	38.84	2.84	1.67	58.61	1.04	0.48	46.48
8.5	1	6.36	4.12	64.85	2.73	1.90	69.60	0.74	0.17	23.16
9.5	1	6.18	3.65	59.04	2.26	0.88	38.92	0.49	0.19	38.43
10.5	1	3.71	2.48	66.72	2.40	1.15	48.11	0.53	0.09	17.88
11.5	1	3.68	2.24	60.95	2.02	1.06	52.57	0.05	1.02	2124.23

Table 63 (D) The diltiazem hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity (n=6)

diltiazem hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	medium								
		0.1 M HCl pH 1.2			PBS pH 6.8			pH-change		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
3.75	0.5	11.68	9.27	79.43	25.46	8.19	32.18	23.45	6.17	26.31
4.25	0.5	30.97	8.88	28.66	27.47	9.96	36.27	36.73	24.40	66.44
4.75	0.5	25.54	6.71	26.27	18.90	4.55	24.07	27.01	6.88	25.46
5.25	0.5	21.12	3.57	16.89	12.60	4.66	37.00	19.38	2.93	15.14
5.75	0.5	15.86	3.19	20.11	9.68	1.77	18.29	8.19	8.22	100.41
6.5	1	10.80	3.86	35.73	5.38	2.46	45.80	9.93	3.78	38.12
7.5	1	8.70	1.61	18.45	4.63	0.94	20.32	4.08	2.62	64.11
8.5	1	4.30	1.38	32.10	1.55	3.58	230.51	4.07	1.60	39.45

Table 64(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity (n=6)

diltiazem hydrochloride release rate (%/hr)							
time point (hr)	time interval (hr)	medium					
		0.1 M HCl pH 1.2			PBS pH 6.8		
		Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	-	-	-	19.54	20.31	103.92
2.25	0.5	7.69	8.18	106.27	12.64	8.48	67.09
2.75	0.5	20.10	15.27	75.97	22.39	20.14	89.94
3.25	0.5	22.16	4.67	21.09	22.12	12.01	54.29
3.75	0.5	19.85	2.70	13.58	18.17	5.68	31.27
4.25	0.5	17.58	5.28	30.04	11.34	4.55	40.10
4.75	0.5	12.96	4.25	32.76	12.64	9.97	78.88
5.25	0.5	10.66	2.99	28.05	4.54	11.29	248.68
5.75	0.5	8.98	1.95	21.68	2.87	3.59	124.95
6.5	1	6.02	1.34	22.20	3.61	2.05	56.79
7.5	1	4.20	0.92	21.80	4.96	3.23	65.15
8.5	1	4.59	1.58	34.42	2.72	2.66	98.01

Table 64(D) The diltiazem hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity (n=6) (continue)

diltiazem hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	pH-change		
		Mean	SD	% CV
2.375	0.75	15.51	4.33	27.93
2.875	0.25	14.99	6.68	44.53
3.25	0.5	20.57	3.18	15.46
3.75	0.5	17.30	4.18	24.15
4.25	0.5	14.12	3.70	26.22
4.75	0.5	9.01	2.19	24.36
5.25	0.5	6.21	2.63	42.33
5.75	0.5	4.06	1.48	36.51
6.5	1	4.57	0.56	12.18
7.5	1	3.49	1.00	28.80
8.5	1	3.31	1.22	36.74

Table 65(D) The propranolol hydrochloride release rate from 0.6 mm orifice size crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity (n=6)

propranolol hydrochloride release rate (%/hr)										
time point (hr)	time interval (hr)	medium								
		0.1 M HCl pH 1.2			0.1 M HCl pH 1.2			0.1 M HCl pH 1.2		
		Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
3.75	0.5	0.35	0.86	244.95	-	-	-	-	-	-
4.25	0.5	0.22	0.54	244.95	-	-	-	4.39	7.27	165.52
4.75	0.5	5.39	7.95	147.43	0.85	2.08	244.95	11.53	8.15	70.66
5.25	0.5	6.82	7.89	115.72	8.85	7.53	85.09	6.56	3.78	57.61
5.75	0.5	2.55	1.65	64.94	3.79	3.31	87.42	6.07	3.14	51.77
6.5	1	4.44	2.58	58.07	5.57	3.43	61.55	8.38	2.60	30.99
7.5	1	3.98	1.55	38.88	6.55	2.11	32.21	7.90	2.80	35.38
8.5	1	4.18	1.33	31.81	5.45	1.00	18.36	5.85	1.00	17.03
9.5	1	4.21	1.00	23.74	5.16	1.13	21.88	4.41	1.48	33.65
10.5	1	3.97	0.80	20.19	4.33	0.75	17.39	4.66	1.83	39.25
11.5	1	3.64	0.54	14.72	4.18	1.23	29.43	3.40	0.85	24.86

Table 66(D) The propranolol hydrochloride release rate from 0.6 mm orifice size non-crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity (n=6)

propranolol hydrochloride release rate (%/hr)							
time point (hr)	time interval (hr)	medium					
		0.1 M HCl pH 1.2			PBS pH 6.8		
		Mean	SD	% CV	Mean	SD	% CV
1.75	0.5	-	-	-	33.05	7.09	21.46
2.25	0.5	18.95	5.82	30.71	20.61	7.44	36.12
2.75	0.5	14.32	11.43	79.84	12.48	5.77	46.26
3.25	0.5	13.48	11.54	85.61	5.97	2.57	43.10
3.75	0.5	6.64	2.18	32.74	4.62	1.21	26.24
4.25	0.5	6.36	2.61	41.01	4.23	2.06	48.66
4.75	0.5	5.12	1.39	27.22	5.86	4.89	83.50
5.25	0.5	6.80	3.71	54.58	4.88	4.46	91.43
5.75	0.5	9.33	5.39	57.73	3.98	2.33	58.65
6.5	1	9.68	3.76	38.81	6.36	2.36	37.11
7.5	1	8.52	4.01	47.07	5.19	2.28	44.01
8.5	1	8.80	7.67	87.14	5.35	2.58	48.30
9.5	1	3.97	2.16	54.32	4.19	2.10	50.07
10.5	1	3.20	1.51	47.04	2.45	1.65	67.42
11.5	1	3.05	1.74	57.20	2.28	1.27	55.81

