เจลคอลลอยดอลซิลิกอนไดออกไซด์ปราศจากน้ำชนิดชอบน้ำและชนิดไม่ชอบน้ำบรรจุยาโปรปราโลนอลไฮโดรคลอไรด์และกรดซาลิไซลิก

Propranolol HCl and Salicylic Acid-loaded Hydrophilic and Hydrophobic Colloidal Silicon Dioxide Anhydrous Gels

นิพนธ์ต้นฉบับ

Original Article

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บทคัดย่อ

วัตถุประสงค์: การศึกษานี้พัฒนาเจลปราศจากส่วนประกอบที่เป็นน้ำโดยการกระจายสารคอลลอยดอลซิลิกอนไดออกไซด์ชนิดชอบน้ำ (คือ Aerosil® 200) และชนิดไม่ชอบน้ำ (คือ Aerosil® R972) ในสารพอลิเอธิลีนไกลคอลสี่ร้อยและน้ำมันแร่ **วิธีการศึกษา:** เจลปราศจากส่วนประกอบที่เป็นน้ำถูกใช้บรรจุยาโปรปราโลนอลไฮโดรคลอไรด์และกรดซาลิไซลิก ซึ่งเป็นยาโมเดลของยาที่มีความชอบน้ำและไม่ชอบน้ำตามลำดับ และทำการประเมินความหนืด การปลดปล่อยยาด้วย Franz diffusion cell **ผลการศึกษา:** พบว่าเจลที่เตรียมจาก Aerosil® 200 ในตัวกลางที่เป็นน้ำมันแร่มีความหนืดสูง การปลดปล่อยยาทั้งสองชนิดจากเจลปราศจากส่วนประกอบที่เป็นน้ำยาวนานขึ้นเมื่อปริมาณคอลลอยดอลซิลิกอนไดออกไซด์มากขึ้น การเพิ่มความชอบน้ำให้ส่วนประกอบของเจลมีผลเพิ่มการปลดปล่อยยาโดยขึ้นกับความเข้มข้นของยา สมบัติทางเคมีกายภาพและลักษณะการปลดปล่อยยาของเจลปราศจากส่วนประกอบที่เป็นน้ำที่บรรจุยาขึ้นกับชนิดและปริมาณของคอลลอยดอลซิลิกอนไดออกไซด์และชนิดของตัวกลางที่สารกระจายตัว **สรุป:** เจลปราศจากส่วนประกอบที่เป็นน้ำที่เตรียมได้ที่มีความหนืดสูงและมีการปลดปล่อยยาดีมีศักยภาพในการนำส่งยาทางผิวหนัง

คำสำคัญ: เจลปราศจากส่วนประกอบที่เป็นน้ำ, โปรปราโนลอลไฮโดรคลอไรด์, กรดซาลิไซลิก, คอลลอยดอลซิลิกอนไดออกไซด์

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Abstract

Objective: To determine the physical properties and the release of propranolol HCl and salicylic acid from both hydrophilic and hydrophobic colloidal silicon dioxide gel formula using different dispersing media including hydrophilic Aerosil® 200 and hydrophobic Aerosil® R972 in polyethylene glycol 400 (PEG 400) and mineral oil. **Method:** Propranolol HCl and salicylic acid were incorporated in these anhydrous gels as the hydrophilic and hydrophobic drugs and evaluated for their viscosities, drug release using Franz diffusion cell method. **Results:** A200 gel using mineral oil as dispersing medium was highly viscous. The release of both drugs from the anhydrous gels was prolonged as the amount of colloidal silicon dioxide was increased. The increased hydrophilicity of the gel component resulted in the increment of drug release with drug concentration dependence. Physicochemical characters and drug release manners of drug- loaded anhydrous gels depended on type and amount of colloidal silicon dioxide and dispersing medium. **Conclusion:** The obtained anhydrous gel with considerable viscosity and high drug release exhibited potential as the transdermal drug delivery.

Keywords: anhydrous gel, propranolol HCl, salicylic acid, colloidal silicon dioxide

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Introduction

Gels are widely used as the semisolid preparations for topical drug delivery which typically is the network of large organic molecules swollen in a liquid medium or small inorganic particles dispersed in liquid media. Gels are obtaining more popularity because of the ease of application and better absorption through the skin layers.[1] There is a three dimensional network of particles or polymeric macromolecule of dispersed phase in gels by interlacing and consequential internal friction between particles or polymers and the liquid dispersion medium which set up the structural viscosity.[2] Subsequently, this increased viscosity behavior immobilizes the liquid media which is mainly responsible for the semisolid state. The typical characteristic feature is the presence of a continuous structure providing semisolid-like properties.[2] The interlinking between the particles or polymeric chains of gelling agents causes the rigidity of a gel. In addition, the nature of the particle or polymer and the type of force responsible for the linkages or interaction could directly influence the structure network and the properties of the gels.[3] The forces of attraction vary from strong primary valencies, as in silicic acid

gels, to weaker hydrogen bonds and Van der Waals forces.[4] Topical gel formulation is a suitable drug delivery system because of its less greasiness and easy removal from the skin. In addition, it exhibits a better application property and physical stability in comparison to cream and ointment.

