FACTORS AFFECTING PHYSICAL PROPERTIES AND DRUG RELEASE FROM HYDROPHILIC AND HYDROPHOBIC COLLOIDAL SILICON DIOXIDE GELS

By

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ปัจจัยที่มีผลต่อคุณสมบัติทางกายภาพและการปลดปล่อยยาจาก เจลคอลลอยดอลซิลิกอนไดออกไซด์ชนิดชอบน้ำและไม่ชอบน้ำ

โดย

นางสาวพจนารถ โตประศรี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

สาขาวิชาเทคโนโลยีเภสัชกรรม

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การเตรียมเจลโดยใช้คอลลอยดอลซิลิกอนไดออกไซด์ชนิดที่ชอบน้ำ (แอโรซิล 200) และชนิดไม่ชอบน้ำ (แอโรซิล อาร์ 972) กระจายในของเหลวตัวกลางชนิดที่ชอบน้ำ และชนิดไม่ชอบน้ำ พบว่า ความหนืดของระบบเพิ่มขึ้นเมื่อปริมาณของคอลลอยดอลซิลิกอนไดออกไซด์ทั้งสองชนิดเพิ่มขึ้น โดยค่าความหนืดเพิ่มขึ้นอย่างมากในปริมาณที่ทำให้เกิดเจล ปัจจัยที่มีผลต่อการเกิดเจล ได้แก่ ความมีขั้วและความหนืดของของเหลวตัวกลาง ความใสของเจลสัมพันธ์กับปริมาณสารก่อเจลและความแตกต่างระหว่างค่าดัชนีการหักเหของแสงของคอลลอยดอลซิลิกอนไดออกไซด์กับของเหลวตัวกลาง ส่วนปัจจัยที่มีผลต่อการปลดปล่อยยาโปรปาโนลอล ไฮโดรคลอไรด์และซาลิซิลิก แอซิด ออกจากเจลคอลลอยดอลซิลิกอนไดออกไซด์ ได้แก่ คุณสมบัติการชอบน้ำของเจลและตัวยา ปริมาณของสารก่อเจลและตัวยาในตำรับ ปฏิกิริยาระหว่างยากับเจลพื้น และชนิดของของเหลวตัวกลางที่ใช้ในการทดสอบการปลดปล่อยยา โดยพบว่า ความหนืดของตำรับมีผลต่อการปลดปล่อยยาน้อยกว่าความสามารถในการดูดซับตัวยาที่ผิวอนุภาคของสารก่อเจลชนิดนี้

สาขาวิชาเทคโนโลยีเภสัชกรรม บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร ปีการศึกษา 2546
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Gels from hydrophilic colloidal silicon dioxide (Aerosil 200) and hydrophobic colloidal silicon dioxide (Aerosil R 972) were prepared by dispersing them in hydrophilic and hydrophobic dispersing media. Viscosity of formulations increased as amount of colloidal silicon dioxide increased. The viscosity markedly increased at amount which the liquid formulations is converted into semisolid gels. The polarity and viscosity of the dispersing media influenced gel formation. The clarity of the gel was related to the amount of colloidal silicon dioxide and refractive index matching between gelling agents and dispersing media. The release of propranolol HCl and salicylic acid from colloidal silicon dioxide gels was influenced by hydrophilic property of the drug and the gel base, the amount of gelling agent and drug loading, the interaction between drug and gel base, and type of receptor medium. Adsorption of the drug on the surface of colloidal silicon dioxide, rather than the gel viscosity, influenced the drug release.

Program of Pharmaceutical Technology Graduate School, Silpakorn University Academic Year 2003

Student's signature ……

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

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LIST OF ABBREVIATIONS

aq	aqueous
ºC	degree celsius
cm	centimeter
cps	centipoise
et al.	and others
g	gram
h	hour
IPM	isopropyl myristate
mg	milligram
ml	milliliter
MO	mineral oil
nm	nanometre
PEG	polyethylene glycol
PG	propylene glycol
RI	refractive index
S.D.	standard deviation
SP	separated from solvent by floating
µg	microgram
µm	micrometre
%w/v	percent weight by volume

CHAPTER I

INTRODUCTION

Gels are semisolid systems consisting of small inorganic particles or large organic molecules dispersing in liquid media. The swelling or network dispersion of molecules or particles should provide an increase of viscosity that can immobilize the liquid media. Thus, gels exhibit the characteristics intermediate to liquids and solids. Gels are divided into inorganic and organic gels on the basis of the nature of the colloidal phase. Bentonite magma is an example of an inorganic gel. Organic gels typically contain polymers as the gel former such as cellulose derivatives. On top of this, the nature of the liquid media determines whether the gel is a hydrogel (i.e. water based) or an organogel (with a non-aqueous media).

The use of gels is quite widespread because of its good appearance e.g. clarity and sparkle. Gels can be used as delivery systems for topical administration. Topical application of drugs e.g. chlorpheniramine maleate (Babar, Bhandari and Plakogiannis 1991 : 2145 - 2146) and lorazepam (Puglia et al. 2001 : 79 - 87), shows some advantages comparing to oral administration, such as a reduction of incidence of systemic toxicity, an absence of hepatic first pass metabolism, etc. Some preparations made from a natural gelling agent might have the problems with microorganism contamination and instability, which can cause undesirable properties after used. The utilization of the synthetic gelling agents can reduce these problems.

Colloidal silicon dioxide or fumed silica or anhydrous silicic acid is a white, amorphous, fluffy powder, spherically shaped inorganic particle. It is manufactured

by hydrolysis of silicon tetrachloride in a hydrogen/oxygen flame (Degussa 2001, 2002). Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products because of its prominent functions such as glidant, binder, suspending agent, thickening agent and adsorbent (Harpaz 1994 : 424 - 427 ; Degussa 2001, 2002). Nonpolar liquids, e.g. olive oil, liquid paraffin or isopropyl myristate, can be converted with colloidal silicon dioxide into translucent gels (Degussa 2001). Colloidal silicon dioxide can be divided into two types: hydrophilic and hydrophobic. The silanol group (Si-OH) on the surface of hydrophilic colloidal silicon dioxide of different particles can interact by hydrogen bond with each other to form the three dimensional network in the dispersing media (Sherriff and Enever 1979 : 842 –845 ; Degussa 2001, 2002). Hydrophobic type is chemically modified by coupling the silanol groups with various silanes or silazanes. The van der Waals forces between each particle are the interaction for the network formation (Raghavan et al. 2002 : 1066 - 1077). Since colloidal silicon dioxide is formed in the oxygen/hydrogen flame at temperature about 1,800 ºC, it is lower in microorganism contamination and higher thermal stability than other gelling agents (Degussa 2002). The factors affecting the gel formation of colloidal silicon dioxide should have further investigation.

To prepare the gel from colloidal silicon dioxide, properties of liquid media i.e. hydrophilicity, viscosity and polarity should be considered. Hydrogen bond formations between silanol groups on the surface of colloidal silicon dioxide particles and polar media might cause some changes in gel strength or gel formation. Theoretically, if the dielectric constant of liquid media is varied by mixing two dispersing media in different ratio and subsequently using it as dispersing media for gel formation form colloidal silicon dioxide, the optimum polarity of the media for gel

forming can be found. Generally, the gels should be clear and should have proper consistency for consumer appeal. For transparent emulsion systems, there are two methods to prepare a transparent emulsion. One is to prepare in form of microemulsions and the other is to calculate and to prepare by refractive index matching between water phase and oil phase (Sun, Erickson and Parr 2003 : 65 - 74). Therefore, it should be possible to prepare the transparent gels using colloidal silicon dioxide incorporated with the media having the similar refractive index.

The therapeutic effectiveness of topical formulation related to the drug release from the formulation. The release of the drug from colloidal silicon dioxide gels has been reported in various studies (Ali, Geneidi and Salama 1978 : 139 – 143 ; Sherriff and Enever 1979 : 842 – 845). The effect of properties of the formulation on drug release was studied (Guy and Hadgraft 1990 : R1 – R3 ; Arellano et al. 1998 : 129 – 135). However, effect of hydrophilicity of colloidal silicon dioxide particles on the release characteristics has not yet been evaluated. Therefore, it is of great importance to study this knowledge as it can give a useful basic information to estimate the drug release from colloidal silicon dioxide gel formulations.

The objectives of this study were to investigate:

1. The suitable characteristics of dispersing medium which used for colloidal silicon dioxide gel formation
2. The factors affecting colloidal silicon dioxide gel formation and gel clarity.
3. The factors affecting drug release from colloidal silicon dioxide gel i.e. type of colloidal silicon dioxide, amount of colloidal silicon dioxide, type

of dispersing medium, type of drug-loaded, type of receptor medium and amount of drug-loaded.

4. Comparative study between hydrophilic and hydrophobic drugs release from colloidal silicon dioxide gel.

CHAPTER II

REVIEW OF RELATED LITERATURE

1. Colloidal silicon dioxide

Colloidal silicon dioxide (colloidal silica or fumed silica or light anhydrous silicic acid or silicic anhydride) is a fine, white, odorless, tasteless, light and amorphous powder consisting of particles about 7 – 40 nm in size.

1.1 Manufacture

Colloidal silicon dioxide is manufactured by chemical hydrolysis chlorosilanes in a hydrogen/oxygen flame.

$$SiCl_4 + 2H_2 + O_2 \longrightarrow SiO_2 + 4HCl$$

The resultant silicon dioxide occurs in the form of an aerosol. Thereafter, it separated from the gaseous phase. The commercial suppliers of colloidal silicon dioxide are Degussa (Aerosil®), Cabot corperation (Cab-O-Sil®), Davison Chemical Devison (Syroid®) and Wacker-Chemie GmbH (Wacker HDK®)

1.2 Types of colloidal silicon dioxides

Colloidal silicon dioxides are divided into hydrophilic and hydrophobic types. Hydrophilic types have silanol (Si-OH) groups on the surface of colloidal silicon dioxide particles (as shown in Figure 1).

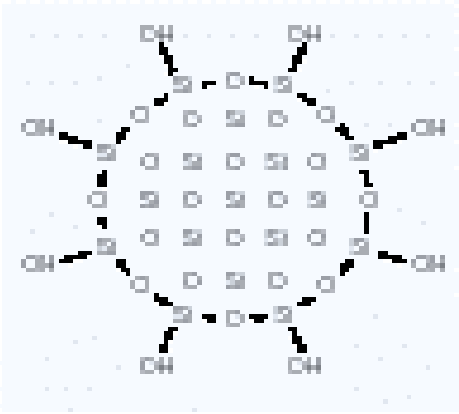


Figure 1 Hydrophilic colloidal silicon dioxide particle

Source: Degussa Aerosil-Fumed silica [on line] 2002

The surface of the colloidal silicon dioxide particles can be chemically modified by react the silanol groups with various silanes and silazanes and this results in the hydrophobic types (as shown in Figure 2).

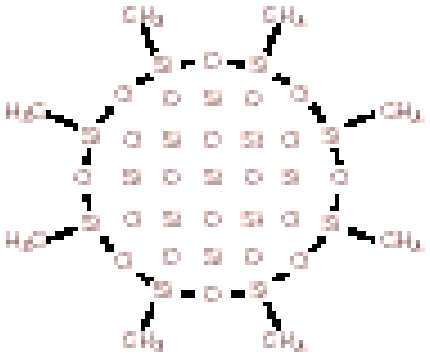


Figure 2 Hydrophobic colloidal silicon dioxide particle

Source: Degussa Aerosil-Fumed silica [on line] 2002

Each type of colloidal silicon dioxides can also have several grades, which are produced by modifying the manufacturing process (see Table 1).

Table 1 Characteristic properties of individual Aerosil grade (data from Degussa)

Types of Aerosil	Behaviour towards water	Appearance	BET surface area (m^2/g)	Average primary particle size (nm)	Tapped density (g/l)	pH value	$\%SiO_2$	%C-content
90	Hydrophilic	Fluffy white powder	90 ± 15	20	80	3.7 – 4.7	> 99.8	-
130			130 ± 25	16	50	3.7 – 4.7	> 99.8	-
150			150 ± 15	12	50	3.7 – 4.7	> 99.8	-
200			200 ± 25	12	50	3.7 – 4.7	> 99.8	-
300			300 ± 30	7	50	3.7 – 4.7	> 99.8	-
380			380 ± 30	7	50	3.7 – 4.7	> 99.8	-
OX 50			50 ± 15	20	30	3.8 – 4.8	> 99.8	-
TT 600			200 ± 50	20	60	3.6 – 4.5	> 99.8	-
MOX 80			80 ± 20	30	60	3.6 –4.5	> 99.8	-
MOX 170			80 ± 20	5	50	3.6 –4.5	> 99.8	-
COK 84			170 ± 30	-	50	3.6 – 4.3	82 - 86	-
R 972	Hydrophobic		110 ± 20	16	50	3.6 – 4.4	> 99.8	0.6 – 1.2
R 974			170 ± 20	12	50	3.7 – 4.7	> 99.8	0.7 – 1.3
R 202			100 ± 20	12	50	4.0 –6.0	> 99.8	3.5 – 5.0
R 805			150 ± 25	12	50	3.5 – 5.5	> 99.8	4.5 – 6.5
R 812			260 ± 30	7	50	5.5 – 7.5	> 99.8	2.0 – 3.0
R 812 S			220 ± 25	7	50	5.5 – 7.5	> 99.8	3.0 – 4.0
R 104			150 ± 25	12	50	> 4.0	> 99.8	1.0 – 2.0
R 106			250 ± 30	7	50	> 3.7	> 99.8	1.5 –3.0
R 8200			160 ± 25	-	20	> 5.0	> 99.8	2.0 – 4.0
R 816			170 ± 25	12	20	4.0 – 5.5	> 99.8	1.2 – 2.2

1.3 Properties

Colloidal silicon dioxide is insoluble in water, organic solvent and mineral acids except hydrofluoric acid. It dissolves in a hot alkali solution to form silicates. The pH of colloidal silicon dioxide is about 3.5 – 4.4 (4% w/v aqueous dispersion). The specific gravity is 2.2 and the refractive index is 1.46. Any modifications can affect the particle size, surface area and density (as shown in Table 1) but cannot affect the silica content, specific gravity, refractive index, color or amorphous form.

1.4 Applications of colloidal silicon dioxides in pharmaceutical products

Colloidal silicon dioxide is widely used in the oral and topical pharmaceutical products as a binder and a glidant in tablets and as a suspending agent and a viscosity modifier in suspensions, ointments and suppositories. It is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas (Degussa 2002). It should not be administered parenterally.

1.4.1 Solid dosage forms

Colloidal silicon dioxide is able to improve the flow and packing characteristics of powders or granules by adhesion onto the surface of powders and absorption the moisture. The utilization of colloidal silicon dioxide in tablet formulations could improve the flow properties and could enhance the crushing strength of tablets and reduce tablet thickness (Chang, Leonzio and Hussain 1999 :

285 - 289). The moisture adsorption capacity of colloidal silicon dioxide related to the particle size (Canefe, Bayel and Unver 1998 : 103 - 119). From this property, it could be used to improve the inhalation properties such as the surface adhesive and cohesive of prunlukast hydrate particles (Kawashima et al. 1998 : 243 -251). The hydrophilic colloidal silicon dioxide (Aerosil 200) could be used as a moisture adsorbent of *Passiflora edulis var. flavicarpa* extractive solution for production of the flavonoid powder (De Sauza et al. 2000 : 331 - 336). Aerosil 200 could also be employed as the viscosity-inducing agent in coating vehicles, which did not affect to the drug release from the coated tablets (Gudsoorkar and Rambhau 1996 : 133 - 136). The use of the hydrophobic colloidal silicon dioxide (Aerosil R 972) as a dry coating agent was previously reported (Sista and Niebergall 1996 : 153 - 158). It was found that the rate of drug release decreased as the amount of Aerosil R 972 increased.

1.4.2 Semisolid dosage forms

The new oily gel base using colloidal silicon dioxide as gelling agent was previously reported by Ali, Geneidi and Salama (1978 : 139 - 143). The rheogram of this gel exhibited a thixotropic area that depends on the nature of oil and concentration of colloidal silicon dioxide incorporated. The hydrophobic colloidal silicon dioxide (Aerosil R 972) could be applied as gelling agent in the hydrophilic/lypophilic microemulsion. This hydrophobic gelling agent contributed to improve a vehicle adhesion to the skin and increased the properties of the microemulsion as a skin enhancer for the lipophilic drugs (Osman-Gardabbou et al. 2000 : 224 - 228). The use of hydrophilic colloidal silicon dioxide in the ointment formulations containing spray-dried extracts of *Achylocline satureioides* could

improve the stability of the formulations owing to the enhancement of a water phase viscosity leading to reduce the release of oil from the inner phase (De Paula et al. 1998 : 235 - 241).

1.4.3 Liquid dosage forms

Colloidal silicon dioxide was also mentioned as a stabilizing agent in suspensions (Muzik, Turan and Stachova 1990 : 1 - 3). Because colloidal silicon dioxide could be used for stabilize the dispersions and prevent the formation of hard and undispersible sediments, which cause a blockage of spray nozzles in the aerosol preparations (Degussa 2001). The stability of organic and water base suspensions could be improved by addition of colloidal silicon dioxide to retard the sedimentation of high density pigments (Cabot corperation laboratories 2003).

1.5 Stability and storage

Colloidal silicon dioxide is inert to all chemicals except the strong alkalis and hydrofluoric acid. It can pick up volatile substances and adsorb water because of its high specific surface area, therefore, colloidal silicon dioxide should be kept in a dry location, in closed containers and should be protected to expose the volatile substances.

2. Gel

2.1 Characteristics of gels (Zatz and Kushla 1989 : 495 – 508 ; Allen 2002)

Gels can be used as a delivery system for oral drug administration, such as capsule shells made from gelatin; for topical drug applied directly to the skin, mucous membranes, or eye; and for long acting dosage forms of drugs injected intramuscularly. Gels have been employed in a wide variety of cosmetics including shampoos, fragrance products, and skin and hair care preparations.

The United States Pharmacopoeia (USP) defines gels as semisolids, being either suspensions of small inorganic particles or large organic molecules interpenetrated with liquid. The inorganic particles, such as bentonite, form a three-dimensional structure throughout the gel. This is a true two-phase system, as the inorganic particles are not soluble, merely being dispersed throughout the continuous phase.

There is an interaction between the units of the colloidal phase, inorganic or organic, which sets up the structural viscosity immobilizing the liquid continuous. Thus, gels exhibit the characteristics intermediate to liquids and solids. Gels are divided into inorganic and organic gels on the basis of the nature of the colloidal phase. Organic gels typically contain polymers as the gel former such as cellulose derivatives. Large organic molecules tend to exist in solution as randomly coiled flexible chains. These molecules, either natural or synthetic polymers, tend to entangle with each other due to their random motion. The organic molecule is dissolved in the continuous phase. Therefore, these systems are actually single phase. Bentonite magma is an example of an inorganic gel. Likewise, the nature of the

dispersing media determines whether the gel is a hydrogel (i.e. water base) or an organogel (with non-aqueous solvent). Thus, both bentonite magma and gelatin are hydrogels. Example of organogels is Plastibase®. The addition of a gelling agent into a formulation should provide a reasonable solidlike nature during storage that can be broken easily when was subjected to the shear forces generated during shaking a bottle or during topical application.

2.2 Gel forming compounds

Ideally, gelling agents for pharmaceuticals and cosmetics should be inert, safe, and nonreactive with other formulation components. The gel should exhibit a little viscosity change under the temperature variations of normal use and storage. Many gels, particularly those of a polysaccharide nature, are susceptible to microbial degradation. Incorporation of a suitable preservative may prevent the contamination and subsequent loss of gel characteristics due to microbial attack.

2.2.1 Natural gums

Natural gums such as alginates, tragacanth, pectin have been used in commercial since the beginning of recorded history. Typically, they are branched chain polysaccharides. Most are anionic, although a few, such as guar gum, are neutral molecules.

Because of their chemical makeup, natural gums could be subjected to microbial degradation and microbial growth. Aqueous systems containing gums should contain a suitable preservative. The cationic antimicrobials

are not generally compatible with the anionic gums; therefore, they should usually be avoided for mixing together.

Gums employed as gel formers may produce the desired effect as a result of simple dispersion in water (e.g. tragacanth) or through chemical interaction (e.g. sodium alginate and calcium). In any case, the gel exists because of crosslinks that tie sections of polysaccharide molecules together while the remainder is solvated.

2.2.2 Carbomer

Carbomer is a resin that was first described in the literature in 1955 and is currently ingredients in a variety of pharmaceutical dosage forms. Carbomer forms gels at concentrations as low as 0.5%. In aqueous media, the polymer, which is marketed in the free acid form, is first uniformly dispersed. After entrapped air has been allowed to escape, the gel is formed by neutralization with a suitable base. The introduction of negative charges along the polymer chain causes it to uncoil and expand. The pH should be adjusted to a neutral value; either insufficient neutralization or excessive pH will adversely affect the gel characteristics (Bonina and Montenegro 1994 : 19 - 24).