propranolol hydrochloride release rate (%/hr)				
time point (hr)	time interval (hr)	pH-change		
		Mean	SD	% CV
2.375	0.75	17.16	6.55	38.19
2.875	0.25	18.85	13.93	73.90
3.25	0.5	10.94	6.68	61.05
3.75	0.5	7.09	4.31	60.79
4.25	0.5	5.53	1.93	34.87
4.75	0.5	7.44	4.79	64.47
5.25	0.5	7.16	4.08	57.02
5.75	0.5	5.92	2.98	50.35
6.5	1	5.49	1.58	28.80
7.5	1	5.50	1.21	22.05
8.5	1	4.77	2.02	42.40
9.5	1	3.58	1.75	48.92
10.5	1	3.39	1.96	57.99
11.5	1	2.45	1.87	76.36

APPENDIX E

Calculations of zero-order equation

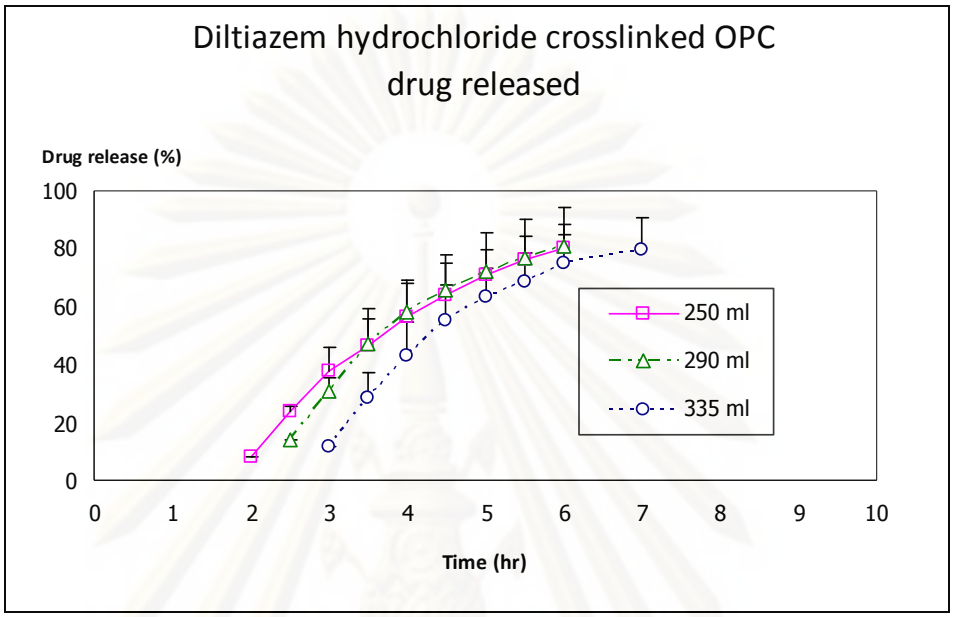


Figure 1(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution in deionized water used for calculations of zero-order equation

Table 1(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution in deionized water

diltiazem hydrochloride crosslinked OPC			
coating level	Qobs*	equation	R^2
250 ml	7.92-80.25	y = 17.661x - 19.192	0.962
290 ml	13.92-80.77	y = 18.581x - 23.324	0.9322
335 ml	11.54-79.55	y = 16.943x - 28.371	0.9055

*Qobs=percentage of drug release interval used for calculation of zero-order equation

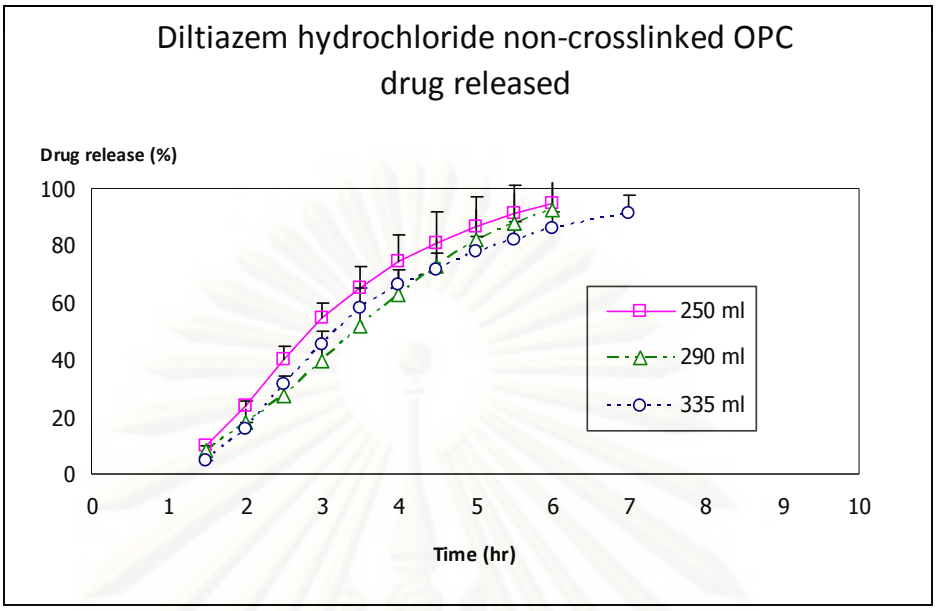


Figure 2(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution in deionized water used for calculations of zero-order equation

