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Formulation and Evaluation of Propranolol Hydrochloride Oral Controlled Release Matrix Tablets

S. VIDYADHARA*, P. RAMA RAO[1] AND J. A. PRASAD
K. V. S. R. Siddhartha College of Pharmaceutical Sciences,
Polyclinic Road, Vijayawada-520010.
[1]Natco Pharma Limited, Hyderabad-500033.

Propranolol hydrochloride was formulated as oral controlled release matrix tablets using hydrophilic polymer such as hydroxypropyl methylcellulose K_4M along with electrolytes. In this work a new attempt was made for *in situ* interactions between drug and electrolytes are devised to control the release of highly water-soluble drugs from oral hydrophilic monolithic systems. Electrolytes such as calcium carbonate, magnesium carbonate, sodium bicarbonate and sodium carbonate were used at different concentrations (5 to 100 mg per tablet) in various formulations, while drug and polymer concentrations were maintained constantly at 1:2 level in all the formulations. These electrolytes were used to monitor matrix swelling and gel properties. Electrolytes at higher concentrations (75 to 100 mg per tablet) exhibited greater inhibition in drug release from the matrix and at low concentrations (5 to 50 mg per tablet) these were accounted for controlled release of the drug. The results indicated that the drug released at a controlled rate which is due to differential swelling rate, matrix stiffening and provides a uniform gel layer. These findings indicated that the swelling and gel formation in the presence of ionisable species with in the hydrophilic matrices provide an attractive alternative for controlled drug delivery from a simple monolithic system.

Recently numerous hydrophilic polymers have been investigated and are currently used in the design of complex controlled release systems[1-3]. The polymers that are most widely used for design of controlled release of a drug include nonionic hydroxypropyl methylcellulose K_4M (Methocel K_4M), polyethylene oxide (PEO) and alginates. The major challenge in the development of new controlled release devices is to achieve optimal drug concentrations at the site of action. To achieve optimal concentration at the site of action, liberation of the drug from the device must be controlled as accurately as possible[4]. The dissolution in a monolithic sense for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. This limitation of hydrophilic polymers may be circumvented through modification of the physical and chemical infrastructure of the polymeric gel system.

*For correspondence
E-mail: svidyadhara@yahoo.com

The drug candidate selected under study is propranolol hydrochloride (PPN), a beta-adrenoceptor blocking agent, is very useful for lowering blood pressure in mild to moderate hypertension and also extremely useful in the management of angina pectoris[5]. It is almost completely absorbed from the gastrointestinal tract after oral administration. It is reported to have plasma half-life of about 3 to 6 h, time of peak plasma concentration occurs about 1 to 2 h, after an oral dose. It is reported to have considerable first pass metabolism[6]. PPN is usually administered as conventional tablet, containing 40 mg, two to three times daily. The drug as hydrochloride is soluble 1 in 20 of water. These bio-pharmaceutical and physicochemical properties reveal that PPN is an ideal candidate to develop into a controlled release

system.

In the present work, a reliable process has been established for inducing *in situ* reactions between pharmaceutically acceptable electrolytes and drug which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix structure. Furthermore, this may produce heterogeneous domains within the swollen gel boundary.

In the past, alkaline compounds or buffers have been included in solid oral formulation of several acidic drugs that undergo dissolution rate-limited absorption[7]. The same principle of addition of buffers, osmotically active agents, surfactants or combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques[8]. However, more specific strategy has been employed to apply the same principle to design a simple directly compressible, monolithic controlled release system. In general the application of buffers and ionizable compounds in dosage form design has essentially been limited to the minimization of localized GIT adverse effects and the pH solubility dependency of poorly soluble compounds[9,10].

The aim of this work was to provide and expand on a means to design, formulate and develop a novel oral monolithic, controlled release tablet dosage form of a drug that may be tailored to provide quasi steady state drug release over an extended period of time[11]. The rationale behind the mechanism and dynamics of electrolytes-induced matrix stiffening and structural changes to the gel is the basis of controlled drug release has also been elucidated.

MATERIALS AND METHODS

Hydroxypropyl methylcellulose K_4M C.R premium grade polymer (Methocel K_4M) was a gift sample received from M/S Colorcon Asia Pvt. Ltd., Mumbai. Propranolol hydrochloride was a gift sample received from M/S Natco Pharma Ltd., Hyderabad. Calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, (S. D. Fine Chemicals Limited, Mumbai) are of analytical grades and procured commercially.

