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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF LABETALOL HYDROCHLORIDE USING HYDROPHILIC POLYMERS

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ABSTRACT

Labetalol hydrochloride is used in treatment of hypertension. It has a short half-life and undergoes extensive first pass metabolism. In the present study, labetalol hydrochloride 100 mg controlled release matrices were prepared by direct compression and in vitro drug dissolution studies were performed to find out the drug release rate and patterns. Hydroxypropyl methylcellulose, Hydroxypropyl cellulose and Hydroxyethyl cellulose were used as rate controlling polymers. Hydroxypropylmethylcellulose was used as primary rate controlling polymer and effects of addition of Hydroxypropyl cellulose and Hydroxyethyl cellulose on in-vitro drug dissolution were studied. Tablets were formulated using total polymer content as 30, 35 and 40 percent with 20 percent standard polymer content of Hydroxypropyl methylcellulose in all batches and varying the concentration of Hydroxypropyl cellulose and Hydroxyethyl cellulose in the range of 10, 15 and 20 percent. *In-vitro* drug release was carried out using USP Type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, followed by 900 ml alkaline dissolution medium (pH 7.4) up to 12 hours. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

KEYWORDS: Labetalol Hydrochloride , Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Hydroxyethyl cellulose, Release Kinetics.

INTRODUCTION:

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages[1].

Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs[2]. The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration[3].

Hydroxypropyl methylcellulose, Hydroxypropyl cellulose and Hydroxyethyl cellulose can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material[4].

Antihypertensive drugs are used for prevention of stroke. Stroke is associated with a wide variety of reasons and hence the presence of adequate amounts of plasma drug levels becomes very necessary for efficient treatment of hypertension. Antihypertensive drugs have short half-lives, extensively metabolized in the liver and are highly bound to plasma proteins. Hence if the release of drug is sustained for a longer period of time, will result in efficient management of hypertension.

Labetalol hydrochloride is a selective α- and nonselective β-adrenergic blocking agent. It is used in management of hypertension, alone or in combination with other classes of antihypertensive agents. Labetalol hydrochloride is one of several preferred initial therapies in hypertensive patients with heart failure, post-MI, high coronary disease risk, or diabetes mellitus. It can be used as monotherapy for initial management of uncomplicated hypertension. Labetalol hydrochloride is also effective in controlling blood pressure in pregnant women with moderate to severe hypertension and severe pregnancy-induced hypertension.

Labetalol hydrochloride has a dosage of, 100 mg twice daily initially. Further the dose is adjusted in increments of 100 mg twice daily every 2 or 3 days until optimum BP response is achieved. For maintenance, manufacturer recommends a usual dosage of 200–400 mg twice daily. Manufacturer states that some adults with severe hypertension may require up to 1.2 g–2.4 g administered in 2 or 3 divided doses daily. Labetalol hydrochloride is rapidly and almost completely absorbed (i.e., 90–100%) from the GI tract following oral administration. It undergoes extensive first-pass

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metabolism in the liver and/or GI mucosa. Absolute bioavailability is about 25%. Therefore to improve bioavailability and patient compliance in this study attempt has been made to develop a controlled release dosage form.

The present study is aimed at formulating sustained release matrix tablets of labetalol hydrochloride using hydrophilic polymers viz. hydroxypropyl methylcellulose, hydroxypropyl cellulose and hydroxyethyl cellulose.

MATERIALS AND METHOD:

MATERIALS:

Labetalol hydrochloride was obtained as gift sample from Meyer Organics Pvt. Ltd. Thane, Maharashtra. Hydroxypropyl methylcellulose (HPMC K 15M) was obtained as gift sample from Signet, Mumbai, Maharashtra. Hydroxypropyl cellulose and hydroxyethyl cellulose were obtained as gift sample from International Specialty Products, Mumbai, Maharashtra. Other materials used were of analytical grade and procured from commercial sources.