Anhydrous gels are usually composed of a liquid organic phase entrapped in a three dimensional cross-linked network.[3] The liquid can be vegetable oil, an organic solvent or mineral oil. Usually, the gel base in an anhydrous gel is mineral oil with polyethylene or fatty oils gelled with colloidal silica or aluminum or zinc soaps.[4] The rheological profiles of anhydrous gels correspond to a physically cross-linked three dimensional gel network.[4] The non-aqueous gel was successfully formulated using ethylcellulose with propylene glycol dicaprylate/dicaprate.[4] Although the hydrogels are widely accepted, the quantity and homogeneity of the drug loading into hydrogels may be limited, especially the hydrophobic drugs. In addition, the high water content and large pore sizes of most hydrogels lead to a relatively rapid drug release.[5] In contrast, the use of anhydrous gels gives rise to their easy method of preparation and inherent long-term stability.[6] They have the ability to accommodate both hydrophilic and hydrophobic compounds within the gel structure. In addition, they can be used as controlled drug delivery systems.[7]

Owing to its prominent features such as amorphous, hydrophilic and anhydrous, with large surface area and controlled particle size[8], colloidal silicon dioxide is widely used in oral and topical pharmaceutical products. It possesses its prominent functions such as a thickening agent, lubricant, glidant, component of tablet coating[9,10], binder, suspending agent, and adsorbent.[11] There are two types of colloidal silicon dioxide namely hydrophilic and hydrophobic. The silanol group (Si-OH) presenting on the surface of the hydrophilic colloidal silicon dioxide such as Aerosil® A200 (A200) can interact with each other via hydrogen bonding to form the three dimensional network in the dispersing media.[12] For hydrophobic colloidal silicon dioxide such as Aerosil® R972 (R972), the silanol groups are chemically modified by coupling with various silanes or silazanes.[12] The hydrophilicity, viscosity and polarity of the dispersing media also influence the physical properties of the viscous fluid comprising colloidal silicon dioxide. The interaction of hydrogen bond formations between silanol groups on the surface of colloidal silicon dioxide and polar media might cause the changes in gel strength or gel formation. R972 could be applied as a gelling agent in the hydrophilic/lypophilic microemulsion.[14] When the amount of R972 as a dry coating agent was increased, the rate of drug release reduced.[15]

Salicylic acid (2-hydroxybenzoic acid) has a molecular weight of 138.12 g/mol, a log P value of 2.26 and a melting point of 159 $^{\circ}$C. Its water solubility is 2.48 mg/mL and it is soluble in oil of turpentine, alcohol and ether.[16] It has a keratolytic action which, when topically applied to the skin, causes the outer layers of the skin to shred away from the pores.[16] Furthermore, it has an anti-inflammatory action by suppressing the activity of cyclooxygenase (COX), an enzyme that is responsible for the production of pro-inflammatory mediators such as prostaglandins.[17] Propranolol hydrochloride has a molecular weight of 295.8 g/mol, a log P value of -0.45 and a melting point of 164.0 °C. Its aqueous solubility is 7.20 mg/mL and it is practically insoluble in ether, benzene, ethyl acetate.[18] It is a beta-adrenoreceptor antagonist to lower the blood pressure in humans by blocking receptors non-selectively and is typically prescribed to treat hypertension, myocardial infarction and cardiac arrhythmias. Because of its short biological half-life (3.9 ± 0.4 h), it is necessary for its administration to consist of two or three times of 40-80 mg per day.[18] Thus, the development into the controlled-release dosage forms such as a topical gel would be advantageous. The drug release rate from a gel formulation is one of the major factors indicating the therapeutic effectiveness. The effect of the drug release was related with the concentration of gelling agent and the initial drug loading which might be due to the alteration of the thermodynamic activity of the drug.[19,20] Moreover, the hydrophilic and hydrophobic properties of gelling agent, type of receptor medium and drug govern the rate of the drug release. The aim of this study was to determine the physical properties and drug release of propranolol HCl and salicylic acid from both hydrophilic and hydrophobic colloidal silicon dioxide gel formula using different dispersing media.

Methods

Materials

Two types of colloidal silicon dioxide, A200 and R972 were purchased from Wacker-Chemie GmBH, Germany. PEG 400 (batch no. P075463) and light mineral oil (batch no. 278607,

Witco, USA) were supplied by P.C. Drug Center Co., Ltd., Bangkok, Thailand. Propranolol hydrochloride (lot no. 030120, Jintan Pharmaceutical Factory, China) was kindly supported by Berlin Pharmaceutical Industry, Thailand and salicylic acid (lot no. 106505, Ajax chemicals, Australia) was used as received.

Preparation of gels

PEG 400 and light mineral oil were selected as the hydrophilic and hydrophobic dispersing media, respectively. In the present study, A200 and R972 at the amount of 4, 6, 8 and 10% by weight were employed as the gelling agents. Propranolol HCl and salicylic acid were used as the hydrophilic and hydrophobic model drugs with the amount of 0.2, 0.4, 0.6, 0.8, 1.0 and 4.0% by weight and 0.2, 0.4, 0.6, 0.8, 1.0, 4.0, 15.0 and 30.0% by weight, respectively. These drugs could dissolve in PEG 400 completely. In the case of mineral oil, the same amounts of both drugs were dissolved in 2 ml 95% ethanol before incorporation with mineral oil. Then A200 and R972 were individually added into the prepared mixtures. The drug free gels were also prepared as the control samples.

Evaluations

Study of the physical properties of anhydrous gels

The viscosity of drug-loaded formulas was measured using a Brookfield viscometer (Model: DV-I, Brookfield Engineering Laboratories, Inc., USA). The pH measurement was conducted using a pH meter (Professional Meter PP-15 Sartorius, Goettingen, Germany).

Determination of solubility of drugs in receptor solutions

Drugs were tested for their solubility in different solvents (water, PEG 400 and mineral oil). Approximately 20 g of a drug was weighed into a test tube. Twenty ml of solvent was added. The test tube was then placed in a water bath shaker at 37 ºC with a shaker speed of 50 rpm for 24 h. The mixture was taken and measured for drug content. The mixture was filtered through a glass membrane filter then was diluted to optimum concentration. The amount of drugs was determined using a UV spectrophotometer (Hitachi U-2000, Japan) at 289 and 298 nm for propranolol HCl and salicylic acid, respectively.

Study of drug release from gels

The drug release through a cellulose acetate membrane with pore size of 0.45 µm from gel systems was determined by a Franz diffusion cell using distilled water or PEG 400 as the receptor solutions. The receptor compartment was filled with 15 ml receptor solution. The 1 g (thickness about 0.2 cm) gel was placed into the donor compartment and tamped down on the cellulose acetate membrane that was previously soaked with the receptor solution. The drugs could solubilize in the receptor fluid and the concentration of both drugs was less than 10% of drug solubility in the receptor solution; thus, the sink condition was maintained through the study.[21] At different 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 a UV spectrophotometer (Hitachi U-2000, Japan) at 289 and 298 nm for propranolol HCl and salicylic acid, respectively. The removed volume of sample solution was replaced with an equal volume of receptor solution to maintain the sink condition. The calculated drug concentrations were plotted as a function of time. The fluxes through the membrane were calculated by plotting the cumulative amount of drug per area against the square root of time. The slope of linear portion of the curve and the X-intercept values (lag time) was determined by linear regression analysis.[22] All of the experiments were done in triplicate.