2.2.3 Cellulose derivatives

Cellulose is a natural structural polymer found in plants. Treatment in the presence of various active substances results in breakdown of the cellulose backbone as well as substitution of a portion of its hydroxyl moieties. The major factors affecting rheological properties of the resulting material are the nature

of the substituent, degree of substitution, and average molecular weight of the resultant polymer.

The cellulose derivatives are subjected to enzymatic degradation; hence they should be protected against the contact with sources of cellulose. Sterilization of aqueous systems or addition of suitable preservatives is used to prevent viscosity reduction resulting from depolymerization due to enzyme production by microorganisms.

2.2.4 Polyethylenes

Various forms of polyethylene and its copolymers are used to form gel with hydrophobic liquids. The result is a soft, easily spreadable semisolid that forms a water-resistant film on the skin surface.

Polyethylene itself is a suitable gellant for simple aliphatic hydrocarbon liquids but may lack the compatibility with many other oils found in personal care products. For these, copolymers with vinyl acetate and acrylic acid may be used, perhaps with the aid of a cosolvent. To form the gels, it is necessary to disperse the polymer in the oil at elevated temperature (above 80 ºC) and then shock cool to precipitate fine crystals that make up the matrix.

2.2.5 Colloidally dispersed solids

Certain finely divided solids can function efficiently as thickening agents in various liquid media. Gel formation depends on the establishment of a network in which the colloidal particles of the solid are connected in an asymmetric fashion.

Microcrystalline silica can function as a gellant in a wide range of liquids. Network formation results from attraction of the particles by polar forces, principally hydrogen bonding. Small concentrations are required in nonpolar liquid; in polar liquids, competition of the medium for hydrogen bonding sites weakens particle-particle interactions, so that higher silica concentrations are required to produce a gel.

Montmorillonite clays are capable of swelling in water due to hydration of exchangeable cations and electrostatic repulsion between the negatively charge faces. At high concentration in water, thixotropic gels can be formed because the particles combine in a flocculated structure in which the face of one particle is attracted to the edge of another. The gels are highly thixotropic, tending to liquify upon agitation. Because of the importance of electrostatic forces in flocculation, it is not surprising that rheological properties of clay dispersions are sensitive to salts (Aldebert et al. 1981 : 669 – 676 ; Simonton, Komarneni and Roy 1988 : 165 –176 ; Abend and Lagaly 2000 : 221 - 227).

The characteristics of gels based on any of these solid particles depend on the method of preparation. High shear is usually required to break the powdered raw material down into primary particles so as to produce the most extensively bonded network.

2.2.6 Surfactants

Combinations of mineral oil, water and high concentrations (typically 20 – 40%) of certain nonionic surfactant can produce clear gels. These combinations result in the formation of microemulsions; the semisolid rheology

encountered is due to the existence of liquid crystalline phases. An adjustment of the proportion and concentration of an ingredient can vary the gel characteristics (Peltola et al. 2003 : 99 – 107 ; Aubrun, Simonet and Alloret 2004).

2.2.7 Other gellants

Various waxy materials such as beeswax, carnauba wax, and cytyl ester wax are employed as gellants in nonpolar media. Aluminum stearate, a hydrophobic soap, has been employed as a bodying agent in oils for many years. These gelling agents are generally incorporated by fusion.

3. Drug release

3.1 Factors affecting drug release

There are various factors affecting the drug release from the dosage form. Some important factors will be presented in the following sections.

3.1.1 Drug solubility and concentration

The solubility of drug in a vehicle influences the partition coefficients of the drug between the formulation and the membrane. Ho et al. (1994 : 636 - 642) found that the increase of the drug solubility in a vehicle decreased the penetration of the drug through the synthetic membrane. In case of ciprofoxacin HCl gel containing propylene glycol and ethanol, the drug release was found to be very low because the drug had high affinity toward these solvents (Chowdary and Kumar 1996 : 47 - 50). The release of chlorpheniramine maleate from hydrophilic ointment base was increased after addition of urea due to the increase of the drug solubility and

increase of in thermodynamic activity of the drug during permeation through the membrane. (Babar, Bhandari and Plakogiannis 1991 : 2145 - 2156). The release of ibuprofen from gel preparation increased as the pH of buffer enhanced due to higher ionization and higher water solubility (Hussain et al. 1999 : 265 – 271). The same relationship was also reported by Suh and Jun (1996 : 13 – 20) for the release of naproxen from gel.

The release of drug was increased with an increase of the initial drug loading. This effect of drug concentration on the drug release was probably due to the increase in thermodynamic activity of the drug, which was related to its concentration in the base (El Gendy, Jun and Kassem 2002 : 823 - 831). Vlachou et al. (1992 : 47 - 52) reported that the doubling of drug concentration in the gel almost doubled its release rate.

3.1.2 Dosage form

The release of ciprofloxacin hydrochloride from gel and cream formulations was studied by Chowdary and Kumar (1996 : 47 - 50). The drug release from gel was higher than that from cream. It might be due to the biphasic nature and the partitioning of the drug in the two phases of cream. Moreover, the increase in drug release was probably due to other factors i.e. drug affinity with the additive and bulk viscosity of the formulations. The comparative study of methyl nicotinate release from topical formulations was investigated by Nastruzzi et al. (1993 : 43 - 50). The rate of drug release from different dosage forms was ranked as followed: hydrophilic gel > w/o cream > o/w cream > liquid crystal. This indicated that the kind of vehicle of the formulation could significantly affect to the drug release rate.

3.1.3 Drug diffusion

Generally, the release of drugs from gels involved the absorption of water into the matrix and simultaneous desorption of drugs via diffusion, as governed by Fick's law (Kim, Bae and Okano 1992 : 283 – 290). Suh and Jun (1996 : 13 - 20) found that as poloxamer content increased, the diffusion coefficient of the drug in the gel decreased, but the bulk viscosity and gel rigidity increased. However, the drug liberation in stirred systems of a poloxamer gel was controlled by gel dissolution rather than the drug diffusion (Moore et al. 2000 : 191 - 202).

3.1.4 Receptor media

The effect of various parameters on drug release from model topical formulations was studied by Shah et al. (1999 : 337 - 385). The results showed that the receptor medium was the most important and was the critical variable affecting the drug release. The drug release was not influenced by alteration of agitation of the medium, using different lots of synthetic membrane or using different stirring speed (Segers, Zatz and Shah 1997 : 70 - 81). Additionally, the stirring speed and membrane did not influence the drug release from ointment base. The release of retinoid from gel was significantly affected by alteration of a receptor fluid and a stirring rate (Keyhani, Nadkarni and Sakr 1995 : 414 - 419).

3.2 Diffusion cell apparatus

The diffusion cell systems are employed in vitro study to quantify the release rate of drugs from topical preparation. In these systems, skin membranes or

synthetic membranes may be employed as barriers to the flow of drug and vehicle to simulate the biological system. The typical diffusion cell has two chambers, one on each side of the test diffusion membrane. A temperature-controlled solution is placed in one chamber and a receptor solution in the others. Drug diffusion may be determined by periodic sampling and assay of the drug content in the receptor solution.

Franz diffusion cell is the most widely used apparatus to determine the drug release profile from the topical drug products because of the reliability and reproducibility. The test specimen was placed in the donor phase, which was separated from the receptor phase by a semipermeable membrane (Figure 3).

The suitable receptor medium is suggested to increase the drug solubility for detection of drug release by the simple method e.g. high-pressure liquid chromatography (HPLC) or ultraviolet spectroscopy.

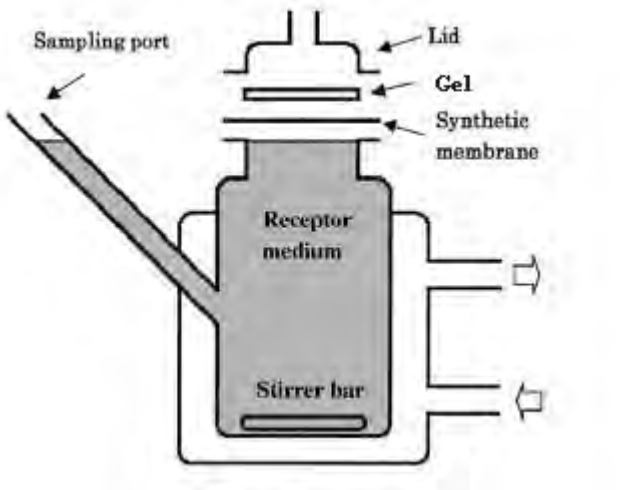


Figure 3 Franz diffusion cell apparatus

4. Dielectric constant

The dielectric constant of a liquid is defined as the ratio of the work required to separate two oppositely charged particles to a given distance in a vacuum to the work required to separate them to that same distance when they are immersed in the liquid (Segal 1985 : 229 - 233). The dielectric constant of a solvent relates to its dipole moment and hydrogen bonding ability and generally reflects the molecule's polarity. The dipole moment is a measure of the degree of polarity of the molecule. Obviously, the degree of bond polarity depends on the difference in electronegativity between the two atoms involved. The greater the difference, the more polar the bond. If a molecule contains more than two atoms, the polarity of the molecule, as a whole will be determined both by the polarity of each bond and the geometry of the molecule (Henry, Moody and Puddephatt 1975 : 91 - 92). Sometimes, the dipole moment is not related to the dielectric constant because the dipole moment is a property of an individual molecule but the dielectric constant is a property of the liquid as a whole that the aggregate of many polar molecules are responsible for the high dielectric constant. However, hydrogen bonding between molecules is the feature that makes this cooperation possible (Segal 1985 : 229 - 233).

5. Refractive index

The ratio of the speed of light in a vacuum to its speed in a substance is called the index of refraction for that substance or the refractive index. The index of refraction of a homogeneous substance is a constant quantity that is a definite physical property of the substance. The identity of such a substance can be determined by

measuring it index of refraction with an instrument known as a refractometer (Beckette and Stenlake 1976 : 23 – 39 ; Bender 1987 : 124 - 130).

CHAPTER III

METHOD OF STUDY

1. Material

1.1 Materials

Castor oil (P.C.Drug Center Co., Ltd., Thailand)

Cellulose acetate membrane pore size 0.45 um. (Sartorius, Germany)

Ceteryl octanoate (Luvitol EHO®) (BASF, Germany)

Colloidal silicon dioxide (Aerosil 200, control no. 1305053 and Aerosil R 972, control no. 1274041) (Wacker-Chemie GmBH, Germany)

Glycerin (P.C.Drug Center Co., Ltd., Thailand)

Isopropyl myristate, IPM (Ake-Trong Chemical 1985 Co., Ltd., Thailand)

Light mineral oil (batch no. 278607, Witco, USA., supplied by P.C.Drug Center Co., Ltd., Thailand)

Polyethylene glycol 400 (PEG 400) (batch no. P075463, Australia, supplied by P.C.Drug Center Co., Ltd., Thailand)

Polyethylene glycol 600 (PEG 600) (batch no. P073026, Australia, supplied by P.C.Drug Center Co., Ltd., Thailand)

Propranolol Hydrochloride (lot no. 030120, Jintan Pharmaceutical Factory, China: Gift from Berlin Pharmaceutical Industry)

Propylene glycol (P.C.Drug Center Co., Ltd., Thailand)

Salicylic acid (lot no. 106505, Ajax chemicals, Australia)

Sorbitol (P.C.Drug Center Co., Ltd., Thailand)

1.2 Apparatus

Analytical balance (Sartorius model BP2100S, Germany)

Brookfield viscometer (Brookfield Engineering Laboratories,Inc.,USA.)

Franz diffusion cell (Crown Bio Scientific Inc., USA)

Refractometer (Schmid & Haensch GmbH Co., Germany)

pH meter (model 220,Corning, Germany)

UV spectrophotometer (Hitachi U-2000, Japan)

Water bath (Julabo, Japan)

Magnetic stirrer (Thermolyne, USA)

2. Method

2.1 Preparation of gels and study of the physical properties

2.1.1 Preparation of gels

The gels were prepared by dispersing hydrophilic colloidal silicon dioxide (Aerosil 200) and hydrophobic colloidal silicon dioxide (Aerosil R 972) at 2, 4, 5, 6, 7, 8, 9 and 10% by weight into hydrophilic dispersing media (water, polyethylene glycol 400, polyethylene glycol 600, propylene glycol, sorbitol and glycerin) and hydrophobic dispersing media (light mineral oil, castor oil, Luvitol EHO® and isopropyl myristate) to make 150 g of the formulations.

2.1.2 Study of the physical properties

The viscosity of all formulations was measured using Brookfield viscometer (Model: DV-I, Brookfield Engineering Laboratories, Inc., USA). The pH measurement of hydrophilic dispersing media was conducted using a

Corning model 220-pH meter. The stability of formulations was evaluated using temperature change for 6 cycles. For one cycle, all formulations were kept at 4°C for 48 h and then at 50°C for 48 h.

2.2 Factors affecting the gel formation and clarity of colloidal silicon dioxide gel

2.2.1 Effect of polarity of the dispersing media on the colloidal silicon dioxide gel formation

The dielectric constant of the dispersing medium was calculated in range of 18 – 40 (Appendix III). To obtain the calculated dielectric constant, pairs of dispersing media (PEG 400–water, PEG 400–PG, PEG 400–glycerin) in weight ratio were gradually mixed. The viscosity of mixed media was measured by Brookfield viscometer. The entire mixed dispersing medium was incorporated with 7.5% w/w of Aerosil 200 and Aerosil R 972. Subsequently, the viscosity of all prepared systems was measured. The relation between the viscosity of the formulation and the dielectric constant was graphically plotted.

2.2.2 Effect of the viscosity of the dispersing media on the colloidal silicon dioxide gel formation

The viscosity of the mixed media before and after incorporation with Aerosil 200 and Aerosil R 972 was measured. At the same dielectric constant, the viscosity of each pairs of dispersing media was compared.

2.2.3 Effect of the refractive index of the dispersing media on the clarity of systems

The refractive index of the systems was measured using a refractometer. The gel clarity was also measured against a blank using UV-Visible spectrophotometer at 480 nm (Yoshioka et al. 1993 : 273 – 275 ; Elorza, Elorza and Chantres 1997 : 173 – 183). The sample in the cuvette was shaken to remove any air bubbles. The air was used as blank. The relation between the refractive index and the absorbance at 480 nm before and after incorporation with Aerosil 200 and Aerosil R 972 was graphically plotted.

2.3 Study of physical properties of drug-loaded gels

PEG 400 and light mineral oil were selected as hydrophilic and hydrophobic gel base because these dispersing media exhibited transparent gels after incorporation with Aerosil. Propranolol hydrochloride at the amount of 0.2, 0.4, 0.6, 0.8, 1.0 and 4.0% by weight and salicylic acid at the amount of 0.2, 0.4, 0.6, 0.8, 1.0, 4.0, 15.0 and 30.0% by weight were dissolved in PEG 400. In case of mineral oil, the same amounts of both drugs were dissolved in 2 ml of 95% ethanol before incorporation with mineral oil. Thereafter, Aerosil 200 and Aerosil R 972 at the amount of 4, 6, 8 and 10% by weight were employed as gelling agent in the mixture of drugs and PEG 400. The mixtures of drug and mineral oil were incorporated with 4, 6, 7 and 8% by weight of both types of Aerosil to make 50 g of the formulations. The physical properties of gel i.e. viscosity, pH and clarity were subsequently investigated.

2.4 Calibration curve of propranolol hydrochloride

2.4.1 Propranolol hydrochloride in water

Propranolol hydrochloride was accurately weighed, dissolved in water and diluted to optimum concentration. This solution was used as a standard stock solution. Optimum volume of this solution was pipetted and adjusted to volume in 25 ml volumetric flask to make approximately 0.008 – 0.030 mg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 289 nm.

2.4.2 Propranolol hydrochloride in PEG 400

Propranolol hydrochloride was accurately weighed, dissolved in 30 ml of ethanol and diluted with PEG 400 to optimum concentration. This solution was used as a standard stock solution. Optimum volume of this solution was pipetted and adjusted with PEG 400 to volume in 25 ml volumetric flask to make approximately 0.010 – 0.060 mg/ml of propranolol HCl. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 289 nm.

The calibration curves of propranolol hydrochloride were conducted and are shown in Figures 19 and 20 (Appendix I).

2.5 Calibration curve of salicylic acid

2.5.1 Salicylic acid in water

Salicylic acid was accurately weighed, dissolved in water and diluted to optimum concentration. This solution was used as a standard stock solution.

Optimum volume of this solution was pipetted and adjusted to volume in 25 ml volumetric flask to make approximately 0.006 – 0.025 mg/ml of salicylic acid. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 298 nm.

2.5.2 Salicylic acid in PEG 400

Salicylic acid was accurately weighed, dissolved in 30 ml of ethanol and diluted with PEG 400 to optimum concentration. This solution was used as a standard stock solution. Optimum volume of this solution was pipetted and adjusted with PEG 400 to volume in 25 ml volumetric flask to make approximately 0.006 – 0.025 mg/ml of salicylic acid. The relationship between concentration and absorbance was determined using UV-spectrophotometer at 298 nm.

The calibration curves of salicylic acid were conducted and are shown in Figures 21 and 22 (Appendix I).

2.6 Content uniformity of drug

The sampling three different positions in gel container were used for drug content analysis of each formulations. Accurately weighed sample of gels (100 mg) was diluted to 50 ml in a volumetric flask. Water and 50% v/v ethanol aqueous solution were used to dissolve propranolol HCl and salicylic acid gels, respectively. The solution was filtered using filter paper (Whatman No. 1). The amount of the drug in the clear solution was determined using UV-spectrophotometer at 289 and 298 nm for propranolol hydrochloride and salicylic acid, respectively.

2.7 Study of drug release from gels

The Franz diffusion cell used in drug release study is shown in Figure 3. The donor compartment with 2.1 cm diameter orifice was utilized. The receptor phase was stirred by a constantly spinning magnetic bar at 600 rpm and thermostated at 37 $\pm$ 0.5 ºC. Distilled water or PEG 400 were used as the receptor solutions. The membrane used in this study was cellulose acetate membrane pore size 0.45 µm. The receptor compartment was filled with 15 ml of receptor solution. About 1 g (thickness about 0.2 cm) of the gel was placed into the donor compartment and tamped down on the cellulose acetate membrane, previously soaked with the receptor solution. Because of the drugs could solubilize in the receptor fluid and the concentration of both drugs were less than 10% of drug solubility in the receptor solution, sink condition are maintained through the study (Ho et al. 1994 : 636 – 642). At appropriate time intervals (0.25, 0.5, 1, 2, 3 h in aqueous receptor solution and 0.5, 1, 2, 3, 6, 12, 25 h in PEG 400 receptor solution), 1 ml of receptor phase was withdrawn. The drug concentration was measured using UV spectrophotometer at 289 and 298 nm for propranolol hydrochloride and salicylic acid, respectively. The volume of sample solution removed was replaced with an equal volume of receptor solution. The calculated drug concentrations were plotted as a function of time and the fluxes were computed from the linear portion of the release profile. All of the experiments were triplicately done, and the mean release rate $\pm$ S.D. were calculated.

2.8 Determination of solubility of drugs in receptor solutions

Drugs were tested for their solubility in different solvent (water, PEG 400 and mineral oil). Approximately 20 g of drug was weighed into a test tube.

Twenty ml of solvent was added. The test tube was then placed in a water bath at 37 ° C. The mixture was taken and measured for the drug content until the content of drug was constant. The mixture was filtered through a glass membrane filter then diluted to optimum concentration. The amount of drugs was determined using UV spectrophotometer at 289 and 298 nm for propranolol hydrochloride and salicylic acid, respectively.

2.9 Calculation of drug release parameter

The fluxes through membrane were calculated by plotting the cumulative amount of drug per area against the square root of time and determining the slope of linear portion of the curve and the X-intercept values (lag time) by linear regression analysis.

2.10 Data evaluation

The significance of the differences between fluxes where $p < 0.05$ was tested using one way ANOVA from SPSS for window version 11.0. The Scheffe test was used as multiple comparisons between groups. In case of the sizes (amount of data using to calculated the fluxes) of the two groups were unequal, the average variance (pooled variance; S_p^2) of the two samples is performed and calculated using the following equation:

$$S_p^2 = \frac{(N_1 - 1)\, S_1^2 + (N_2 - 1)\, S_2^2}{N_1 + N_2 - 2} \qquad \text{Equation 1}$$

The equation for the calculation of the *t* statistic include the pooled variance term is calculated as described equation:

$$t = \frac{(X_1 - X_2)}{S_p\sqrt{(1/N_1 + 1/N_2)}} \quad \text{Equation 2}$$

Where X_1 and X_2 are the mean values of the two groups of sample data (termed 1 and 2); N_1 and N_2 are the number of observations in the two data groups; S_p^2 is the pooled variance; $(N_1 - 1)$ and $(N_2 - 1)$ are the numbers of degrees of freedom associated with sample 1 and sample 2, respectively; and $N_1 + N_2 - 2$ is the total number of degree of freedom for a two independent sample *t* test.