METHODS:

PREPARATION OF SUSTAINED RELEASE MATRIX TABLETS OF LABETALOL HYDROCHLORIDE:

Sustained release tablets of labetalol hydrochloride were prepared by direct compression method[5] using microcrystalline cellulose as directly compressible vehicle. Hydroxypropyl methylcellulose (HPMC K 15M), Hydroxypropyl cellulose and Hydroxyethyl cellulose were used as retardant material for preparation of tablets[6]. Other excipients were magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. For preparation of Controlled release tablets of miglitol, drug and polymer were weighed accurately, all the ingredients were sieved through 40 mesh screen and mixed with other ingredients and the powder mixture was compressed using 16 station rotary tablet compression machine using 5 mm punches. Tablet compression weight was adjusted to 50 mg. In total, 6 formulations containing different amounts of HPC (F1, F2, F3), and HEC (F4, F5, F6) were prepared.

The formula for various formulations attempted have been given in **Table 1**: Composition of sustained release labetalol hydrochloride tablets

Table 1: Composition and physical characters of sustained release labetalol hydrochloride tablets

Ingredient	F1	F2	F3	F4	F5	F6
Labetalol hydrochloride	100	100	100	100	100	100
HPMC K 15M	40	40	40	40	40	40
HPC 2M	20	30	40			
HEC 2M				20	30	40
MCC	36	26	16	36	26	16
Aerosil	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2

PHYSICAL CHARACTERIZATION OF FABRICATED TABLETS[7]:

The quality control tests for the tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used

Dial tablet hardness tester. Friability was determined b y Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the weight variation was calculated. Physical characters observed for various batches are given in **Table 2**: Evaluation of Physical characters of labetalol hydrochloride tablets.

ESTIMATION OF DRUG CONTENT[8]:

An UV/Vis spectrophotometric method is used based on the measurement of absorbance at 395 nm for the estimation of labetalol hydrochloride. From each batch of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 50 mg of labetalol hydrochloride was weighed accurately on an analytical balance and dissolved in distilled water and diluting to 50 mL in calibrated flask with water to give a stock solution of 1 mg/mL. Solution is filtered and10 mL of filtered solution was further diluted with distilled water to 100 mL in a volumetric flask to obtain 100 mcg/mL solution. To a 25 mL volumetric flask add 1.5 mL of 0.029 M 4-aminobenzenesulfonic acid, 1.5 mL of 0.29 M sodium nitrate and 2 mL of 0.2 M HCl were pipetted and kept in an ice-bath (0 - 3 ^{0}C) for 10 mins to complete diazotization reaction. After 10 mins 1 mL of 100 mcg/mL stock solution of labetalol hydrochloride is added followed by 4 mL of

0.28 M sodium carbonate solution and then diluted to volume using distilled water. The resulting solution containing 4 mcg/mL of labetalol hydrochloride is estimated by measuring the absorbance of both standard and sample solutions at 395 nm using UV/Vis spectrophotometer (Systronic 2201). Results are tabulated in **Table 3**: Drug content and In-vitro drug release studies of labetalol hydrochloride tablets.

IN-VITRO RELEASE STUDIES:

The *in-vitro* dissolution studies were performed using USP type 2 dissolution apparatus (paddle) at 50 rpm. The dissolution medium consisted of 1.2 pH medium for first 2 hours and for subsequent 10 hours in phosphate buffer pH 7.4 (900 ml), maintained at 37±0.5 ^{o}C. The release studies were conducted in triplicate. Aliquot of samples (5ml) were withdrawn at specific time intervals and drug content was determined spectrophotometrically at 395 nm. Results are tabulated in **Table 3**: Drug content and In-vitro drug release studies of labetalol hydrochloride tablets. Results of *in-vitro* dissolution studies are shown graphically in **Figure 1:** Plot of Cumulative % drug released v/s Time for different formulation (F1-F6).

KINETICS OF _IN-VITRO_ DRUG RELEASE[9]:

In-vitro release data obtained was treated to zero order rate equation, Higuchi's equation and Korsmeyer-Peppas equation to know precisely the mechanism of drug release from matrix tablet.

Release data obtained is treated with following modes of data treatment.

Zero order equation - Cumulative percentage drug release vs. Time in hours.

Firdt order equation – Log cumulative percentage drug remained vs. Time in hours.

Higuchi's Diffusion equation - Cumulative percentage drug release vs. Square root time. Korsmeyer- Peppas equation - Log cumulative percentage of drug release vs. Log time.

Results are tabulated in **Table 4**: Different kinetic models for labetalol hydrochloride tablets.