Statistical analysis

Mean with standard devidation was presented for all outcomes. The significance of the differences of the obtained viscosity data was tested using the one-way ANOVA from SPSS for window version 11.0. The significance level was set at P-value < 0.05.

Results and Discussion

Determination for the solubility of drugs in receptor solutions

Propranolol HCl was more soluble in water than PEG 400 while salicylic acid gave higher solubility in PEG 400 because the dielectric constant of water is higher than PEG 400 (Table 1). The dielectric constant of water and PEG 400 was 78.5 and 12.4, respectively. The rank order of solubility of propranolol HCl in receptor solutions was water > PEG 400 > mineral oil, where that of salicylic acid was PEG 400 > water > mineral oil. The solubility values of these two compounds would be applied for discussion about their release behavior from the prepared gels.

Table 1 Solubility of propranolol HCl and salicylic acid at 37 ºC (mg/ml) (n = 3).

Dispersing media	Propranolol HCl (mg/ ml)	Salicylic acid (mg/ ml)
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

Physical properties of drug-loaded gels

The physical appearances of all propranolol HCl and salicylic acid-loaded gels are shown in Table 2 and 3. The drug-loaded gels comprising PEG 400 were transparent, viscous and smooth whereas those in mineral oil were turbid. By comparison, both systems using mineral oil as the dispersing medium exhibited a higher viscosity than that of the systems using PEG 400 as a dispersing medium. The increase in amount of Aerosil® made the formulations more viscous because the higher network formation between particles caused the solvent to be immobilized as previously mentioned.[12,23] In polar dispersion medium, the silanol group on the A200 could interact more with the hydroxyl group of dispersion medium than that of the silanol-silanol interaction which led to a much weaker structure system.[23] Thus, the systems with high polarity medium exhibited a low viscosity. The dielectric constant of mineral oil is 2.1 and that of PEG 400 is 12.4. Thus, when A200 was added, the viscosity of drug-loaded PEG systems showed a lower viscosity than that of the systems containing mineral oil significantly (*P*-value < 0.05) (Table 2 and 3). On the other hand, when the R972 (containing both non-polar (dimethyldichloro) and polar (residual silanol) components on surface) was added into the PEG system, the viscosity was significantly less than that of the system using mineral oil as a dispersing medium (*P*-value < 0.05). The interaction of dimethyldichloro groups of R972 to cluster together depended on the extent of mismatch characters between particle surface and liquid dispersing media.[12]

As the concentration of propranolol HCl was increased, the viscosity of the PEG systems containing colloidal silicon dioxide was also increased (Table 2). The molecule such as propranolol HCl could interact with hydroxyl groups of the polar dispersing medium. Thus, there was a more silanol-silanol interaction which increased the viscosity of the system. When A200 was added into the PEG system containing salicylic acid, the viscosity of the system was initially increased (Table 3A). The salicylic acid could reduce the polarity of the system which promoted the system to increase the viscosity whereas the further increase in concentration of the salicylic acid to 0.6% decreased the viscosity. This might be due to the ability of salicylic acid to provide the H-bond formation with other molecules which might reduce the tendency for silanol-silanol interaction. However, in case of the PEG system containing R972 (Table 3B), there was a fluctuation in the viscosity. This proved that the degree of interaction of dimethyldichloro groups of R972 to cluster together depended on the extent of mismatching between particle surface and polar dispersing media.[24] The systems comprising propranolol HCl showed the higher pH value than that of the systems comprising salicylic acid owing to the more acidic property of salicylic acid.

***In vitro* drug release of gels**

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

From the determination of content uniformity, the content of propranolol hydrochloride and salicylic acid in the prepared gels was in the range of 95 to 110 percent. The 0.2% propranolol HCl-loaded Aerosil® gel containing both types of colloidal silicon dioxide in PEG showed a higher amount of drug release than that of the 0.2% salicylic acid-loaded colloidal silicon dioxide gel. The propranolol HCl has a log P of -0.45[25]; therefore, it was more soluble in an aqueous receptor medium and diffused out into the receptor medium higher than salicylic acid with a log P of 2.26.[25] By comparison, the release of 0.2% propranolol HCl from the gel using PEG 400 as a dispersing medium containing hydrophilic colloidal silicon dioxide (A200) was different from gel using hydrophobic colloidal silicon dioxide (R972) (Figure 1A). When PEG contacted with the receptor medium, it diffused out and the receptor medium penetrated into the gel matrix. The viscosity of A200 gels was higher than that of R972 gels. However, the gel systems containing hydrophilic A200 dispersed in PEG 400 offered a less resistance for the diffusion of aqueous receptor medium into the gel matrix than that of the gel containing hydrophobic silicon dioxide (R972). The release of salicylic acid from the gel using PEG as a dispersing medium showed the similar result. By comparison, the propranolol HCl released from the gel using PEG as a dispersing medium was apparently higher than systems using mineral oil (Figure 1).

The release of drugs from the gels involved the absorption of water into matrix and simultaneous desorption of drugs via diffusion as expressed by Fick's law.[26] The trend of the viscosity of the system containing 4% colloidal silicon dioxide in mineral oil gel base was as follows: salicylic acid+A200 < propranolol HCl+A200

Table 2 Physical appearance of propranolol HCl-loaded A200 gel (A) and R972 gel (B).

