

Preparation and Evaluation of Once a Day Extended Release Tablet of Propranolol Hydrochloride

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ABSTRACT

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The objective of the present investigation was to develop once a day extended release tablet formulation of propranolol hydrochloride employing hydroxypropyl methylcellulose (HPMC). Different batches of propranolol hydrochloride extended release tablets were prepared by using different grades of HPMC (Methocel K4M, Methocel K15M and Methocel K100M) in order to get desired release profile. The optimized batch criteria were selected considering USP limits of dissolution study for extended release propranolol hydrochloride tablets. The physical parameters (crushing strength and friability) of all formulated batches were within acceptable limits. The results of dissolution study indicated that as amount of higher viscosity grade HPMC in tablet composition increases there is retardation of drug release. The optimized batch S8 containing 30% w/w of Methocel K100M showed highest similarity factor (f_2) value of 73.8. The mean dissolution time of batch S8 was 7.27 h. The kinetics of drug release was best explained by Korsmeyer and Peppas model. The optimized batch passed stability study carried out at $25 \pm 2^\circ\text{C}$ and $60 \pm 5\% \text{RH}$ for 6 months.

Ke words: Propranolol Hydrochloride, Extended release tablet, Hydroxypropyl methylcellulose, Release kinetics, Stability Study.

INTRODUCTION

Extended-release pharmaceutical dosage forms have received much attention in recent years and are highly desirable for providing a constant level of pharmaceutical agent to patient. The nature of the delivery system is dictated by the properties and dose of the drug, desired release profile and physiological factors. Such dosage form not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side-effects, as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations.¹ Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing sustained release dosage forms because it makes such manufacturing easy.²

Hydroxypropyl methylcellulose (HPMC) is the excipient chosen by most formulators for the preparation of hydrophilic

matrix system most probably due to its claim as a fast gel formation to control initial release, and formation of strong, viscous gel to control prolong drug release.³ Hydroxypropyl methylcellulose displays good compression properties, can accommodate high levels of drug loading, and is considered non-toxic.⁴ The mechanisms of drug release from these systems are complex, involving up to three moving boundaries, usually termed the swelling, diffusion, and erosion fronts.⁵ The rate of drug release from HPMC matrix is dependent on various factors such as type of polymer, polymer/drug ratio, drug, particle size of drug and polymer, and the type and amount of fillers used in the formulation.⁶⁻⁸

Propranolol hydrochloride, a nonselective beta-adrenergic blocking agent, is widely used for treatment of hypertension, angina pectoris, phaeochromocytoma and cardiac arrhythmias.⁹ Propranolol hydrochloride undergoes extensive first-pass metabolism following oral administration, with a reported systemic bioavailability between 15% and 23%.¹⁰⁻¹¹ Half life of 4 h, high aqueous solubility and frequent administration of drug makes propranolol hydrochloride an ideal candidate for preparing extended release formulation.¹²

¹⁴ The objective of the present study was to develop extended release tablets of propranolol hydrochloride and to examine the effects of hydrophilic polymer on in-vitro drug release. Selection of optimized batch among the different prepared batches was done by finding f_2 (similarity) value¹⁵ and mean *in vitro* dissolution time (MDT).¹⁶

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MATERIALS AND METHODS

Materials:

Propranolol hydrochloride was received as a gift sample from Zydus Cadila (Ahmedabad, India). Various grades of hydroxypropyl methylcellulose (Methocel K4M, Methocel K15M, and Methocel K100M) were obtained as a gift sample from Colorcon Asia Pvt. Ltd. (Goa, India). Dibasic calcium phosphate (DCP) and magnesium stearate were purchased from Laser chemicals (Ahmedabad, India). Polyvinylpyrrolidone (PVP K30) was purchased from Laser laboratories (Ahmedabad, India). Talc was purchased from Ravi chemicals (Mumbai, India).

Methods:

The extended release monolithic tablet formulation was prepared by direct compression of propranolol hydrochloride, Methocel and DCP using PVP K30 as a dry binder. The polymer concentration was varied while drug content (80mg) and the total tablet weight (300 mg) were kept constant. The composition of various tablet formulation are given in Table 1. The ingredients were individually passed through 40# and mixed for 15 m. The mixture was lubricated with magnesium stearate (1%) and talc (2%) and then compressed into a tablet using a single punch machine (Cadmach Machinery, Ahmedabad) using concave punch of 13/23". The compressed tablets were evaluated for crushing strength, drug content, friability and *in vitro* dissolution study. Results of the test are shown in Table 2.

EVALUATION:

Crushing strength:

Crushing strength of 10 randomly selected tablets were determined using Dr. Scheleuniger tablet hardness tester (Pharmatone 8, Germany).