RESULTAND DISCUSSION:

In present work an attempt has been made to formulate controlled release matrix tablets of labetalol hydrochloride using three retardants namely hydroxypropyl methylcellulose used as primary rate controlling polymer and effect on in vitro drug dissolution were studied by addition of hydroxypropyl cellulose and hydroxyethyl cellulose different concentrations and combinations.

PHYSICAL CHARACTERIZATION OF TABLETS:

The formulation of tablets was done by using direct compression technique which was found acceptable. All the formulations were prepared according to the formula given in **Table 1**. The prepared matrix tablets were evaluated for various physical properties as indicated in **Table 2.**

Table 2: Evaluation of Physical characters of labetalol hydrochloride tablets

Formulation code	Thickness (mm)**	Weight variation (%)	Hardness (N)**	Friability (%)*
F1	3.32 ± 0.05	0.79 ± 0.05	42.51 ± 1.54	0.14 ± 0.02
F2	3.34 ± 0.04	1.18 ± 0.16	42.96 ± 2.63	0.12 ± 0.03
F3	3.36 ± 0.08	1.24 ± 0.08	44.19 ± 1.71	0.12 ± 0.01
F4	3.35 ± 0.03	1.36 ± 0.12	38.41 ± 2.58	0.18 ± 0.04
F5	3.37 ± 0.07	1.27 ± 0.19	39.27 ± 2.79	0.16 ± 0.02
F6	3.33 ± 0.02	0.97 ± 0.06	40.62 ± 3.42	0.15 ± 0.02

*****All the values are expressed as a mean ± SD., n = 3

****** All the values are expressed as a mean ± SD., n = 6

The results of evaluation studies can be summarized as follows:

The thickness of the formulations was found to be in the range of 3.32 ± 0.05 mm to 3.37 ± 0.07 mm. The crushing strength of tablets was in the range of 38.41 ± 2.58 N to 44.19 ± 1.71 N. The loss in total weight of the tablets due to friability was less than 0.5% for all the formulations the high value of crushing strength and low friability indicated that the compressibility of labetalol hydrochloride and adjuvant was good.

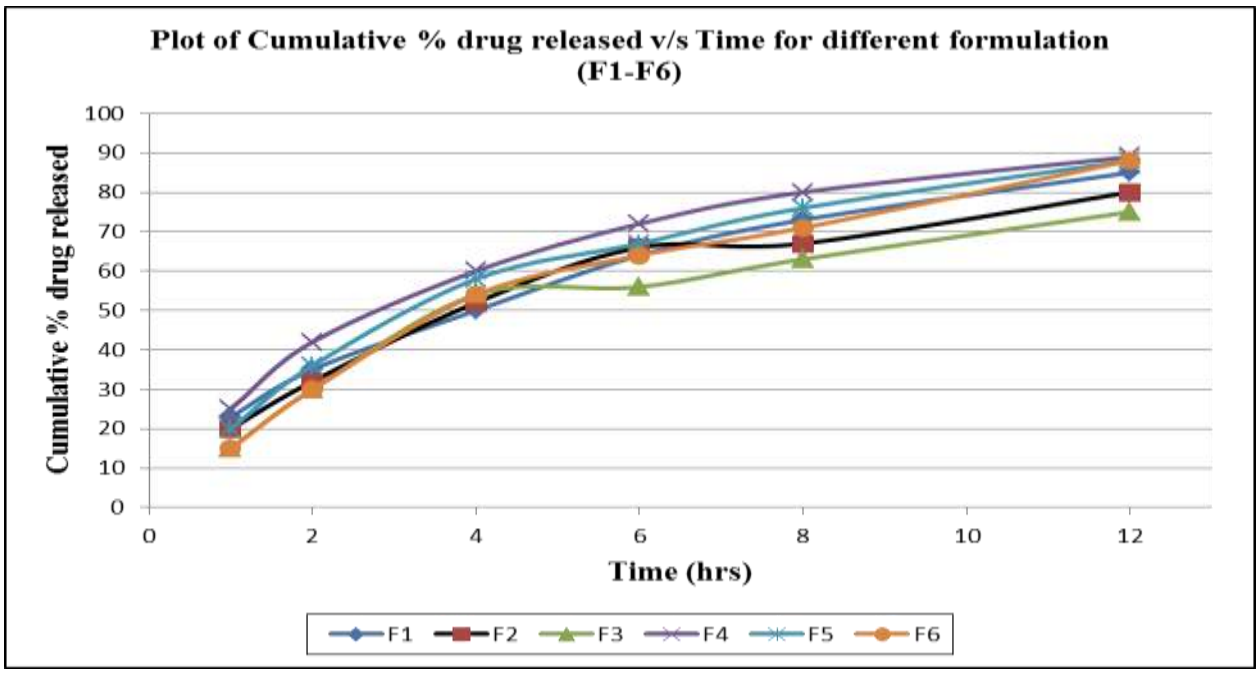
DRUG CONTENT AND IN-VITRO DRUG RELEASE OF TABLETS:

Drug content and in-vitro drug release studies are indicated in T**able 3**.

