Original Article

# A Programmable 'Tablet-In-Capsule' Drug Delivery Device for Oral Administration of Propranolol Hydrochloride

**R. Archana*, B.V. Basavaraj[1], S. Bharath[1], R. Deveswaran[1], V. Madhavan[2]**

[1] Department of Pharmaceutics, M.S.Ramaiah College of Pharmacy, M.S.R.Nagar, M.S.R.I.T Post, Bangalore-560 054, Karnataka, India
[2] Department of Pharmacognosy, M.S.Ramaiah College of Pharmacy, M.S.R.Nagar, M.S.R.I.T Post, Bangalore-560 054, Karnataka, India

## ABSTRACT

The objective of the present study was to develop a programmable novel 'tablet-in-capsule' drug delivery device using a swellable hydrophilic polymer Hydroxypropylmethylcellulose K 15 (HPMC K 15) as a plug material for chronotherapeutic delivery of a model drug propranolol hydrochloride. The hard gelatin capsule body was made water insoluble by formaldehyde and heat treatment. The erodible HPMC K 15 tablet plugs were prepared by direct compression. Powder plug batches were also formulated by manually filling the capsule with the drug-polymer blend and the drug and slightly compressed to form a compact plug. The influence of formulation blend of powder plug and tablet plug were studied for the release pattern of propranolol hydrochloride. The batch $PP_2$ (Powder Plug) with 130 mg HPMC K 15, 90 mg dicalcium phosphate (DCP) satisfied the criteria of lag time i.e. less than 10% drug release within 4 h. At the end of 8 h, the batch $PP_2$ showed percentage drug release up to 56.99%. Tablet plugs showed a lag time of only 2 h. The drug release from the tablet plug batches after the lag time was in an extended fashion. It was shown that increasing the concentration of lactose resulted in faster erosion of the plug and thus shorter lag time. Batch $TP_3$ (Tablet Plug) with HPMC K 15: lactose in the 1:1 ratio (200 mg) showed complete drug release within 8 h due to faster erosion of the plug material. In conclusion tablet-in-capsule propranolol hydrochloride delivery system can be suggested as an appropriate device for chronotherapeutic delivery of drug.

**Keywords:** HPMC K 15, Propranolol hydrochloride, lag time, chronotherapeutic delivery.

## INTRODUCTION

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day.[1] One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated.[2] The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity.[1]

Chronotherapeutics deals with the medical treatment according to the human daily working cycle that corresponds to a person's daily, monthly, seasonal or yearly biological clock or in order to maximize the health benefits and minimize the adverse effects. The main goal of Chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness.[3]

Currently, there are antihypertensive products in the market that are Chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm.[4] A delayed release profile, where the drug is released

**Received Date** : 23-03-2012
**Revised Date** : 15-05-2012
**Accepted Date** : 25-05-2012
**DOI:** 10.5530/rjps.2012.2.5

**Address for correspondence**
***Mr. B.V. Basavaraj,***
Asst. Professor,
Dept. of Pharmaceutics,
M.S. Ramaiah College of Pharmacy,
Bangalore - 560 054.
Email: bvbasu@rediffmail.com

**www.rjps.in**

completely after a defined lag time, $t_L$, has advantage over sustained release dosage forms for drugs which develop biological tolerance, with an extensive first pass metabolism, targeted to a specific site in the intestinal tract and for the adaptation of therapeutic needs to circadian rhythms of body functions or diseases.[5] The lag time is defined as the time until 10% of drug has been released. Pulsatile delivery is defined as the rapid and transient release of certain amounts of drug molecules within a short time period immediately after a predetermined off-release period, i.e, lag time. These deliver the drug at the right time and at the right place and in the right amount thus increasing patient compliance.[6] Pulsincap is a delivery system which releases drug contents at a predetermined time or at a specific site within the gastrointestinal tract.[7] Each capsule is composed of a water insoluble body and a water soluble cap, and also contains the drug dose which is sealed with a hydrogel plug.[4] On oral administration, the water soluble capsule cap dissolves in the gastric juices and the hydrogel plug swells. At predetermined time point after the ingestion, the swollen plug is ejected from the Pulsincap dosage form after which the encapsulated dosage formulation is then released into the small intestine fluid.[8] A Swellable hydrophilic polymer, HPMC K15 was selected as plug material so as to induce delayed release of the drug.