(A)

Propranolol HCl (%)	A200 (%)	Dispersing medium	State	Clarity	Homogeneity	pH	Viscosity (cps)
0.2	4	PEG 400	Liquid	+5	+5	5.78 ± 0.05	478.67 ± 30.55
0.2	6	PEG 400	Liquid	+5	+5	6.33 ± 0.16	1,121.33 ± 65.03[a]
0.2	8	PEG 400	Gel	+5	+5	4.77 ± 0.13	11,946.67 ± 922.89[b]
0.2	10	PEG 400	Gel	+5	+5	4.26 ± 0.05	22,093.33 ± 3,545.44
0.2	4	Mineral oil	Liquid	+3	+4	N/A	481.33 ± 6.11
0.2	6	Mineral oil	Gel	Turbid	+3	N/A	1,693.33 ± 323.32[a]
0.2	7	Mineral oil	Gel	Turbid	Coarse	N/A	7,653.33 ± 2,097.74
0.2	8	Mineral oil	Gel	Turbid	Coarse	N/A	180,733.33 ± 7,814.97[b]
0.4	8	PEG 400	Gel	+5	+5	7.31 ± 0.06	12,586.67 ± 310.70
0.6	8	PEG 400	Gel	+5	+5	7.35 ± 0.01	13,413.33 ± 782.13
0.8	8	PEG 400	Gel	+5	+5	7.39 ± 0.01	14,026.67 ± 589.69
1.0	8	PEG 400	Gel	+5	+5	7.32 ± 0.01	12,733.33 ± 582.87

(B)

Propranolol HCl (%)	R972 (%)	Dispersing medium	State	Clarity	Homogeneity	pH	Viscosity (cps)
0.2	4	PEG 400	Liquid	+5	+5	5.08 ± 0.15	245.33 ± 4.62[a]
0.2	6	PEG 400	Liquid	+5	+5	4.84 ± 0.01	513.33 ± 2.31[b]
0.2	8	PEG 400	Liquid	+5	+5	4.78 ± 0.05	1,025.33 ± 24.11[c]
0.2	10	PEG 400	Liquid	+5	+5	4.93 ± 0.11	1,629.33 ± 16.65
0.2	4	Mineral oil	Gel	+3	+3	N/A	2,068.00 ± 106.51[a]
0.2	6	Mineral oil	Gel	Turbid	Coarse	N/A	8,973.33 ± 794.31[b]
0.2	8	Mineral oil	Gel	Turbid	Coarse	N/A	21,533.33 ± 1620.53[c]
0.4	6	PEG 400	Liquid	+5	+5	7.55 ± 0.00	1,780.00 ± 323.57
0.6	6	PEG 400	Liquid	+5	+5	7.45 ± 0.02	1,986.67 ± 92.92
4.0	6	PEG 400	Liquid	+4	+5	7.21 ± 0.03	3,290.00 ± 36.06

Note: N/A = not available; higher numbers of + indicates more clarity and homogeneity of formula. The superscripts of a, b and c represent a significant difference (*P*-value < 0.05).

Table 3 Physical appearance of salicylic acid-loaded A200 gel (A) and R972 gel (B).

(A)

Salicylic acid (%)	A200 (%)	Dispersing medium	State	Clarity	Homogeneity	pH	Viscosity (cps)
0.2	4	PEG 400	Liquid	+5	+5	5.39 ± 0.24	497.33 ± 16.17
0.2	6	PEG 400	Liquid	+5	+5	4.29 ± 0.08	1,265.33 ± 40.27
0.2	8	PEG 400	Liquid	+5	+5	4.07 ± 0.10	4,013.33 ± 479.31[a]
0.2	10	PEG 400	Gel	+5	+5	4.01 ± 0.03	17,906.67 ± 151.44
0.2	4	Mineral oil	Liquid	Turbid	+3	N/A	469.33 ± 10.07
0.2	6	Mineral oil	Gel	Turbid	Coarse	N/A	866.67 ± 140.48
0.2	7	Mineral oil	Gel	Turbid	Coarse	N/A	11,213.33 ± 1,784.53
0.2	8	Mineral oil	Gel	Turbid	Coarse	N/A	48,000.00 ± 2,588.59[a]
0.4	8	PEG 400	Liquid	+5	+5	5.09 ± 0.03	4,236.67 ± 231.81
0.6	8	PEG 400	Liquid	+5	+5	4.55 ± 0.02	3,653.33 ± 64.29

(B)

Salicylic acid (%)	R972 (%)	Dispersing medium	State	Clarity	Homogeneity	pH	Viscosity (cps)
0.2	4	PEG 400	Liquid	+5	+5	4.04 ± 0.02	330.67 ± 6.11[a]
0.2	6	PEG 400	Liquid	+5	+5	3.85 ± 0.02	900.00 ± 18.33[b]
0.2	8	PEG 400	Liquid	+5	+5	3.90 ± 0.05	3,210.67 ± 64.66[c]
0.2	10	PEG 400	Liquid	+5	+5	3.89 ± 0.03	7,920.00 ± 1,087.38
0.2	4	Mineral oil	Gel	Turbid	Coarse	N/A	1,426.67 ± 140.48[a]
0.2	6	Mineral oil	Gel	Turbid	Coarse	N/A	9,986.67 ± 715.91[b]
0.2	7	Mineral oil	Gel	Turbid	Coarse	N/A	14,733.33 ± 1,248.57
0.2	8	Mineral oil	Gel	Turbid	Coarse	N/A	26,026.67 ± 771.84[c]
0.4	8	PEG 400	Liquid	+5	+5	6.31 ± 0.01	4,950.00 ± 65.57[d]
0.6	8	PEG 400	Liquid	+5	+5	5.42 ± 0.04	4,326.67 ± 445.01[e]
0.8	8	PEG 400	Liquid	+5	+5	4.57 ± 0.03	5,510.00 ± 104.40[f]
1.0	8	PEG 400	Liquid	+5	+5	3.60 ± 0.01	4,473.33 ± 185.02[g]
4.0	8	PEG 400	Liquid	+5	+5	2.60 ± 0.01	5,210.00 ± 0.00
15	8	PEG 400	Liquid	+4	+5	2.39 ± 0.09	4,106.67 ± 46.19
30	8	PEG 400	Liquid	+3	+4	2.57 ± 0.02	3,413.33 ± 61.10
0.4	6	Mineral oil	Gel	Turbid	+2	N/A	8,106.67 ± 700.09[d]
0.6	6	Mineral oil	Gel	Turbid	+2	N/A	8,746.67 ± 560.48[e]
0.8	6	Mineral oil	Gel	Turbid	+2	N/A	9,000.00 ± 523.07[f]
1.0	6	Mineral oil	Gel	Turbid	+2	N/A	10,626.67 ± 438.79[g]

Note: N/A = not available; higher numbers of + indicates more clarity and homogeneity of formula. The superscripts of a, b and c represent a significant difference (*P*-value < 0.05).