Table 2(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution in deionized water

diltiazem hydrochloride non-crosslinked OPC			
coating level	Qobs*	equation	R^2
250 ml	9.92-94.9	y = 18.824x - 8.4696	0.9463
290 ml	8.17-92.66	y = 19.793x - 19.922	0.989
335 ml	4.58-91.1	y = 16.15x - 8.0278	0.9182

*Qobs=percentage of drug release interval used for calculation of zero-order equation

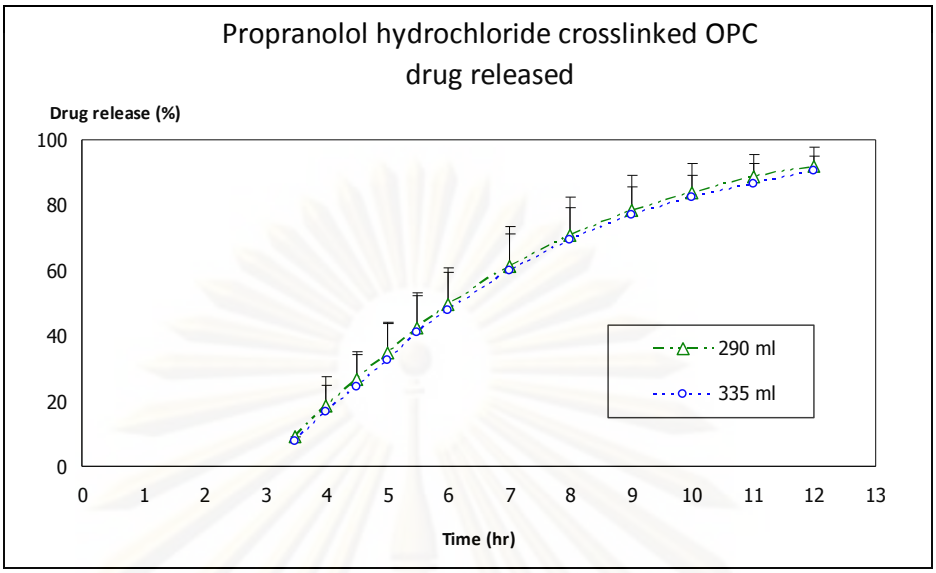


Figure 3(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution in deionized water used for calculations of zero-order equation

Table 3(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice size crosslinked OPC coating with various amounts of CA solution in deionized water

propranolol hydrochloride crosslinked OPC			
coating level	Qobs*	equation	R^2
290 ml	9.02-92.04	y = 9.8159x - 16.993	0.9478
335 ml	7.58-90.4	y = 9.8013x - 15.246	0.9502

*Qobs=percentage of drug release interval used for calculation of zero-order equation

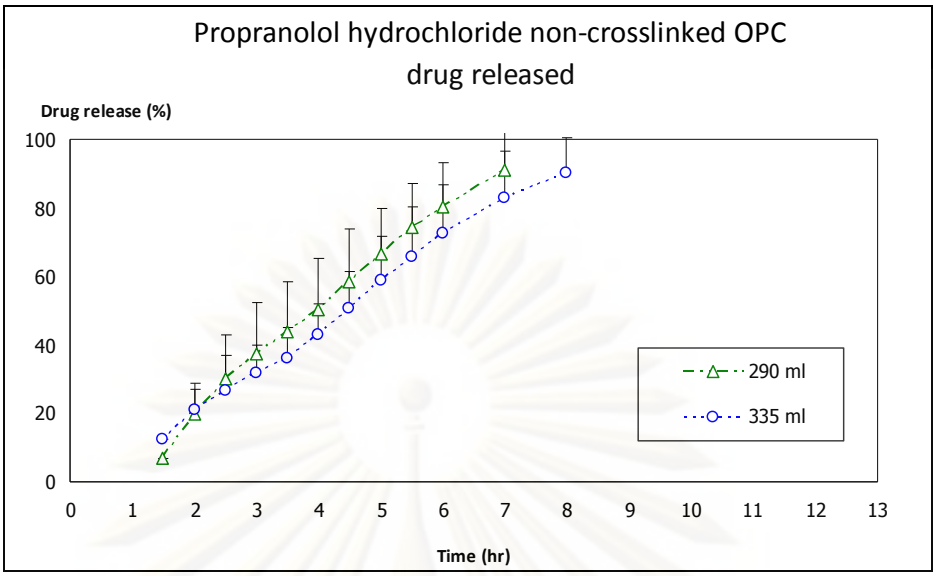


Figure 4(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution in deionized water used for calculations of zero-order equation

Table 4(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice size non-crosslinked OPC coating with various amounts of CA solution in deionized water

propranolol hydrochloride non-crosslinked OPC			
coating level	Qobs*	equation	R^2
290 ml	6.74-90.78	y = 15.023x - 10.027	0.9897
335 ml	12.5-90.11	y = 12.386x - 4.857	0.9928

*Qobs=percentage of drug release interval used for calculation of zero-order equation