Propranolol hydrochloride was chosen as a model active pharmaceutical agent, as it is a non selective beta-blocker used to treat tremors, angina (chest pain), hypertension (high blood pressure), heart rhythm disorders, and other heart or circulatory conditions.[9] It is highly lipophilic, rapidly and completely absorbed after oral administration. It readily crosses the blood brain barrier and the plasma half-life is only about 2 to 3 hours. However, it undergoes an extensive hepatic metabolism and on an average only about 25% reaches the systemic circulation.[10]

## OBJECTIVE

The objective of the study was to develop a 'tablet-in-capsule' drug delivery device for Propranolol hydrochloride using swellable hydrophilic polymer HPMC K15 as a plug material for chronotherapeutic delivery in the treatment of hypertension.

## MATERIALS AND METHODS

### Materials

Propranolol hydrochloride was received as gift sample from Unidrug Innovative Pharma Technologies Ltd, Indore, Madhyapradesh. Dicalciumphosphate and HPMC K15 (Himedia Laboratories Pvt. Ltd, Mumbai); Formaldehyde (RFCL limited, NewDelhi); All the formulation ingredients used were of high quality AR grade.

### Preparation of impermeable/insoluble capsule body

The body portion of the hard gelatin capsules were cross-linked by the combined effect of formaldehyde and heat treatment.[8] The body and the cap of the hard gelatin capsules (size 0) were separated. Capsule bodies were exposed to formaldehyde vapors for six hours in desiccator at room temperature and dried at 50°C for 24 hours in hot air oven. Afterwards the capsule body and the untreated soluble cap were stored in desiccator for further use.

### Disintegration test for empty capsules[8]

Disintegration test for formaldehyde treated empty capsules was carried out in a standard USP tablet disintegration test apparatus (Remi equipments). The open upper surface of the basket rack assembly was closed by means of a 10 # wire gauge. Six capsules were used for the study. The time required for disintegration/dissolution of capsules was noted.

### Powder plugs

Accurately weighed quantity of dicalcium phosphate (DCP) was manually filled into the capsule body which was previously treated with formaldehyde. Drug (Propranolol hydrochloride, 80 mg) was added next to DCP. Weighed quantity of the hydrophilic swellable polymer (HPMC 15K) was placed on top and compressed lightly using a rod to form a compact plug. The total weight of the powder mass was 300 mg. The soluble cap of the capsule was placed on the top of the body. The composition of different batches is shown in the Table 1.

### Tablet plugs

Accurately weighed amounts of HPMC K15 were directly compressed into tablets using a 6 mm round concave punches in a rotary tablet machine 5 (Rimek, RSB-4 mini press Cadmach, Ahmedabad, India). Weighed quantity of drug (Propranolol 80 mg) was filled into the capsules of size 0 and then HPMC K15 tablet plug was inserted into the capsule body. Finally the soluble cap was fitted to the capsule body. The composition of different batches is shown in the Table 2.

### *In-vitro* dissolution studies of the capsules

*In-vitro* dissolution studies of all the formulations were performed in USP XXIII Type-I dissolution test apparatus (Labindia DS 8000) using 0.1N HCl as dissolution medium for first 2 h at 37 ± 1°C. Capsule was

**Table 1: Powder plugs**

| Batch code* | Weight of HPMC K 15 (mg) | Weight of DCP (mg) | Weight of drug (mg) | Total weight of the plug (mg) |
|---|---|---|---|---|
| $PP_1$ | 100 | 120 | 80 | 300 |
| $PP_2$ | 130 | 90 | 80 | 300 |
| $PP_3$ | 150 | 70 | 80 | 300 |
| $PP_4$ | 150 | 130 | 80 | 360 |

*PP- powder plug.

