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Research Article

FORMULATION AND EVALUATION OF ORAL CONTROLLED RELEASE DOSAGE FORM OF ANTI-HYPERTENSIVE AGENT

Lakshmi Parvathi A, Senthil Kumar Krishnan*, Mohammad Gulzar Ahmed, Abdul Naser Kurnool, B.Ramesh
Department of Pharmaceutics, Sri Adhichunchanagiri College of Pharmacy, B.G.Nagara, Karnataka, India
*Email: senthilsomesh2005@gmail.com

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ABSTRACT

The aim of present investigation is preparation, characterization and evaluation of oral controlled release matrix tablets of Propranolol HCl in order to improve efficacy and to reduce the side effects. Tablets were prepared by direct compression method using different polymers like Guar gum, HPMC K4M, PVP and MCC used as the directly compressible vehicle. The granules were evaluated for pre-formulation characteristics and the tablets were subjected to post compression parameters, drug content and *in-vitro* dissolution release studies. *In-vitro* dissolution studies were carried out for 12 hrs and the results showed that among the nine formulations F8 and F9 showed good dissolution profile to control the drug release respectively. The drug release follows first order kinetics and the mechanism was found to be diffusion controlled for all the formulations (except F-9). The mechanism of drug release from F-9 was diffusion coupled with erosion. The Stability studies were carried out according to ICH guideline which indicates that the selected formulations (F8 and F9) were stable. In conclusion the results suggest that the developed matrix tablets of Propranolol HCl could perform therapeutically better than conventional dosage form, leading to improved efficacy and better patient compliance.

Keywords: Controlled release, Matrix tablets, Propranolol HCl, Formulations, *In-vitro* dissolution studies.

INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes that have been explored for the systemic delivery of drugs in case of different dosage forms. The oral controlled-release system is usually made of polymers, and the mechanisms of release are generally regulated by diffusion, bioerosion or degradation, and swelling or generation of osmotic pressure. Diffusion occurs when the drug–polymer mixture is exposed to the gastrointestinal fluid, resulting in release of the drug from the tablet or capsule.[1] Oral controlled – release drug delivery is thus a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.

In the exploration of oral controlled – release drug administration, one encounters three areas of potential challenges:

- Development of a drug delivery system
- Modulation of gastrointestinal transit time
- Minimization of hepatic first pass metabolism

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug.[2,3]

In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.

Cardiovascular diseases are one of the life threatening diseases of mankind and hypertension is the most common cardiovascular disease, which requires constant monitoring. Control of hypertension reverses the risk of congestive cardiac failure; whereas the risk of coronary disease is not reversed rapidly[4]. It is very much essential to control the hypertension and maintain sufficient blood circulation to heart to reduce the morbidity and make the patient to lead a near normal life. Hypertension is defined as a systolic blood pressure (SBP) = 140 mmHg and a diastolic blood pressure (DBP) = 90 mmHg for persons up to 60 years of age and for subjects with diabetes mellitus or familiar hypercholesterolemia and as a SBP = 160 mmHg and a DBP = 90 mmHg for persons of 60 years and older without diabetes mellitus or familiar hypercholesterolemia. Hypertension is a risk factor for myocardial infarction, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease. The World Health Organization reported that suboptimal blood pressure (SBP > 115 mmHg) is responsible for 62% of all cerebrovascular diseases and 49% of all ischemic heart diseases[5].

One approach to the manufacture of controlled release dosage forms is the direct compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternatively, retardant drug blends may be granulated prior to compression. Matrix tablets are considered to be the commercially feasible controlled action dosage forms.

The objective of the present investigation was to Formulation and evaluation of oral controlled release dosage form of Anti-hypertensive agent. Propranolol hydrochloride was formulated as an oral controlled release dosage form using various polymers like $HPMCK_4$, Guargum, MCC and PVPK90.