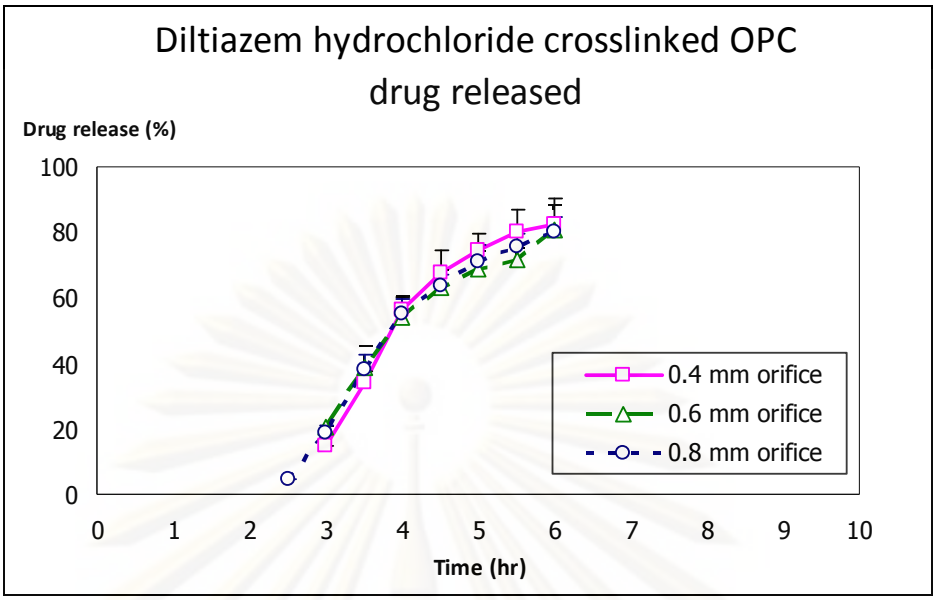


Figure 5(E) The release profiles of diltiazem hydrochloride from various orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water used for calculations of zero-order equation

Table 5(E) Zero-order equations of release profiles of diltiazem hydrochloride from various orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water

diltiazem hydrochloride crosslinked OPC			
orifice size	Qobs*	equation	R^2
0.4 mm	14.94-82.53	y = 22.337x - 41.981	0.9015
0.6 mm	20.51-80.94	y = 18.722x - 27.35	0.9283
0.8 mm	4.59-80.25	y = 21.985x - 42.52	0.9351

*Qobs=percentage of drug release interval used for calculation of zero-order equation

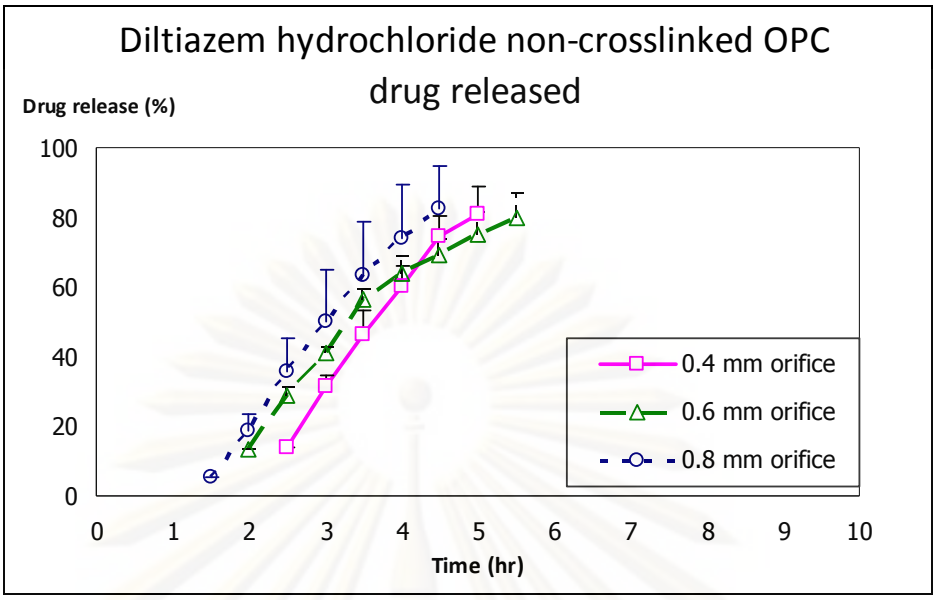


Figure 6(E) The release profiles of diltiazem hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water used for calculations of zero-order equation

Table 6(E) Zero-order equations of release profiles of diltiazem hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water

diltiazem hydrochloride non-crosslinked OPC			
orifice size	Qobs*	equation	R^2
0.4 mm	13.66-80.7	y = 27.325x - 51.402	0.9853
0.6 mm	13.12-79.92	y = 18.836x - 17.242	0.9496
0.8 mm	5.48-82.35	y = 26.377x - 32.049	0.9902

*Qobs=percentage of drug release interval used for calculation of zero-order equation

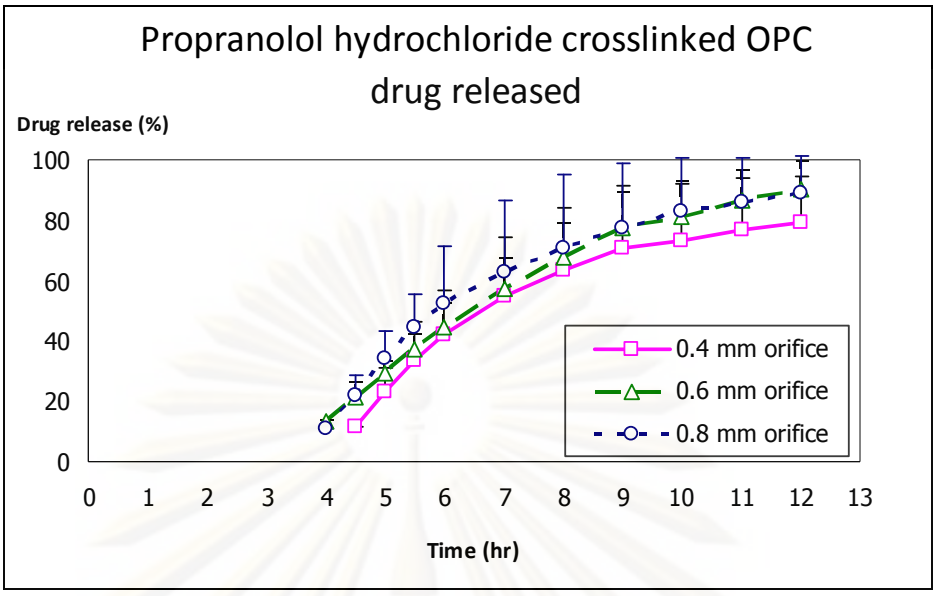


Figure 7(E) The release profiles of propranolol hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water used for calculations of zero-order equation