**Table 2: Tablet plugs**

| Batch code* | Composition of plug | Weight of plug (mg) | Weight of drug (mg) |
|---|---|---|---|
| $TP_1$ | HPMC K15 | 200 | 80 |
| $TP_2$ | HPMC K15 | 150 | 80 |
| $TP_3$ | HPMC K15 : lactose (1:1) | 200 | 80 |
| $TP_4$ | HPMC K15 : lactose (1:0.5) | 150 | 80 |
| $TP_5$ | HPMC K15 : lactose (4:1) | 250 | 80 |

*TP- tablet plug.

placed in the basket and was rotated at 50 rpm. After 2 hours, 0.1N HCl was replaced with phosphate buffer pH 6.8 and dissolution was continued. The aliquots with suitable dilution were analyzed using Shimadzu UV-Visible spectrophotometer at 290 nm.

### Drug release kinetics

The dissolution data of all batches were fitted to zero-order, first-order, Hixson-Crowell, Higuchi and Korsemeyer and Peppas models to predict the drug release mechanism.

## RESULTS AND DISCUSSION

### Effect of formaldehyde treated hard gelatin capsules on lag time

Gelatin is readily soluble in biological fluids at body temperature. On exposure of empty hard gelatin capsule bodies to formaldehyde vapours followed by heat treatment, the solubility of the capsules was modified. Capsule bodies were exposed to formaldehyde vapours for six hours in desicator at room temperature and dried at 50ºC for 24 h in hot air oven so that a complete reaction between formaldehyde and gelatin will take place.[11] Formaldehyde is known to cause cross linking between the aminoacid chains of gelatin.[12] Initial formation of gelatin methylol compound which leads to a methylene ether crosslink between a gelatin amino-methylol compound and an unspecified gelatin-methylol compound.[13] The results of disintegration test revealed that, all the untreated six capsule caps disintegrated and solubilised within 30 min but formaldehyde treated capsule body remained intact for more than 24 h. This shows that the drug will be released only from the open end of the hard gelatin capsule body.

### Powder plugs

In case of powder plugs, Batch $PP_2$ (130 mg HPMC K 15, 90 mg DCP, 80 mg drug) satisfied the criteria of lag time i.e. less than 10% drug release within 4 h. But the release of the drug was delayed even after 4 h lag time. The extent of drug release depends on rate of erosion of the plug material. The batches $PP_1$, $PP_4$ showed 3 h lag time followed by burst release of the drug.

### Tablet plugs

In case of tablet plug batches a tight fit is necessary between the impermeable capsule body wall and the tablet plug for good results, as it minimizes the penetration of water to the capsule content and drug release prior to complete erosion or ejection of the plug. Batches $TP_2$, $TP_4$, $TP_5$ showed lag time of only 2 h followed by burst release of the drug. So tablet plug batches have failed to meet the criteria of lag time.

### Effect of lactose

Among the batches $TP_3$, $TP_4$, $TP_5$ containing lactose along with HPMC K15, the batches $TP_4$ and $TP_5$ showed comparatively better results. This shows that on increasing the concentration of lactose, the drug release got increased due to faster erosion of the plug. The percentage drug release from both powder plug and tablet plug batches within 4 h were shown in the Tables 3 and 4 respectively. The dissolution profiles of powder plug and tablet plug batches are shown in the Figures 1 and 2 respectively.

