

Release of Propranolol Hydrochloride from Matrix Capsules/Disc: Effect of Matrix Additives

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Abstract—Propranolol Hydrochloride (PPH), non-cardio selective beta blocker, has been widely used to manage the hypertension, phaeochromocytoma, angina pectoris, myocardial infarction and cardiac arrhythmias. PPH has a short half-life (3–4 hours) so it was selected as a model drug for controlled release to minimize the fluctuations of blood pressure. The aim of this research was to develop the controlled release PPH with the various additives i.e., Ethylcellulose (EC), Hydroxypropyl Methylcellulose (HPMC), Hydrogenated Vegetable Oil (HVO) and Glyceryl Monostearate (GMS). Eighty milligrams of PPH was mixed with the different types (EC, HPMC, HVO or GMS) and concentrations (30 to 60 %w/w) of the additives. The mix powders were granulated into granule using wet granulation, and then the fine granule was filled into the capsules or compressed into the tablets discs. The PPH labeled amount and release characteristics were further evaluated according to the United States Pharmacopoeia (USP31). The results show that PPH matrixes were successfully prepared by wet granulation method. For all formula, the PPH content was within the range of 90–110 %. The release of PPH from formulation containing 30% w/w of HPMC and HVO was significantly retarded. Moreover, the release kinetics of PPH disc was followed by Higuchi's model. The PPH release was governed by diffusion mechanism. In conclusion, these HPMC and HVO matrixs can be effectively controlled the PPH release.

Index Terms—Propranolol Hydrochloride (PPH), matrix additives, controlled release

I. INTRODUCTION

In general, controlled release dosage forms are intended to maintain the relative steady concentrations of the drug in the blood, tissues, and target organs. In these systems, the loading dose is released first and followed by the release of the maintenance dose of the drug at a constant rate. However, drug release of controlled release dosage forms involves more than one mechanism, and the drug release rates of controlled release dosage forms could vary at different release stages [1]. The criterion of controlled release dosage forms is different from conventional dosage forms, in order to ensure that there is no dose dumping. According to the USP *in vitro* dissolution test requirement for a conventional dosage form, most of the drug needs to be released from the dosage forms within a short period of time, whereas, for a

controlled release dosage form, a desired drug release profile is required.

Nowadays, there are two main techniques for the development of controlled release dosage forms that include the matrix systems and coated (membrane) systems. For matrix system, the drug is dispersed in the swellable hydrophilic substances, the insoluble matrix of rigid non swellable hydrophobic materials or the plastic materials. On the other hand, coated (membrane) systems can be prepared using four basic approaches that include pan coating with the solvent evaporation, fluidized-bed coating with the solvent evaporation, compaction coating and melt coating.

Polymer matrix systems have been widely developed due to the low cost, less manufacturing process and green environment and the lack of use organic solvent. Apart from active ingredients each systems are usually formulated using polymer alone or combinations of polymers, waxy materials, and supplementary functional excipients. The Ethylcellulose (EC), Hydroxypropyl Methylcellulose (HPMC), Hydrogenated Vegetable Oil (HVO) and Glyceryl Monostearate (GMS) are the polymers and waxy materials that can be used as the matrix materials for the controlled release dosage forms.

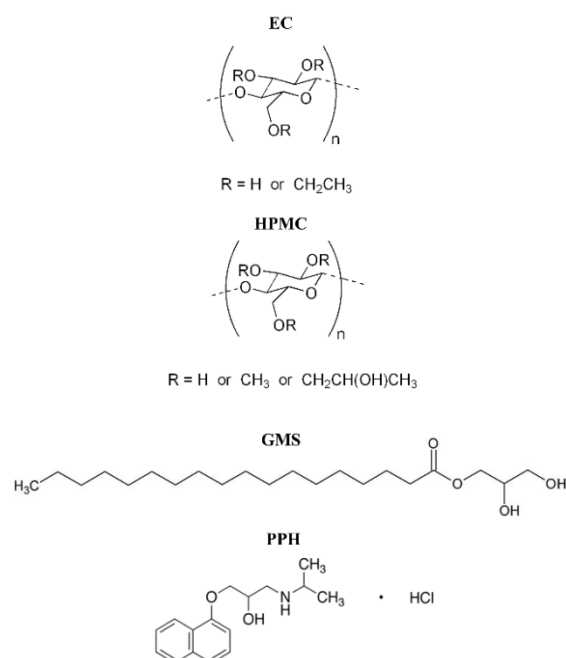


Figure 1. Molecular structure of compounds.

EC, Fig. 1 with complete ethoxy substitution (DS=3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_n C_{12}H_{23}O_5$ where n can be varied that provide a wide variety of molecular weights. EC, an ethyl ether of cellulose, is a long chain polymer of β -anhydroglucose units jointed together by acetal linkages. It is a tasteless, free-flowing, white to light tan-colored powder.

