Role of Xanthan Gum on Propranolol HCl Release from Single and Double Layered Suppositories

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ABSTRACT

Single and double layered propranolol HCl suppositories were fabricated with molding technique using 7:3 PEG 4000: PEG 400 or hydrogenated myristyl esters of olive oil (Phytowax®), melting point of 40°C (L40) and 25°C (L25), as suppository base. Xanthan gum could promote the drug release from hydrophobic L25 and L40 base whereas it could effectively prolong drug release for hydrophilic PEG base. The incorporated xanthan gum into outer part more effectively sustained drug release than an addition into inner part of double layered suppository. The drug release in distilled water was slower than that in phosphate buffer pH 7.4. Both fabricating into double layer and using different base with different hydrophilicity could modulate the drug release for suppository dosage forms.

Keywords: Layered suppository, Propranolol HCl, Xanthan gum, Release

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INTRODUCTION

Suppositories generally consist of an active compound loaded into an inert matrix, which may be either a rigid or semi-rigid base. After administration, the role of the suppository is to liberate the active compound, either by melting due to body temperature or by dissolving in the local mucosal fluids, and then to release the active compound to produce a local effect or to move to the mucosal barriers into the systemic circulatory to produce a pharmacological effect [1]. Typically the physicochemical factors of the active compound affecting the drug release including the solubility of drug in lipid and in water and the particle size of a dispersed drug whereas that of base including its ability to melt, soften, or dissolve at body temperature, its ability to release the drug substance, and its hydrophilic or hydrophobic properties [2,3]. The substances employed as a suppository base are the waxy substances that can melt or dissolve in rectal or vagina fluids. Separation of the active compounds into outer or inner layer of the double layer-type suppository could be performed and also the release characteristic of active compounds could be modulated as fast or prolonged release by using different base in each layer of this suppository.

Sustained release suppository containing progesterone with a double-layered structure was fabricated which hydroxypropylcellulose and carbopol-934P were used as bases of the inner layer and Witepsol W35 was used as a base of the outer layer [4]. Vaginal double layer suppositories were fabricated to load probiotics in core and antibacterial drugs in the outer layer for simultaneous treatment of bacterial vaginosis and vagina recolonization by lactobacilli [5]. The combination of Novata ABPH in the core and Witepsol H-15 in the outer layer as bases was a more suitable vehicle for preparation of this double layer vaginal suppository.

Polymer has been employed as adhesive enhancing promoter or controlled drug release material for suppositories. The addition of carbopol 934 P together with antiemetic drug such as ramosetrol HCl in witepsol H15 could enhance the drug bioavailability with sustained release behavior [6]. Clotrimazole vaginal suppository was prepared using semisynthetic triglyceride as base which an addition of polycarboxyl, HPMC or hyaluronic sodium salt could retain the drug release in this area [7]. Sustainable suppository has been fabricated by mixing sodium alginate and calcium salt into Witepsol [8]. Polyethylene glycol which was hydrophilic waxy material was used as the hydrophilic or fast release suppository base in this study. Hydrogenated myristyl esters of olive oil (Phytowax®) were applied in this study as the hydrophobic meltable suppository base.

Xanthan gum is the cellulosic polymer composed with β-1,4-D-glucan cellulosic backbone having trisaccharide side chain containing β-D-mannose-(1,4)- β-D-glucuronic acid-(1,2)-α-D-mannose [9]. Glucoronic acid and pyruvic groups on its structure promote the anionic charge on its structure. Xanthan gum is widely used as the thickening agent in food industry, and in the pharmaceutical industry. Xanthan gum has been also used as an effective excipient for sustained release formulations; it not only retards drug release, but also provides time-dependent release kinetics [9, 10]. One of the unique characteristics of this polymer is its dramatic gel generating property in aqueous system [11, 12]. Propranolol hydrochloride was employed as the model drug for this study. The aim of this study was to investigate the role of xanthan gum on the drug release from double layer-type fast and
sustained release suppositories fabricated by fusion method. The double layer-type fast and sustained release suppositories were prepared using PEG 4000:PEG400 in a ratio of 70:30 as a fast release base and hydrogenated myristyl esters of olive oil as a hydrophobic base.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride (Batch No. 941002) was purchased from China National Chemical Imp. & Exp., China. Polyethylene glycol was purchased from PC Drug, Thailand. The hydrogenated myristyl esters of olive oil (Phytowax®) having melting point of 40°C (L40) and 25°C (L25) were purchased from Sophim, Parc de la Cassine, France was passed through sieve No. 60 before use. Potassium dihydrogen phosphate (Ajax Finechem, New South Wales, Australia), citric acid (B/NO. AF609161, Seven Hills, NSW, Australia) and anhydrous Na₂HPO₄ (B/No.AF405300, Ajax Fineche, Australia) were used as received. Other chemicals were of reagent grade purchased from PC Drug, Thailand.