Table 7(E) Zero-order equations of release profiles of propranolol hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water

propranolol hydrochloride crosslinked OPC			
orifice size	Qobs*	equation	R^2
0.4 mm	11.28-79.5	y = 8.6714x - 14.678	0.8946
0.6 mm	13.59-90.18	y = 9.7697x - 17.725	0.9535
0.8 mm	11.21-89.24	y = 9.3077x - 11.809	0.9053

*Qobs=percentage of drug release interval used for calculation of zero-order equation

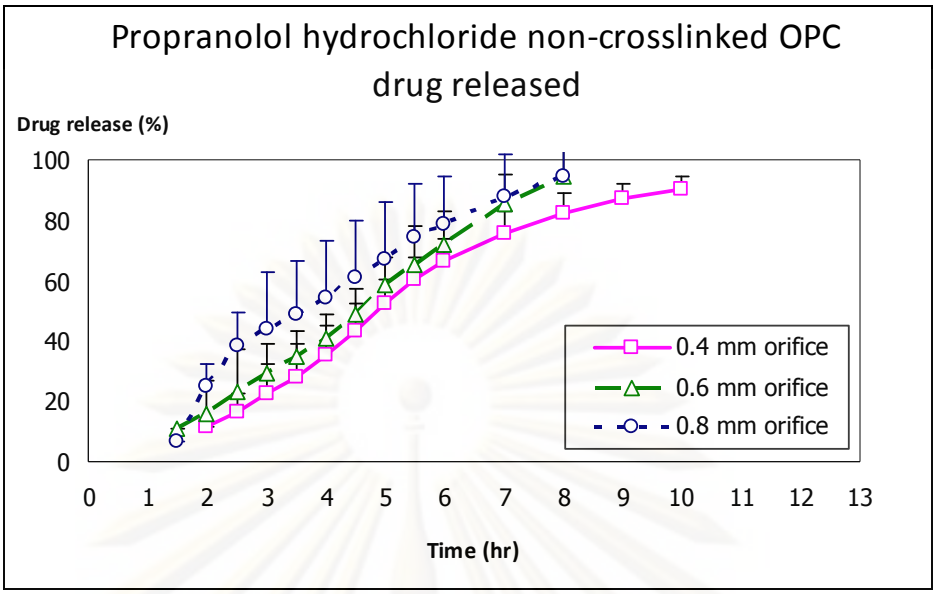


Figure 8(E) The release profiles of propranolol hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water used for calculations of zero-order equation

Table 8(E) Zero-order equations of release profiles of propranolol hydrochloride from various orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water

propranolol hydrochloride non-crosslinked OPC			
orifice size	Qobs*	equation	R^2
0.4 mm	11.68-90.52	y = 10.735x - 6.1376	0.9593
0.6 mm	10.79-94.35	y = 13.478x - 10.696	0.9958
0.8 mm	6.77-94.66	y = 12.581x + 1.6732	0.9529

*Qobs=percentage of drug release interval used for calculation of zero-order equation

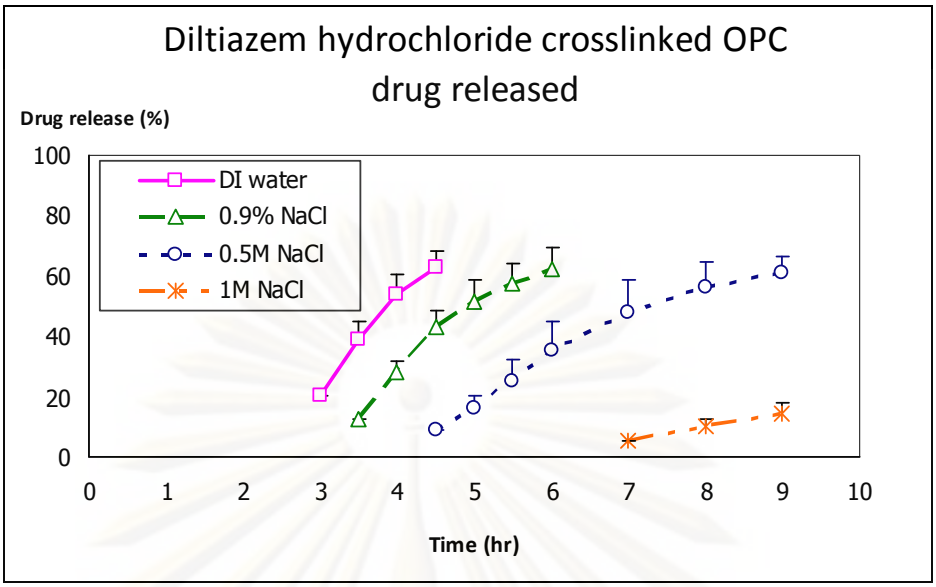


Figure 9(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions used for calculations of zero-order equation

Table 9(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions

diltiazem hydrochloride crosslinked OPC			
medium	Qobs*	equation	R^2
DI water	20.51-63.12	y = 28.63x - 63.217	0.9787
0.9 % NaCl	12.69-62.16	y = 19.662x - 50.793	0.9438
0.5 M NaCl	8.79-60.98	y = 11.931x - 40.866	0.9553
1 M NaCl	3.90-7.37	y = 4.4371x - 25.583	1.000

*Qobs=percentage of drug release interval used for calculation of zero-order equation