Drug content:

One tablet was transferred to 100 ml volumetric flask containing 5 ml of dilute hydrochloric acid and shaken until

the tablet disintegrates. After complete disintegration of the tablet the solution was diluted with 75 ml of methanol and mixture was sonicated for 15 m. The obtained solution was filtered through a 45µm filter membrane. The total amount of drug within the tablet was analyzed after appropriate dilution of the test solution by using Shimadzu-1700 UV/visible spectrophotometer at 287 nm.

Friability:

Friability was evaluated as the percentage loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, India) for 4 m at 25 rpm.¹² The tablets were then dedusted and the loss in weight caused by fracture or abrasion was recorded as the percentage friability.

In vitro dissolution study:

The *in vitro* drug release study was carried out for 24 h in a calibrated dissolution test apparatus (Electrolab, TDT 06-T, Mumbai) equipped with basket employing 900 ml of 1.2 pH phosphate buffer solution for first 1.5 h and finally pH 7.2 phosphate buffer solution for the remaining period as a dissolution medium.¹² The baskets were rotated at 100 rpm and maintained at a temperature of $37 \pm 0.5^\circ$ throughout the experiment. After pre determined time interval (1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours) 10 ml of samples were withdrawn and analyzed spectrophotometrically at 287 nm using Shimadzu-1700 UV/visible spectrophotometer. An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($R^2=0.99$).

Model fitting:

In vitro drug release data were analyzed by different kinetic models in order to evaluate the release mechanism of propranolol hydrochloride from the polymer matrices. The FORTRAN software, developed in-house was used. The

Table 1: Composition of propranolol hydrochloride extended release matrix tablet

Batch Code (mg/tablet)	Ingredient								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
Propranolol hydrochloride	80	80	80	80	80	80	80	80	80
Methocel K4M	90	120	150	-	-	-	-	-	-
Methocel K15M	-	-	-	90	120	150	-	-	-
Methocel K100M	-	-	-	-	-	-	90	120	150
Dicalcium phosphate	106	75.99	45.99	106	75.99	45.99	106	75.99	45.99
PVP K30	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6

Table 2: Comparison of various tests performed on different batches

Test	Batch Code								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
Crushing strength (K-Pascal)	10.54 ± 0.28	10.50 ± 0.24	10.67 ± 0.2	10.44 ± 0.13	10.60 ± 0.19	10.31 ± 0.14	10.40 ± 0.21	10.55 ± 0.17	10.65 ± 0.21
% friability	0.310	0.40	0.284	0.43	0.32	0.51	0.46	0.34	0.29
f ₂ value	50.44	64.74	70.47	60.33	70.61	71.24	50.46	73.80	65.81
MDT	4.99	6.55	7.13	5.89	7.06	7.80	4.69	7.27	8.49

Fischer's value (F-value) and SSR values were used to test the applicability of the release models.

Mean dissolution time:

The mean dissolution time (MDT) was measured using equation 1.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} * \Delta M}{\sum_{i=1}^{i=n} \Delta M} \dots\dots\dots(1)$$

Where i, dissolution sample number; n, the number of dissolution sample time; t_{mid} , the time at the midpoint between i and i - 1 and ΔM , the additional amount of drug dissolved between i and i - 1.¹⁶ Higher the MDT, slower the drug release rate. Linder and Lippold found that MDT provides a more accurate drug release rate than the t_x % approach.¹⁷

Similarity factor:

The similarity factor f_2 was calculated from the mean dissolution data according to the equation 2.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} * 100 \right\} \dots\dots\dots(2)$$

Where n, the number of pull points; R_i , the reference profile at time point t and T_i , the test profile at the same time point. The value of f_2 should be between 50 and 100.¹⁵ An f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between releases profiles increases.

Stability study

Stability study of optimized batch S8 was carried at room temperature ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$) for 6 months. The samples were evaluated for crushing strength, friability and *in vitro* drug release study at the end of 6 months.

Fourier transformation infra red spectroscopy study

Propranolol hydrochloride, batch S8 with and without drug (blank) were separately mixed with IR grade potassium bromide. Infrared spectra were taken using an infrared

spectrophotometer (Model FTIR-8400S, Shimadzu, Japan) by scanning samples over a wave number of 4000 to 400 cm^{-1} .