**Table 3: Drug release from powder plugs within 4 h**

| Time (h) | $PP_1$ (%) | $PP_2$ (%) | $PP_3$ (%) | $PP_4$ (%) |
|---|---|---|---|---|
| 1 | 2.81 | 1.12 | 2.81 | 1.68 |
| 2 | 2.27 | 1.13 | 10.1 | 5.08 |
| 3 | 5.65 | 4.51 | 18.02 | 7.33 |
| 4 | 19.18 | 9.61 | 32.18 | 14.1 |

**Table 4: Drug release from tablet plugs within 4 h**

| Time (h) | $TP_1$ (%) | $TP_2$ (%) | $TP_3$ (%) | $TP_4$ (%) | TP5 (%) |
|---|---|---|---|---|---|
| 1 | 2.81 | 2.25 | 20.81 | 6.1 | 6.81 |
| 2 | 16.3 | 8.46 | 22.73 | 10.1 | 10.19 |
| 3 | 21.4 | 13.52 | 41.57 | 19.18 | 18.63 |
| 4 | 30.45 | 20.89 | 52 | 31.1 | 29.9 |

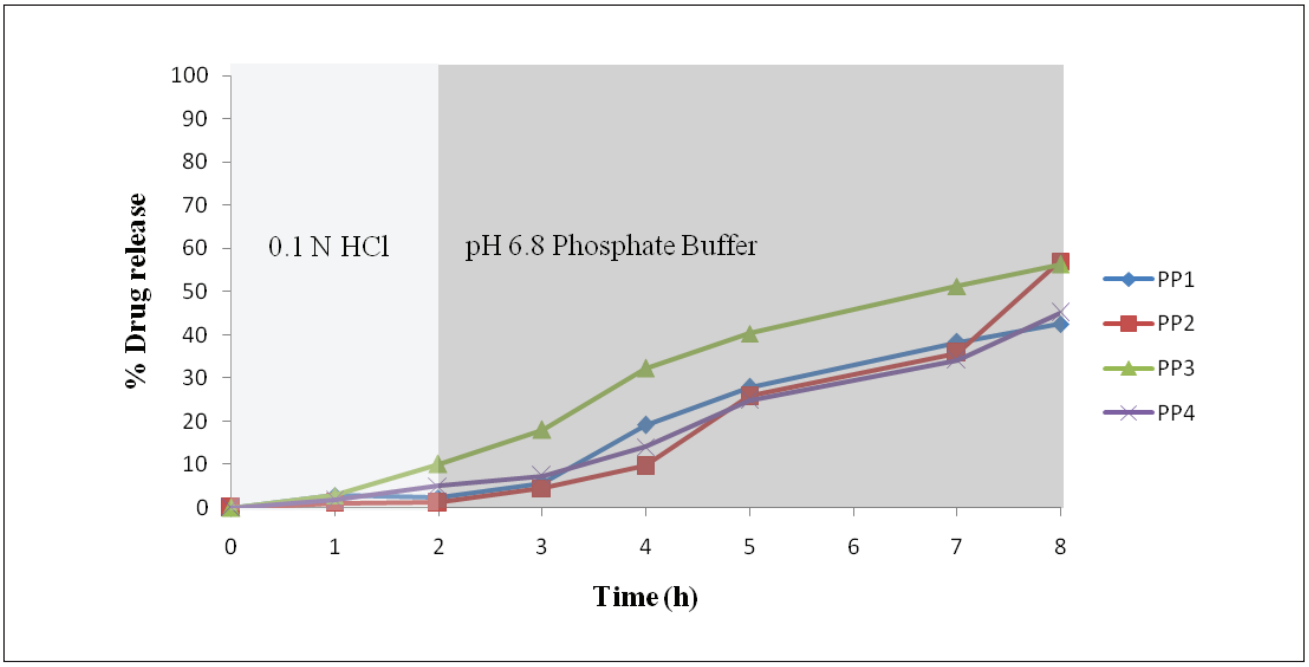


**Figure 1:** Dissolution profile of powder plugs.

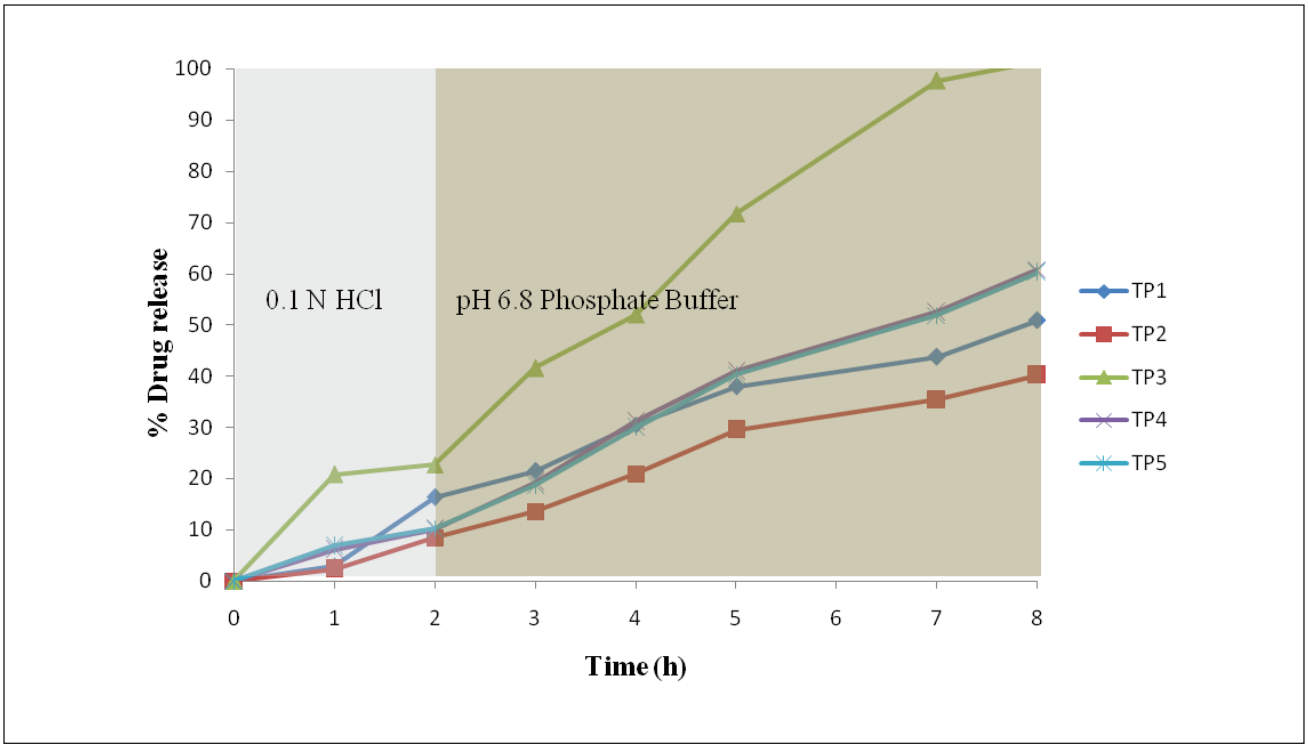


**Figure 2:** Dissolution profile of tablet plugs.

**Table 5: Drug release kinetics**

| | Drug release kinetics | | | |
|---|---|---|---|---|
| **Batches** | $r^2$ | *k* | *n* | **Model** |
| $PP_1$ | 0.9594 | 1.5411 | 1.6314 | Zero-order |
| $PP_2$ | 0.9615 | 0.5644 | 0.8710 | Peppas |
| $PP_3$ | 0.9867 | 3.1623 | 1.4919 | Zero-order |
| $PP_4$ | 0.9948 | 1.4302 | 1.6634 | Peppas |
| $TP_1$ | 0.9927 | 4.0341 | 1.3312 | First-order |
| $TP_2$ | 0.9899 | 2.7278 | 1.3824 | Zero-order |
| $TP_3$ | 0.9913 | 16.9165 | 0.8784 | Zero-order |
| $TP_4$ | 0.9935 | 5.5526 | 1.1769 | Zero-order |
| $TP_5$ | 0.9933 | 5.2855 | 1.1894 | Peppas |

### Drug release kinetics

The predicted drug release mechanism by PCP Disso V3 software indicated that all the prepared batches showed $r^2$ value between 0.9594–0.9948. Batch $PP_2$ showed $r^2$ value of 0.9615, *k* value of 0.5644 and *n* value of 0.8710. The drug release kinetics of all the powder plug and tablet plug batches are shown in the Table 5. It can be predicted that the drug release exhibited peppas model with the drug release by diffusion process.