CHAPTER IV

ANALYSIS OF THE DATA

1. Preparation of gels and study of physical properties

The physical appearance of all systems is shown in Figures 23 – 29 (Appendix II) and is summarized in Table 2. All systems showed an increase in viscosity as the amount of both types of colloidal silicon dioxide was increased. The obvious increase in viscosity was found at the amount of colloidal silicon dioxide converting the liquid formulations into semisolid gels e.g. viscosity of system containing mineral oil (Figure 4). By comparison at the same amount used, the systems incorporated with Aerosil 200 were more viscous than that incorporated with Aerosil R 972 (Figure 4). Aerosil R 972 could not be incorporated into water, sorbitol, and glycerin (Figure 5).

Table 2 Physical appearance of the systems containing hydrophilic and hydrophobic colloidal silicon dioxide particles

Dispersing medium	Clarity		Homogeneity	
	Aerosil 200	Aerosil R 972	Aerosil 200	Aerosil R 972
Water	+1	SP	+3	SP
PEG 400	**+5**	**+4**	**+5**	**+5**
PEG 600	**+5**	**+4**	**+5**	**+5**
Propylene glycol	+3	+1	+4	+4
Sorbitol	+2	SP	+4	SP
Glycerin	+3	SP	+4	SP
Light mineral oil	**+5**	**+5**	**+4**	**+5**
Luvitol EHO®	+3	+3	+4	+4
Castor oil	+4	+3	+5	+5
Isopropyl myristate	+2	+1	+4	+4

***** +1 to +5 = the rank order score of clarity and consistency from low to high
****** SP = separated from dispersing media by floating

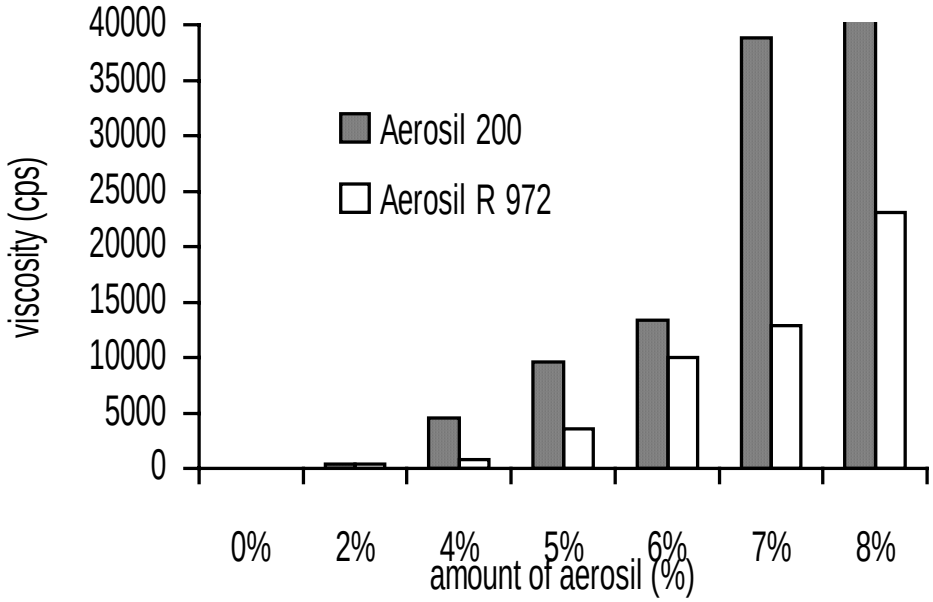


Figure 4 The viscosity of systems containing mineral oil after addition of Aerosil 200 and Aerosil R 972

Figure 5 The immiscibility of Aerosil R 972 with water, sorbitol and glycerin

The criteria to specify the gel formation in this study was that the systems could alter the characteristic from sol to gel. The 5 grams of systems was transferred into test tube of 1.5 cm diameter and the tubes were turned upside down. The systems must stay only in a test tube and did not flow down for at least 30 seconds. The guideline for this technique was applied from the determination of gel–sol transition state suggested by Guzmán (1994 : 2041 - 2048). The dispersing media converted into gels after incorporation with Aerosil 200 were polyethylene glycol 400 and 600, light mineral oil, castor oil, isopropyl myristate and Luvitol EHO® at concentrations of 8, 5, 6, 7, 7 and 7% by weight, respectively. Aerosil R 972 could convert light mineral oil and Luvitol EHO® into gel at concentrations of 7 and 10% by weight, respectively. The viscosity of the gel systems was 13 – 2600 folds (560 – 118, 733.33 cps) compared to the initial viscosity of the dispersing media (Table 3). Table 4 shows the decrease of pH of the systems after incorporated with colloidal silicon dioxide. The appearance of the systems prepared from polyethylene glycol 400, 600 and light mineral oil was clear, but the others were turbid. There were no phase separation or color changes of the systems after the stability test with a temperature change of 6 cycles. The gel formulations exhibited very little change of pH and viscosity after stability testing (Tables 3 and 4).

2. Factors affecting the gel formation and clarity of colloidal silicon dioxide gel

Aerosil 200 could convert all non-polar dispersing media and some polar dispersing media i.e. PEG 400 and 600 into gels. The effect of polarity of the dispersing medium and other effects were further investigated.

Table 3 The viscosity of the Aerosil gel formulations

Dispersing media	Type of Aerosil	viscosity of the dispersing media(cps)	viscosity of the dispersing media after temperature change (cps)	Viscosity of the gel (cps)	Viscosity after temperature change (cps)
PEG 400	A 200	114 ± 6.93	105.33 ± 1.15	13,293.33 ± 6497.27	12,613.33 ± 61.10
PEG 600	A 200	135.67 ± 0.58	167.00 ± 1.00	1,775.33 ± 49.37	1,253.33 ± 310.70
Mineral oil	A 200	45.67 ± 1.15	44.00 ± 0.00	13,373.33 ± 1,473.14	10,760.00 ± 1,009.55
	R 972	45.67 ± 1.15	44.00 ± 0.00	118,733.33 ± 18,094.57	149,466.67 ± 601.01
Castor oil	A 200	753.00 ± 28.16	697.33 ± 0.58	10,466.67 ± 257.16	12,600.00 ± 144.22
Luvitol EHO®	A 200	27.00 ± 2.00	35.00 ± 0.00	5,733.33 ± 1,012.98	4,106.67 ± 532.67
	R 972	27.00 ± 2.00	35.00 ± 0.00	560.00 ± 120.00	640.00 ± 105.83

Table 4 The pH of the Aerosil gel formulations

Dispersing media	Type of Aerosil	Amount used to convert into gel (%)	pH of the dispersing media	pH of the dispersing media after temperature change	pH of the gel	pH after temperature change
PEG 400	A 200	8	3.19 ± 0.02	3.06 ± 0.01	3.19 ± 0.03	3.00 ± 0.01
PEG 600	A 200	5	3.67 ± 0.02	3.85 ± 0.14	3.73 ± 0.22	4.10 ± 0.01
Mineral oil	A 200	6	N/A*	N/A	N/A	N/A
	R 972	7	N/A	N/A	N/A	N/A
Castor oil	A 200	7	N/A	N/A	N/A	N/A
Luvitol EHO®	A 200	7	N/A	N/A	N/A	N/A
	R 972	10	N/A	N/A	N/A	N/A

*N/A = not available

2.1 Effect of the polarity of the dispersing media on the colloidal silicon dioxide gel formation

Pairs of dispersing media (PEG 400–water, PEG 400–PG, PEG 400–glycerin) were prepared in weight ratio to obtain the dielectric constant values of 18 – 40. The viscosity of all mixed media with various dielectric constants was subsequently measured as shown in Figures 6 and 7.

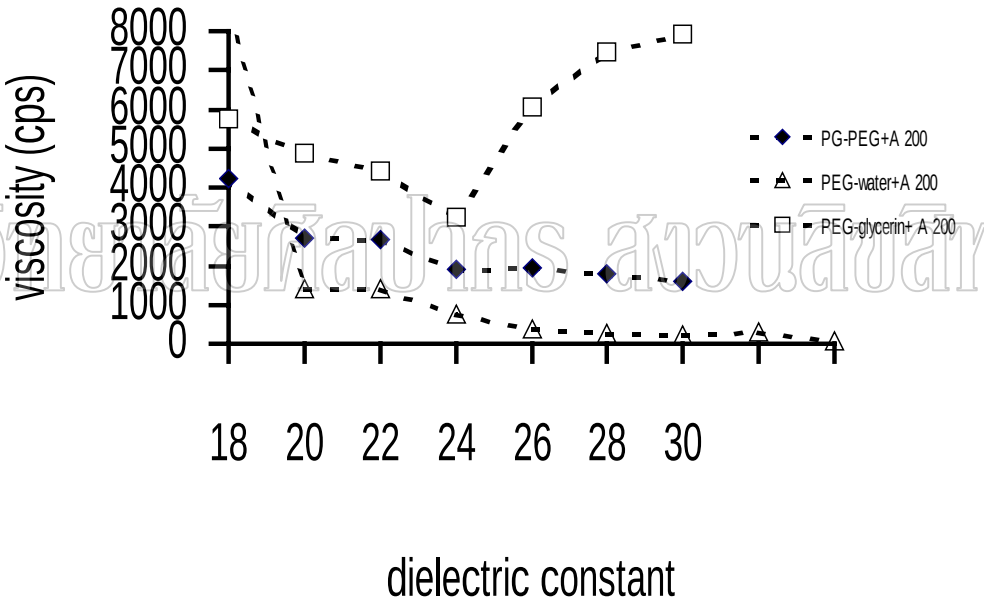


Figure 6 The viscosity of various mixed media after incorporation with Aerosil 200

The viscosity of the mixed media of PEG–PG and PEG–water decreased as the dielectric constant increased. In contrast, the viscosity of PEG 400 and glycerin mixture obviously increased as the dielectric constant enhanced

(Appemdix III). After the Aerosil 200 was incorporated into the mixed media, all systems showed the enhancement of a viscosity, especially, the formulations having low dielectric constant (Figure 6) and vice versa in case of Aerosil R 972 (Figure 7). As the dielectric constant of dispersing media containing PEG 400 and glycerin increased, the viscosity of the systems incorporated with Aerosil 200 decreased. However, the viscosity was slightly increased after the dielectric constant was greater than 24. The physical appearances of all formulations are presented in Figures 30 – 35 (Appendix II).

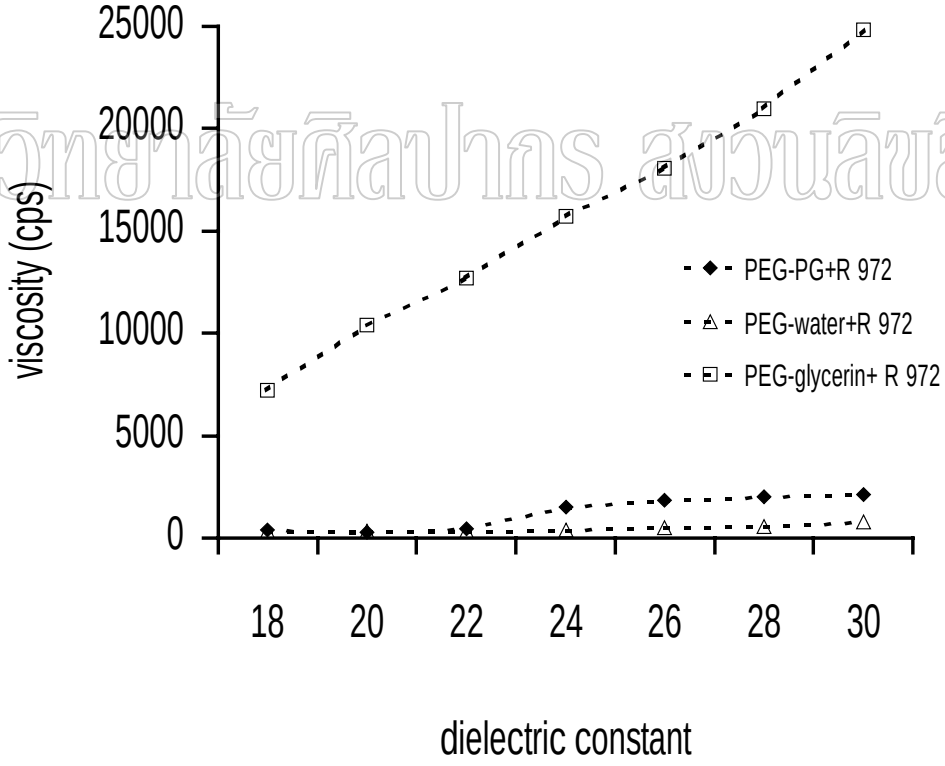


Figure 7 The viscosity of various mixed media after incorporation with Aerosil R 972

2.2 Effect of the viscosity of dispersing media the colloidal silicon dioxide gel formation

The viscosity of the mixed dispersing media having the same dielectric constant was different. At the dielectric constant values of 20 – 30, the rank order of the viscosity of mixed media was PEG 400–glycerin> PEG 400–water> PEG 400–PG (Table 14, Appendix III), and after Aerosil 200 was incorporated, the rank order was PEG 400–glycerin> PEG 400–PG > PEG 400–water. Except a dielectric constant of 18, the rank order was PEG 400–water > PEG 400–glycerin > PEG 400–PG (Figure 6). In case of the incorporation of Aerosil R 972 into mixed media, the rank order of viscosity was PEG 400–glycerin> PEG 400–PG > PEG 400–water (Figure 7). All of PEG 400–glycerin mixtures were obviously converted into gel, while PEG only were not converted with Aerosil R 972 into gel.

2.3 Effect of the refractive index of dispersing media on the clarity of systems

The refractive index of all systems is presented in Figure 8. The mixed media between PEG 400–PG, and PEG 400–water showed the decrease of refractive index when the dielectric constant increased, whereas the refractive index of systems containing PEG–glycerin remained constant (1.464) at all dielectric constant values. Generally, the refractive index values of the system (RI_{mix}) can also be calculated from weight and refractive index of each component as shown in Equation 3. Where RI_i is the refractive index of each component; W_i and W_T are weight of each component and total weight of the system, respectively.

$$RI_{mix} = [\Sigma W_i * RI_i] / W_T \qquad \text{Equation 3}$$

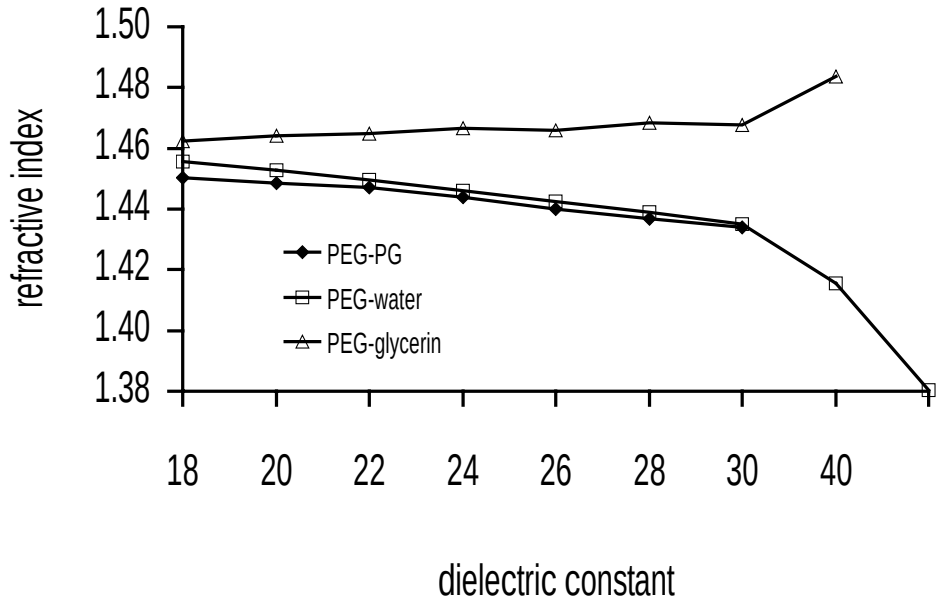


Figure 8 The refractive index of various mixed dispersing media

The refractive index values from this experiment compared to the calculated values are presented in Figure 9. It was apparent that the experimental values deviated only slightly from the calculated values. The rank order of the clarity of the formulations was PEG 400–PG < PEG 400–water < PEG 400–glycerin. This evidence was similar to the clarity conducted using UV- Visible spectrophotometer (Figure 10).

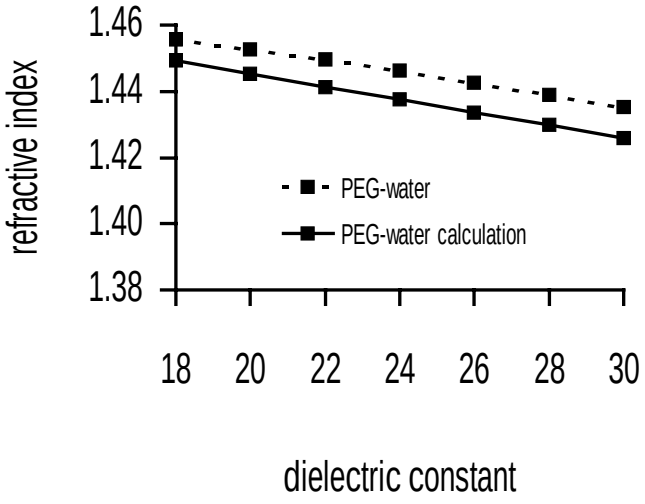


Figure 9 The refractive index of gels containing PEG–water from experiment and calculation

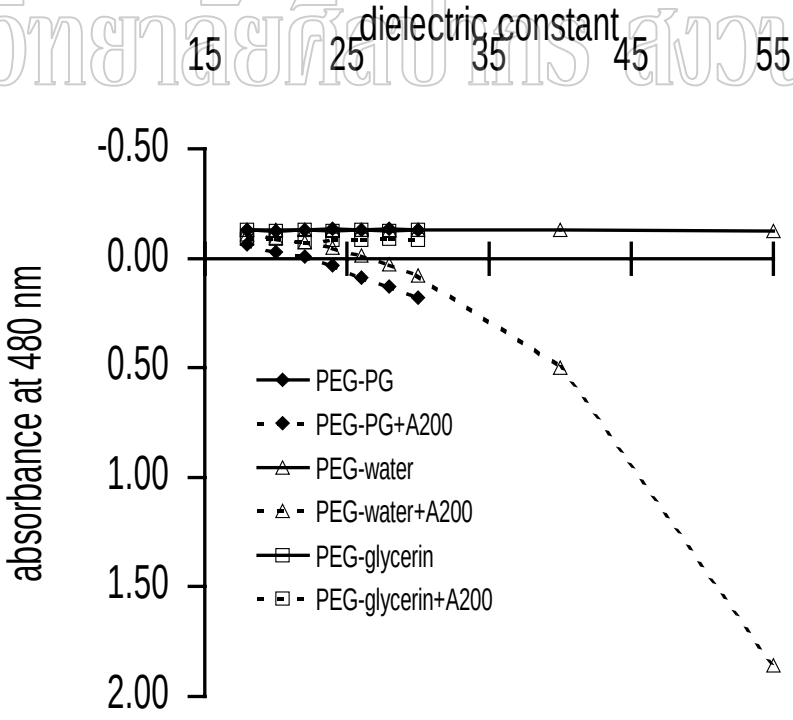


Figure 10 The absorbance of various mixed dispersing media after incorporation with Aerosil 200

3. Physical properties of drug-loaded gels

PEG 400 and mineral oil were selected as hydrophilic and hydrophobic gel bases, respectively, because they could be converted into transparent gels using colloidal silicon dioxide as gelling agent. After the selected gels were added with propranolol hydrochloride (formulations 1 – 23, Figures 36 - 37) and salicylic acid (formulations 24 – 61, Figures 38 - 39), the physical appearances of all formulations were investigated and summarized in Tables 5 – 6 and Figures 36 – 39 (Appendix II).