Methods

Preparation of suppositories

There were two main suppository bases: the hydrophilic and hydrophobic suppository bases. The double layer-type suppositories containing hydrophilic component (PEG base) and hydrophobic component (hydrogenated myristyl esters of olive oil (Phytowax®), melting point of 40°C (L40) and 25°C (L25)), were fabricated using the special suppository mold as shown in Fig. 1A and B. The suppository base was melted on water bath and then was mixed with propranolol HCL and the mixture was filled into the stainless steel suppository mold. This mold composed of the stainless steel rods to place into selected component during setting to be the semisolid in used mold cavity and then the rods were removed before another component without or with polymer were subsequently filled into the created cavity. The O ring was used to adjust the distance of the rods into the cavity. The suppository was also prepared with different amount of drug and polymer loaded in each layer.

Fig. 1 Suppository mold with stainless steel rods (A,B) and appearance of double layer-type suppositories (C).
Evaluations of suppositories

A test of drug liberation was undertaken using a dissolution apparatus (Prolabo, France) with the basket method at 25 rpm. A volume of 700 ml of phosphate buffer, pH 7.4 equilibrated at 37°C was utilized as dissolution fluid. Five milliliters of dissolution medium was withdrawn at predetermined intervals. The volume of dissolution medium was kept at 700 ml by adding a fresh medium. The samples were assayed by an UV-Vis spectrophotometer (Perkin-Elmer, Germany) at the wavelength of 320 nm (n=3).

RESULTS AND DISCUSSION

Hydrogenated myristyl esters of olive oil (Phytowax®), melting point of 40°C (L40) and 25°C (L25), were employed as the suppository base. The homogeneous propranolol HCl suppositories were obtained. In vitro drug release into phosphate buffer pH 7.4 (Fig. 2) indicated the apparent low drug release from L40 and 50:50 L40:L25 which showed the steady release after 60 min. An addition of lower melting point L25 could slightly enhance the drug release from this oleaginous base. The rather high xanthan gum loading (25%) significantly increased the drug release from these oleaginous bases with near zero order release. High hydrophilic molecular structure of this polymer was owing to glucose, mannose and glucuronic acid linked with 1,4 β-glycosidic linkage hence their hydration could absorb the water to dissolve the dispersed drug particles and subsequently the dissolved drug molecules could diffuse outward from environmental hydrophobic matrix into the dissolution medium [9, 10]. Xanthan gum should disperse particularly and homogeneously in oleaginous base as proposed and presented in Fig. 3. The deposited xanthan gum on suppository surface could hydrate and swell which promoted the pore formation and water penetration into the suppository matrix to dissolve the incorporated drug gradually.

Fig. 2 Dissolution profiles of 75 mg propranolol HCl released from L40 or L25 simple suppositories without or containing 25% xanthan gum in phosphate buffer pH 7.4.
Fig. 3 Schematic indicating the dispersion of xanthan gum in L40 or L40:L25 suppository bases.

Propranolol HCl released from 70:30 PEG4000:PEG400 suppository base comprising xanthan gum is shown in Fig. 4. The addition of 0.5% xanthan gum did not notably change the drug release. Prolongation of drug release was evident as the amount of xanthan gum loading was higher. The low and nearly steady release was observed for systems comprising xanthan gum loading higher than 15%. The fast drug dissolution from this suppository base without xanthan gum was due to its high hydrophilicity and solubility. Gel formation with generating the viscous environment from xanthan gum hydration apparently sustained the drug release. Xanthan gum gel as presented in Fig. 5 could modulate the penetration rate and amount of medium and also the drug diffusion into the test medium. Ketoprofen released from PEG base faster than that from Witepsol H 15 and Massa Estarinum B whereas the incorporated HPMP prolonged the drug release from PEG base [13].

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Fig. 4 Dissolution profiles of 75 mg propranolol HCl released from 7:3 PEG 4000: PEG 400 simple suppositories containing different amount of xanthan gum in phosphate buffer pH 7.4.
Fig. 5 Schematic gel formation owing to the hydration of xanthan gum around the propranolol HCl suppository using 7:3 PEG 4000: PEG 400 as suppository base.