HPMC, Fig. 1, a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. It is an odorless and tasteless, white or creamy white fibrous or granular powder.

HVO is a mixture of triglycerides of fatty acid. It's present in various forms *i.e.*, fine powder, flakes, or pellets. The colors of the materials depend on the manufacturing process and the forms. In general, the material is white to yellowish-white with the powder grades appearing more white-colored than the coarser grades.

GMS, Fig. 1, consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$) and glyceryl monopalmitate ($C_{19}H_{38}O_4$) is a white to cream-colored, waxlike solid in the form of beads, or powder. It is waxy to the touch and has a slightly fatty odor and taste.

The drugs having high water solubility, short biological half-life (3-4 h) and rapidly eliminate from the body are mainly selected to develop the controlled release dosage forms. The controlled release dosage form decrease fluctuation in plasma drug concentration, maintain drug concentration in plasma and improved the efficiency of treatments by increasing the patient compliance especially with long-term treatment for chronic diseases.

Propranolol hydrochloride (PPH, Fig. 1), non-cardio selective beta blocker affect the heart and circulation (blood flow through arteries and veins), has been widely used management of hypertension, pheochromocytoma, angina pectoris, myocardial infarction, cardiac arrhythmias and other heart or circulatory conditions [2]. PPH has a short half-life (3-4 hours) and is an acid-soluble basic drug [3]. Due to these characteristics, it was selected as a model drug for controlled release to minimize the fluctuations of blood pressure. The hydrophilic polymer matrix systems delay the drug release by creating the polymer hydration, diffusion and erosion-resistant gel layer.

The aim of this research was to develop the controlled release PPH with the various additives. The different types (EC, HPMC, HVO or GMS) and concentrations (30 to 60 %w/w) of the additives was selected as matrix materials. The matrix of PPH and additives was prepared using wet granulation and then developed as capsules and tablets discs. The PPH labeled amount and release characteristics were evaluated.

II. MATERIALS AND METHODS

A. Materials

Propranolol hydrochloride (PPH, Sigma, St. Louis, MO, USA.), Ethocel[®] (ethylcellulose (EC), Rama chem.,

Thailand), Methocel[®] F4M (hydroxypropyl methylcellulose (HPMC), Srichand-united dispensary Ltd, Thailand), Lubritab[®] (hydrogenated vegetable oil (HVO) mahta group trading Ltd., PART., India) and glyceryl monostearate (GMS, Rama Production Co., Ltd. Thailand).

B. Methods

Preparation of PPH Capsule/Tablets discs: Eighty milligrams of PPH was mixed with the different types (EC, HPMC, HVO or GMS) and concentrations (30 to 60 %w/w) of the matrix additives (Table I) in the plastic bags. The mix powders were granulated into granule using wet granulation technique. The wetted mass passed through the sieve and dried under hot air oven. The dried granule was filled into the capsules (No. 1) using capsule filling machine (Model Panviv A-01) or compressed into the tablets discs using hand hydraulic press machine (Specac P/N 15011/25011, UK) at a constant force (40 kN) using stainless flat-face punches with a diameter of 9.53 mm.

TABLE I. COMPOSITION OF PPH FORMULATION

Rx	1	2	3	4	5	6	7
PPH (mg)	80	80	80	80	80	80	80
EC (mg)	-	120	-	-	-	-	-
HPMC (mg)	-	-	120	-	-	60	60
HVO (mg)	-	-	-	120	-	60	-
GMS (mg)	-	-	-	-	120	-	60

The PPH Labeled Amount: Twenty capsules were taken randomly, opened and poured in a mortar. A portion of the crushed powder was weighed and transferred into a 100 volumetric flask containing a portion of methanol (AR grade, RCI Lab Scan, Ltd, Thailand). The mixture was stirred on a magnetic stirrer, diluted and adjusted the volume with methanol and then assayed using UV-visible spectrophotometer (Spectronic[®] Genesyn 5, Rochester, U.S.A.) at a wavelength of 290 nm. The PPH content was calculated and expressed a % labeled amount.

In Vitro Dissolution Studies: The dissolution test was performed using dissolution apparatus 1 (VANKEL Technology Group Cary, North Carolina). In the first hour, 900 mL of pH 1.2 was used as the dissolution medium and then the medium was change to buffer pH 7.5 until 12 h. at temperature $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Five milliliter of sample was withdrawn from the dissolution apparatus at designated intervals, and then the same milliliter of the fresh dissolution medium was replaced immediately. Samples were filtered through a $0.45 \mu\text{m}$ membrane filter and the released drug absorbance was measured at 289 nm using a UV/visible spectrophotometer (Spectronic genesys 5, U.S.A.).