Table 5 Physical appearance of propranolol HCl gel

Formula	Name	Dosage	Clarity	Homo-geneity	pH	Viscosity (cps)
1	0.2 P 4 Ap	Liquid	+5	+5	5.78 ± 0.05	478.67 ± 30.55
2	0.2 P 6 Ap	Liquid	+5	+5	6.33 ± 0.16	1,121.33 ± 65.03
3	0.2 P 8 Ap	Gel	+5	+5	4.77 ± 0.13	11,946.67 ± 922.89
4	0.2 P10 Ap	Gel	+5	+5	4.26 ± 0.05	22,093.33 ± 3,545.44
5	0.2 P 4 Rp	Liquid	+5	+5	5.08 ± 0.15	245.33 ± 4.62
6	0.2 P 6 Rp	Liquid	+5	+5	4.84 ± 0.01	513.33 ± 2.31
7	0.2 P 8 Rp	Liquid	+5	+5	4.78 ± 0.05	1,025.33 ± 24.11
8	0.2 P 10 Rp	Liquid	+5	+5	4.93 ± 0.11	1,629.33 ± 16.65
9	0.2 P 4 Am	Liquid	+3	+4	N/A	481.33 ± 6.11
10	0.2 P 6 Am	Gel	Turbid	+3	N/A	1,693.33 ± 323.32
11	0.2 P 7 Am	Gel	Turbid	Coarse	N/A	7,653.33 ± 2,097.74
12	0.2 P 8 Am	Gel	Turbid	Coarse	N/A	180,733.33 ± 17,814.97
13	0.2 P 4 Rm	Gel	+3	+3	N/A	2,068.00 ± 106.51
14	0.2 P 6 Rm	Gel	Turbid	Coarse	N/A	8,973.33 ± 794.31
15	0.2 P 8 Rm	Gel	Turbid	Coarse	N/A	21,533.33 ± 1620.53
16	0.4 P 8 Ap	Gel	+5	+5	7.31 ± 0.06	12,586.67 ± 310.70
17	0.6 P 8 Ap	Gel	+5	+5	7.35 ± 0.01	13,413.33 ± 782.13
18	0.8 P 8 Ap	Gel	+5	+5	7.39 ± 0.01	14,026.67 ± 589.69
19	1.0 P 8 Ap	Gel	+5	+5	7.32 ± 0.01	12,733.33 ± 582.87

Table 5 (continued)

Formula	Name	Dosage	Clarity	Homo-geneity	pH	Viscosity (cps)
20	4.0 P 8 Ap	Liquid	+5	+5	7.10 ± 0.01	1,813.33 ± 220.30
21	0.4 P 6 Rp	Liquid	+5	+5	7.55 ± 0.00	1,780.00 ± 323.57
22	0.6 P 6 Rp	Liquid	+5	+5	7.45 ± 0.02	1,986.67 ± 92.92
23	4.0 P 6 Rp	Liquid	+4	+5	7.21 ± 0.03	3,290.00 ± 36.06

* The first number is percentage of drug in the formulation
The second number is percentage of Aerosil in the formulation
P = propranolol HCl, S = salicylic acid, A = Aerosil 200, R = Aerosil R 972, p = PEG 400, m = mineral oil
** N/A = not available

Table 6 Physical appearance of salicylic acid gel

Formula	Name	Dosage	Clarity	Homo-geneity	pH	Viscosity (cps)
24	0.2 S 4 Ap	Liquid	+5	+5	5.39 ± 0.24	497.33 ± 16.17
25	0.2 S 6 Ap	Liquid	+5	+5	4.29 ± 0.08	1,265.33 ± 40.27
26	0.2 S 8 Ap	Liquid	+5	+5	4.07 ± 0.10	4,013.33 ± 479.31
27	0.2 S10 Ap	Gel	+5	+5	4.01 ± 0.03	17,906.67 ± 151.44
28	0.2 S 4 Rp	Liquid	+5	+5	4.04 ± 0.02	330.67 ± 6.11
29	0.2 S 6 Rp	Liquid	+5	+5	3.85 ± 0.02	900.00 ± 18.33
30	0.2 S 8 Rp	Liquid	+5	+5	3.90 ± 0.05	3,210.67 ± 64.66
31	0.2 S 10 Rp	Liquid	+5	+5	3.89 ± 0.03	7,920.00 ± 1,087.38
32	0.2 S 4 Am	Liquid	Turbid	+3	N/A	469.33 ± 10.07
33	0.2 S 6 Am	Gel	Turbid	Coarse	N/A	866.67 ± 140.48
34	0.2 S 7 Am	Gel	Turbid	Coarse	N/A	11,213.33 ± 1,784.53
35	0.2 S 8 Am	Gel	Turbid	Coarse	N/A	48,000.00 ± 2,588.59
36	0.2 S 4 Rm	Gel	Turbid	Coarse	N/A	1,426.67 ± 140.48
37	0.2 S 6 Rm	Gel	Turbid	Coarse	N/A	9,986.67 ± 715.91
38	0.2 S 7 Rm	Gel	Turbid	Coarse	N/A	14,733.33 ± 1,248.57
39	0.2 S 8 Rm	Gel	Turbid	Coarse	N/A	26,026.67 ± 771.84
40	0.4 S 8 Ap	Liquid	+5	+5	5.09 ± 0.03	4,236.67 ± 231.81
41	0.6 S 8 Ap	Liquid	+5	+5	4.55 ± 0.02	3,653.33 ± 64.29

Table 6 (continued)

Formula	Name	Dosage	Clarity	Homo-geneity	pH	Viscosity (cps)
42	0.8 S 8 Ap	Liquid	+5	+5	3.48 ± 0.00	2,833.33 ± 35.12
43	1.0 S 8 Ap	Liquid	+5	+5	2.97 ± 0.23	2,476.67 ± 109.70
44	4.0 S 8 Ap	Liquid	+5	+5	2.57 ± 0.00	4,826.67 ± 23.09
45	15 S 8 Ap	Gel	+4	+5	2.55 ± 0.00	6,653.33 ± 61.10
46	30 S 8 Ap	Gel	+3	+4	2.60 ± 0.01	7,826.67 ± 922.89
47	0.4 S 8 Rp	Liquid	+5	+5	6.31 ± 0.01	4,950.00 ± 65.57
48	0.6 S 8 Rp	Liquid	+5	+5	5.42 ± 0.04	4,326.67 ± 445.01
49	0.8 S 8 Rp	Liquid	+5	+5	4.57 ± 0.03	5,510.00 ± 104.40
50	1.0 S 8 Rp	Liquid	+5	+5	3.60 ± 0.01	4,473.33 ± 185.02
51	4.0 S 8 Rp	Liquid	+5	+5	2.60 ± 0.01	5,210.00 ± 0.00
52	15 S 8 Rp	Liquid	+4	+5	2.39 ± 0.09	4,106.67 ± 46.19
53	30 S 8 Rp	Liquid	+3	+4	2.57 ± 0.02	3,413.33 ± 61.10
54	0.4 S 6 Am	Gel	Turbid	+4	N/A	1,613.33 ± 272.27
55	0.6 S 6 Am	Gel	Turbid	+4	N/A	1,453.33 ± 378.07
56	0.8 S 6 Am	Gel	Turbid	+4	N/A	1,826.67 ± 704.65
57	1.0 S 6 Am	Gel	Turbid	+4	N/A	4,373.33 ± 786.21
58	0.4 S 6 Rm	Gel	Turbid	+2	N/A	8,106.67 ± 700.09
59	0.6 S 6 Rm	Gel	Turbid	+2	N/A	8,746.67 ± 560.48
60	0.8 S 6 Rm	Gel	Turbid	+2	N/A	9,000.00 ± 523.07
61	1.0 S 6 Rm	Gel	Turbid	+2	N/A	10,626.67 ± 438.79

The formulations containing the drugs in PEG 400 (1 – 8, 16 – 31 and 40 – 53) were transparent, viscous and smooth. However, those in mineral oil (9 – 15, 32 – 39 and 54 – 61) were turbid and coarse. The increase in amount of Aerosil 200 and Aerosil R 972 made the formulations more viscous. At high amount of propranolol HCl (4% w/w), the viscosity of the formulations containing Aerosil 200 decreased and vice versa in Aerosil R 972. In case of salicylic acid, the viscosity of formulations

containing Aerosil 200 increased as the amount of this drug increase. In contrary, the viscosity of formulations containing Aerosil R 972 decreased as the amount of this drug increase.

4. Content uniformity of drug

The content uniformity of drug in drug-loaded gels was analyzed using spectrophotometry, and the results are shown in Table 7. The content of propranolol hydrochloride and salicylic acid in these gels were varied from 80 – 120 percent.

Table 7 Percentage of label amount of propranolol HCl and salicylic acid in gel preparations (n = 3)

Formula	Name	% Label amount	S.D.
1	0.2 P 4 Ap	113.00	2.77
2	0.2 P 6 Ap	119.24	4.08
3	0.2 P 8 Ap	114.41	5.09
4	0.2 P10 Ap	103.83	5.85
5	0.2 P 4 Rp	112.04	4.41
6	0.2 P 6 Rp	113.32	1.19
7	0.2 P 8 Rp	112.36	7.40
8	0.2 P 10 Rp	118.39	0.99
9	0.2 P 4 Am	93.22	7.86
10	0.2 P 6 Am	94.92	7.30
11	0.2 P 7 Am	108.21	6.79
12	0.2 P 8 Am	98.32	2.85
13	0.2 P 4 Rm	88.21	7.60
14	0.2 P 6 Rm	89.03	6.35
15	0.2 P 8 Rm	85.62	3.61
16	0.4 P 8 Ap	90.74	2.00

Table 7 (continued)

Formula	Name	% Label amount	S.D.
17	0.6 P 8 Ap	94.70	4.45
18	0.8 P 8 Ap	98.47	9.57
19	1.0 P 8 Ap	88.59	6.03
20	4.0 P 8 Ap	101.51	7.61
21	0.4 P 6 Rp	94.62	4.43
22	0.6 P 6 Rp	99.43	6.91
23	4.0 P 6 Rp	106.80	3.46
24	0.2 S 4 Ap	99.80	0.54
25	0.2 S 6 Ap	97.73	0.77
26	0.2 S 8 Ap	100.18	0.24
27	0.2 S10 Ap	102.07	1.24
28	0.2 S 4 Rp	92.28	0.96
29	0.2 S 6 Rp	97.39	11.55
30	0.2 S 8 Rp	103.07	0.60
31	0.2 S 10 Rp	103.68	1.63
32	0.2 S 4 Am	86.05	2.76
33	0.2 S 6 Am	85.50	5.50
34	0.2 S 7 Am	103.70	2.64
35	0.2 S 8 Am	102.41	6.28
36	0.2 S 4 Rm	91.04	3.10
37	0.2 S 6 Rm	89.55	6.66
38	0.2 S 7 Rm	91.56	3.86
39	0.2 S 8 Rm	87.80	6.88
40	0.4 S 8 Ap	84.73	1.99
41	0.6 S 8 Ap	102.71	13.71
42	0.8 S 8 Ap	92.25	5.53
43	1.0 S 8 Ap	86.56	2.78
44	4.0 S 8 Ap	91.44	2.73
45	15 S 8 Ap	88.24	2.26
46	30 S 8 Ap	99.11	9.47

Table 7 (continued)

Formula	Name	% Label amount	S.D.
47	0.4 S 8 Rp	89.48	4.56
48	0.6 S 8 Rp	89.95	2.29
49	0.8 S 8 Rp	103.62	20.70
50	1.0 S 8 Rp	88.07	1.85
51	4.0 S 8 Rp	90.34	0.33
52	15 S 8 Rp	84.70	4.12
53	30 S 8 Rp	90.65	3.08
54	0.4 S 6 Am	90.58	5.84
55	0.6 S 6 Am	96.53	3.01
56	0.8 S 6 Am	97.86	15.69
57	1.0 S 6 Am	94.13	15.24
58	0.4 S 6 Rm	82.98	0.52
59	0.6 S 6 Rm	101.82	12.17
60	0.8 S 6 Rm	92.25	6.06
61	1.0 S 6 Rm	90.74	6.69

5. Studies of drug release from gels

The cumulative amounts of drug release from the colloidal silicon dioxide gels were plotted as a function of square root of time. The plots were linear as present with correlation coefficient (r^2) as shown in Tables 8 and 9. The fluxes were calculated from the slope of the linear region of the release profile between the cumulative amount ($\mu g/cm^2$) and square root of time ($h^{1/2}$) (Wang et al. 2001 : 89 – 104 ; Kim and Shin 2004 : 23 - 27). The X-intercepts were described as lag time. The percentage of cumulative release of propranolol HCl and salicylic acid into both types of receptor medium was shown in Tables 16 – 19 (Appendix V). Tables 8 and 9 exhibited the drug release from most formulations appearing to fit the Higuchi's

equation (Higuchi 1962 : 802 – 804). However, the release of formulations 9, 13 – 15, 21, 23, 40, 41, 44 – 47, 53 – 57 into PEG 400 receptor medium seem to be according to other kinetics ($r^2 < 0.99$).

5.1 Effect of the type of colloidal silicon dioxide on the drug release

The release of propranolol HCl from PEG gel containing Aerosil 200 was significant difference than that from PEG gel containing Aerosil R 972 (Table 20, Appendix VI). In Figure 11 (a), the release of propranolol HCl from the hydrophilic colloidal silicon dioxide (Aerosil 200) gel (using PEG 400 as dispersing medium) was higher than that of hydrophobic colloidal silicon dioxide (Aerosil R 972) gel. The release of salicylic acid from PEG and mineral oil bases showed the similar result as shown in Table 17 (Appendix V). There was no propranolol HCl released from mineral oil gel containing Aerosil R 972 into aqueous receptor medium (Figure 11 (b)). Table 8 shows the fluxes and lag times of the formulations consisting of Aerosil 200 and Aerosil R 972. It is seen that the fluxes of the formulations 3, 26 and 33 was higher than that of the formulations 7, 30 and 37.

5.2 Effect of amount of the colloidal silicon dioxide on the drug release

The effect of amount of Aerosil 200 and Aerosil R 972 on drug released from gels was investigated. The data showed that an increase of the concentration of both types of Aerosil from 4 – 10% (w/w) tended to decrease the cumulative amount of drug released after 3 h. In Figure 12, the cumulative release of salicylic acid at 3 h decreased from 30.77 to 24.29 ($\mu g/cm^2$) when the concentration of Aerosil 200 was increased from 4 to 10%. The significant difference between fluxes

of the formulations 9 – 12 and 32 – 35 was found. In propranolol gel (formulations 9 - 12 and 32 – 35), the fluxes decreases from 36.39 ± 1.55 to 12.37 ± 2.67 and from 38.28 ± 1.89 to 25.48 ± 4.75 µg/ cm^2/ $h^{½}$, respectively (Table 8).

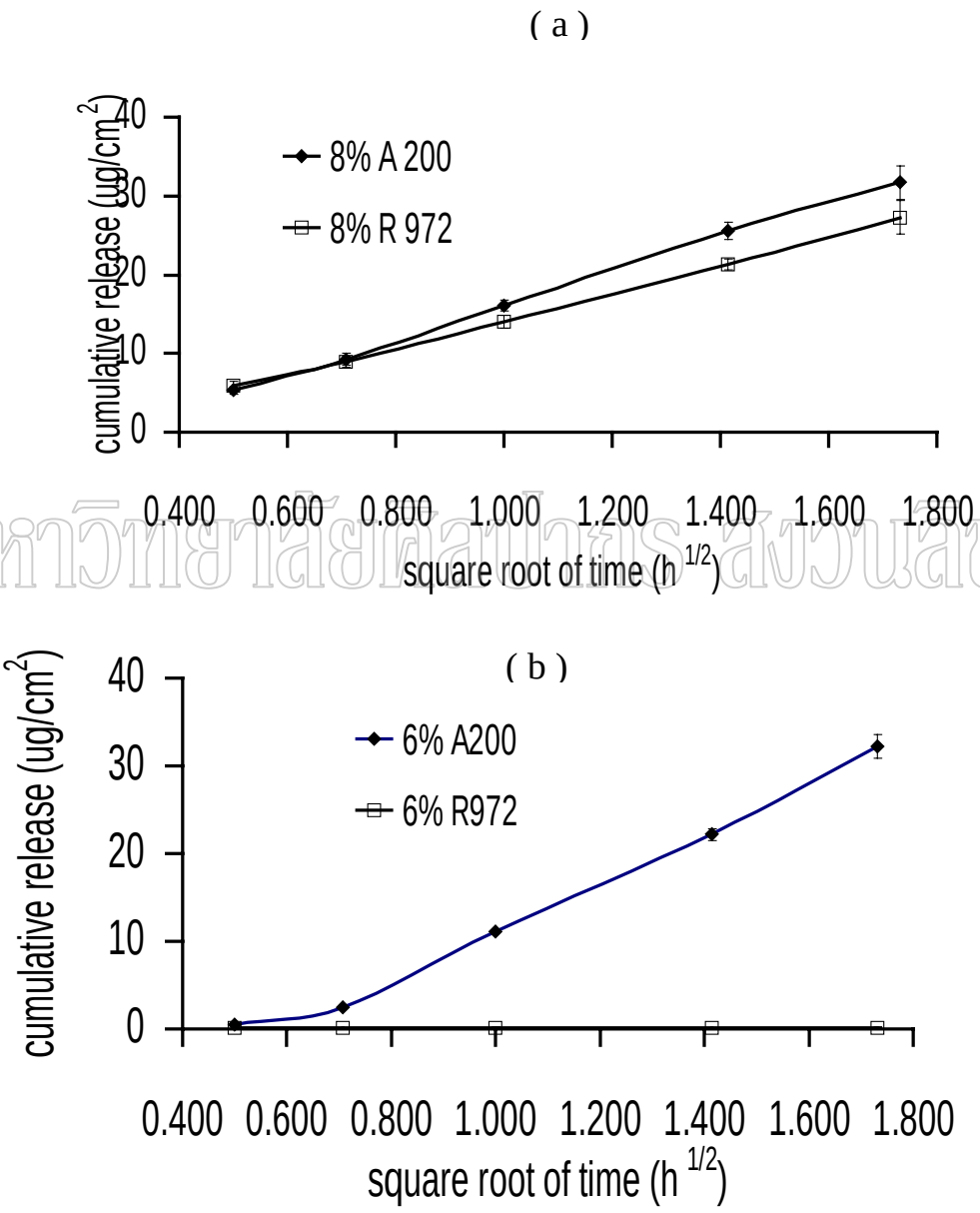


Figure 11 Effect of the types of Aerosil on the release of 0.2% propranolol HCL in Aerosil gel (a) PEG gel base, (b) mineral oil gel base

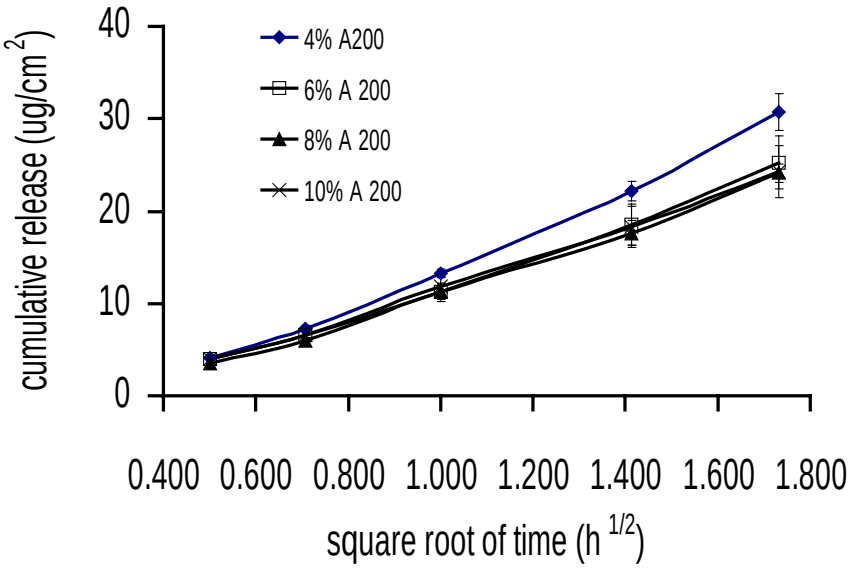


Figure 12 Effect of the Aerosil concentration on the release of 0.2% salicylic acid in PEG gel containing Aerosil 200

5.3 Effect of the type of dispersing medium on a drug release

The effect of the hydrophilic and hydrophobic gel bases on drug release into aqueous receptor medium is shown in Figure 13. Figure 13 (a) showed that the release of propranolol HCl from PEG base was higher than that from mineral oil, and vice versa in case of salicylic acid (Figure 13 (b)). The flux of propranolol HCl from PEG gel base (formulation 3) was higher than that from mineral oil gel base (formulation 12) (Table 8). In contrary, the flux of salicylic acid from PEG gel base (formulation 26) was significantly lower than that from mineral oil gel base (formuation 35).