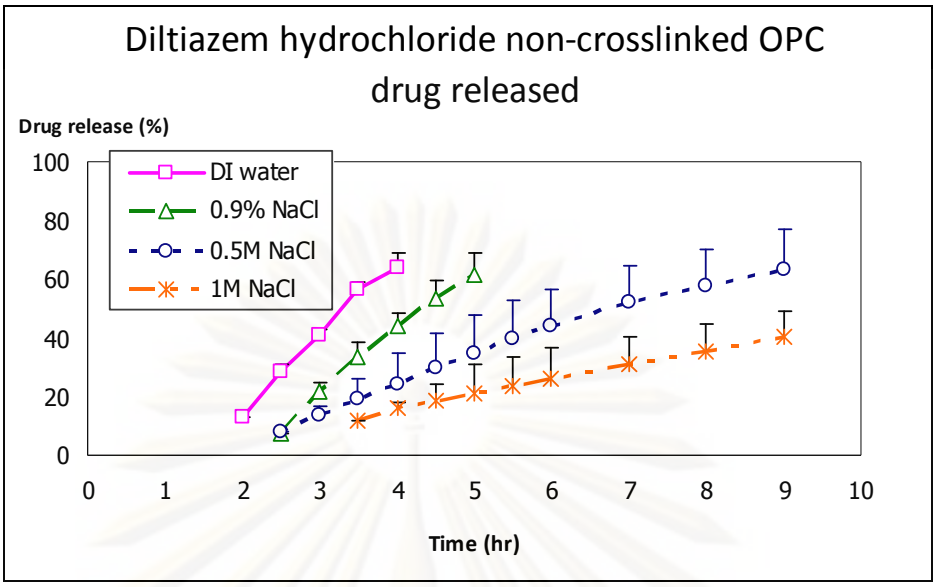


Figure 10(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions used for calculations of zero-order equation

Table 10(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions

diltiazem hydrochloride non-crosslinked OPC			
medium	Qobs*	equation	R^2
DI water	13.12-63.95	y = 25.868x - 36.978	0.9895
0.9 % NaCl	7.25-61.36	y = 21.513x - 43.711	0.9891
0.5 M NaCl	8.21-63.14	y = 8.6339x - 10.32	0.9831
1 M NaCl	12.00-40.18	y = 4.9743x - 4.026	0.9955

*Qobs=percentage of drug release interval used for calculation of zero-order equation

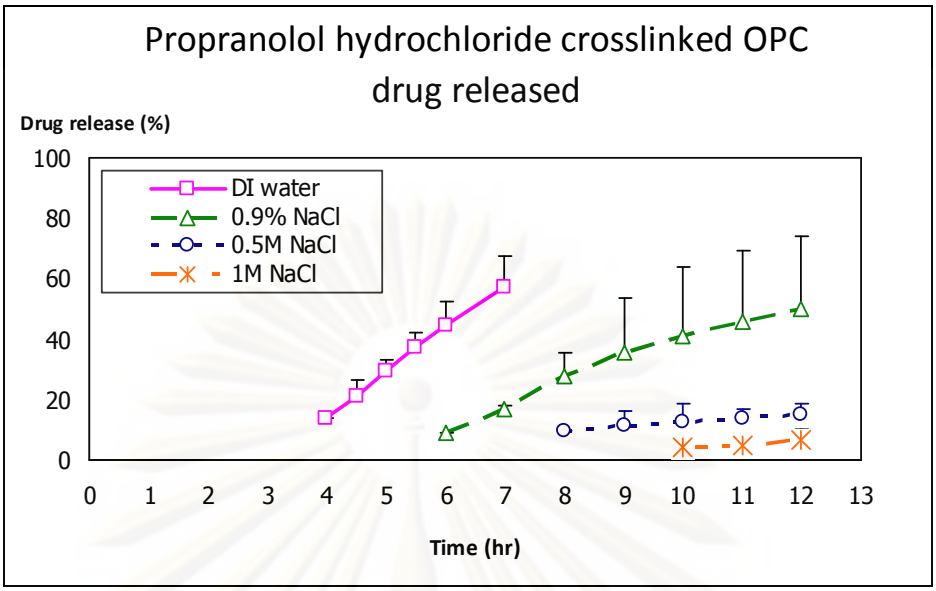


Figure 11(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions used for calculations of zero-order equation

Table 11(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions

propranolol hydrochloride crosslinked OPC			
medium	Qobs*	equation	R^2
DI water	13.59-57.32	y = 14.674x - 44.412	0.9976
0.9 % NaCl	8.94-50.14	y = 6.9478x - 30.263	0.9717
0.5 M NaCl	9.75-15.25	y = 1.3759x - 1.1904	0.9991
1 M NaCl	4.33-6.40	y = 1.0352x - 6.2162	0.9005

*Qobs=percentage of drug release interval used for calculation of zero-order equation

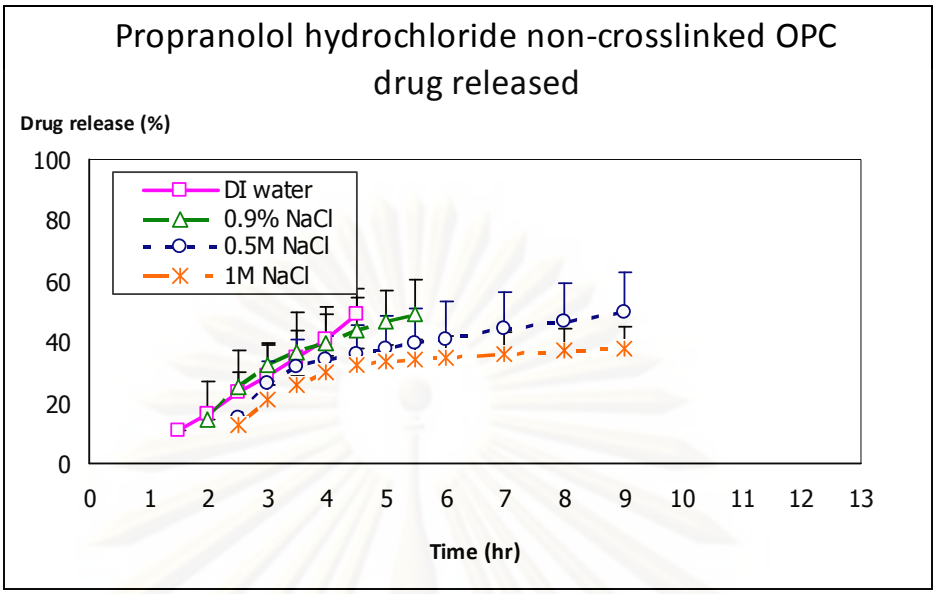


Figure 12(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions used for calculations of zero-order equation