RESULTS AND DISCUSSION

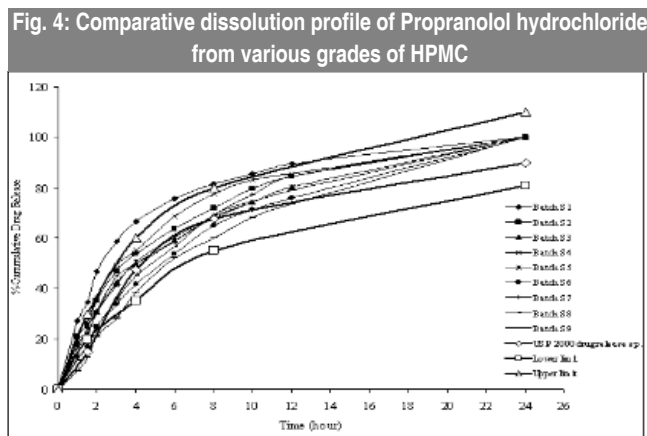
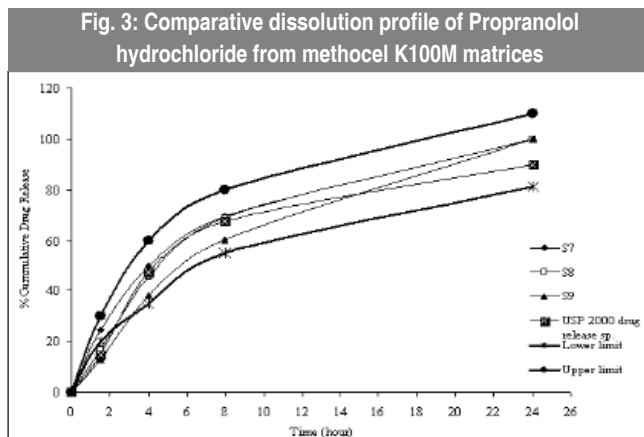
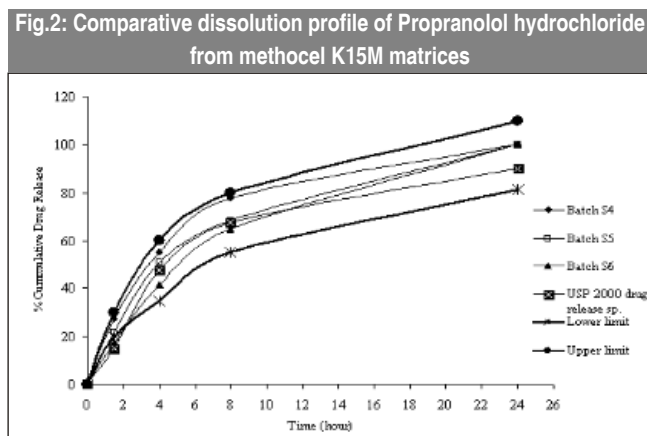
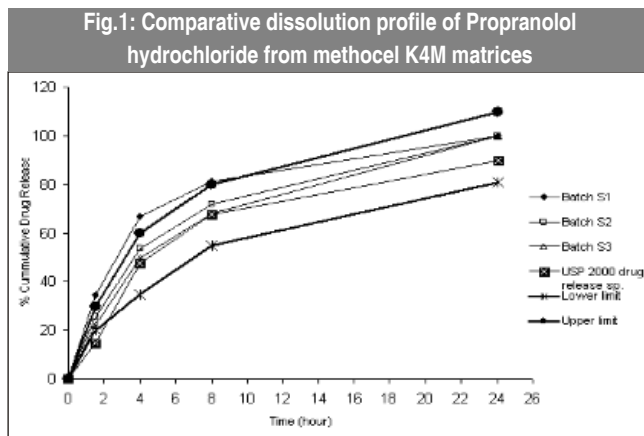
All the formulations were prepared according to the Table 1. The prepared formulated batches S1-S9 were evaluated for various physical properties such as hardness and friability as indicated in Table 2. All the formulated batches were produced under similar conditions to avoid processing variables. Once a day extended release tablet should perfectly release the loading dose in initial stage and the remaining drug should be released at a fairly constant rate. Table 2 displays that the crushing strength of all formulated batches (S1-S9) ranged from 10 to 11 K-Pascal. The loss in total weight of the tablets due to friability was less than 0.55% at 100 RPM. The drug content in the formulated tablets was within the range from 97.25 ± 2.12 to 101.88 ± 1.51 %. The 24 h release pattern of propranolol hydrochloride extended release tablet mentioned in USP XXIX, NF XIV was considered as a reference release pattern.¹² The criteria of the optimized batch were selected as: middle values of the limit of % drug released at given time point mentioned in USP XXIX, NF XIV (Y_{90} , percentage drug released at the end 90 min should not be more than 30 %, Y_{240} , percentage drug released at the end of 4 h should be between 35 to 60 %, Y_{480} , percentage drug released at the end of 8 h should be between 55 to 80 %, Y_{1440} , percentage drug released at the end of 24 h should be between 81 to 110 % and value of mean dissolution time should be between 7-9 h).⁹