MATERIALS AND METHODS

Propranolol Hydrochloride was obtained as gift sample from Yarrow chem Products, Mumbai. Hydroxy propyl methyl cellulose K4M, Guargum, Magnesium stearate and Talc were obtained from S d fine-chem limited, Mumbai. Microcrysttaline cellulose was obtained from Signet, Mumbai. PVPK90 was obtained from Loba chemie pvt.ltd, Mumbai.

The formula for preparation of matrix tablets:

Preparation of matrix tablets:[6]

Matrix tablets containing Propranolol were prepared by direct compression method using varying ratios of different polymers as shown in the table no 1.

All the ingredients were weighed accurately & mixed. Propranolol was first mixed with the polymer and directly compressible Microcrystaline cellulose for 10 min to obtain uniform mixture. Then the mixture is passed through 60# sieve. Finally, the mixture is blended with talc and magnesium stearate.

Pre-compression parameters

I. Bulk density:[7,8]

Loose bulk density and Taped bulk density was calculated by the following formulae

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}} \quad (a)$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}} \quad (b)$$

Carr's Compressibility Index:

% Carr's Index can be calculated by using the following formula

$$\text{Carr's Index (\%)} = \frac{TBD - LBD}{TBD} \times 100 \quad (c)$$

Hausner's ratio:[9]

Hausner ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula

Hausner's ratio = (Tapped density)/(Bulk density) (d)

Angle of repose:

Angle of repose (θ) can be calculated from the following formula

where

$\tan\theta = h/r$ (e)

h=height of pile and r=radius of the base of pile.

Post-compression parameters

a) Friability test:[7] Previously weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rpm for 4 minutes. The results are given in table-2.

b) **Hardness test:**[7] Hardness of the tablets was tested using "Monsanto" hardness tester. The physical properties of the tablets are shown in table-2.

c) **Uniformity of weight**: Average weight of the tablet was calculated by weighing 20 tablets individually and all together. The results are given in table-2.

d) **Drug content uniformity of the tablets**:[6]

Twenty tablets were weighed and powdered. The quantity equivalent to 100mg of Propranolol HCl was weighed accurately and taken in 100ml volumetric flask. The volume was made up to 100ml with pH6.8 and filtered. From this, 1ml was pipetted into 10ml volumetric flasks and the volume made with pH 6.8. The absorbance was measured at the 289nm by using pH 6.8 as a blank.. The results are given in table-2.

e) *In-vitro* dissolution studies:[6]

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The dissolution medium consisted of 900 ml of pH 1.2 buffer (0.1N HCl) for first two hours and the phosphate buffer pH 6.8 from 3- 12 hours maintained and the temperature of the medium was set at 37±0.5° C. The rotational speed of the paddle was set at 100 rpm. 5 ml of sample was withdrawn at predetermined time interval of 1 hr upto 12 hr and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10ml with pH 6.8, filtered and analyzed on UV spectrophotometer at 289 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

f) Stability studies:[10]

Short-term stability studies were performed at temperature 40±2°C over a period of two months on the matrix tablet formulation F9. Sufficient number of tablets (10) were packed in amber colored screw capped bottles and kept in stability chamber maintained at 40±2°C.

g) Kinetics of Drug Release:[11]

The cumulative amount of Propranolol hydrochloride released from controlled released matrix tablets at different time intervals was fitted to zero-order, first order kinetics, Higuchi's model and Korsmeyer's peppas models.

RESULTS AND DISCUSSION

Determination of λ_{max} of Propranolol HCl:

Drug was identified by UV scanning method which showed a λ_{max} at 289 nm as reported in the literature. IR spectrum was also in concordant with the reference spectrum of Propranolol HCl.

Pre-compression parameters:

The method employed for tabletting in this study was direct compression for which the drug or the mixture of drug and polymer should possess good flow properties. Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder blend, to achieve constant uniformity of tablet weight.

Angle of repose (θ):

The data obtained for angle of repose for all the formulations were tabulated in the table no16. The values were found to be in the range of 24°56' to 27°82'. which reveals the good flow property.

Bulk density:

The Loose bulk density and tapped bulk density for the entire formulation blend varied from 0.236g/ml - 0.370 g/ml and 0.266 g/ml - 0.410 g/ml respectively.