Fig. 6 is the dissolution profile of propranolol HCl released from double layered suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) containing drug of (70%) with different amount of xanthan gum and inner layer (I) comprising drug of 11.25 mg (30%) in phosphate buffer pH 7.4. The rather initial rapid drug release was mainly from the basal area of the inner suppository which there was no xanthan gum addition combined with the drug dissolved from the outer layer especially for the low xanthan gum loading in this part. However the slower drug release was attained for the higher xanthan gum loading into the outer part. Some of xanthan gum gel might expand and then close the hole of the inner suppository at basal part therefore the apparent slow drug release was seen and the initial abrupt drug release was less than 30%.
Drug dissolution profiles of double layer suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) containing drug of 37.5 mg with different amount of xanthan gum and inner layer containing drug of 37.5 mg in distilled water and phosphate buffer pH 7.4 are shown in Fig. 7. This result indicated the influence of dissolution medium on the role of xanthan gum to control the drug release. The drug released slower in distilled water than in phosphate buffer pH 7.4. Propranolol HCl, an anionic basic drug with a pKa of 9.45, should be more soluble in acidic environment than in neutral and alkaline environment, respectively. Typically, the propranolol should dissolve easier in the free ion environment to avoid the salting out or common ion effect. The decline of solubility in HCl buffer pH 1.2 was attributed to the common-ion (chloride) effect, which provided an unexpected trend in solubility of this drug in the presence of chloride ion in this acidic medium. This related evidence was noted by Rekhi et al. (1989) [14] and Takka et al. (2001) [15]. In addition, the pH dependence on dissolution of this drug from matrices containing HPMC and carbopol was reported previously [16]. Therefore this was not the reason for this obtained evidence. For xanthan gum, this anionic polymer could freely hydrate in aqueous system hence the other anionic ion could suppress the hydration and recoil properties and that the gel formation could be diminished. The high anionic ions from phosphate buffer could decrease the viscous gel from xanthan gum resulted in the lower efficacy to control the drug release from suppository whereas the higher gel formation in distilled water effectively retarded the drug release.

![Graph](image)

Fig. 7 Dissolution profiles of propranolol HCl release from double layer suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) containing drug of 37.5 mg with different amount of xanthan gum and inner layer containing drug of 37.5 mg in distilled water (W) and phosphate buffer pH 7.4 (P).

By comparison, to study the role of xanthan gum deposited in iner or outer parts of suppository, the more rapid drug release was found for the addition of xanthan gum into iner part since the fast drug release was attainable from the outer layer (Fig. 8). More than 50% initial drug liberated into dissolution medium was attained from test systems because the rapid dissolution of the outer layer. The controlled drug release owing to the hydration...
of xanthan gum was evident for the inner suppository after 60 min. The drug release from suppository containing xanthan gum in outer layer was notably slower as seen in Fig. 8. Because the suddenly hydrating of xanthan gum effectively modulate the drug release both from outer and also inner parts of these systems. The efficacy of xanthan gum for sustainable drug release from layered tablets has been reported from our research work [17]. However the low xanthan gum as 1% did not clearly demonstrate this behavior owing to its too minimal interconnected polymer network to form the sufficient strong viscous gel.

![Graph](image_url)

*Fig. 8* Dissolution profiles of propranolol HCl release from double layer suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) containing drug of 37.5 mg with different amount of xanthan gum and inner layer (I) containing drug of 37.5 mg with different amount of xanthan gum in phosphate buffer pH 7.4 (P).

The use of PEG base as outer part and L40 as inner part of double layer suppository was conducted. The rapid drug released from outer part was observed and then there was nearly no drug release from inner layer (Fig. 9). However the higher addition of xanthan gum promoted the higher drug release from the inner layer. As seen from Fig. 2, the 25% xanthan gum addition could apparently enhance the drug release from this oleaginous base. Metoprolol tartrate mini-tablet prepared by hot melt extrusion comprising ethylcellulose/dibutyl sebacate as matrix base could be promoted the drug release by an addition of xanthan gum [18]. This enhancement effect depended on the amount of xanthan gum loading. The greater amount of xanthan gum, the higher matrix swelling and drug liberation. Therefore the small amount xanthan gum was difficult to promote the drug release effectively from L40. An addition of xanthan gum into the outer suppository still more effective to control the drug release from prepared systems containing the different drug loading in outer and inner parts as seen in Figs. 10 and 11, respectively.
Fig. 9 Dissolution profiles of propranolol HCl release from double layer suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) composed of drug 37.5 mg and L40 inner layer (I) composed of drug 37.5 mg with 2.5% xanthan gum in phosphate buffer pH 7.4 (P).

Fig. 10 Dissolution profiles of propranolol HCl release from double layer suppositories comprising 7:3 PEG 4000: PEG 400 outer layer (E) and 7:3 PEG 4000: PEG 400 inner layer (I) containing 2.5% xanthan gum at different part with different drug amount in distilled water (W).
CONCLUSION

Double layered suppository could be fabricated using PEG or hydrogenated myristyl esters of olive oil as hydrophilic and hydrophobic suppository base, respectively. Xanthan gum could promote the drug release from hydrophobic base whereas it could prolong the drug release from hydrophilic base with dose manner.

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REFERENCES