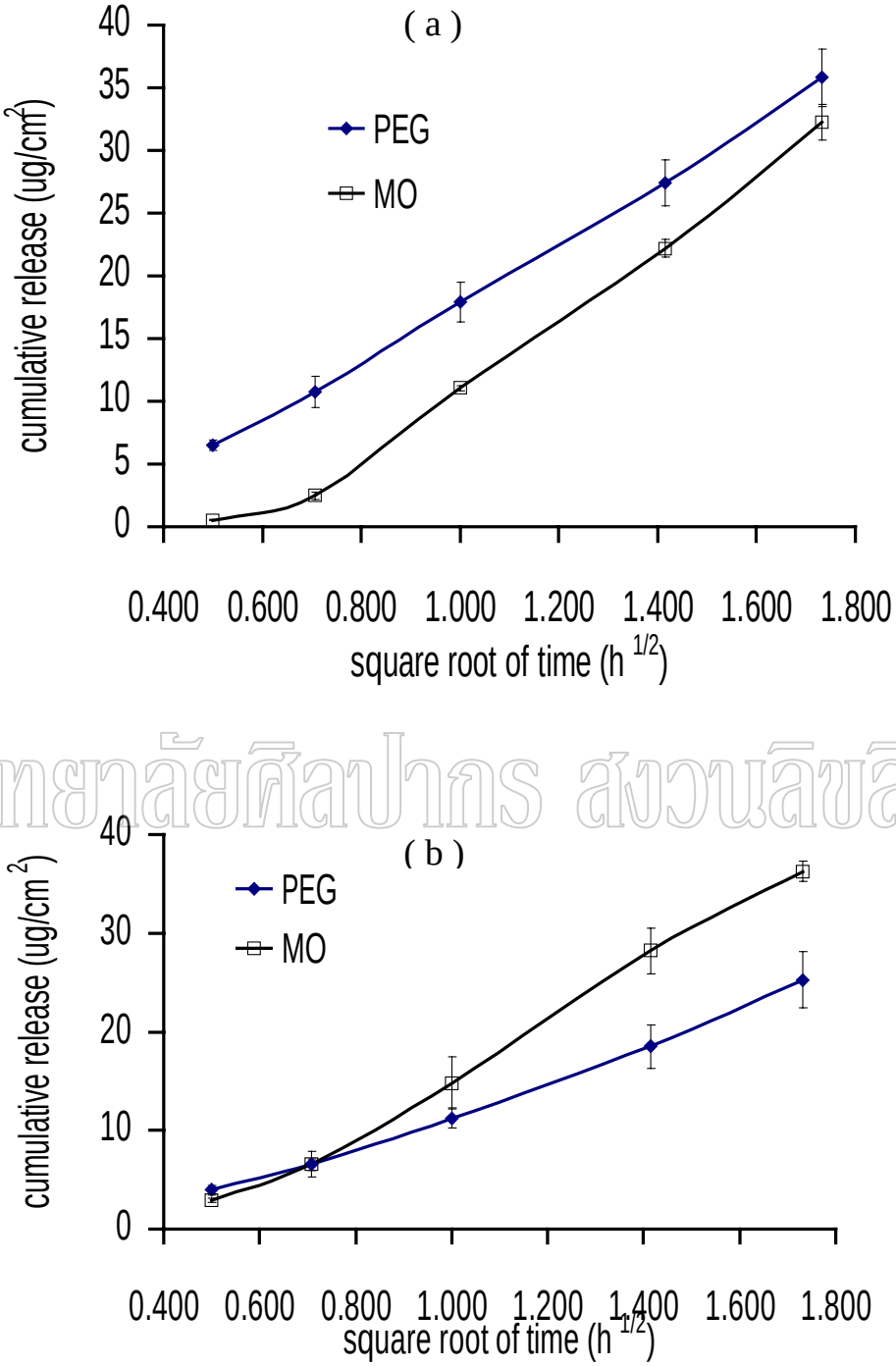


Figure 13 Effect of the type of gel base on the release of 0.2% drug in 8% Aerosil 200 gel (a) propranolol HCl, (b) salicylic acid

5.4 Effect of the type of drug-loaded on the drug release

In PEG base, the release of propranolol HCl into aqueous medium was significantly higher than that of salicylic acid, whereas, in mineral oil base, the release of salicylic acid into aqueous medium was higher than that of propranolol HCl (Figure 14 (a) and (b)). The fluxes of propranolol HCl and salicylic acid releasing from PEG base were 21.83 $\pm$ 1.22 and 16.75 $\pm$ 0.94 µg/ cm^2/ $h^{½}$, respectively (formulations 3 and 26, Table 8). From mineral oil gel base, The fluxes of propranolol HCl and salicylic acid releasing were 26.46 $\pm$ 0.92 and 28.06 $\pm$ 0.67 µg/ cm^2/ $h^{½}$, respectively (formulations 10 and 33, Table 8).

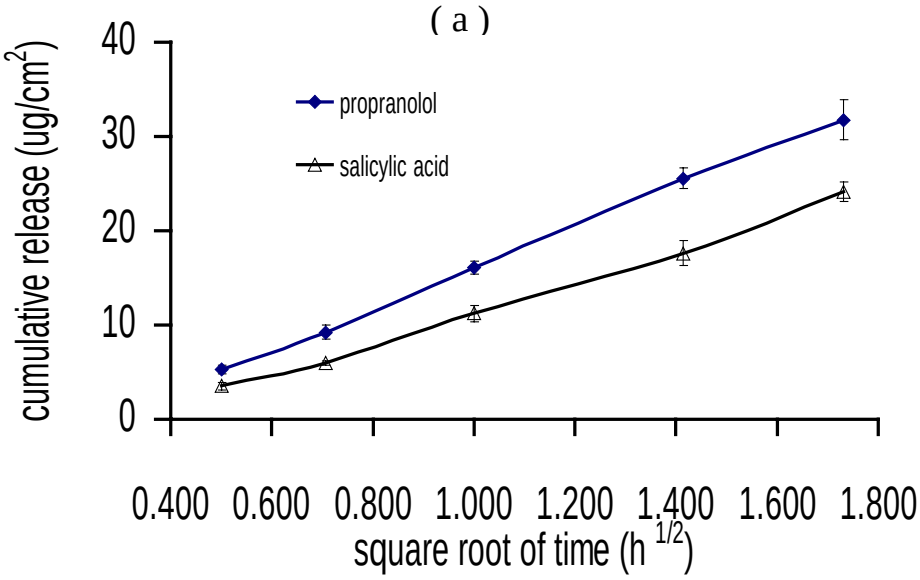
5.5 Effect of the receptor medium on the drug release

The system containing Aerosil R 972 in mineral oil showed an absence of propranolol HCl released into aqueous receptor medium (Figure 11 (b)). Therefore, PEG 400 was used alternatively as receptor medium in this study. The effect of receptor solution on drug release is shown in Figure 15. In aqueous receptor medium, the release of propranolol HCl was higher than that of salicylic acid (Figure 15 (a)), and vice versa in PEG 400 receptor medium (Figure 15 (b)). In PEG 400 receptor medium, the lag times from release profiles presented the longer duration compared with that in aqueous medium. The lag times of formulation 9 in aqueous medium and PEG medium were 0.22 $\pm$ 0.02 and 5.80 $\pm$ 0.17 h, respectively. The fluxes from aqueous medium were significantly higher than that from PEG 400. In aqueous medium, the fluxes of propranolol HCl and salicylic acid were 21.83 $\pm$ 1.22 (formulation 3) and 16.75 $\pm$ 0.94 µg/ cm^2/ $h^{½}$, respectively (formulation 26).

Whereas, the fluxes of these formulations from PEG 400 receptor medium were 4.32 $\pm$ 0.05 and 6.81 $\pm$ 0.28 µg/ cm^2/ $h^{½}$, respectively.

5.6 Effect of the drug loading on the drug release

The effect of the drug loading on the drug release from the gel was studied. The concentration of propranolol HCl and salicylic acid was 0.2 – 4.0% (w/w) and 0.2 – 30.0% (w/w), respectively. The receptor medium used was PEG 400. The data showed that the release of drug in all cases significantly increased as the initial drug loading in the bases increased. The fluxes of 0.2 – 4.0% propranolol HCl gels (formulations 7, 21 – 23) were 5.30 $\pm$ 0.17 to 120.57 $\pm$ 6.73 µg/ cm^2/ $h^{½}$ (Table 9). The fluxes of 0.2 – 30% salicylic acid gels using Aerosil 200 and Aerosil R 972 as gelling agents (formulations 26, 40 – 46 and 30, 47 - 53) were 6.81 $\pm$ 0.28 to 1,168.71 $\pm$ 391.12 and 6.11 $\pm$ 1.46 to 964.84 $\pm$ 279.33 µg/ cm^2/ $h^{½}$, respectively. Figures 16 and 38 show the increase of propranolol HCl and salicylic acid released from various systems, respectively. The plot of drug flux (µg/cm^2/$h^{1/2}$) versus the percentage of drug concentration showed a good linearity for 0.2 – 4.0% propranolol HCl in 8% Aerosil R 972 gel PEG, 0.2 – 30% salicylic acid in 8% Aerosil 200 and Aerosil R 972 gel PEG (R squared of 0.9989, 0.9984 and 0.9859, respectively (Figure 18).



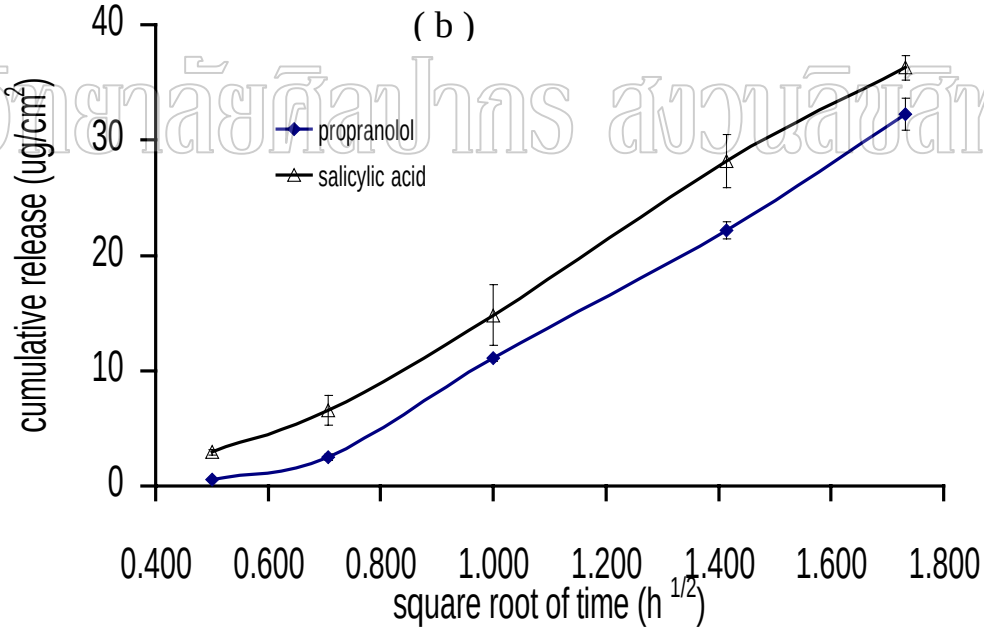


Figure 14 Effect of the types of drug-loaded on the release of 0.2% drug in 8% Aerosil 200 gel (a) PEG base, (b) mineral oil base

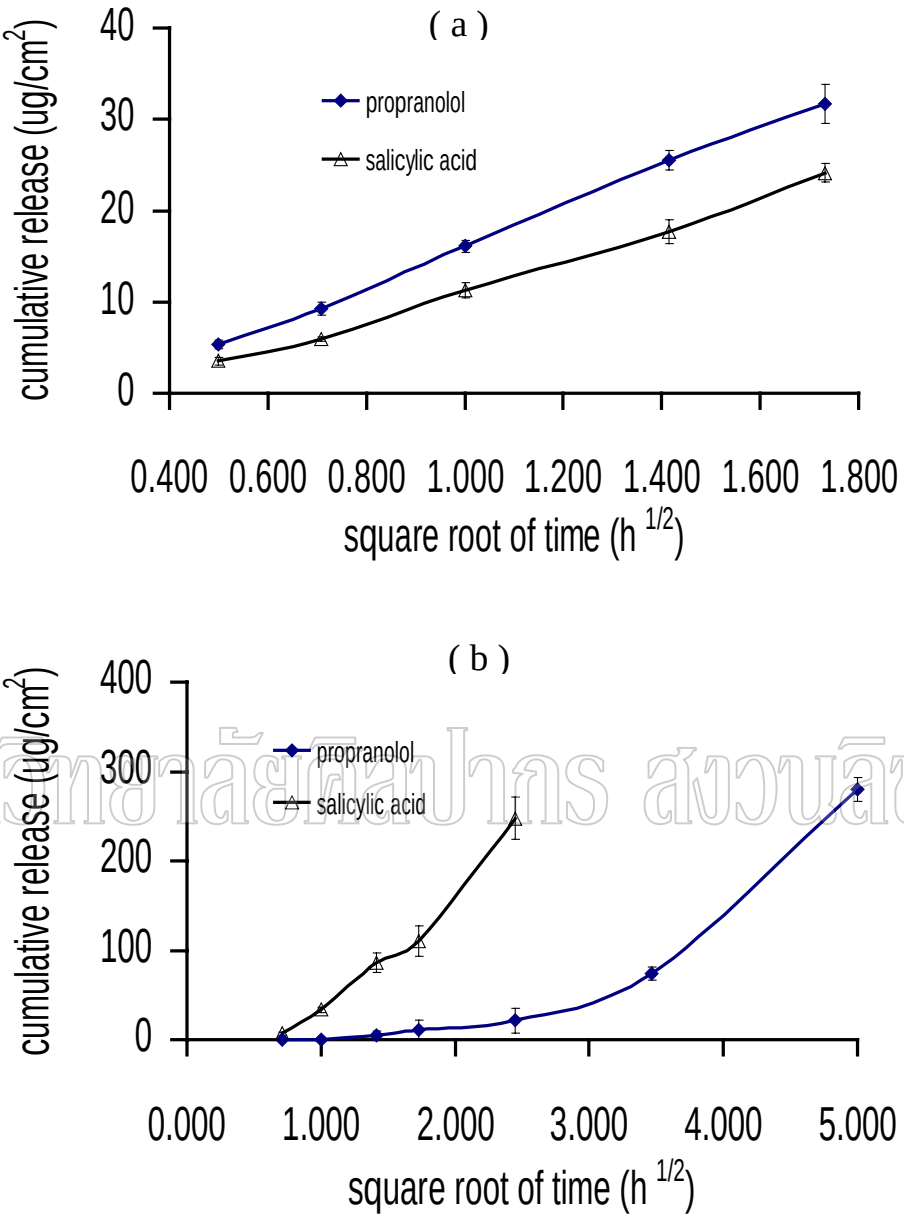


Figure 15 Effect of the receptor medium on the release of drug from PEG gel containing 8% Aerosil 200 into (a) aqueous medium, (b) PEG 400 medium

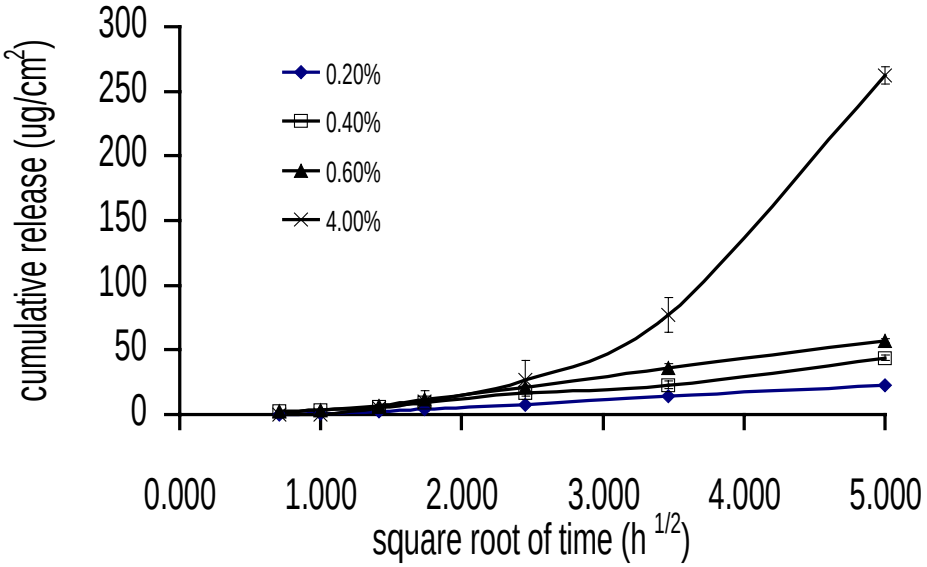


Figure 16 Effect of the drug loading dose on the release of propranolol HCl from PEG gel containing 8% Aerosil R 972

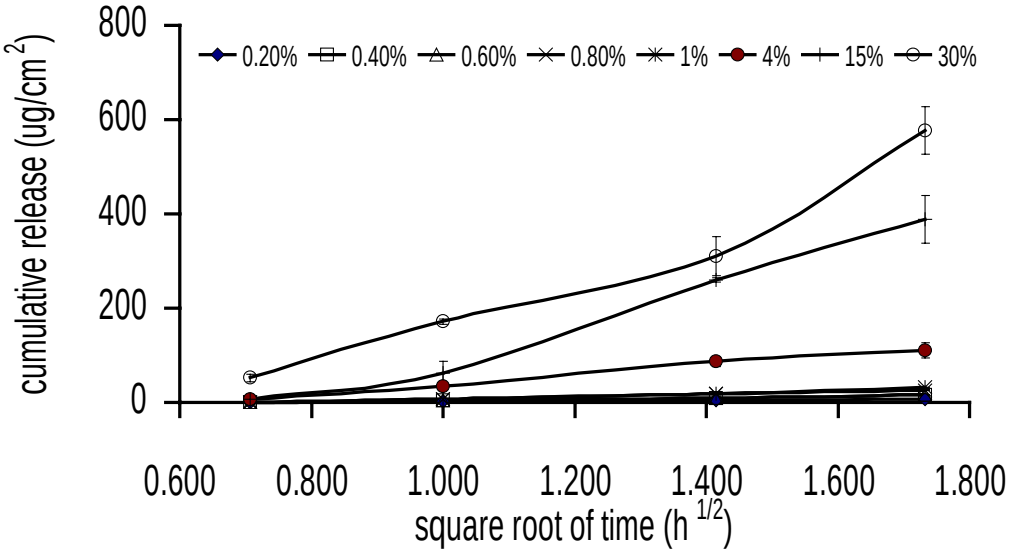


Figure 17 Effect of the drug loading dose on the release of salicylic acid from PEG gel containing 8% Aerosil 200

Table 8 Correlation coefficient, average flux and lag time of drug release from gels into aqueous medium (n = 3)

Formula	Name	Correlation coefficient (r^2)	flux (μg/cm^2/h $^{1/2}$)		lag time (h)	
			mean	S.D.	mean	S.D.
1	0.2 P 4 Ap	0.9987	21.84	0.62	0.04	0.04
2	0.2 P 6 Ap	0.9995	23.78	1.44	0.06	0.00
3	0.2 P 8 Ap	0.9995	21.83	1.22	0.07	0.00
4	0.2 P10 Ap	0.9985	20.44	1.09	0.05	0.02
5	0.2 P 4 Rp	0.9993	19.80	0.67	0.03	0.01
6	0.2 P 6 Rp	0.9997	17.47	0.95	0.03	0.02
7	0.2 P 8 Rp	0.9995	17.43	1.45	0.04	0.02
8	0.2 P 10 Rp	0.9996	16.82	0.85	0.02	0.10
9	0.2 P 4 Am	0.9923	36.39	1.55	0.22	0.02
10	0.2 P 6 Am	0.9942	26.46	0.92	0.31	0.00
11	0.2 P 7 Am	0.9935	13.61	3.08	0.09	0.09
12	0.2 P 8 Am	0.9930	12.37	2.67	0.08	0.08
16	0.4 P 8 Ap	0.9985	48.33	0.82	0.08	0.01
17	0.6 P 8 Ap	0.9998	65.36	1.95	0.05	0.01
18	0.8 P 8 Ap	0.9992	96.82	12.81	0.08	0.02
19	1.0 P 8 Ap	0.9979	123.18	1.80	0.06	0.01
24	0.2 S 4 Ap	0.9967	21.61	1.75	0.12	0.03
25	0.2 S 6 Ap	0.9970	17.34	2.04	0.10	0.01
26	0.2 S 8 Ap	0.9979	16.75	0.94	0.10	0.01
27	0.2 S10 Ap	0.9989	16.55	2.28	0.08	0.02
28	0.2 S 4 Rp	0.9967	17.17	1.73	0.05	0.02
29	0.2 S 6 Rp	0.9973	17.09	1.75	0.09	0.01
30	0.2 S 8 Rp	0.9957	15.26	0.62	0.08	0.01
31	0.2 S 10 Rp	0.9984	13.56	0.18	0.06	0.00
32	0.2 S 4 Am	0.9945	38.28	1.89	0.31	0.13
33	0.2 S 6 Am	0.9976	28.06	0.67	0.19	0.03
34	0.2 S 7 Am	0.9981	26.81	1.31	0.13	0.01

Table 8 (continued)

Formula	Name	Correlation coefficient (r^2)	flux (µg/cm^2/h $^{1/2}$)		lag time (h)	
			mean	S.D.	mean	S.D.
35	0.2 S 8 Am	0.9965	25.48	4.75	0.19	0.16
36	0.2 S 4 Rm	0.9927	16.62	1.18	0.07	0.01
37	0.2 S 6 Rm	0.9971	18.07	0.94	0.05	0.01
38	0.2 S 7 Rm	0.9977	13.08	1.86	0.01	0.02
39	0.2 S 8 Rm	0.9968	13.60	0.74	0.03	0.02
40	0.4 S 8 Ap	0.9917	42.99	0.11	0.21	0.01
41	0.6 S 8 Ap	0.9962	47.60	5.27	0.18	0.02
42	0.8 S 8 Ap	0.9967	65.02	6.46	0.21	0.03
43	1.0 S 8 Ap	0.9957	66.88	11.47	0.17	0.05