C. Drug Release Kinetics

To investigate the drug release kinetics of all formulations, data obtained from *in vitro* release study was analyzed according to the zero, first and, Higuchi's models [4].

1) Zero-order model

The data obtained from *in vitro* PPH release studies. The cumulative amounts of PPH released (Q_t) vs. time (t) were plotted. This model describes the PPH release pattern, assuming that the PPH release rate is independent with the concentration, as Eq. (1):

$$Q_t = k_0 t \quad (1)$$

where Q_t is the amount of PPH released at time t ; k_0 is the zero-order release constant, expressed in units of concentration/time; and t is the time.

2) First-order model

The data obtained were plotted as the natural logarithm ($\ln$) of the cumulative percentage of PPH remaining vs. time (t). This model describes the PPH release pattern, assuming that the PPH release rate is dependent with the concentration, as Eq. (2):

$$\ln C = \ln C_0 - k_1 t \quad (2)$$

where C_0 is the initial concentration of the PPH, k_1 is the first-order rate constant, and t is the time

3) Higuchi model

This model describes PPH release from a matrix system as a process that is dependent on the square root of time, based on Fickian diffusion, as Eq. (3):

$$Q_t = kt^{1/2} \quad (3)$$

where Q_t is the cumulative amount of PPH released at time t , k is the Higuchi release rate constant, and t is the time. A straight line can be obtained by plotting Q_t vs. t . The resultant slope is the Higuchi rate constant.

III. RESULTS AND DISCUSSION

The wet granulation of PPH/additives and PPH capsules were successfully prepared using wet granulation method. Also, the granules could be compressed into the tablets disc. PPH was fixed at 80 mg per capsule/disc and matrix additives were varied in the range of 30-60 % weight by weight (w/w) (60-120 mg) as seen in Table I. The amount of PPH was based on the treatment dose of PPH.

A. The PPH Label Amount

The PPH labeled amount of PPH capsules/discs was displayed in Table II. The content of PPH was between 98.6-109.1 %. The results showed that PPH content from all formulations have been in accordance with the USP criteria (90-110 % LA), indicating the homogeneous mixture was obtained from this method [5], [6]. This approach could provide the content uniformity of PPH.

TABLE II. THE PPH LABELED AMOUNT OF PPH/MATRIX ADDITIVES CAPSULES AND DISCS

Rx	PPH labeled amount (%)
1	N.D.*
2	98.6 ± 0.5
3	101.4 ± 1.4
4	108.0 ± 2.6
5	109.3 ± 0.9
6	109.1 ± 1.5
7	101.1 ± 0.6

* N.D. = not determined

B. In Vitro Dissolution Studies

In Vitro dissolution test of PPH capsules was also investigated. The results shown that PPH was rapidly released (almost 90%) from capsules containing HVO and GMS within 20 min, as seen in Fig. 2(A). This might be due to the GMS that showed negligible swelling property and it was not sufficient enough to control the rapid release [7]. Capsule containing HPMC and EC showed a slower released than those of HVO and GMS. PPH was approximately released 43 to 53%, respectively. The slowest PPH release was observed in HPMC matrix capsules. This could be attributed to an increase in the viscosity of the hydrated gel layer (HPMC, EC) with the increase in mucilage concentration while HVO and GMS without this feature. This results in agreement with the research of Cai *et al.* [8].

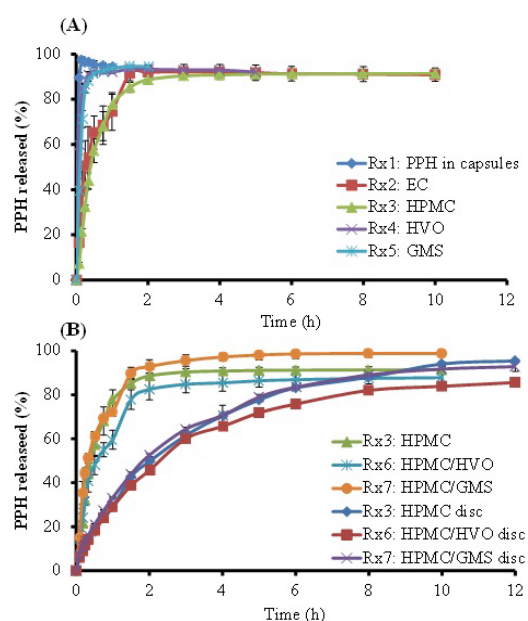


Figure 2. The release profiles of PPH from capsules or discs (A) different matrix additives, compared to PPH in capsules, (B) mixing of HPMC and other additives.