## CONCLUSION

A tablet-in-capsule propranolol hydrochloride drug delivery system was developed for oral use, using HPMC K 15 as an erodible plug in a water insoluble capsule body. This system provided a delayed drug release showing a lag time with an extended release up to 8 h. Burst release of the drug can also be obtained by including $NaHCO_3$ in the formulation which pushes off the plug material by generating $CO_2$. Thus, it can be used for chronotherapeutic drug delivery of propranolol hydrochloride for preventing early morning heart stroke.

## REFERENCES


1. Prasanthi NI, Swathi G, Manikiran SS. Chronotherapeutics: A New Vista In Novel Drug Delivery Systems. Int J Pharm Sci Rev Res 2011;**6** (2): 66–75.
2. Pranay Wal, Ankita Wal, Awani K Rai, Ashutosh Saxena. Chronopharmaceutics As A Novel Approach For Drug Delivery. J Pharm Sci Tech 2009;**1**(2):59–62.
3. Rupali Singh, Pramod Kumar Sharma and Rishabha Malviya. Review on Chronotherapeutics - A New Remedy in the Treatment of Various Diseases. Eur J Bio Sci 2010;**2**(3):67–76.
4. Sajan J, Cinu TA, Chacko AJ, Litty J and Jaseeda T. Chronotherapeutics and Chronotherapeutic Drug Delivery Systems. Tropical J Pharm Res 2009;**8**(5):467–475.
5. Mohammad Barzegar-Jalalia B, Mohammad Reza Siyahi-Shadbada, Azim Barzegar-Jalaic, Khosro Adibkiaa D, Ghobad Mohammadie, Behnaz Aghaia, Mahdi Zeraatia. Design and Evaluation of Delayed-Release Osmotic Capsule of Acetaminophen. Iranian J Pharm Sci Spring 2006;**2**(2):65–72.
6. Anantha Nayaki Ravula, Bairi Agaiah Goud. A review on-Recent Advances In Oral Pulsatile Drug Delivery. J Adv Pharm Sci 2011;**1**(1): 132–145.
7. Hedben J, Wilson C, Spiller R, Gilchrist P, Blackshaw E, Frier M Perkins A. Regional differences in quinine absorption from the undisturbed human colon assessed using a timed release delivery system. Pharm Res 1999;**16**:1087–1092.
8. Mukesh C Gohel, Manhapra Sumitra G. Modulation of active pharmaceutical material release from a novel 'tablet in capsule system' containing an effervescent blend. J of Controlled Rel 2002;**79**:157–164.
9. Laurence LB, John SL, Keith LP. Goodman Gilman's The Pharmacological Basis 0f Therapeutics. 11th ed. USA: Mc Graw-Hill Companies; 2006;272.
10. Sweetman SC. Martindale: The Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005; 989–990.
11. Khan A Waris, Ahmed Mohammed Gulzar, Ramesh B. Formulation and evaluation of novel sustained release capsules of terbutaline sulphate. Int Res J Pharm 2011;**2**(1):249–255.
12. Charbel Tengroth, Ulla Gasslander, Fredrik O Andersson and Sven P Jacobsson. Cross-linking of gelatin capsules with formaldehyde and other aldehydes: an FTIR spectroscopy study. Pharma Dev Tech 2005; **10**(3): 405–412.
13. Davis P, Tabor BE. Kinetic study of the crosslinking of gelatin by formaldehyde and glyoxal. J Polymer Sci 2003;**1**(2):799–815.