Table 9 Correlation coefficient, average flux and lag time of drug release from gels into PEG 400 medium (n = 3)

Formula	Name	Correlation coefficient (r^2)	flux (µg/cm^2/h $^{1/2}$)		lag time (h)	
			mean	S.D.	mean	S.D.
9	0.2 P 6 Am	0.9047	1.44	0.41	5.80	0.17
13	0.2 P 4 Rm	0.9887	5.55	0.83	1.90	0.69
14	0.2 P 6 Rm	0.9809	5.37	0.59	2.01	0.51
15	0.2 P 8 Rm	0.9781	4.92	0.43	2.18	0.33
3	0.2 P 8 Ap	0.9939	4.32	0.05	0.92	0.04
7	0.2 P 8 Rp	0.9954	5.30	0.17	0.72	0.07
21	0.4 P 8 Rp	0.9897	9.58	0.68	0.50	0.06
22	0.6 P 8 Rp	0.9969	13.22	0.59	0.58	0.02
23	4.0 P 8 Rp	0.9250	120.57	6.73	7.97	0.83

Table 9 (continued)

Formula	Name	Correlation coefficient (r^2)	flux (µg/cm^2/h $^{1/2}$)		lag time (h)	
			mean	S.D.	mean	S.D.
26	0.2 S 8 Ap	0.9965	6.81	0.28	0.59	0.04
40	0.4 S 8 Ap	0.9823	25.19	0.93	1.16	0.11
41	0.6 S 8 Ap	0.9802	25.63	0.95	1.14	0.08
42	0.8 S 8 Ap	0.9964	29.15	0.97	0.57	0.03
43	1.0 S 8 Ap	0.9957	33.38	3.04	0.58	0.01
44	4.0 S 8 Ap	0.9858	113.58	13.29	0.45	0.01
45	15 S 8 Ap	0.9831	560.37	173.01	0.99	0.19
46	30 S 8 Ap	0.9591	1,168.71	391.12	1.34	0.34
30	0.2 S 8 Rp	0.9923	6.11	1.46	1.88	1.72
47	0.4 S 8 Rp	0.9899	15.65	1.95	1.00	0.05
48	0.6 S 8 Rp	0.9958	18.27	0.43	0.60	0.03
49	0.8 S 8 Rp	0.9949	27.26	3.92	0.60	0.09
50	1.0 S 8 Rp	0.9916	36.63	4.03	0.91	0.18
51	4.0 S 8 Rp	0.9976	100.30	1.85	0.45	0.08
52	15 S 8 Rp	0.9926	603.68	78.04	0.88	0.21
53	30 S 8 Rp	0.9727	964.84	279.33	1.15	0.39
54	0.4 S 6 Am	0.9082	6.85	1.09	6.17	0.37
55	0.6 S 6 Am	0.9226	6.63	2.23	5.50	2.39
56	0.8 S 6 Am	0.9468	14.51	2.08	4.65	1.00
57	1.0 S 6 Am	0.9753	11.81	3.12	3.39	1.26
58	0.4 S 6 Rm	0.9926	19.40	0.43	0.63	0.01
59	0.6 S 6 Rm	0.9942	33.85	7.35	0.83	0.29
60	0.8 S 6 Rm	0.9946	38.59	2.54	0.54	0.03
61	1.0 S 6 Rm	0.9969	45.72	4.69	0.54	0.07

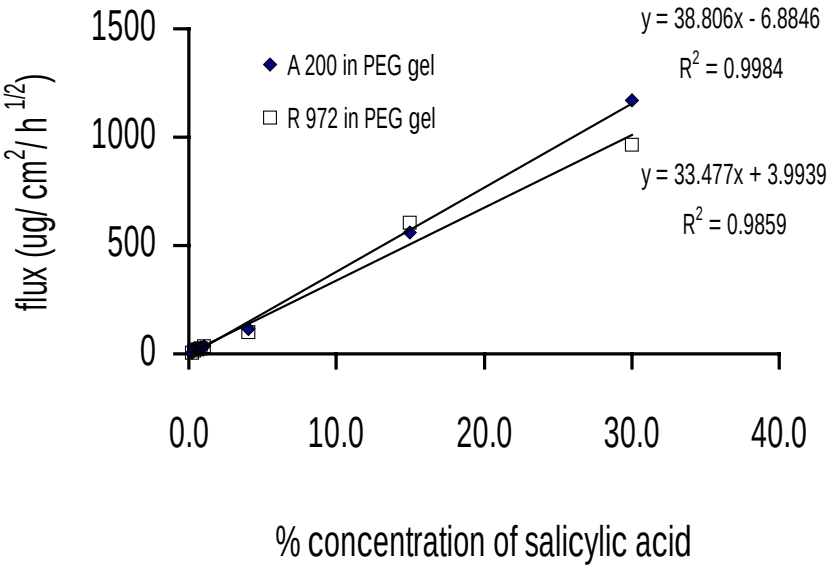


Figure 18 Correlation between flux and drug concentration

6. Determination for the solubility of drugs in receptor solutions

The solubility of the drugs in several receptor solutions at 37 ºC is listed in Table 10. The rank order of solubility of propranolol HCl in receptor solutions was water> PEG 400> mineral oil, where those of salicylic acid was PEG 400> water> mineral oil.

Table 10 Solubility of propranolol HCl and salicylic acid at 37 ºC (mg/ ml)

Dispersing media	Propranolol HCl	Salicylic acid
Water	7.00 ± 0.04	2.98 ± 0.04
PEG 400	0.04 ± 0.00	22.67 ± 0.08
Mineral oil	Insoluble	0.39 ± 0.01

7. Data evaluation

Effect of the type of colloidal silicon dioxide, the amount of colloidal silicon dioxide, the type of dispersing medium, the type of drug loaded, the type of receptor medium and the amount of drug loading on drug release was evaluated. The significance of the differences between groups ($p < 0.05$) was tested using ANOVA and *t* test. The significance result was shown in Tables 20 and 21 (Appendix VI). The effect of the type of colloidal silicon dioxide on the drug released was considered to be significantly different between pair of propranolol HCl gel (formulations 0.2 P 8 Ap and 0.2 P 8 Rp). The effect of the amount of colloidal silicon dioxide on the drug released was insignificantly different. The effect of the type of dispersing medium on the drug released was considered to be significantly different between pair of salicylic acid gel (formulations 0.2 S 6 Ap and 0.2 S 6 Am). The effect of the type of drug loaded on the drug released was considered to be significantly different between pair of formulations 0.2 P 8 Ap and 0.2 S 8 Ap. The effect of type of receptor medium on the drug released from the formulations 0.2 P 8 Ap and 0.2 S 8 Ap was considered to be significantly different, whereas the effect of drug loading on the drug released from all formulations, except pairs of formulations 40–41, 42–43, 45-46 and 52–53, was found to be significantly different.

CHAPTER V

DISCUSSION

In this study, all of the systems showed the increase of the viscosity after the incorporation with colloidal silicon dioxide. The pH of the systems was lower than that of initial dispersing media because of the acid property of colloidal silicon dioxide (Degussa 2002). The pH measurement of hydrophobic dispersing media was not investigated. Because pH is a measure of the concentration of hydrogen ion which should be measured only in aqueous solution since there are no suitable reference materials for calibrating a pH meter in non-aqueous systems or hydrophobic dispersing media. Some liquids i.e. PEG 400, PEG 600, light mineral oil, castor oil, isopropyl myristate and Luvitol EHO® could be converted into gels using 5 – 8% by weight of Aerosil 200, whereas water, glycerin, sorbitol and PG only showed the viscosity enhancement. The silanol groups on the surface of different particles of Aerosil 200 could interact via hydrogen bond with each other to form connecting bridges (Sherriff and Enever 1979 : 842 – 845 ; Degussa 2001, 2002 ; Allen 2002). A thickening effect was found after three-dimensional structure was developed (Degussa 2001, 2002). At a suitable amount of colloidal silicon dioxide, the three-dimensional network led to the immobilization of a dispersing medium and the gel formation (Sherriff and Enever 1979 : 842 – 845 ; Degussa 2001, 2002 ; Allen 2002). This phenomenon typically occurred when there was a mismatch between the chemical nature of the particle surface and that of the liquid. Thus, if the particle surfaces were rendered polar (silanol group), and the dispersion medium was nonpolar, there would

be a tendency for the polar surfaces to associate to form connecting bridge (Raghavan et al. 2000 : 1066 - 1077). From Table 11, the dispersing media could be classified into high polarity (i.e. water, sorbitol and glycerin), rather high polarity (PG), and low polarity (i.e. PEG 400, castor oil and mineral oil).

Table 11 The dielectric constant value of the dispersing media (data from Merck index)

Dispersing media	Dielectric constant
Water	78.5
Sorbitol	62
Glycerin	42.5
PG	32.1
PEG 400	12.4
PEG 600	N/A*
Isopropyl myristate	N/A
Castor oil	4.5
Mineral oil	2.1
Luvitol EHO®	N/A

*N/A = not available

The dispersing media having high and rather high polarity are composed of an excess of hydroxyl groups. Therefore, the probability of silanol-hydroxyl interactions was higher than that of silanol-silanol interactions. This fact accounted for the much weaker network structure exhibited by these systems when compared

with the low polar dispersing media as described by Sherriff and Enever (1979 : 842 - 845).

Aerosil R 972 could convert only light mineral oil and Luvitol EHO® into gels, while it could not convert high polar dispersing media i.e. water, sorbitol, glycerin and PG into gels. Aerosil R 972 is the hydrophobic type of colloidal silicon dioxide. The silanol groups on the surface of Aerosil R 972 were chemically modified with dimethyldichlorosilane (Degussa 2001). Therefore, it is hydrophobic and hard to be wet with high polar dispersing media i.e. water, sorbitol and glycerin. Generally, the non polar surfaces of Aerosil R 972 might have a tendency to form connecting bridges in polar dispersing medias, but the failure in gel formation was found in rather high polar dispersing media such as PG, which could be incorporated with Aerosil R 972. Both nonpolar (dimethyldichloro) and polar (residual silanol) components on Aerosil R 972 surface can exhibit either polar or nonpolar characteristics. Depending on the extent of mismatch between particle surface and liquid, the nonpolar dimethyldichloro groups would tend to cluster together in highly polar dispersing media (Raghavan et al. 2000 : 1066 - 1077). On the other hand, the polar silanol would tend to associate in nonpolar dispersing media. In this study, light mineral oil and Luvitol EHO® might have some suitable properties which could be converted into gel with Aerosil R 972. However, the behavior of Aerosil R 972 was considerably more complicated and must be further studied.

The goal of this study was to prepare the transparent gel with colloidal silicon dioxide. Therefore, the dispersing media providing only an increase of viscosity, low consistency and low clarity after incorporation with colloidal silicon dioxide i.e. water, sorbitol, glycerin, polyethylene glycol, isopropyl myristate and

Luvitol EHO® were excluded. In this study, the clarity of the colloidal silicon dioxide gel was influenced by two factors: viscosity and refractive index of dispersing medium. Firstly, at low concentration of colloidal silicon dioxide, the viscosity of the dispersing system was not enough to suspend the Aerosil particles. The relationship between velocity of the particle and the relative viscosity of colloidal system was previously reported by Mills, Rubi and Quemada (1980 : 639 - 643). At low viscosity, the velocity of the moving colloidal silicon dioxide particles in the system were higher than that at high viscosity; thus the particles tended to accumulate and aggregate in a large mass and related to the turbidity of the system or precipitate. Secondly, it was the mismatch of refractive index of dispersing media and colloidal silicon dioxide. The different of refractive index between Aerosil and dispersing media is shown in Table 12. This phenomenon could change the transparent property of dispersing media by alteration optical density and change the light transmission (Sun, Erickson and Parr 2003 : 65 - 74). Thus, the systems prepared with the dispersing fluid i.e. water, PG, isopropyl myristate and Luvitol EHO® were turbid.

From temperature change testing, pH and viscosity of the prepared gels had very little change. Therefore, gel preparation from both gelling agents had good stability under temperature cycling change. In addition, colloidal silicon dioxide is formed at temperature about 1,800 ºC leading to high temperature stability (Degussa 2002). The little change of pH and viscosity of dispersing media without incorporating Aerosil were also found (Tables 7 and 8). This might be due to an individual property of the dispersing media.

Table 12 The refractive index value of the dispersing medium

Dispersing medium	Refractive index (RI)	$RI_{dispersing\ medium} - RI_{Aerosil}$
Water	1.333 ± 0.001	**- 0.127**
Sorbitol	1.462 ± 0.001	0.002
Glycerin	1.469 ± 0.000	0.009
PG	1.418 ± 0.001	**- 0.042**
PEG 400	1.461 ± 0.001	0.001
PEG 600	1.467 ± 0.000	0.007
Castor oil	1.473 ± 0.000	0.013
Mineral oil	1.456 ± 0.000	- 0.004
IPM	1.433 ± 0.000	**- 0.027**
Luvitol	1.445 ± 0.001	**- 0.015**

Effect of the polarity of the dispersing media on the colloidal silicon dioxide gel formation

Aerosil 200 could not convert the highly polar dispersing media having the dielectric constant value more than 32.1 into gel and vice versa in case of the dispersing media having the dielectric constant lower than 12.4. Hence, the conversion of the dispersing media into gel with this gelling agent could be predicted by the polarity of the media. In this study, the decrease of polarity of the highly polar dispersing media i.e. water, propylene glycol and glycerin by mixing with PEG 400 could increase the viscosity of the system after incorporation of Aerosil 200. Because the binary system lowered the polarity of the dispersing medium leading to the decrease in the interference of H- bonding between colloidal silicon dioxide particles.

In case of glycerin, the contrary result was obtained after the dielectric constant was higher than 24 (Figure 6) which was mainly due to the high viscosity of this dispersing media. The effect of the viscosity will be discussed in the next section. The addition of Aerosil R 972 into dispersing medium with higher dielectric constant provided higher viscosity of the system because of the mismatch of the polarity between particles and dispersing media.

Effect of the viscosity of the dispersing media on the colloidal silicon dioxide gel formation

The viscosity of PEG-PG and PEG-water systems decreased as the dielectric constant increased because of an increased of amount of low viscosity dispersing media i.e. PG and water (Appendix III). In contrary, the viscosity of PEG-glycerin system increased as the dielectric constant increase because the amount of viscous glycerin increased. The viscosity of all systems at the same dielectric constant was particularly different. The viscosity of PEG 400–glycerin system before and after incorporated with both types of Aerosil was higher than the others. This evidence could be explained that the initial viscosity of PEG 400–glycerin system might prolong the duration of particle dispersion leading to complete connecting-bridge formation. Tetreault (2003) also reported that the loading percentage of Aerosil for desired thickening effect was dependent on the initial viscosity condition of the system. Thus, the viscosity of the media was one of the main factors influencing the gel-forming properties.

Effect of the refractive index of the dispersing media on the gel clarity of the systems

Equation 3 indicated that the reduction in refractive index of mixture corresponded to an increased of amount of dispersing media which have low refractive index value. As the dielectric constant of the system increased, the system exhibited the decrease of refractive index because of an increased amount of low dielectric constant dispersing media i. e. water and PG (Figure 8). Particularly, PEG 400–PG and PEG 400–water showed an obviously numeral difference of refractive index value between its system and both types of Aerosil as the increase of dielectric constant. Aerosil 200 and Aerosil R 972 have refractive index of 1.46. When the mixed media were incorporated with this gelling agent, the mixture became more turbid as the dielectric constant of the mixed media increased, except in the systems containing PEG–glycerin which have constant refractive index at all dielectric constant value (Figure 10). Thus, the turbidity was noticeably assessed by a variation of the refractive index value of dispersing medium and Aerosil.

Physical properties of the drug-loaded gel

The formulations containing the drug in mineral oil base were more turbid and coarse than that in PEG base. In this study, the drugs were dissolved by 95% ethanol of 2 ml before incorporated into gel because the drugs could not be solubilized in the base. The polarity and refractive index of incorporated ethanol might change the apparence of mineral oil gel causing low clarity and less homogeneity. When high amount of polar molecule, propranolol HCl, was dissolved in PEG 400, the system was increased in the polarity. The decrease in viscosity of the

formulation was found after incorporation with Aerosil 200 because the interference of H-bonding between Aerosil 200 particles increased as the polarity of the system was increased. The interference might not occur in Aerosil R 972 system. Therefore, the viscosity of this system increased as the amount of propranolol HCl increased. Salicylic acid was dissolved in PEG 400 and Aerosil 200 was incorporated into the drug mixture. The viscosity of the formulation decreased as the drug concentration increased to 1% w/w. Thereafter, the viscosity of the formulation increased as concentration of salicylic acid increased. Salicylic acid is the low polarity molecule and also capable to provide H-bond formation with other molecules. The silanol groups of Aerosil 200 were available for drug-particle interaction (Sherriff and Enaver 1979 : 842 – 845). The drug-silanol interaction was higher than silanol-silanol interaction. This fact accounted for the much weaker network structure exhibited by the decrease of viscosity. In further addition of salicylic acid, the number of silanol groups in the system might reach the saturation point that all silanol groups were involved in particle-particle or drug-particle interaction. Therefore, salicylic acid might reduce the polarity of the system led to increase of system viscosity after incorporation with Aerosil 200 and vice versa in case of Aerosil R 972.

The preliminary experiment revealed that the order of mixing used to prepare gel could influence gel viscosity. The viscosity of the formulation which the drug solution was incorporated after gel formation was higher than that of the drug was firstly mixed with dispersing media before incorporation with Aerosil. In mineral oil base, ethanol was used to dissolve the drug might influence the viscosity of the formulations

The content of both drugs in colloidal silicon dioxide gel was presented in wide range (80 – 120%). This might be due to the low content uniformity of drugs in the formulations, the adsorption of drugs on the surface of Aerosil 200 (Gallacher, Trottet and Puddephatt 2003 : 37 – 45) and the interference of Aerosil particles leaving in the filtrate. The test for content uniformity and multiple extraction of drug in the formulation might include in further study.

***In vitro* release of drug from colloidal silicon dioxide gel**

A simplified Higuchi diffusion equation (Higuchi 1962 : 802 – 804) for drug release from one side of a semisolid layer is described as follows:

$$Q = 2C_0 (Dt / ¶)^{½} \qquad \text{Equation 4}$$

Where Q is the cumulative amount of drug released per unit surface area. C_0 is the initial drug loading, D is the diffusion coefficient, t is the time after commencement of diffusion and ¶ is a constant.

According to the Higuchi theory, equation 4 is valid if (*a*) the percentage released is less than 30% of the total drug in the vehicle, (*b*) only a single drug species is present in the vehicle, (*c*) the diffusion coefficient is invariant with respect to time or position within the vehicle layer, (*d*) only the drug diffuses out of the vehicle, and (*e*) the drug reaching the receptor side is removed rapidly. The experimental conditions in the present study appeared to match the above assumptions favorably in most formulations. Some formulations did not exhibit a linear release profile into PEG 400 receptor medium because of the high viscosity of this medium.

The network formation within the gels led to the resistance of drug diffusion from gel matrix. This revealed that the rate-controlling step was the process of drug

diffusion through the gel matrix (Arellano et al. 1998 : 129 -135). Therefore, the cumulative release of the drug through the matrix was linear relationship with square root of time. The molecular weight cut–off of cellulose membrane was around 12,000 – 14,000, therefore; the channels in membrane allow the drug molecules to diffuse freely. Appendix IV shows that the membrane had negligible resistance to the diffusion of propranolol HCl and salicylic acid. Thus, the properties of the formulation might be the factor controlling the release of the drug (Guy and Hadgraft 1990 : R1 – R3). Some factors affecting drug release were investigated and described as followed:

Effect of the type of colloidal silicon dioxide on the drug release

The types of colloidal silicon dioxide (Aerosil 200 and Aerosil R 972) affected drugs released from gel. Aerosil R 972 could not convert PEG 400 into gel. The viscosity of Aerosil 200 gel was higher than that of Aerosil R 972 (11,946.67 and 1,025.33 cps, respectively). The release of drugs from Aerosil 200 gel was higher than that from Aerosil R 972. This implied that the resistance to the diffusion of a receptor medium through the gel matrix of hydrophilic Aerosil 200 was lower than that of hydrophobic Aerosil R 972. Generally, the greater the viscosity of the formulation, the lower the release (Chowdary and Kumar 1994 : 47 – 50 ; Tehrani and Mehramizi 2000 : 409 - 414). Therefore, the hydrophilicity of Aerosil particles might be a significant factor affecting the drug release.