Table 12(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in deionized water and various concentration NaCl solutions

propranolol hydrochloride crosslinked OPC			
medium	Qobs*	equation	R^2
DI water	10.79-49.02	y = 12.517x - 8.4663	0.9967
0.9 % NaCl	14.42-49.34	y = 9.2611x + 1.2423	0.9377
0.5 M NaCl	14.80-49.65	y = 4.3649x + 13.53	0.8520
1 M NaCl	12.36-37.57	y = 3.1174x + 13.971	0.7018

*Qobs=percentage of drug release interval used for calculation of zero-order equation

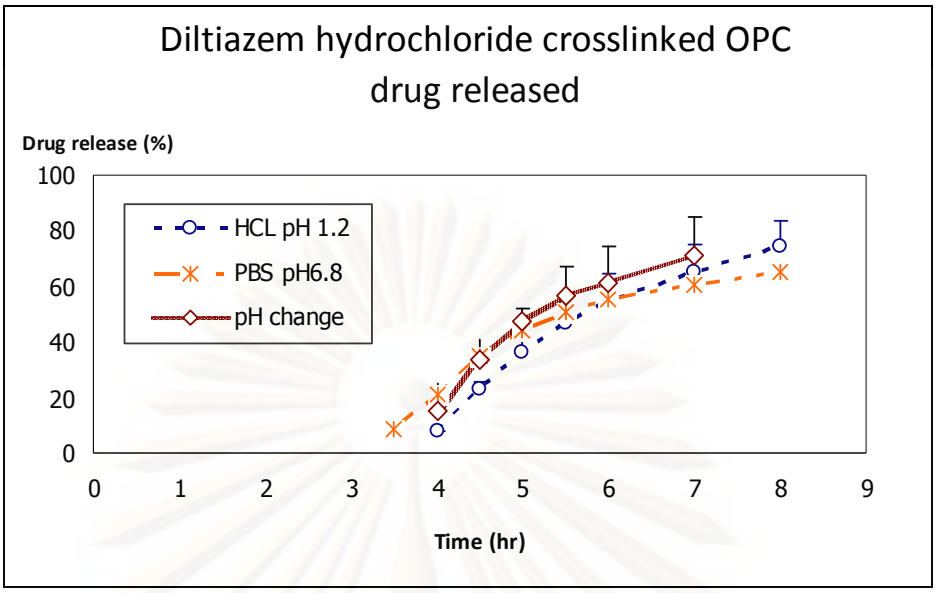


Figure 13(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity used for calculations of zero-order equation

Table 13(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity

diltiazem hydrochloride crosslinked OPC			
medium	Qobs*	equation	R^2
HCl	7.82-74.07	y = 16.051x - 47.74	0.9372
PBS	8.23-65.30	y = 12.237x - 24.075	0.8740
pH-change	15.24-70.82	y = 17.841x - 47.742	0.9085

*Qobs=percentage of drug release interval used for calculation of zero-order equation

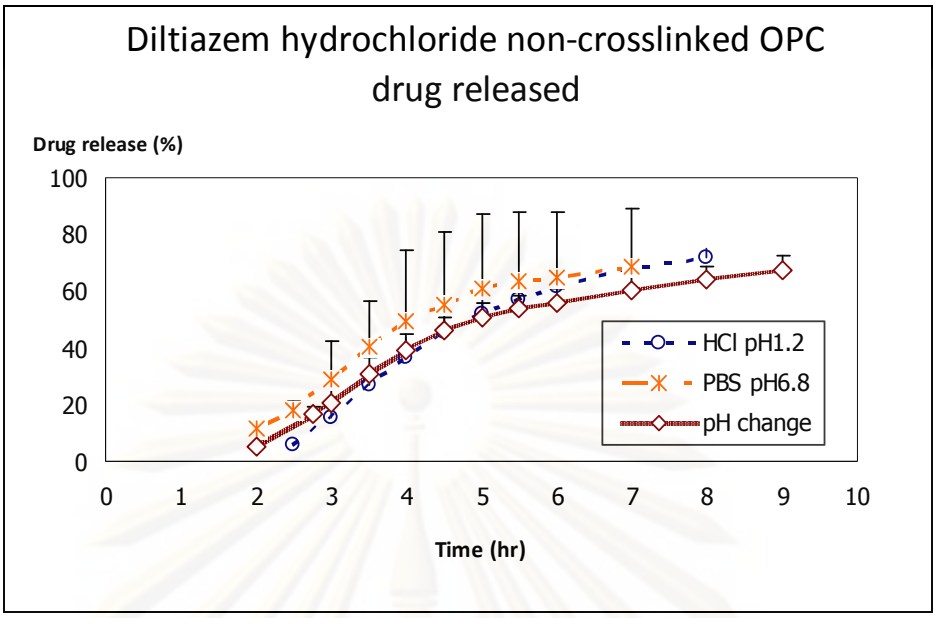


Figure 14(E) The release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity used for calculations of zero-order equation