From the above results, HPMC matrix capsules was selected to combine with the other additives (HVO/GMS) and then compressed into disc in order to provide the controlled release of PPH. The PPH matrix of HPMC/HVO and HPMC/GMS capsules provided the different PPH release profiles. HPMC/GMS matrix capsule showed the increased release of PPH when compare to HPMC only, while HPMC/HVO matrix capsule showed the decreased PPH release as seen in Fig. 2(B). On the other hand, HPMC discs with and without HVO or GMS retarded the release of PPH. The insignificant difference in PPH release profiles between the discs was observed. The controlled PPH release was seen over 6 h of test. However, HPMC/HVO discs obtained the best controllable way for PPH. The slight lower dissolution rate of PPH was achieved, compared to the other disc. These might be because the HVO acted as the wet granulation binder to promote the stiffen granules of the discs. They prolonged the diffusion between the

PPH and release medium during the dissolution test, and resulted in the controlled release profile. According to the results, the matrix of HPMC and HVO in term of disc may be a candidate to be a controlled release carrier for PPH.

C. Drug Released Kinetics

In this research, various mathematical equation have been propose for kinetic analysis of PPH from formulations. The release kinetic analysis of the release profile of PPH from HPMC/HVO matrix disc was conducted by fitting to a zero order, first order and Higuchi's model. The zero order describes the system that drug release is independent from its concentrations while the first order describes the system that drug release is concentration dependent. For Higuchi's model, drug release from the matrix is directly proportional to the square root of time [9].

Table III shows the correlation coefficients (R^2) of kinetic analysis. The highest R^2 was detected by Higuchi's model, indicating the release of PPH from HPMC/HVO matrix disc was followed by Higuchi's model and governed by diffusion mechanism

TABLE III. KINETICS MODELS OF PPH RELEASE PROFILE OF HPMC/HVO MATRIX DISC

Release model	Correlation Coefficients (R^2)
Zero-order	0.8214
First-order	0.6290
Higuchi	0.9657

IV. CONCLUSION

In conclusion, the proper amount of HPMC and HVO offered as usable matrix polymers for developing PPH controlled dosage forms. HPMC/HVO matrix disc could slow down the release profile of PPH. The gel layer of HPMC, hydrophobic nature of HVO and the compaction of matrix controlled the hydration and diffusion of PPH. This approach may be suitable for development of controlled delivery of highly soluble drugs such as PPH.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

AUTHOR CONTRIBUTIONS

Benchawan Chamsai conducted the research, analyzed the data and wrote the manuscript. Wipada Samprasit proofed and gave the comment on the manuscript. All authors had approved the final version.

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REFERENCES

- [1] J. Patel and A. Patel, "Artificial neural networking in controlled drug delivery," *Artificial Neural Network for Drug Design, Delivery and Disposition*, pp. 195-218, 2016.
- [2] S. C. Sweetman, *Martindale 36th ed.: The Complete Drug Reference*, London: Pharmaceutical Press, 2007, p. 1380.
- [3] N. D. Zaharuddin, M. I. Noordin, and A. Kadivar, "The use of hibiscus esculentus (Okra) gum in sustaining the release of propranolol hydrochloride in a solid oral dosage form," *BioMed Research International*, vol. 2014, p. 735891, 2014.
- [4] S. Dash, P. N. Murthy, L. Nath, and P. Chowdhury, "Kinetic modeling on drug release from controlled drug delivery systems," *Acta Poloniae Pharmaceutica*, vol. 67, no. 3, pp. 217-223, 2010.
- [5] C. Bharti, S. Isha, C. Lovish, and H. Hemant, "Design, development & evaluation of solid dispersion incorporated transdermal gel of benzoyl peroxide," *International Journal of Scientific Research and Reviews*, vol. 3, no. 3, pp. 70-81, 2014.
- [6] Y. Chen, *et al.*, "Initial drug dissolution from amorphous solid dispersions controlled by polymer dissolution and drug-polymer interaction," *Pharmaceutical Research*, vol. 33, no. 10, pp. 2445-2458, 2016.
- [7] H. Al-Zein, K. Sakeer, and F. K. Alanazi, "Designing an extended release waxy matrix tablet containing nicardipine-hydroxy propyl β cyclodextrin complex," *Saudi Pharmaceutical Journal*, vol. 19, pp. 245-253, 2011.
- [8] Z. Cai, *et al.*, "Preparation and evaluation of sustained-release solid dispersions co-loading gastrodin with borneol as an oral brain-targeting enhancer," *Acta Pharmaceutica Sinica*, vol. 4, no. 1, pp. 86-93, 2014.
- [9] M. Saeedi, K. Morteza-semnani, and M. Sagheb-doust, "Evaluation of *Plantago major* L. seed mucilage as a rate controlling matrix for sustained release of propranolol hydrochloride," *Acta. Pharm.*, vol. 63, pp. 99-114, 2013.

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