Preparation of tablets:

The controlled release monolithic tablet formulation consisted of a polymer, drug and electrolyte. The ratio of drug:polymer was always maintained at 1:2 level, while the electrolyte content was varied. The composition of various tablets formulations were given in Table 1. The materials are individually passed through sieve no. 60 and mixed for 15 min. The powder mixture was lubricated with talc and compressed into tablets using a Cadmac single punch machine. To minimize processing variables, all batches of tablets were compressed under identical conditions. The compressed tablets were evaluated for physical parameters such as weight uniformity, hardness, friability and drug content.

Drug release studies:

Dissolution studies on each formulation were performed in a calibrated three station dissolution test apparatus equipped with paddles, employing 900 ml of 1.2 pH buffer solution for the first 1.5 h and pH 6.8 buffer solution for the remaining period as dissolution medium. The paddles were operated to rotate at 100 rpm and maintained the temperature at 37 ± 1^0 throughout the experiment. Samples were withdrawn at regular intervals up to 12 h and each time were replaced with equal volume of fresh medium to maintain the volume of dissolution medium constant through out the experiment. Drug content of the samples was determined by ultraviolet spectroscopy at 320 nm[12], after suitable dilution of the samples. Necessary corrections were made for the loss of drug due to each sampling and plotted the cumulative amount of drug release Vs square root of time period to calculate the drug release rate constant.

Photomicrographs:

For photomicrographs, the tablets on which dissolution studies have been completed are collected, a thin layer of the swollen matrix was taken and mounted on a glass slide. The slides were observed under a compound microscope at 10X magnification. The photomicrographs of the gel structure were taken by fixing a camera to the magnifying lens.

RESULTS AND DISCUSSION

The present study was undertaken to design and evaluate the controlled release matrix tablets of propranolol hydrochloride with methocel K_4M by employing electrolytes as drug release retardants. All batches of tablets were produced under similar conditions to avoid processing variables. These tablets were preliminarily evaluated for various physical parameters such as weight uniformity, hardness, friability and drug content. All the batches of tablets with different electrolyte composition were within the weight range of 230 mg to 350 mg. The hardness of all the tablets were maintained in the range of 6 to 8 kg/cm^2. The loss in total weight of the tablets due to friability was in the

TABLE 1: COMPOSITION OF VARIOUS TABLET FORMULATIONS

Formulations	Ingredients (mg / tablet)						
	Propranolol HCl	Methocel K_4M	Cal. carbonate	Mag. carbonate	Sod. bicarbonate	Sod. carbonate	Talc
F	80	160	-	-	-	-	2.4
F1	80	160	25	-	-	-	2.65
F2	80	160	50	-	-	-	2.9
F3	80	160	75	-	-	-	3.15
F4	80	160	100	-	-	-	3.4
F5	80	160	-	15	-	-	2.55
F6	80	160	-	25	-	-	2.65
F7	80	160	-	50	-	-	2.9
F8	80	160	-	75	-	-	3.15
F9	80	160	-	100	-	-	3.4
F10	80	160	-	-	25	-	2.65
F11	80	160	-	-	50	-	2.9
F12	80	160	-	-	75	-	3.15
F13	80	160	-	-	100	-	3.4
F14	80	160	-	-	-	5	2.45
F15	80	160	-	-	-	25	2.65
F16	80	160	-	-	-	50	2.9
F17	80	160	-	-	-	75	3.15
F18	80	160	-	-	-	100	3.4

range of 0.1 to 0.2%. The drug content in different tablet formulations was highly uniform and in the range of 98 to 104%.

From the *in vitro* dissolution studies, it was observed that formulations F_9 and F_{18} showed greater inhibition of release rate of propranolol hydrochloride from the tablet matrix. By the incorporation of electrolyte into hydrophilic monolithic tablet matrices, it was possible to reduce the release rate of drug over an extended period of time. With an increase in electrolyte concentration from 0 to 100 mg per tablet, the release rate of propranolol reduced indicating greater inhibition in comparison to the control formulation F. The effect of electrolyte concentration on drug release from the tablet matrix was shown in fig. 1. Under the given experimental conditions, the formulations F_3, F_5, F_{10}, F_{11} and F_{14} were considered optimal as they exhibited a linear release pattern, which might meet the USP extended release test 1 profiles for propranolol hydrochloride. The other formulations given in Table 1 have also showed greater inhibition (fig. 2) of rate of release of propranolol hydrochloride from the matrix tablets. The dissolution rate constants for various formulations were recorded in Table 2.