< propranolol HCl+ R972 < salicylic acid+ R972. For the drug release from the colloidal silicon dioxide gel in mineral oil into the aqueous receptor medium, 0.2% salicylic acid-loaded A200 gel showed the highest drug release which was followed by 0.2% propranolol HCl-loaded A200 gel and 0.2% salicylic acid-loaded R972 gel, respectively (Figure 1B). The release of salicylic acid from PEG and mineral oil bases showed the similar result. There was no propranolol HCl released from the mineral oil gel containing R972 into aqueous receptor medium (Figure 1B). The hydrophobicity of both R972 and mineral oil led to the prevention of water diffusion into the gel matrix which retarded the drug release. In addition, this cumulative drug release complied with the viscosity of the gels described above as shown in Table 2. Therefore, the hydrophilicity of Aerosil® particles might be a significant factor affecting the drug release which could affect the prolongation of the drug release.

The drug release from most formulas fitted well with the Higuchi's equation with high correlation coefficient (r^2). For PEG 400 base, the release of propranolol HCl into an aqueous medium was higher than that of salicylic acid. It was probably due to a strong affinity of salicylic acid to PEG 400.[27] On the other hand, colloidal silicon dioxide particles have the ability to bind molecules of the drug via H-bond.[12,28] while in the case of R972, there may be the hydrophobic and electrostatic interactions. All factors caused the drug adsorption on its surfaces which this drug adsorption on the surface of colloidal silicon dioxide particles made the drug unavailable for release from the system. However, for mineral oil gel base, the release of salicylic acid into an aqueous medium was higher than that of propranolol HCl. The molecular size of salicylic (138.12) which was smaller than propranolol HCl (295.84)[29] gave a higher release due to high rate of the diffusion through the internal phase. The fluxes of propranolol HCl and salicylic acid released from PEG base were 21.83 ± 1.22 and 16.75 ± 0.94 μg/cm^2/h^{½}, respectively (Table 4 and 5). For the mineral oil gel base, the fluxes of propranolol HCl and salicylic acid released were 26.46 ± 0.92 and 28.06 ± 0.67 μg/cm^2/h^{½}. The results indicated that the amount of both drugs from mineral oil gel base penetrated more through the membrane and diffused out than those systems using PEG gel base.

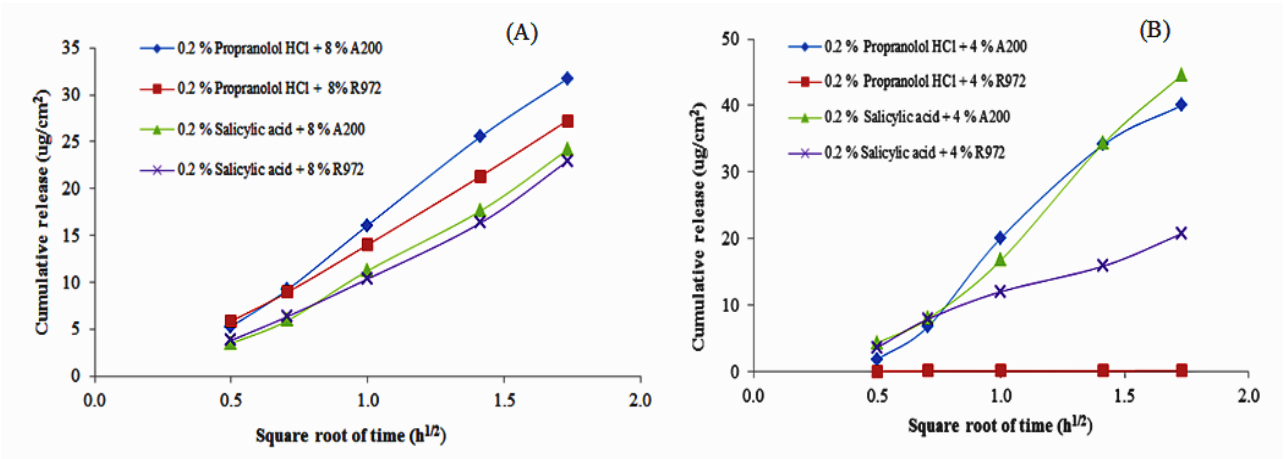

Figure 1 Comparison of cumulative release of 0.2% propranolol HCl and 0.2% salicylic acid from gel containing A200 and R972 dispersed in PEG 400 (A) and mineral oil (B) into aqueous medium (n = 3).

Table 4 Correlation coefficient, average flux and lag time of propranolol HCl release from A200 gels (A) and R972 gels (B) into aqueous medium (n = 3).