Table 14(E) Zero-order equations of release profiles of diltiazem hydrochloride from 0.6 mm orifice sizes non-crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity

diltiazem hydrochloride non-crosslinked OPC			
medium	Qobs*	equation	R^2
0.9 % NaCl	7.25-71.02	y = 18.322x - 32.784	0.9695
HCl	5.64-72.01	y = 12.227x - 15.794	0.9200
PBS	11.56-68.53	y = 12.206x - 6.3925	0.9082
pH-change	4.89-67.27	y = 8.7552x - 1.4628	0.8774

*Qobs=percentage of drug release interval used for calculation of zero-order equation

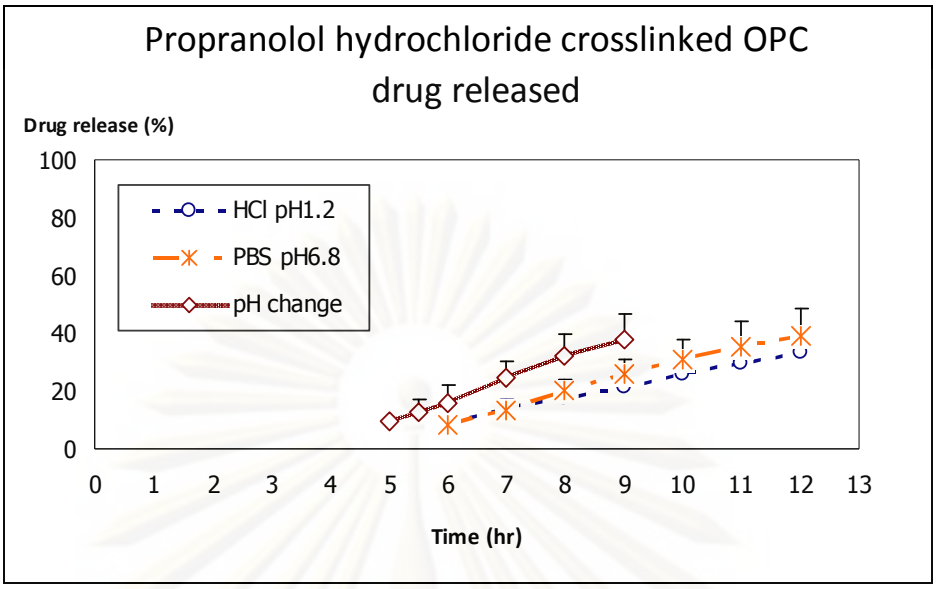


Figure 15(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity used for calculations of zero-order equation

Table 15(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity

propranolol hydrochloride crosslinked OPC			
medium	Qobs*	equation	R^2
0.9 % NaCl	8.94-40.98	y = 8.3106x - 40.455	0.9869
HCl	9.09-33.50	y = 4.0818x - 15.153	0.9994
PBS	7.93-39.15	y = 5.2592x - 22.801	0.9942
pH-change	9.56-38.02	y = 7.3351x - 27.389	0.9971

*Qobs=percentage of drug release interval used for calculation of zero-order equation

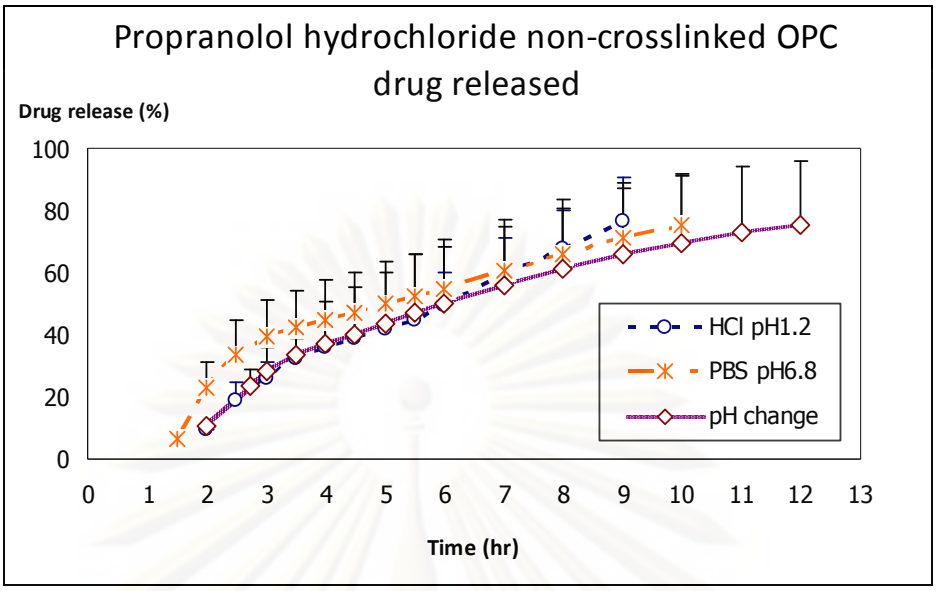


Figure 16(E) The release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity used for calculations of zero-order equation

Table 16(E) Zero-order equations of release profiles of propranolol hydrochloride from 0.6 mm orifice sizes crosslinked OPC coating with 335 ml CA solution in different pH media with isotonicity

propranolol hydrochloride non-crosslinked OPC			
medium	Qobs*	equation	R^2
0.9 % NaCl	14.61-75.06	y = 7.9117x + 5.9338	0.9751
HCl	9.16-76.67	y = 8.8922x - 2.7019	0.9833
PBS	6.58-75.5	y = 6.7004x + 13.479	0.8977
pH-change	10.61-75.41	y = 5.9277x + 10.824	0.9436

*Qobs=percentage of drug release interval used for calculation of zero-order equation

VITAE

Miss Nijarat Wichianprasit was born on August 5, 1984. She received the Bachelor of Sciences in Pharmacy in 2006 from the faculty of pharmaceutical Sciences, Chulalongkorn University, Thailand. She entered studying in the Master's Degree in Industrial Pharmacy Program in the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand in 2007.