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ORIGINAL ARTICLE

Drug release behavior of polymeric matrix filled in capsule

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Abstract A single unit sustainable drug release system was developed using hydroxypropyl methylcellulose (HPMC)-based matrices filled in capsule as the drug delivery device. Release behavior of propranolol HCl from these capsules was investigated and least square fitting was performed for the dissolution data with the different mathematical expressions. Effect of diluent, polymer, pH and hydrodynamic force on the drug release from the developed systems was investigated. The utilization of HPMC as a matrix former extended the drug release longer than 8 h. HPMC viscosity grades affected the drug release, that is, increasing the amount of fillers such as lactose and dibasic calcium phosphate enhanced the drug release rate of HPMC matrices. The hydrodynamic force, type and amount of incorporated polymer apparently influenced the drug release. The physiochemical properties of polymers and interaction between HPMC and other polymers were important factors for prolongation of the drug release. The release mechanism from HPMC-based matrices in capsules was the non-Fickian transport in which the sustainable drug release of HPMC capsules could be achieved by the addition of polymeric matrix.

1. Introduction

Typically, hard gelatin capsule is commonly used for filling large number of drugs including antibiotics. The production of pharmaceutical products in the form of capsules is both cost- and process-effective. The utilization of capsules as a controlled drug delivery device is also interesting. The lipid system in a molten state can be directly filled into hard gelatin capsules to control the drug release. A diffusion-controlled system was obtained with Gelucire® containing lithium sulfate, which remained inert in the aqueous environment at 37 °C. On the contrary, the erosion was proved to control the release of indomethacin when the dispersible Gelucire® was added to the non-dispersible Gelucire® (Vial-Bernasconi et al., 1995). Some retardation in urinary excretion was obtained for total salicylate when administering capsules of aspirin mixed with Gelucire® 50/13 (Djimbo et al., 1984). For colon drug delivery with a chitosan capsule, an additional outer enteric coating prevented the drug release in the stomach owing to the solubility of chitosan under acidic conditions. Resultant enteric-coated chitosan dispersed system capsules reached the large

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intestine within 1–3 h after oral administration and they gradually degraded in the colon (Shimono et al., 2002). Pulsatile drug delivery system has been developed using a water insoluble capsule body and a hydrophilic plug (HPMC or guar gum). The body portion was cross-linked by formaldehyde and heat treatment which the drug was liberated from a limited surface area of the open end of this hard gelatin capsule. This design was similar to the Pulsincap™ system which had an insoluble capsule body (Gothoskar et al., 2004). In addition, the type of hydrophilic agent (HPMC or guar gum) and the molecular weight of HPMC affected the drug release (Mukesh and Sumitra, 2002).

Propranolol HCl (PPH) is widely used in therapeutics for its antihypertensive and antiarrhythmic actions. It has a short plasma half-life of about 2–6 h. Consequently, it has to be frequently taken in order to maintain the plasma concentration in the therapeutic range. The main purpose of the extended release product is to reduce side effects and prolong the drug intake interval and, thus, it is also convenient for drug administration. Furthermore, being highly water soluble drug (Lund, 1994) it is suitable to be used as model drug for this study to assess the efficacy of the developed system for prolongation of its release.

HPMC capsules do not become brittle when exposed to low humidity and they are chemically stable. In addition, the slower drug release from HPMC capsule than that from gelatin capsules has been reported (Cole et al., 2004). HPMC capsules were used in this study to minimize the effect of charge interaction, especially the positive charge of propranolol and the negative charge of gelatin. HPMC has been employed extensively as a hydrophilic matrix former in oral controlled-release dosage forms for various drugs. This popularity can be attributed to its non-toxic nature, its capability to accommodate high levels of drug loading in matrix and a small influence of processing variables on drug release (Ganga et al., 1992; Taylan et al., 1996; Chattaraj and Das, 1996). There are many disadvantages for manufacturing matrix tablet including the longer period and higher energy-consuming process. In addition, some polymer using as matrix former renders the granules elastic and the elastic deformation during the compression leads to soft tablets with not adequate hardness. For matrix filled in capsule, the cost of production will be minimized because of the lesser production steps and excipients in formula. Although the single-unit matrices of PPH sustained release tablets have been widely developed, in order to reduce the frequency of dosing and to produce steady pharmacological effects, the development of this drug into single HPMC matrix filling into capsules has not been reported. The purpose of this study was to develop PPH sustained release capsules using different polymers as a matrix former and to investigate the factors affecting the drug release from the prepared capsules , which is the simplest way to make prolonged release formulations. Authors need to highlight draw backs of matrix tablets such as.

2. Materials and methods

2.1. Materials

PPH was purchased from China National Chemical Imp. & Exp., Shanghai, China. HPMCs (Methocel® K 4M, Methocel® K 15M, Methocel® K 100M and Methocel® E 15LV were purchased from Colorcon Asia Pacific Pvt., Ltd., Bangkok, Thailand. Chitosan (Aqua premier, Chonburi, Thailand) with a degree of deacetylation of 99.3% and a molecular weight of 70 kDa was passed through sieve No. 80 mesh before being used. Dibasic calcium phosphate (DPC) (Sudeep Pharma Ltd., India), HCl (Baker Analyzed, A.C.S. Reagent, USA), and xanthan gum (Xantural 75®, CP Kelco U.S., Inc. USA.) were used as received. Monobasic potassium phosphate, sodium hydroxide pellets, sodium bicarbonate and sodium chloride were purchased from P.C. Drug Center Co., Ltd., Thailand. HPMC capsules size No.1 were kindly supplied by Capsugel, Pranakorn Sriauthuthaya, Thailand and used as received.

2.2. Formulation and preparation of single-unit controlled release capsules

Hard HPMC capsules (size No. 1 with a volume of 0.49 ± 0.01 mL) were filled with the drug and matrix component. The amount of PPH per capsule was 40 mg. Different viscosity grades of HPMC, i.e. Methocel® type K4M, K15M, K100M and E15LV, were utilized as a matrix former to investigate the effect of viscosity grade of HPMC on the drug release. A study was also performed for the effect of types and amounts of diluents (lactose, dibasic calcium phosphate (DPC) and sodium bicarbonate ($NaHCO_3$)) and polymers (chitosan and xanthan gum) on the drug release from HPMC matrices. The tapped density of the excipients (Table 1) was used to determine the amount to fill into capsules. The capsule formula presenting the excipient composition is shown in Table 2. The powders were mixed manually with a mortar and pestle for 5 min to obtain the homogeneous powder mix and filled in capsules using a capsule filling machine No. 1 (S.T.P No.1 B.M., Bangkok, Thailand).

2.3. Evaluation of physical properties of capsule

Weight variation of capsules was determined by using an analytical balance. Twenty capsules were individually weighed. The contents of each capsule were removed by using a suitable means. The empty shells were individually accurately weighed and calculated for the net weight of its contents by subtracting the weight of the shell from the respective gross weight.

Table 1 Tapped density of drug and materials (mean ± SD, $n = 3$).

Materials	Tapped density (g/mL)
PPH	0.42 ± 0.00
Chitosan (180 mesh passed)	0.32 ± 0.01
Dibasic calcium phosphate	0.86 ± 0.01
Ethyl cellulose	0.32 ± 0.00
HPMC K15M	0.46 ± 0.01
HPMC K4M	0.49 ± 0.00
HPMC K100M	0.48 ± 0.01
HPMC E15LV	0.51 ± 0.01
Lactose	0.67 ± 0.00
Sodium bicarbonate	0.67 ± 0.00
Xanthan gum	0.69 ± 0.02