(A)

Propranolol HCl (%)	A200 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h $^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	4	PEG 400	0.9987	21.84	0.62	0.04	0.04
0.2	6	PEG 400	0.9995	23.78	1.44	0.06	0.00
0.2	8	PEG 400	0.9995	21.83	1.22	0.07	0.00
0.2	10	PEG 400	0.9985	20.44	1.09	0.05	0.02
0.2	4	Mineral oil	0.9923	36.39	1.55	0.22	0.02
0.2	6	Mineral oil	0.9942	26.46	0.92	0.31	0.00
0.2	7	Mineral oil	0.9935	13.61	3.08	0.09	0.09
0.2	8	Mineral oil	0.9930	12.37	2.67	0.08	0.08
0.4	8	PEG 400	0.9985	48.33	0.82	0.08	0.01
0.6	8	PEG 400	0.9998	65.36	1.95	0.05	0.01
0.8	8	PEG 400	0.9992	96.82	12.81	0.08	0.02
1.0	8	PEG 400	0.9979	123.18	1.80	0.06	0.01

(B)

Propranolol HCl (%)	R972 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h $^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	4	PEG 400	0.9993	19.80	0.67	0.03	0.01
0.2	6	PEG 400	0.9997	17.47	0.95	0.03	0.02
0.2	8	PEG 400	0.9995	17.43	1.45	0.04	0.02
0.2	10	PEG 400	0.9996	16.82	0.85	0.02	0.10

Table 5 Correlation coefficient, average flux and lag time of salicylic acid release from A200 gel (A) and from R972 gels (B) into aqueous medium (n = 3).

(A)

Salicylic acid (%)	A200 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	4	PEG 400	0.9967	21.61	1.75	0.12	0.03
0.2	6	PEG 400	0.9970	17.34	2.04	0.10	0.01
0.2	8	PEG 400	0.9979	16.75	0.94	0.10	0.01
0.2	10	PEG 400	0.9989	16.55	2.28	0.08	0.02
0.2	4	Mineral oil	0.9945	38.28	1.89	0.31	0.13
0.2	6	Mineral oil	0.9976	28.06	0.67	0.19	0.03
0.2	7	Mineral oil	0.9981	26.81	1.31	0.13	0.01
0.2	8	Mineral oil	0.9965	25.48	4.75	0.19	0.16
0.4	8	PEG 400	0.9917	42.99	0.11	0.21	0.01
0.6	8	PEG 400	0.9962	47.60	5.27	0.18	0.02
0.8	8	PEG 400	0.9967	65.02	6.46	0.21	0.03
1.0	8	PEG 400	0.9957	66.88	11.47	0.17	0.05
1.0	8	PEG 400	0.9957	66.88	11.47	0.17	0.05

(B)

Salicylic acid (%)	R972 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	4	PEG 400	0.9967	17.17	1.73	0.05	0.02
0.2	6	PEG 400	0.9973	17.09	1.75	0.09	0.01
0.2	8	PEG 400	0.9957	15.26	0.62	0.08	0.01
0.2	10	PEG 400	0.9984	13.56	0.18	0.06	0.00
0.2	4	Mineral oil	0.9927	16.62	1.18	0.07	0.01
0.2	6	Mineral oil	0.9971	18.07	0.94	0.05	0.01
0.2	7	Mineral oil	0.9977	13.08	1.86	0.01	0.02
0.2	8	Mineral oil	0.9968	13.60	0.74	0.03	0.02

Table 6 Correlation coefficient, average flux and lag time of propranolol HCL release from A200 gels (A) and R972 (B) into receptor PEG 400 medium (n = 3).

(A)

Propranolol HCl (%)	A200 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	6	Mineral oil	0.9047	1.44	0.41	5.80	0.17
0.2	8	PEG 400	0.9939	4.32	0.05	0.92	0.04

(B)

Propranolol HCl (%)	R972 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	4	Mineral oil	0.9887	5.55	0.83	1.90	0.69
0.2	6	Mineral oil	0.9809	5.37	0.59	2.01	0.51
0.2	8	Mineral oil	0.9781	4.92	0.43	2.18	0.33
0.2	8	PEG 400	0.9954	5.30	0.17	0.72	0.07
0.4	8	PEG 400	0.9897	9.58	0.68	0.50	0.06
0.6	8	PEG 400	0.9969	13.22	0.59	0.58	0.02
4.0	8	PEG 400	0.9250	120.57	6.73	7.97	0.83

Effect of the receptor medium on the drug release

The system containing R972 in mineral oil showed an absence of a propranolol HCl release into the aqueous receptor medium. Therefore, PEG 400 was used alternatively as a receptor medium. Previous studies of the use of PEG 400 as a receptor medium in the release has been reported for a low solubility drug.[30] The effect of receptor solution type on drug release is shown in Figure 2. In an aqueous receptor medium, the release of propranolol HCl was higher than that of salicylic acid (Figure 2A), and vice versa in PEG 400 receptor medium (Figure 2B). For the PEG 400 receptor medium, the lag times from release profiles presented the longer duration compared with that in the aqueous medium. The fluxes of drug release through the aqueous medium (Table 4 and 5) were higher than that through PEG 400 (Table 6 and 7). For the aqueous medium, the fluxes of propranolol HCl and salicylic acid were 21.83 ± 1.22 and 16.75 ± 0.94 μg/cm^2/h^{½}, respectively. The fluxes of these formulations from the PEG 400 receptor medium were 4.32 ± 0.05 and 6.81 ± 0.28 μg/cm^2/h^{½}, respectively (Table 6 and 7). Typically, when the receptor medium entered into the gel matrix, the drug dissolved into it and the dissolved drug molecules diffused out into the medium of the receptor compartment. Propranolol HCl showed higher solubility in the aqueous medium than in PEG 400 (Table 1) which supported that the release of it into the aqueous medium was greater than salicylic acid. On the other hand, salicylic acid which had high solubility in PEG 400 showed the notably higher drug release into the PEG 400 receptor medium than propranolol HCl (Figure 2).

Generally, the drug release exhibited a lag period followed afterwards by an instantaneous release.[31] The prediction of lag time is fundamental for a time-delayed delivery system.[32] When compared with the aqueous receptor medium, the delay in lag time occurred in the drug release of mineral oil gel system into the PEG 400 receptor medium. When the receptor medium was water, the lag time for the mineral oil gel base system was rather longer than the PEG gel. Regarding the hydrophilic property of PEG 400, the water could be absorbed into the gel and this influx of water into the gel system initiated the diffusion out of the drug from the gel system.

Table 7 Correlation coefficient, average flux and lag time of salicylic acid release from A200 gels (A) and R972 (B) into PEG 400 medium (n = 3).