Carr's consolidation index and Hausners ratio:

The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 5.541 to 13.33%. the powder blend showed excellent compressibility index values upto 15% result in good to excellent flow properties. It was further supported by Hausner's ratio ranged from 1.0416 to 1.153. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Evaluation parameters:

Physicochemical Properties:

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, weight variation, friability and drug content. Evaluation studies indicated that, the values of various parameters were within the pharmacopoeial permissible limits for all the nine formulations.

Table No.1: Ingredients used in the formulation

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propranolol HCl	40	40	40	40	40	40	40	40	40
Guargum	160	180	200	-	-	-	80	90	100
$HPMCK_4$	-	-	-	160	180	200	80	90	100
MCC	122	102	82	122	102	82	122	102	82
$PVPK_{90}$	20	20	20	20	20	20	20	20	20
Mg.stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4

Table No.2: Evaluation parameters of pre-formulation characteristics

Formulation code	Angle of Repose(θ)	Loose Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	%Compressibility	Hausner's ratio
F1	24°56 ±0.02	0.37±0.04	0.408±0.03	9.524±0.07	1.095±0.03
F2	27°25′±0.04	0.37±0.04	0.387±0.02	5.541±0.06	1.045±0.05
F3	26°93'±0.03	0.324±0.05	0.337±0.03	8.76±0.04	1.041±0.03
F4	25°.07'±0.06	0.236±0.06	0.266±0.04	11.428±0.03	1.129±0.05
F5	24°.39'±0.02	0.259±0.054	0.286±0.02	9.406±0.02	1.103±0.03
F6	27°.82'±0.04	0.382±0.087	0.404±0.06	5.547±0.03	1.047±0.04
F7	27°.82'±0.04	0.272±0.076	0.314±0.03	13.33±0.04	1.153±0.08
F8	26°.93'±0.06	0.350±0.065	0.382±0.02	8.444±0.02	1.090±0.02
F9	25°.92'±0.04	0.326±0.076	0.354±0.06	7.998±0.04	1.086±0.03

Table No.3: Evaluation Parameters of Matrix Tablets

Formulation code	Thickness	Hardness (kg/cm^2)	Friability (%)	weight variation (mg)	Drug Content (%)
F1	2.53±0.03	6± 0.956	0.357±0.02	350± 0.0418	96.98±0.02
F2	2.31±0.04	5.5± 0.856	0.357±0.05	350± 0.0354	97.54±0.05
F3	2.34±0.02	6.5± 0.887	0.282±0.06	350± 0.0317	98.03±0.06
F4	2.12±0.02	6± 0.835	0.288±0.03	350± 0.0314	97.02±0.08
F5	2.52±0.03	5.7± 0.934	0.375±0.05	350± 0.0423	95.34±0.13
F6	2.45±0.01	5.5± 0.884	0.287±0.04	350± 0.0427	96.92±0.07
F7	2.36±0.05	5± 0.879	0.167±0.12	350± 0.0324	98.54±0.08
F8	2.37±0.06	6.5± 0.856	0.155±0.06	350± 0.0334	98.67±0.07
F9	2.47±0.03	6± 0.923	0.156±0.06	350± 0.0325	99.95±0.06

Table No 4: Kinetic data of various models for release study of Propranolol HCl tablets

Formulation code	Zero order release plots	First order release Plots	Higuchi's plots	Korsmeyer-Peppas plots	
	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Regression coefficient (R^2)	Exponential value (n)
F1	0.9963	0.9811	0.9964	0.9928	0.5045
F2	0.9924	0.9732	0.9967	0.9856	0.5886
F3	0.9912	0.9824	0.9934	0.9948	0.4447
F4	0.9822	0.9883	0.9944	0.9868	0.5399
F5	0.9962	0.9942	0.9821	0.9688	0.5312
F6	0.9852	0.9957	0.9872	0.9872	0.5842
F7	0.9662	0.9897	0.9731	0.9908	0.6291
F8	0.9872	0.9467	0.9922	0.9981	0.5890
F9	0.9962	0.9358	0.9707	0.9985	0.7180