The inclusion of electrolyte within the swollen matrix for controlling the release rate of propranolol hydrochloride might lead to the formation of free base of propranolol and fundamental structural changes in gel boundary, thus inducing the textural variations in the swollen matrix. It appears that electrolyte-induced buffer threshold within the matrix plays an essential role in effective interaction with drug and textural changes. Further it may be due to higher

pKa values of electrolytes, which can display higher buffer threshold for maintaining suitable pH inside the matrix. Electrolytes such as magnesium carbonate and sodium carbonate with pH values greater than 10 might exert a better and desired control on drug release from matrix tablets.

The photomicrographs (figs. 3a and 3b) of swollen matrix gel layer showed that formulation F (3a, without electrolyte) had highly transparent swollen gel layer with glassy surface, indicating rapid drug release. Formulation F_5 (3b, with 15 mg magnesium carbonate) exhibited less swollen gel layer with glassy surface that is indicative of an interaction between the electrolyte and the drug, which resulted in controlled drug release. On the basis of photomicrographic examination, the following mechanism might prevail during the period of drug release from the swollen intragel structure. As the dissolution medium enters the periphery of the tablet, there is a rapid electrolyte water interaction with significant chemical reaction through electrolyte solubilization and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process the electrolyte present in the gel boundary could have been converted to chloride form (for example sodium carbonate/ magnesium carbonate to sodium chloride/magnesium

TABLE 2: DISSOLUTION RATE CONSTANTS FOR VARIOUS FORMULATIONS

Formulations	Release rate constant ($mg/h^{1/2}$)
F	21.70
F_1	20.00
F_2	20.00
F_3	17.60
F_4	17.25
F_5	17.25
F_6	14.25
F_7	14.00
F_8	13.35
F_9	12.55
F_{10}	18.00
F_{11}	17.80
F_{12}	15.60
F_{13}	15.15
F_{14}	17.25
F_{15}	14.00
F_{16}	13.85
F_{17}	13.10
F_{18}	13.00

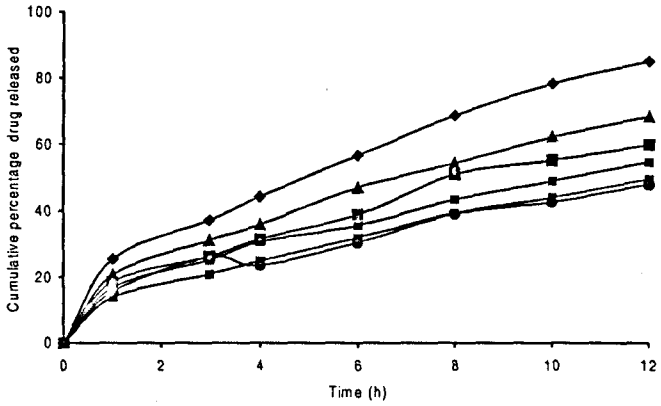


Fig. 1: Release of propranolol hydrochloride from different formulations.

Release of propranolol hydrochloride from formulations containing different concentration of magnesium carbonate in pH 1.2 buffer solution for first 1.5 h and pH 6.8 buffer solution for the remaining period. F (-♦-), F5 (-▲-), F6 (-◘-), F7 (-x-), F8 (-*-), F9 (-●-).