(A)

Salicylic acid (%)	A200 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	8	PEG 400	0.9965	6.81	0.28	0.59	0.04
0.4	8	PEG 400	0.9823	25.19	0.93	1.16	0.11
0.6	8	PEG 400	0.9802	25.63	0.95	1.14	0.08
0.8	8	PEG 400	0.9964	29.15	0.97	0.57	0.03
1.0	8	PEG 400	0.9957	33.38	3.04	0.58	0.01
4.0	8	PEG 400	0.9858	113.58	13.29	0.45	0.01
15	8	PEG 400	0.9831	560.37	173.01	0.99	0.19
30	8	PEG 400	0.9591	1,168.71	391.12	1.34	0.34
0.4	6	Mineral oil	0.9082	6.85	1.09	6.17	0.37
0.6	6	Mineral oil	0.9226	6.63	2.23	5.50	2.39
0.8	6	Mineral oil	0.9468	14.51	2.08	4.65	1.00
1.0	6	Mineral oil	0.9753	11.81	3.12	3.39	1.26

(B)

Salicylic acid (%)	R972 (%)	Dispersing medium	Correlation coefficient (r^2)	Flux (μg/cm^2/h$^{1/2}$)		Lag time (h)	
				mean	S.D.	mean	S.D.
0.2	8	PEG 400	0.9923	6.11	1.46	1.88	1.72
0.4	8	PEG 400	0.9899	15.65	1.95	1.00	0.05
0.6	8	PEG 400	0.9958	18.27	0.43	0.60	0.03
0.8	8	PEG 400	0.9949	27.26	3.92	0.60	0.09
1.0	8	PEG 400	0.9916	36.63	4.03	0.91	0.18
4.0	8	PEG 400	0.9976	100.30	1.85	0.45	0.08
15	8	PEG 400	0.9926	603.68	78.04	0.88	0.21
30	8	PEG 400	0.9727	964.84	279.33	1.15	0.39
0.4	6	Mineral oil	0.9926	19.40	0.43	0.63	0.01
0.6	6	Mineral oil	0.9942	33.85	7.35	0.83	0.29
0.8	6	Mineral oil	0.9946	38.59	2.54	0.54	0.03
1.0	6	Mineral oil	0.9969	45.72	4.69	0.54	0.07

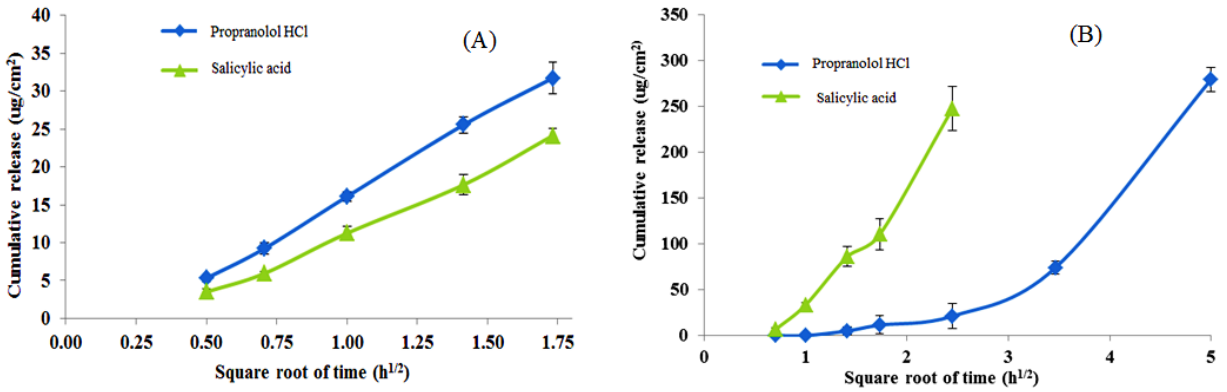

Figure 2 Effect of the receptor medium on the release of the drug from gels using PEG as dispersing medium containing 8% A200 into (A) aqueous medium, (B) PEG 400 medium.

Effect of the colloidal silicon dioxide on the drug release

The increase of concentration of both types of Aerosil® from 4 to 10% (w/w) tended to decrease the cumulative amount of drug released after 3 h (Figure 3 and 4). The cumulative release of salicylic acid at 3 h decreased from 30.77 to 24.29 μg/cm^2 when the concentration of A200 was increased from 4 to 10% (Figure 3A). The significant difference between fluxes was found in propranolol HCl gel. The increased amount of Aerosil® caused the greater complexity of interaction between neighboring particles. The more rigid structure increased the viscosity of the solvent which made it difficult for the drug to diffuse through the network.[22] Thus, the increase in concentration of both types of Aerosil® caused the drug release to decrease from drug-loaded gels (Figure 3 and 4). The data showed that an increase of concentration of A200 from 4 to 10% (w/w) tended to decrease the cumulative amount of drug released after 3 h (Figure 3A). The cumulative release of salicylic acid at 3 h decreased from 30.77 to 24.29 μg/cm^2 while that of propranol HCl at 3 h decreased from 35.79 to 30.103 μg/cm^2, respectively (Figure 3A). Thus, the drug release from the gel system could be controlled by the incorporation of an increased amount of Aerosil®.

Effect of the type of dispersing medium on a drug release

The release of propranolol HCl from the PEG base was higher than that from mineral oil (Figure 5A), and vice versa in case of salicylic acid (Figure 5B). The flux of propranolol HCl from the PEG gel base was higher than that from the mineral oil gel base (Table 4). On the contrary, the flux of salicylic acid from the PEG gel base was lower than that from the mineral oil gel base (Table 5). When the aqueous receptor medium entered into the gel matrix, it could disrupt the connecting bridge between hydrophilic silicon dioxide and the dispersing medium because the silanol groups on the particle surface had more affinity for the hydroxyl group on aqueous receptor media. Thus, the diffusion in the aqueous receptor medium and diffusion out of PEG 400 occurred. Meanwhile, the dissolved propranolol HCl with a low log P (-0.45)[25] was released into the aqueous medium. Therefore, the release of propranolol HCl from the PEG base was higher than that of salicylic acid (Figure 5A). On the contrary, when mineral oil was used as the gel base, the salicylic acid-loaded colloidal silicon dioxide gel comprising of A200 showed a higher drug release. Thus, depending on the polarity of the dispersing medium, the release of the drug from the gel system could be predicted. In addition, the more of an increase in viscosity of the propranolol HCl-loaded gel in mineral oil exhibited a slower release of drug from the gel matrix.