The excipients did not show absorbance at 287 nm. The UV spectrum remained unchanged during *in vitro* drug release study, indicating photosensitive stability of propranolol hydrochloride during the analytical procedure. Release profiles of the tablets of batches S1 to S9 are shown in Figs.1-4. Fig.1. concludes that the release rate is greatly influenced by formulation factors such as the amount of HPMC and dicalcium phosphate. The drug dissolution can be either controlled by disentanglement or diffusion and it depends on the polymer molecular weight and the thickness of the diffusion boundary layer.¹⁸ Slow drug release ($Y_{60} = 12.64$ %) was observed from the formulation containing 30 &

40 % w/w of Methocel® K100M of total weight of tablet and a relatively faster drug release ($Y_{60} > 15\%$) was observed from formulations containing Methocel® K4M, Methocel® K15M and 20% of Methocel® K100M. Increasing polymer level from 20% w/w to 50% w/w dramatically retard the release of propranolol hydrochloride from the tablets prepared by direct compression method. As the polymer level was increased, the polymer gel formed is more likely to be resistant to drug diffusion and gel erosion.¹⁹ As the release rate limiting polymer changes from a glassy state to rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release of drug since it has to diffuse through this gel barrier in to the bulk phase. The strength of gel depends on the chemical structure and molecular size of polymer.²⁰⁻²¹ The faster drug release in case of formulation containing low amount of Methocel® K100M may be due to less tortuous diffusion path (r). It is known that higher viscosity grade polymer (Methocel K100M) hydrates faster and therefore is capable of forming a gel structure faster than medium viscosity grade (Methocel K15M) and low viscosity grade (Methocel K4M) polymer. The release rate was significantly dependent on the proportion and type of the polymer used.²²

The results shown in Figs.1-4 displays that the low viscosity grade (Methocel K4M) was not able to extend the drug release up to 24 h. While with medium viscosity grade polymer (Methocel K15M) the release was extended further (beyond 12 h) with burst release. The required release profile with suitable drug release in first hour (between 20-30 %) was obtained with batches S3, S5, S6, S8 and S9 as shown in Fig. 4. Similarity factor (f_2) was employed for selection of best batches among S3, S5, S6, S8 and S9. Batch S8 showed highest f_2 value of 73.8 and hence, considered as optimized batch.

The *in vitro* drug dissolution data was analyzed for establishing kinetics of drug release. Model fitting was done using an in-house program developed by the authors. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models were tested. Korsmeyer-Peppas model showed the least of sum of square of residuals (SSR) and therefore it was used for further data analysis. To find out release mechanism the *in vitro* release data were applied in Korsmeyer-Peppas equation. The slope and intercept values for the formulations S3, S5, S6, S8 and S9 were 0.1733, 0.1739, 0.1759, 0.1780, 0.1773 and 0.1149, 0.1124, -0.0117, 0.0237, -0.0952 respectively. The release exponent n was determined and observed 0.5480, 0.5666, 0.6677, 0.6945 and 0.8122 for batches S3, S5, S6,



S8 and S9, respectively. Formulations of Batches S3, S5, S6 and S8 showed ($n=0.51$ to 0.7) Anomalous (non-Fickian) diffusion. The formulation of batch S9 showed ($n=0.88$ to 1.20) super case-II diffusion principle.²³

Short-term stability study of the optimized batch S8 was carried out for six months at $25\pm 2^\circ\text{C}$ and $60\pm 5\% \text{RH}$. The crushing strength (10.89 ± 0.18 K-Pascal), friability (0.31%) and in vitro drug release profile of batch S8 remained unchanged during the study. The similarity factor (f_2) and mean dissolution time (MDT) of batch S8 at the end of stability study were 75.2 and 7.36 h respectively. The infrared spectra of propranolol hydrochloride and powder blend of batch S8 were comparable. Propranolol hydrochloride showed prominent peak at 3467 cm^{-1} because of presence of NH group. This peak was retained in sample of batch S8 containing drug and absent in blank indicating presence and stability of propranolol during processing.

CONCLUSION

In the present research extended release hydrophilic matrix tablet of propranolol hydrochloride was developed using Methocel. The results of this investigation enable us to state that the hydrophilic matrices are an interesting way of formulating oral extended release matrix tablets using a fabrication process that is easy and inexpensive and does not require special production equipment. The matrices had high mechanical strength. The drug release profile from optimized batch S8 containing 30% of Methocel K100M satisfying dissolution criteria of USP passed stability study carried out at $25\pm 2^\circ\text{C}$ and $60\pm 5\% \text{RH}$ for 6 months.

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