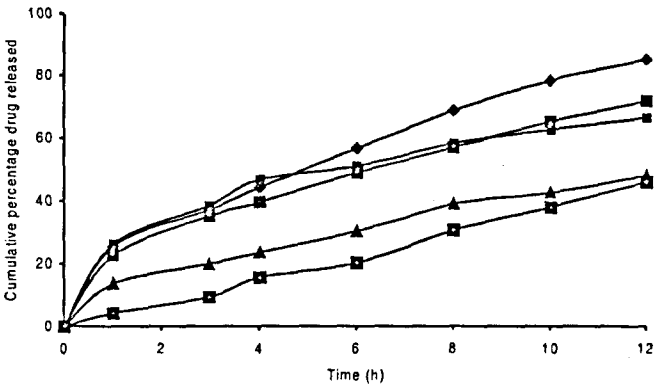
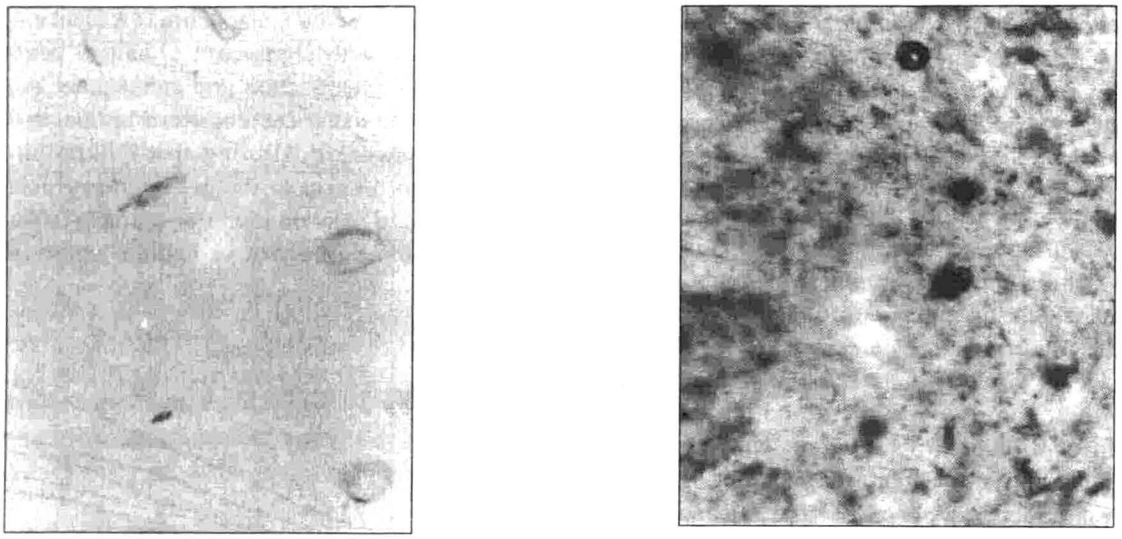


Fig. 2: The influence of different electrolytes (100 mg) on release of propranolol hydrochloride from tablet formulations.

The influence of different electrolytes (100 mg) on release of propranolol hydrochloride from tablet formulations in pH 1.2 buffer solution for first 1.5 h and pH 6.8 buffer solution for the remaining period. F (-♦-), F_4 (-◘-), F_9 (-▲-), F_{13} (-x-), F_{18} (-*-).



A B

Fig. 3: Photomicrographs of Formulation F and F_5

a. Photomicrograph of swollen matrix of propranolol hydrochloride tablet formulation F (10X Magnification) and b. Photomicrograph of swollen matrix of propranolol hydrochloride tablet formulation F_5 (10X Magnification).

chloride) due to interaction with the hydrochloride form of propranolol, which lead to the formation of free base of propranolol. The formation of free base might cause matrix stiffening. The passive and actively formed electrolytes with in the gel matrix would compete for water leading to dehydration of polymer molecules, thus leading to suppression of initial swelling which was seen up to 2 to 3 h with formulations containing high concentration of electrolytes. After 3 h the water attracted by electrolytes into the polymer matrix, could result in solubilizing the drug molecules which would diffuse out, creating a capillary network for more water penetration leading to enhancement of swelling, that was observed after 3 h. From these alterations and mechanisms of intragel changes, it appears possible to inhibit drug dissolution rate. This inhibition in dissolution rate appears to be a time-dependant phenomenon. Since, as more water enters the gel matrix layer-by-layer the electrolytes and their byproducts are diluted and any drug base may revert to its hydrochloride form, which is subsequently released.

From the above discussion, it may be concluded that electrolytes can be used as aids to controlled delivery in the formulation of water soluble drugs from tablet matrix. Among the various formulations of propranolol developed, the formulations F_5 and F_{14} appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

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