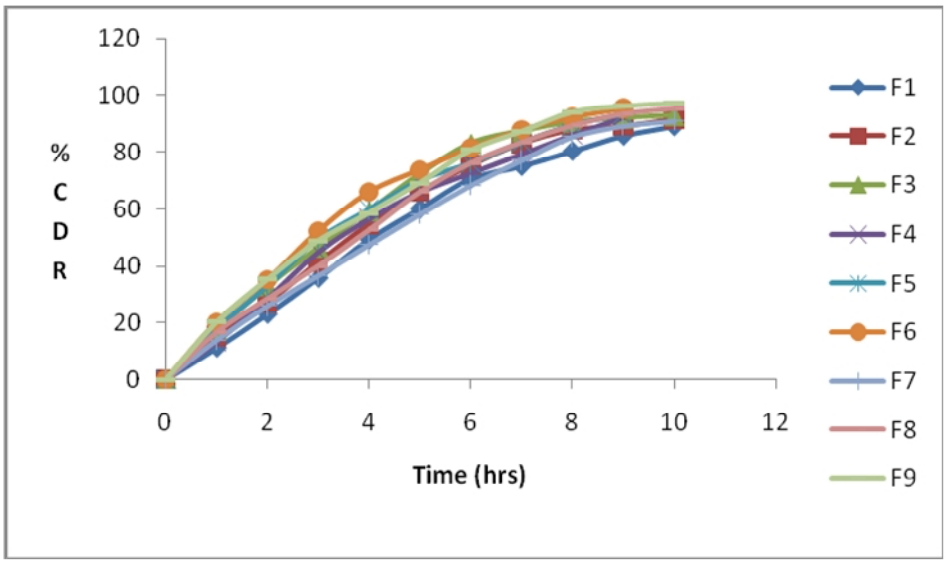

Figure no 1*: In-vitro* Cumulative percentage drug released V/S Time for All the Formulations

***In-vitro* Drug Release Profile:**

In-vitro drug release studies were carried out on dissolution test apparatus USP XXIII with paddles in 900ml of 0.1N HCl for 2 hours and phosphate buffer 6.8 pH for the next remaining 12 hours. The release rate of the drug from the matrix tablets decreased with an increase in polymer proportion because of increase in gel strength as well as the formation of a gel layer with a longer diffusional path.

Based on the results of *in-vitro* release studies F8&F9 were selected as best released formulations. These selected formulations are subjected for stability studies.

Data analysis:

When the data was plotted according to the first-order equation, the formulation showed a fair linearity, with regression values between 0.9358 and 0.9957. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or higuchi's kinetics.

In the experiments, the *in-vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2: 0.9707 to 0.9967). To confirm the diffusion mechanism, the data was fit into korsmeyer-peppas eqution. The formulations F1 to F8 showed good linearity (R^2: 0.9856 to 0.9981), with slope (n) values ranging from 0.4447 to 0.6291,indicating that diffusion is the dominant mechanism of drug release with these formulations. When plotted according to korsmeyer-peppas equation, F9 also showed high linearity (R^2: 0.9985), with a comparatively high slope (n) value of 0.7180. This end value, however appears to indicate a coupling of diffusion and erosion mechanism so called anomalous diffusion.

Stability Studies:

Stability studies were carried out for the best controlled released formulations F8, F9 as per ICH guidelines at one temperature. The formulations showed good stability and the values were within permissible limits.

CONCLUSION

As the concentration of HPMC K4M & Guar gum was increased, the percentage of drug release was found to be increased. Guar gum shows more time release compared to HPMC K4M. On combination of both the polymers (HPMC K4M and Guar gum) shows more release time than used individually. All the formulations were fitted into Krosmeyer's-Peppas model and n-exponent value ranged between 0.4447 to 0.7180. Selected best formulations were found to be stable for a period of 2 months.

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