Effect of the amount of colloidal silicon dioxide on the drug release

The fluxes had a trend to inversely relate with the amount of Aerosil. This might be attributed to the increase in the number of the networks formed at the higher amount of colloidal silicon dioxide. In addition, the higher Aerosil amount the shorter the inter-particle distance, leading to greater complexity of cross-links between neighboring particles and a greater number of networks per unit volume (Zhang et al. 2002 : 73 - 81). A more rigid structure caused the increase in the viscosity of vehicles and the decrease in the rate of drug release (Wang et al. 2001 : 89 – 104 ; Moore et al. 2000 : 191 - 202) because an incorporated drug might be difficult to diffuse through the networks.

Effect of the type of dispersing medium on the drug release

The fluxes of propranolol HCl from PEG base was higher than that from mineral oil base. The vehicles or bases used in the topically applied formulations can greatly influence the rate of drug release from a formulation (Guzmán et al. 1994 : 2041 - 2048). The release of drugs from the gels involved the absorption of water into the matrix and simultaneous desorption of drugs via diffusion, as expressed by Fick's law (Kim, Bae and Okano 1992 : 283 - 290). The hydrophilic property of PEG 400 could absorb aqueous receptor medium into its gel matrix better than mineral oil. Therefore, the absorption of water into the matrix would result in the transformation of the gel. After this point, the surface of the gel sometimes became irregular, causing an increase of drug released (Chawdary and Kumar 1996 : 47 – 50). However, the high absorption of water from skin into gel could not occur when the gel is applied. Thus, propranolol HCl was able to release from PEG base better than from mineral

oil. In addition, this might be due to propranolol HCl remaining inside the alcohol droplet, result in the drug was entrapped by mineral oil gel matrix. In case of salicylic acid, the lower release profile in PEG gel than mineral oil was found. It was probably due to a strong affinity of salicylic acid to PEG 400 (Al Khamis, David and Hadgraft 1987 : 111 - 118). Moreover, it was probable that the thermodynamic activities of drug in the two gel bases might be different (Takahashi et al. 2002 : 179 - 186). This indicated that the factor other than hydrophilic property of a gel base such as drug interaction with a gel base also affected the drug release.

Effect of the type of drug-loaded on the drug release

The release of propranolol HCl from PEG base was higher than that of salicylic acid. This was closely related to the solubility of the drug in both the donor and receptor phases. In this study, propranolol HCl was more soluble in the aqueous receptor solution than salicylic acid. On the other hand, salicylic acid was more soluble in PEG 400 (Table 10). Therefore, the release of propranolol HCl from PEG base was greater than the latter. This might impede the drug diffusion toward the external medium. Such a reduction in drug diffusivity might be resulted from the reduced thermodynamic activity of salicylic acid molecules which markedly solubilized in PEG 400. El-Khordagui (1991 : 25 - 32) found that the release of riboflavin was influenced by its solubility in sodium salicylate, which was used as gelling agent. Furthermore, such effects were profoundly influenced by possible interaction between drug and gelling agent such as Methocel (Bonina and Montenegro 1993 : 19 – 24) and chitosan (Knapczyk 1993 : 233 - 237). Colliodal silicon dioxide particles have a capacity to bind molecules of drug via H-bond (Sherriff and Enerver

1979 : 842 – 845 ; De Paula et al. 1998 : 235 - 241), leading to drug adsorption on its surfaces. When drug molecules had the ability to bind to the silanol group of Aerosil 200, there would be a competition for the binding sites between drug and Aerosil particles, leading to the more decrease of bulk viscosity (Sherriff and Enerver 1979 : 842 - 845). There was a decrement of the system viscosity of the PEG gel base, 0.2% propranolol HCl PEG gel base and salicylic acid PEG gel base (13,293.33 $\pm$ 6,497.27, 11,946.67 $\pm$ 922.89 and 4,013.33 $\pm$ 479.31 cps, respectively). These showed that Aerosil 200 had affinity to adsorb salicylic acid on its surface higher than propranolol HCl. The similar results were also observed in the case of Aerosil R 972. From the hydrophobic characteristic of Aerosil R 972, the drugs might be adsorbed by hydrophobic and electrostatic interactions. Thus, the adsorption of drug on the surface of colloidal silicon dioxide particles made the drug unavailable for release from the system. Gallagher, Trottet and Heard (2003 : 37 - 45) also reported that retardation of the drug release was primary due to the adsorption to colloidal silicon dioxide, rather than due to the change in a viscosity. In the case of mineral oil base, both drugs were found to be poorly soluble in mineral oil. The result showed that the release of salicylic acid was more than that of propranolol HCl. In addition, this might be explained by the molecular size of the drugs (Gallardo et al. 2001 : 33 - 40) The molecular weight of propranolol HCl and salicylic acid are 295.84 and 138.12, respectively (USP 25 2002 : 1474 – 1475, 1548 - 1549). Thus, in the mineral oil gel base, the smaller molecular size of salicylic acid would have a higher released due to high rate of the diffusion through the internal phase.

Effect of the receptor medium on the drug release

A more rapid release of propranolol HCl was observed when the release medium was aqueous solution. This result was related to a greater solubility of propranolol HCl in this medium and vice versa in the case of salicylic acid, which had high solubility in PEG base. From the result, propranolol HCl could not release freely from the hydrophobic gel system. This phenomenon might be due to the hydrophobicity of both Aerosil R 972 and mineral oil, leading to prevention of the diffusion of water into the gel matrix. Then the low polar dispersing media, PEG 400 was used alternately as a receptor medium. The hydrophilicity and low polarity properties of PEG 400 led to the miscibility with Aerosil R 972 and mineral oil. PEG 400 in various aqueous concentrations was widely used as receptor medium in the release studies of low solubility drugs such as steroids because of its solubilizing property (Shin and Byun 1996 : 95 – 102 ; and Shin and Lee 2002 : 201 - 206). However, only PEG 400 was recently used as receptor medium in the study of ketoprofen release from colloidal silicon dioxide gel (Gallagher, Trottet and Heard 2003 : 37 - 45). The release of salicylic acid, which had high solubility in this medium, was higher than that of propranolol HCl for the similar reason. Shin and Lee (2002 : 201 – 206) also reported that the rate of tripolidine permeation was found to increase with the increase of volume fraction of drug solubilizer i.e. PEG 400 in the receptor solution.

Effect of the drug loading dose on the drug release

The fluxes were enhanced as a drug concentration was increased. The increase in release rate with the increment in the loading dose might be due to the

increase in thermodynamic activity of the drug, which was related to its concentration in the base. (Vlachou et al. 1992 : 47 - 52) The similar results were also reported by El Gendy, Jun and Kassem (2002 : 823 – 831) and Yoshida et al. (2004 : 55 – 64).

CHAPTER VI

CONCLUSION

Colloidal silicon dioxide could convert some liquids into gel. The dispersing media that could be converted into gel with hydrophilic colloidal silicon dioxide (Aerosil 200) were PEG 400, PEG 600, light mineral oil, castor oil, IPM and Luvitol EHO®. However, the dispersing media that could be converted into gel with hydrophobic colloidal silicon dioxide (Aerosil R 972) were light mineral oil and Luvitol EHO®. Some physical properties of dispersing media such as polarity and viscosity influenced on the network forming capability of colloidal silicon dioxide. Thus, these led to the difference in gel forming ability of colloidal silicon dioxide in each media. The clarity of colloidal silicon dioxide gels preparation depended on the initial viscosity and the difference between the refractive index of dispersing media and colloidal silicon dioxide.

The release of propranolol HCl was increased as the hydrophilicity of the gel component (hydrophilic colloidal silicon dioxide and hydrophilic dispersing medium) increased. The interaction between salicylic acid and PEG 400 or the adsorption of salicylic acid on the surface of Aerosil 200 decreased the release of salicylic acid. The release of both drugs from colloidal silicon dioxide gel increased as the amount of colloidal silicon dioxide decreased. The release of propranolol HCl and salicylic acid increased as the concentration of both drugs increased. The type of receptor solution also affected the drug release, the higher solubility of the drug in receptor solution, the higher the release was found.

From this study, the characteristics of dispersing media such as polarity, viscosity and refractive index should be considered for transparent colloidal silicon dioxide gel preparations. The interaction between drugs and gel base might be used to estimate the drug release from gels. The rheology of colloidal silicon dioxide gel and drug permeability though skin membrane should be further investigated.

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APPENDICES

APPENDIX I

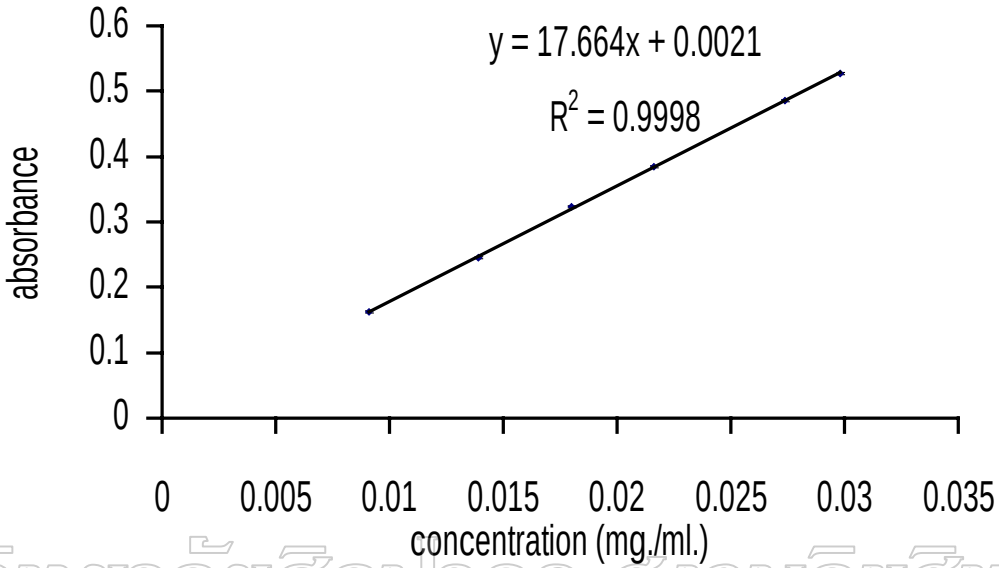

Figure 19 Calibration curve of propranolol hydrochloride in water

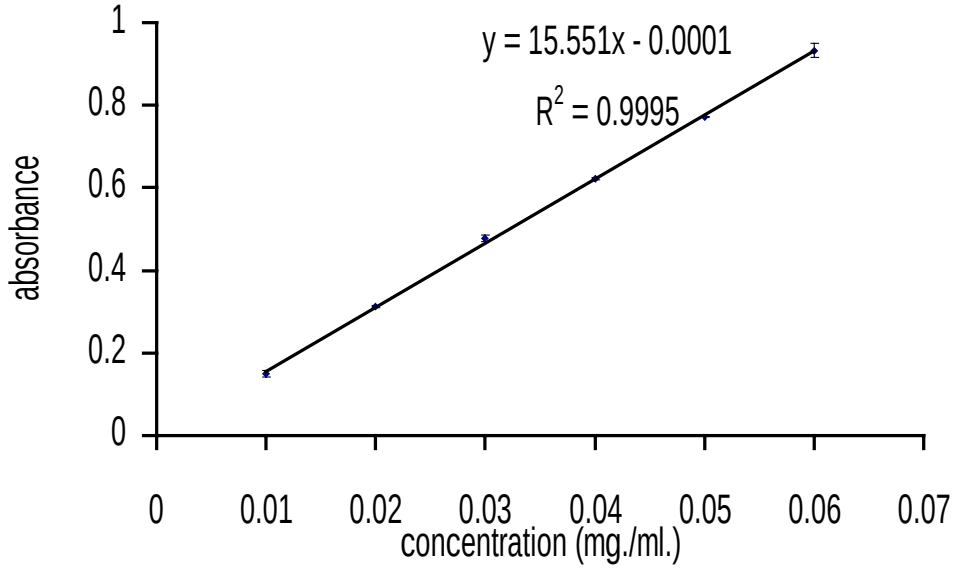

Figure 20 Calibration curve of propranolol hydrochloride in PEG 400

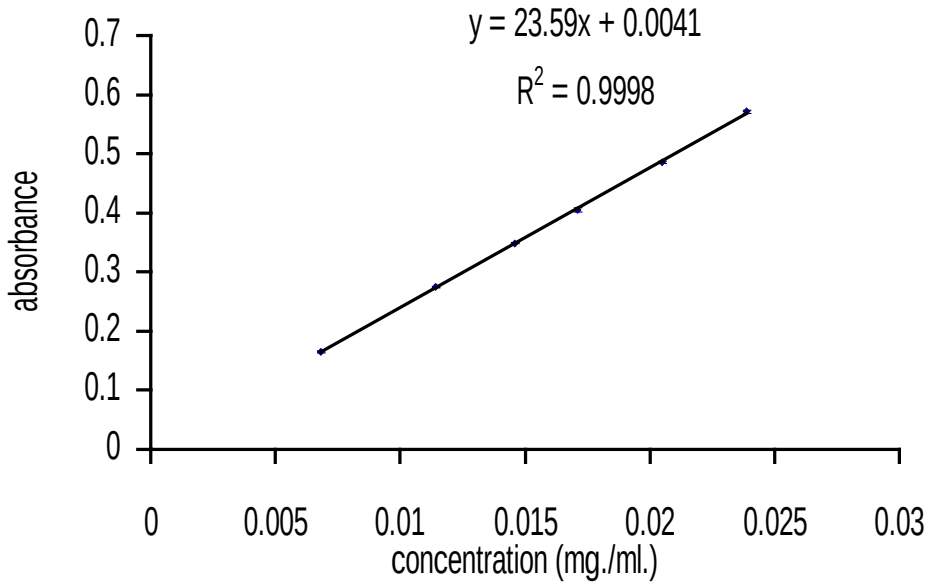

Figure 21 Calibration curve of salicylic acid in water

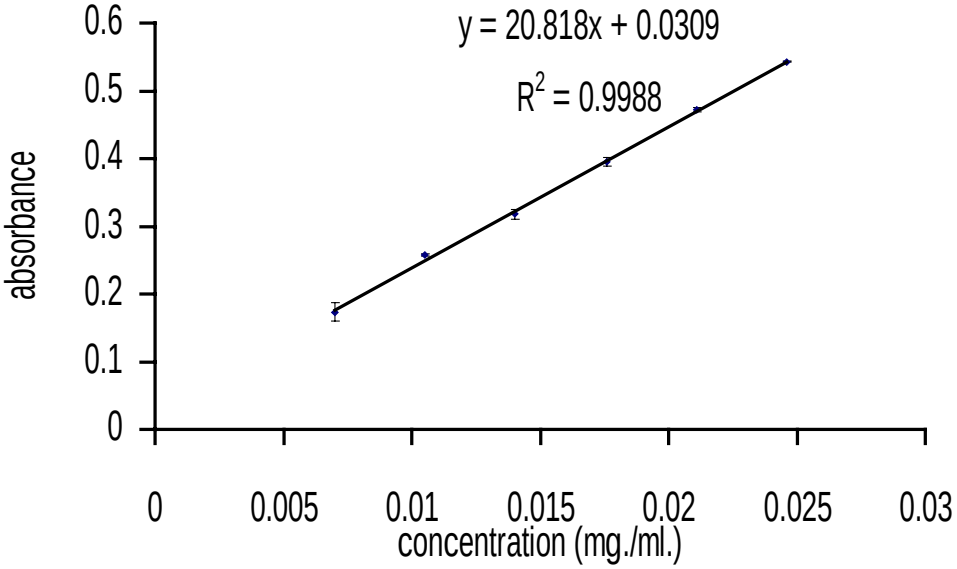

Figure 22 Calibration curve of salicylic acid in PEG 400

APPENDIX II

Physical apparent of the systems containing colloidal silicon dioxide

Figure 23 The incorporation of water with Aerosil 200

Figure 24 The incorporation of PEG 400 with Aerosil 200

Figure 33 The mixture of PEG 400 and propylene glycol after incorporation with Aerosil R 972

Figure 34 The mixture of PEG 400 and glycerin after incorporation with Aerosil 200

Figure 35 The mixture of PEG 400 and glycerin after incorporation with Aerosil R 972

Figure 36 PEG 400 gel bases containing propranolol HCl

Figure 39 Mineral oil gel bases containing salicylic acid

APPENDIX III

Table 13 The amount of dispersing media in different weight ratio to prepare the dispersing medium having various dielectric constant

dielectric constant	Dispersing media (g)					
	PEG - PG		PEG - water		PEG - glycerin	
	PEG 400	PG	PEG 400	Water	PEG 400	Glycerin
18	107.35	42.65	137.29	12.71	122.09	27.91
20	92.13	57.87	132.75	17.25	112.13	37.87
22	76.9	73.1	128.22	21.78	102.16	47.84
24	61.68	88.32	123.67	26.33	92.19	57.81
26	46.44	103.56	119.13	30.87	82.23	67.77
28	31.22	118.78	114.6	35.4	72.26	77.74
30	15.99	134.01	110.06	39.94	62.29	87.71
40	-	-	87.37	62.63	12.46	137.54

Table 14 The viscosity of mixed-dispersing media at various dielectric constant

dielectric constant	Viscosity (cps)		
	PEG - PG	PEG - water	PEG - glycerin
18	86.67 $\pm$ 0.58	101.00 $\pm$ 0.00	171.33 $\pm$ 1.15
20	83.67 $\pm$ 1.15	93.00 $\pm$ 1.00	197.67 $\pm$ 5.69
22	79.67 $\pm$ 1.15	87.33 $\pm$ 0.58	227.33 $\pm$ 5.51
24	76.33 $\pm$ 1.53	81.67 $\pm$ 0.58	270.67 $\pm$ 7.64
26	75.00 $\pm$ 1.00	75.33 $\pm$ 0.58	307.33 $\pm$ 7.57
28	74.00 $\pm$ 0.00	70.00 $\pm$ 0.00	378.00 $\pm$ 12.53
30	69.00 $\pm$ 0.00	64.33 $\pm$ 0.58	446.67 $\pm$ 2.52
40	-	40.00 $\pm$ 0.00	737.00 $\pm$ 16.09

APPENDIX IV

Table 15 The percentage of cumulative release of propranolol HCl and salicylic acid from aqueous solution into aqueous medium

Time (h)	0.02% propranolol HCl					0.02% salicylic acid				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.03	5.91	4.78	5.91	5.53	0.65	0.00	0.00	0.00	0.00	0.00
0.08	25.71	27.47	28.46	27.21	1.39	27.16	17.76	19.05	21.32	5.10
0.17	49.18	54.59	45.95	49.91	4.37	48.56	44.75	41.54	44.95	3.51
0.25	65.84	75.48	63.01	68.11	6.54	70.66	61.53	55.91	62.70	7.44
0.5	94.54	97.18	87.78	93.17	4.85	89.63	84.86	80.72	85.07	4.46
1	94.15	96.46	94.16	94.92	1.33	97.38	93.09	93.48	94.65	2.37
2	97.20	98.68	88.78	94.89	5.34	97.84	94.45	96.12	96.14	1.70
3	91.73	97.66	82.98	90.79	7.39	96.76	92.95	95.72	95.14	1.97
6	82.43	89.92	83.89	85.41	3.97	96.03	92.80	94.52	94.45	1.62

APPENDIX V

Table 16 The percentage of cumulative release of propranolol HCl from gel into aqueous medium

Time (h)	0.2 P 4 Ap					0.2 P 6 Ap					0.2 P 8 Ap					0.2 P 10 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	9.53	9.15	7.23	8.64	1.23	8.64	9.5	8.86	9.00	0.45	10.24	9.51	9.59	9.78	0.40	11.23	8.62	9.01	9.62	1.41
0.5	14.45	13.61	13.00	13.69	0.73	13.79	14.52	16.47	14.93	1.39	18.62	17.18	15.48	17.09	1.57	17.42	15.69	13.84	15.65	1.79
1	23.16	23.43	22.36	22.98	0.56	23.68	24.05	26.64	24.79	1.61	32.79	28.26	28.26	29.77	2.62	27.95	27.65	24.08	26.56	2.15
2	35.64	34.71	34.26	34.87	0.70	36.31	38.16	39.56	38.01	1.63	51.99	44.66	45.12	47.26	4.11	44.23	44.25	38.85	42.44	3.11
3	47.29	46.46	45.51	46.42	0.89	47.9	49.06	51.8	49.59	2.00	62.96	57.1	55.69	58.58	3.86	53.47	53.91	46.08	51.15	4.40

Time (h)	0.2 P 4 Rp					0.2 P 6 Rp					0.2 P 8 Rp					0.2 P 10 Rp				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	9.55	9.17	9.23	9.32	0.20	8.54	7.77	7.20	7.84	0.67	7.37	8.54	8.39	8.10	0.64	9.92	8.54	8.92	9.13	0.71
0.5	15.33	13.98	14.13	14.48	0.74	12.70	12.31	11.37	12.13	0.68	11.73	12.91	12.44	12.36	0.59	15.34	12.88	13.12	13.78	1.36
1	23.34	22.57	23.20	23.04	0.41	19.60	19.00	18.69	19.10	0.46	18.75	19.49	19.71	19.32	0.50	22.96	19.80	21.78	21.51	1.60
2	34.81	32.29	34.28	33.79	1.33	30.54	28.07	29.76	29.46	1.26	30.08	28.29	29.92	29.43	0.99	32.71	28.38	31.43	30.84	2.22
3	45.73	41.80	44.51	44.01	2.01	37.96	35.04	37.04	36.68	1.49	37.09	35.41	40.18	37.56	2.42	42.02	35.36	40.39	39.26	3.47