Effect of the drug loading on the drug release

The release of drug in all cases increased as the initial drug loading in the bases increased (Figure 6A and 6B). The fluxes of 0.2 to 4.0% propranolol HCl gels were 5.30 ± 0.17 to 120.57 ± 6.73 μg/cm^2/h^{½} (Table 6). The fluxes of 0.2 – 30% salicylic acid gels using A200 and R972 as gelling agents were 6.81 ± 0.28 to 1,168.71 ± 391.12 and 6.11 ± 1.46 to 964.84 ± 279.33 μg/cm^2/h^{½}, respectively (Table 7). Owing to the increase in thermodynamic activity of the drug in the base, increments of the drug loading dose increased in release rate.[19,20]

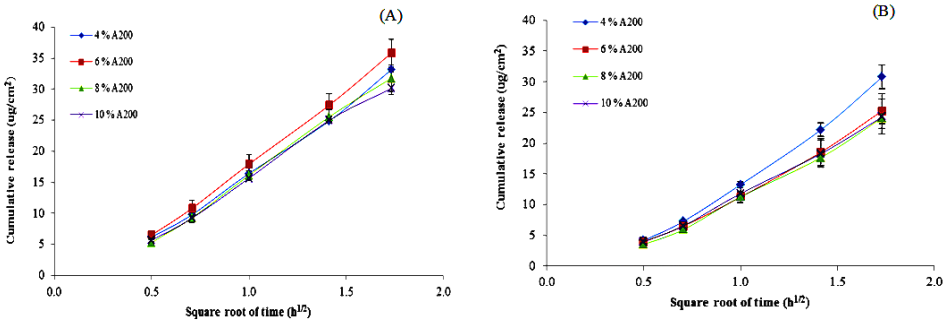

Figure 3 Effect of A200 concentration on the release of 0.2% propronolol HCl (A) and 0.2% salicylic acid (B) dispersed in PEG (n = 3).

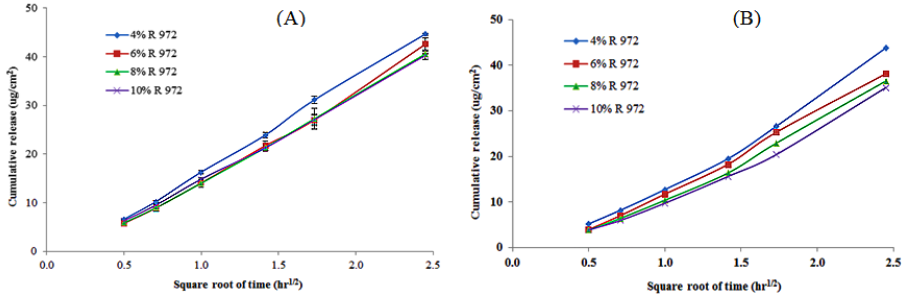

Figure 4 Effect of R972 concentration on the release of 0.2% propranolol HCl (A) and 0.2% salicylic acid (B) dispersed in PEG (n = 3).

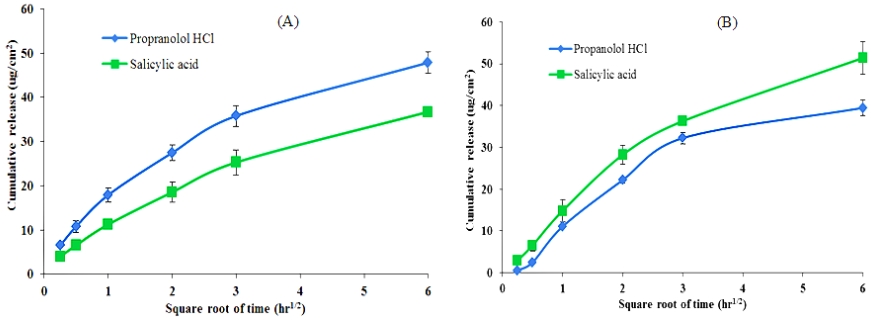

Figure 5 Comparison of (a) 0.2 % propranolol HCl and 0.2 % salicylic dispersed in PEG (A) and mineral oil (B) containing 6% A200 (n = 3).

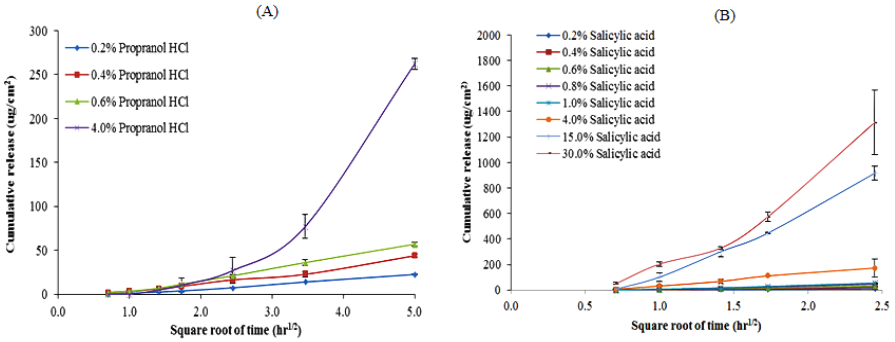

Figure 6 Effect of propranolol HCl (A) and salicylic acid (B) loading dose on cumulative drug release from R972 gels (n = 3).

Conclusion

The release of propranolol HCl 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 A200 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. The obtained gelling system with considerable viscosity and high flux exhibited the potential as the dosage form for retardation or prolongation of drug release.

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Disclosure

The authors report no conflicts of interest in this work.

Declaration of interest:

The authors declare that they have no conflict of interest with this investigation.

Statement of human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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