Table 3: Drug content and in-vitro drug release studies of labetalol hydrochloride tablets

Formulation code	Drug content (%)	Cumulative % drug release
F1	100.43 ± 1.31	84.47 ± 0.12
F2	98.91 ± 0.94	81.36 ± 0.21
F3	101.69 ± 0.97	76.13 ± 0.05
F4	100.42 ± 1.37	88.92 ± 0.08
F5	101.72 ± 0.78	87.46 ± 0.18
F6	99.61 ± 1.34	87.28 ± 0.09

All the values are expressed as a mean ± SD, n = 3



Drug content was found to be uniform among different formulation of tablets and ranged from 98.91 ± 0.94 % to 101.72 ± 0.78 %. In-vitro drug release studies revealed that formulations F1, F2 and F3 containing combination of hydroxypropyl methylcellulose and hydroxypropyl cellulose showed release between 84.47 ± 0.12 and 76.13 ± 0.05 at the end of 12 hours. Cumulative release decreased as the concentration of polymer increased. Decrease in release indicates rate controlling effect of hydroxypropyl cellulose in addition to hydroxypropyl methylcellulose. Also the standard deviation is low which is usually observed by using single hydroxypropyl methylcellulose in similar concentration. In-vitro drug release studies revealed that formulations F4, F5 and F6 containing combination of hydroxypropyl methylcellulose and hydroxyethylcellulose showed release between 88.92 ± 0.08 and 87.28 ± 0.09 at the end of 12 hours. There is no significant decrease in cumulative percent release indicating no additional retarding effect of hydroxyethyl cellulose in addition to hydroxypropyl methylcellulose.

KINETICS OF DRUG RELEASE:

There are various applied mathematical models for dissolution data of miglitol controlled release tablet are shown in **table 4**. Formulations F1, F2 and F6 have Korsmeyer - Peppas as best fit kinetic model for drug release. Formulations F1 and F2 follow Fickian mechanism for drug transport indicating drug release follows the diffusion process as described by Ficks 2nd law of diffusion through thin films and is generally observed when water diffusion controls the drug release process whereas formulation F6 follows anomalous mechanism for drug transport indicating drug release deviates from Ficks law and where drug release is both diffusion and swelling controlled. Formulations F3, F4 and F5 have First Order as best fit kinetic model for drug release indicating the percentage of drug dissolved at a certain time point may be equivalent to the percentage surface area at that time point.

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer - Peppas			Best fit model
				R^2	n	k	
F1	0.863	0.952	0.961	0.978	0.467	1.403	Korsmeyer - Peppas
F2	0.853	0.955	0.953	0.960	0.485	1.366	Korsmeyer - Peppas
F3	0.827	0.977	0.934	0.923	0.521	1.295	First Order
F4	0.786	0.967	0.913	0.943	0.423	1.477	First Order
F5	0.805	0.964	0.925	0.941	0.491	1.393	First Order
F6	0.817	0.924	0.931	0.937	0.580	1.288	Korsmeyer - Peppas

CONCLUSION:

Results of present research work demonstrate that the combination of hydrophilic polymers was successfully employed for formulation of labetalol hydrochloride sustained release tablets. It is observed that combination of polymers produce a more linear release from matrix tablets with low standard deviation. Hydroxypropyl methylcellulose and hydroxypropyl cellulose showed more retardation effect than combination of hydroxypropyl methylcellulose and hydroxyethyl cellulose for oral controlled release tablets of labetalol hydrochloride. In all the formulations, drug release rate is inversely proportional to the concentration of polymer. From this study, it is possible to design promising oral controlled release matrix tablets containing labetalol hydrochloride for the management of hypertension with more efficacy and better patient compliance.

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