Time (h)	0.2 P 4 Am					0.2 P 6 Am					0.2 P 7 Am					0.2 P 8 Am				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	3.50	3.30	3.94	3.58	0.33	1.18	1.13	0.90	1.07	0.15	7.44	3.71	23.93	11.69	10.76	4.15	5.99	11.36	7.17	3.75
0.5	13.75	11.40	14.36	13.17	1.56	4.70	5.45	4.84	5.00	0.40	11.83	8.47	37.98	19.43	16.16	6.28	10.17	18.71	11.72	6.36
1	41.07	34.56	40.26	38.63	3.55	22.97	21.44	22.44	22.28	0.78	19.75	19.42	57.84	32.34	22.09	12.62	17.39	26.69	18.90	7.16
2	64.35	67.26	64.73	65.45	1.58	45.15	44.06	44.87	44.69	0.57	33.62	35.53	74.96	48.04	23.34	21.30	25.35	33.23	26.63	6.07
3	74.27	81.12	75.04	76.81	3.75	66.71	65.87	62.24	64.94	2.38	39.24	44.03	72.32	51.86	17.88	25.80	29.87	35.55	30.41	4.90

Time (h)	0.4 P 8 Ap					0.6 P 8 Ap					0.8 P 8 Ap					1.0 P 8 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	8.56	8.46	9.79	8.94	0.74	9.01	8.54	8.24	8.60	0.39	9.12	7.20	7.51	7.94	1.03	10.31	8.84	9.30	9.48	0.75
0.5	14.12	13.77	17.27	15.05	1.93	16.54	13.93	13.30	14.59	1.72	15.28	12.94	13.36	13.86	1.25	16.52	13.90	15.18	15.20	1.31
1	22.92	24.12	31.29	26.11	4.53	24.60	23.40	21.81	23.27	1.40	25.89	22.40	24.48	24.26	1.76	26.89	24.14	25.87	25.63	1.39
2	40.80	41.36	49.01	43.72	4.59	38.17	36.35	34.95	36.49	1.61	39.96	37.86	40.83	39.55	1.53	44.48	40.41	42.44	42.44	2.04
3	50.53	51.55	59.22	53.77	4.75	46.98	45.98	43.48	45.48	1.80	49.55	47.67	49.56	48.93	1.09	52.49	49.00	51.41	50.97	1.79

Table 17 The percentage of cumulative release of salicylic acid from gel into aqueous medium

Time (h)	0.2 S 4 Ap					0.2 S 6 Ap					0.2 S 8 Ap					0.2 S 10 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	5.22	6.04	6.13	5.80	0.50	5.48	5.03	6.21	5.57	0.60	5.59	4.24	4.88	4.90	0.68	7.70	6.77	6.85	7.11	0.52
0.5	10.25	10.47	9.99	10.24	0.24	9.37	8.34	9.89	9.20	0.79	9.03	8.03	7.91	8.32	0.61	14.18	11.13	10.41	11.91	2.00
1	19.51	17.67	18.55	18.58	0.92	15.84	14.57	17.05	15.82	1.24	17.33	15.77	14.03	15.71	1.65	23.06	19.95	20.38	21.13	1.69
2	32.40	29.27	31.53	31.07	1.62	25.45	23.80	28.99	26.08	2.65	27.45	24.30	22.17	24.64	2.66	35.17	30.39	32.49	32.68	2.40
3	47.06	39.50	42.97	43.18	3.78	34.79	32.68	39.26	35.58	3.36	36.48	33.12	31.47	33.69	2.55	46.98	40.46	42.95	43.46	3.29

Time (h)	0.2 S 4 Rp					0.2 S 6 Rp					0.2 S 8 Rp					0.2 S 10 Rp				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	8.17	7.21	7.93	7.77	0.50	5.87	5.68	5.29	5.61	0.30	5.69	5.13	5.50	5.44	0.28	6.27	5.39	6.33	6.00	0.53
0.5	13.06	11.48	12.17	12.24	0.79	10.67	9.76	9.55	9.99	0.60	9.38	8.74	9.10	9.07	0.32	9.65	8.43	9.65	9.24	0.70
1	20.83	17.75	18.65	19.08	1.58	17.21	15.05	17.89	16.72	1.48	14.89	14.18	15.16	14.74	0.51	15.61	13.49	16.25	15.12	1.44
2	33.02	26.61	28.21	29.28	3.34	26.6	24.17	27.43	26.07	1.69	23.42	22.47	23.81	23.23	0.69	25.00	22.10	25.50	24.20	1.84
3	47.23	35.10	37.95	40.09	6.34	37.17	33.36	37.88	36.14	2.43	32.84	31.25	33.59	32.56	1.19	32.96	28.97	33.16	31.70	2.36

Time (h)	0.2 S 4 Am					0.2 S 6 Am					0.2 S 7 Am					0.2 S 8 Am				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	8.87	4.21	3.77	5.62	2.83	4.35	3.19	5.11	4.22	0.97	7.06	6.28	7.00	6.78	0.43	2.86	12.76	5.42	7.01	5.14
0.5	13.54	6.14	12.11	10.60	3.93	10.99	5.60	12.66	9.75	3.69	13.02	12.04	12.70	12.59	0.50	4.99	20.05	9.15	11.40	7.78
1	26.69	12.73	26.96	22.13	8.14	25.17	12.88	27.92	21.99	8.01	27.07	28.21	27.63	27.64	0.57	12.67	32.57	16.82	20.69	10.50
2	54.03	29.05	51.36	44.81	13.72	47.20	27.67	49.04	41.30	11.84	38.02	50.21	50.93	46.39	7.25	26.79	52.37	30.84	36.67	13.75
3	68.64	41.16	63.53	57.78	14.62	58.76	38.42	60.69	52.62	12.34	58.86	63.75	64.60	62.40	3.10	39.98	61.68	39.00	46.89	12.82

Time (h)	0.2 S 4 Rm					0.2 S 6 Rm					0.2 S 7 Rm					0.2 S 8 Rm				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	4.70	3.69	3.59	3.99	0.61	4.25	5.87	5.23	5.12	0.82	6.32	7.98	5.76	6.69	1.15	4.06	6.98	10.10	7.05	3.02
0.5	9.75	8.68	7.61	8.68	1.07	11.40	14.31	11.75	12.49	1.59	11.56	13.27	9.83	11.55	1.72	6.96	10.29	16.69	11.31	4.95
1	15.12	12.2	12.21	13.18	1.68	17.29	22.03	17.77	19.03	2.61	17.47	19.82	14.68	17.32	2.57	10.96	15.11	25.03	17.03	7.23
2	20.43	16.33	15.54	17.43	2.63	25.88	33.19	26.15	28.41	4.14	24.36	27.26	19.21	23.61	4.08	16.05	21.48	34.81	24.11	9.65
3	28.17	22.02	18.63	22.94	4.84	31.39	42.31	33.64	35.78	5.77	33.00	34.06	24.09	30.38	5.48	22.35	29.30	46.56	32.74	12.47

Table 17 (continued)

Time (h)	0.4 S 8 Ap					0.6 S 8 Ap					0.8 S 8 Ap					1.0 S 8 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.25	4.27	4.80	4.80	4.62	0.31	3.67	2.74	3.55	3.32	0.51	3.59	2.77	2.82	3.06	0.46	2.49	2.56	3.00	2.68	0.28
0.5	8.40	7.96	7.92	8.09	0.27	6.16	5.15	6.63	5.98	0.76	6.07	5.50	5.22	5.60	0.43	5.16	5.97	6.35	5.83	0.61
1	15.40	14.36	16.08	15.28	0.87	12.79	12.01	16.85	13.88	2.60	13.95	11.79	10.33	12.02	1.82	9.99	10.95	11.23	10.72	0.65
2	30.69	28.90	29.15	29.58	0.97	19.57	21.10	26.58	22.42	3.69	22.93	27.09	17.86	22.63	4.62	16.78	19.58	19.38	18.58	1.56
3	42.43	39.29	41.01	40.91	1.57	30.07	28.14	37.10	31.77	4.72	32.16	30.60	24.97	29.24	3.78	24.80	27.60	27.69	26.70	1.64

Table 18 The percentage of cumulative release of propranolol HCl from gel into PEG 400 medium

Time (h)	0.2 P 6 Am					0.2 P 4 Rm					0.2 P 6 Rm					0.2 P 8 Rm				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.26	0.00	0.11	0.12	0.13	0.00	0.00	0.00	0.00	0.00	2.34	3.63	2.83	2.93	0.65	2.66	3.07	4.02	3.25	0.70
1	0.55	0.19	0.34	0.36	0.18	0.73	0.97	0.87	0.86	0.12	3.68	4.10	2.82	3.53	0.65	2.96	3.29	4.00	3.42	0.53
2	0.86	0.40	0.36	0.54	0.28	1.67	2.17	2.14	1.99	0.28	3.81	5.42	3.89	4.37	0.91	3.73	4.88	5.39	4.67	0.85
3	0.91	0.56	0.38	0.62	0.27	3.29	3.84	2.82	3.32	0.51	5.27	6.93	5.32	5.84	0.94	4.54	6.44	6.80	5.93	1.21
6	1.78	0.73	0.57	1.03	0.66	7.56	8.79	14.75	10.37	3.85	10.07	12.83	10.75	11.22	1.44	9.44	11.64	11.63	10.90	1.27
12	4.69	1.97	1.73	2.80	1.64	19.35	19.56	24.87	21.26	3.13	19.28	23.79	18.57	20.55	2.83	17.62	21.45	21.51	20.19	2.23
25	17.54	8.44	6.32	10.77	5.96	32.70	31.89	41.84	35.48	5.53	37.30	43.72	32.23	37.75	5.76	33.73	41.92	37.86	37.84	4.10

Time (h)	0.2 P 8 Ap					4.0 P 8 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.38	0.54	0.59	0.50	0.11	0.00	0.00	0.00	0.00	0.00
2	2.14	2.05	2.51	2.23	0.24	0.50	0.69	0.03	0.41	0.34
3	3.63	3.08	3.63	3.45	0.32	0.77	1.95	0.12	0.95	0.93
6	8.91	8.67	10.39	9.32	0.93	1.48	2.71	2.28	2.16	0.62
12	14.76	15.29	13.29	14.45	1.04	5.56	6.47	5.50	5.84	0.54
25	25.17	25.74	26.82	25.91	0.84	17.87	26.76	22.12	22.25	4.45

Table 18 (continued)

Time (h)	0.2 P 8 Rp					0.4 P 8 Rp					0.6 P 8 Rp					4.0 P 8 Rp				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.54	0.52	0.54	0.53	0.01	1.71	1.55	1.58	1.61	0.09	1.20	1.06	0.98	1.08	0.11	0.00	0.00	0.00	0.00	0.00
1	1.85	1.55	1.72	1.71	0.15	2.50	2.52	2.39	2.47	0.07	1.98	1.73	1.62	1.78	0.18	0.00	0.00	0.00	0.00	0.00
2	4.09	3.27	3.98	3.78	0.45	4.85	4.37	4.99	4.74	0.33	3.55	3.71	3.44	3.57	0.14	0.38	0.22	0.57	0.39	0.18
3	5.72	4.76	6.12	5.53	0.70	5.96	6.76	7.81	6.84	0.93	6.22	5.81	5.44	5.82	0.39	1.19	0.31	0.78	0.76	0.44
6	11.10	9.33	11.56	10.66	1.18	10.49	12.75	14.25	12.50	1.89	11.64	10.73	9.87	10.75	0.89	1.17	3.96	1.68	2.27	1.49
12	20.00	19.55	20.35	19.97	0.40	14.50	18.11	19.27	17.29	2.49	19.94	18.70	16.37	18.34	1.81	4.25	6.24	8.72	6.40	2.24
25	33.20	31.12	32.55	32.29	1.06	31.01	34.93	34.10	33.35	2.07	30.18	29.23	27.50	28.97	1.36	16.45	22.76	25.20	21.47	4.52

Table 19 The percentage of cumulative release of salicylic acid from gel into PEG 400 medium

Time (h)	0.2 S 8 Ap					0.4 S 8 Ap					0.6 S 8 Ap					0.8 S 8 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.04	0.00	0.02	0.02	0.02	0.19	0.33	0.00	0.17	0.17	0.69	0.24	0.00	0.31	0.35	0.14	0.20	0.14	0.16	0.03
1	2.62	1.89	1.17	1.89	0.73	3.35	3.44	1.88	2.89	0.88	2.41	2.16	1.72	2.10	0.35	2.51	2.39	2.07	2.32	0.23
2	6.21	5.57	3.05	4.94	1.67	7.55	7.17	5.79	6.84	0.93	4.44	5.03	5.25	4.91	0.42	6.84	6.67	8.36	7.29	0.93
3	10.19	8.70	4.78	7.89	2.79	12.53	11.59	10.55	11.56	0.99	7.61	7.59	7.86	7.69	0.15	10.71	9.61	9.54	9.95	0.66
6	17.95	17.66	8.89	14.83	5.15	27.42	25.44	25.06	25.97	1.27	17.75	17.86	17.74	17.78	0.07	19.01	20.16	18.53	19.23	0.84

Time (h)	1.0 S 8 Ap					4.0 S 8 Ap					15.0 S 8 Ap					30.0 S 8 Ap				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.26	0.19	0.25	0.23	0.04	0.68	0.44	0.94	0.69	0.25	0.20	0.06	0.02	0.09	0.09	0.41	0.43	0.46	0.43	0.03
1	2.20	2.07	2.36	2.21	0.15	3.75	2.53	3.61	3.30	0.67	1.04	0.47	1.11	0.87	0.35	1.15	1.42	1.83	1.47	0.34
2	4.99	6.64	6.35	5.99	0.88	9.01	6.35	10.33	8.56	2.03	3.06	3.60	4.62	3.76	0.79	1.81	2.81	3.41	2.68	0.81
3	9.47	9.35	10.24	9.69	0.48	10.06	8.92	13.62	10.87	2.45	4.48	6.04	6.24	5.59	0.96	4.04	5.15	5.45	4.88	0.74
6	16.38	17.97	19.57	17.97	1.60	23.27	21.49	28.01	24.26	3.37	9.79	13.78	15.28	12.95	2.84	11.93	14.00	11.10	12.34	1.49

Time (h)	0.2 S 8 Rp					0.4 S 8 Rp					0.6 S 8 Rp					0.8 S 8 Rp				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	1.10	0.00	0.00	0.37	0.64	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	0.30	0.19	0.16
1	2.24	2.31	0.32	1.62	1.13	1.96	1.68	1.42	1.69	0.27	1.71	2.07	2.24	2.01	0.27	0.82	2.56	2.12	1.83	0.90
2	4.96	5.75	2.66	4.46	1.61	6.53	4.83	4.65	5.34	1.04	4.65	5.95	5.52	5.37	0.66	6.65	6.04	5.50	6.06	0.58
3	7.95	9.22	4.26	7.14	2.58	10.31	7.84	6.49	8.21	1.94	7.96	8.13	8.77	8.29	0.43	9.79	9.22	8.81	9.27	0.49
6	15.88	16.27	9.48	13.88	3.81	21.09	16.13	15.19	17.47	3.17	15.53	16.04	16.52	16.03	0.50	20.78	17.04	16.56	18.13	2.31

Table 19 (continued)

Time (h)	1.0 S 8 Rp					4.0 S 8 Rp					15.0 S 8 Rp					30.0 S 8 Rp				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.65	0.27	0.22	0.38	0.24	0.44	0.97	0.44	0.62	0.31	0.17	0.15	0.15	0.16	0.01	0.55	0.58	0.41	0.51	0.09
1	2.13	2.22	1.87	2.07	0.18	2.54	3.51	2.30	2.78	0.64	1.39	3.23	2.00	2.21	0.94	1.97	2.02	2.18	2.06	0.11
2	5.08	5.47	4.70	5.08	0.39	4.90	8.15	5.30	6.12	1.77	6.46	6.27	6.47	6.40	0.11	3.44	3.16	3.43	3.34	0.16
3	8.95	8.68	8.35	8.66	0.30	9.12	10.16	10.47	9.92	0.71	9.30	11.04	8.54	9.63	1.28	5.70	5.69	6.12	5.84	0.25
6	17.94	15.52	16.64	16.70	1.21	7.68	17.17	22.64	15.83	7.57	19.82	22.74	16.55	19.70	3.10	15.64	14.25	10.20	13.36	2.83

Time (h)	0.4 S 6 Am					0.6 S 6 Am					0.8 S 6 Am					1.0 S 6 Am				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.21	0.02	0.00	0.08	0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.19	0.13	0.00	0.11	0.10	0.00	0.00	0.00	0.00	0.00	0.55	0.08	0.65	0.43	0.30	0.03	0.14	0.43	0.20	0.21
2	0.37	0.41	0.00	0.26	0.23	0.00	0.00	0.17	0.06	0.10	0.81	0.37	1.17	0.78	0.40	0.28	0.38	1.18	0.61	0.49
3	0.44	0.64	0.00	0.36	0.33	0.00	0.00	0.34	0.11	0.20	0.95	0.90	1.51	1.12	0.34	0.58	0.60	2.90	1.36	1.33
6	0.58	0.68	0.66	0.64	0.05	0.00	0.08	1.03	0.37	0.57	1.71	1.87	2.58	2.05	0.46	1.44	1.57	4.33	2.45	1.63
12	2.96	3.43	6.10	4.16	1.69	3.46	1.55	3.48	2.83	1.11	4.39	6.97	5.47	5.61	1.30	2.51	3.20	6.57	4.09	2.17
25	11.95	15.42	16.48	14.62	2.37	13.57	8.97	5.36	9.30	4.11	14.28	19.22	12.17	15.22	3.62	6.87	8.68	13.34	9.63	3.34

Time (h)	0.4 S 6 Rm					0.6 S 6 Rm					0.8 S 6 Rm					1.0 S 6 Rm				
	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.	1	2	3	mean	S.D.
0.5	0.23	0.10	0.14	0.16	0.07	0.73	0.47	0.31	0.50	0.21	0.95	0.56	0.62	0.71	0.21	0.69	0.08	0.49	0.42	0.31
1	3.06	3.80	3.13	3.33	0.41	4.18	6.40	3.80	4.79	1.40	5.71	5.17	4.64	5.17	0.54	3.32	2.13	3.94	3.13	0.92
2	10.24	9.79	8.39	9.47	0.96	10.20	14.47	8.44	11.04	3.10	11.78	11.10	10.45	11.11	0.67	8.96	11.07	12.06	10.70	1.58
3	16.88	16.66	13.29	15.61	2.01	16.77	26.52	14.94	19.41	6.23	21.45	19.97	19.80	20.41	0.91	15.92	18.29	17.23	17.15	1.19
6	32.56	33.60	26.72	30.96	3.71	30.44	40.83	32.34	34.54	5.53	36.48	32.24	34.63	34.45	2.13	25.67	31.11	27.81	28.20	2.74

APPENDIX VI

Table 20 One way ANOVA significant statistical data

Comparison between groups		Sig.
0.2 P 8 Ap	0.2 P 8 Rp	0.017
0.2 P 8 Ap	0.2 S 8 Ap	0.034
0.2 S 6 Ap	0.2 S 6 Am	0.000
0.2 P 8 Rp	0.4 P 8 Rp	0.000
0.2 P 8 Rp	0.6 P 8 Rp	0.000
0.2 P 8 Rp	0.8 P 8 Rp	0.000
0.4 S 6 Am	0.8 S 6 Am	0.019

Table 21 Statistical testing for two independent samples include the pooled variance

Comparison between groups		df	$t_{0.025}$	$t_{calculated}$
0.2 P 8 Ap (aqueous)	0.2 P 8 Ap (PEG)	10	2.228	38.721
0.2 S 8 Ap (aqueous)	0.2 S 8 Ap (PEG)	6	2.447	22.612
0.2 S 8 Ap	0.4 S 8 Ap	6	2.447	- 43.365
0.2 S 8 Ap	0.6 S 8 Ap	6	2.447	- 43.591
0.2 S 8 Ap	4 S 8 Ap	6	2.447	- 19.038
0.2 S 8 Ap	15 S 8 Ap	6	2.447	- 7.588
0.2 S 8 Ap	30 S 8 Ap	6	2.447	- 7.045
0.2 S 8 Rp	0.6 S 8 Rp	6	2.447	- 18.242
0.2 S 8 Rp	0.8 S 8 Rp	6	2.447	- 8.757
0.2 S 8 Rp	4 S 8 Rp	5	2.571	- 72.275
0.4 S 6 Rm	0.6 S 6 Rm	6	2.447	- 4.651

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