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Research Paper

Formulation and Evaluation of Sustained Release Matrix Tablet of Antihypertensive Drugs Using Hydrophobic and Hydrophilic Matrix Polymers

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Most of the drug does not reach the site of action in appropriate concentration in treating Hypertension if conventional drug delivery system is used. Thus Sustained release delivery systems have shown to be of better significance in release rate for drug**.** The present work was an attempt to study the effect of different polymers like hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) on release of the sustained release tablets of the Atenolol and indapamide .The objective of the present study was to develop based matrix sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. The formulation of Atenolol and indapamide matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Atenolol and indapamide was studied. The prepared formulations were evaluated with precompression parameters like bulk density, compressibility index, hausner's ratio, angle of repose and postcompression parameters like weight variation, thickness, hardness, friability. In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II at 50 rpm.

Key Words: Atenolol, indapamide, Water insoluble, Matrix tablet, Hydrophobic, Hydrophilic, Polymer

INTRODUCTION

Hypertension is the most common cardiovascular diseases. For hypertension β-blockers are presently most important class of drug. The first therapeutic drug shown to posses and ability to membrane-stabilising properties is Atenolol [(4-2 – hydroxy-3 – isopropyl - aminopropoxy) phenylacetamide] is a cardioselective β-blocker. It is reported to lack intrinsic sympathomimetic activity and is one of the emerging molecules in case of Hypertension; successful treatment means maintenance of blood pressure at normal physiological level, for which a constant and uniform supply of drug is desired. It may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin and α- methyldopa[1]. Besides being one of the most widely used β - blockers clinically, it has often been used as a reference drug in randomized controlled trials of hypertension[2-5].The elimination half-life of atenolol is 6 to 7 hours and there is no alteration of kinetic profile of drug by chronic administration.

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Following intravenous administration peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5 to 10 fold) during the first 7 hours. Following oral doses of 50 mg or 100 mg both β -blocking and anti-hypertensive effects persist for at least 24 hours. The drug accumulates in patients with renal failure and dosage should be adjusted for patients whose creatinine clearance is less than 35 ml/min/1.73m^2.[6] Indapamide (thiazide-type diuretics) is indoline derivatives of chlorosulphonamide (4-Chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide. Indapamide is also an anti-hypertensive diuretic related to the thiazides. The anti-hypertensive effect is associated with an improvement in arterial compliance and a reduction in total and arteriolar peripheral resistance. Indapamide as a first step antihypertensive, has two properties beyond diuresis. First, there is added vasodilation[7]. A second unusual property is a high concentration class I and III antiarrhythmic effect[8]. Indapamide has a terminal half-life of 14 to 16 hours and effectively lowers the blood pressure over 24 hours. The initial dose is 1.25 mg once daily for 4 weeks, then if needed 2.5 mg daily. Indapamide appearsto be more lipid neutral than other thiazides[9] but seems equally likely to cause other metabolic problems such as hypokalemia, hyperglycemia or hyperuricemia. Indapamide (2.5 mg daily) does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance. To reduce the administered dose and to improve patient convenience and compliance, a sustained release matrix tablet formulation of combined atenolol and indapamide is desirable. The drug is freely soluble in water and hence selections of both hydrophobic and hydrophilic polymer matrix system are widely used in oral controlled drug delivery to obtain a desirable drug release, patient compliance and cost–effectiveness.

Hence in the present study work an attempt has been made to develop sustained release matrix tablet of Atenolol and idapamide using hydrophobic and hydrophilic polymers. Matrix material such as (HPMC) hydroxyl propyl methyl cellulose and ethyl cellulose, Pvp, Gaur gum, Xanthan gum. The drug release for extended duration, particularly for highly water soluble drug using a hydrophilic matrix system is restricted because of the rapid diffusion of the dissolved drug though the hydrophilic network. For such drug with high water solubility hydrophobic polymers are suitable, along with a hydrophilic matrix for developing

Table No. :1 Formulation of Atenolol and Indapamide Sustained Release Matrix Tablet

Ingredients	F1	F2	F3	F4	F5	F6
Atenolol(mg)	40	40	40	40	40	40
Indapamide(mg)	1.5	1.5	1.5	1.5	1.5	1.5
Xanthan Guam	60	60	60	60	60	60
Gaur gum	60	60	60	60	60	60
HPMC	18	18		36		
PVP		18	18		36	
Ethyl cellulose	18		18			36
Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	50	50	50	50	50	50
Total	250	250	250	250	250	250

sustained release dosage forms. Therefore in this study both the hydrophilic and hydrophobic polymer was used as matrix material. The main objective of the study is to formulate several hydrophilic and hydrophobic matrix systems by polymer material to investigate the effect of both.

MATERIALS AND METHODS

HPMC, Ethyl cellulose, Gaur gum, Zanthan gum, Pvp, Magnesium starate, Talc, all the ingredients used were of analytical grade. Formulation chart of Tablet is given in Table 1.

Preformulation Studies:

It is one of the important prerequisite in development of any drug delivery system. Preformulations studies were performed on the drug[10].

Organoleptic characteristics

The colour, odor and taste of the drug were characterized and recorded in Table 2. [10,11]

Table 2: Organoleptic properties

S. No.	Properties	Results	
		Atenolol	Indapamide
1.	Description	Solid(Crystalline powder)	Solid (powder)
2.	Taste	Bitter	Bitter
3.	Odor	Odorless	Odorless
4.	Colour	White to off White	White

Determination of Melting Point

Melting point of Atenolol and Indapamide was determined by capillary method. Fine powder of Atenolol and Indapamide was filled in capillary tube (previously sealed at one end). The capillary tube inserted in sample holder of melting point apparatus and a thermometer is also placed in the apparatus. The temperature at which powder melted was noticed**.** [11]

Solubility

Preformulation solubility analysis was done to select suitable solvent system to dissolve the drug as well as various excipients used for formulation and also to test drugs solubility in the dissolution medium, which was to be used, which was to be used in Table 3. [12]

Table 3: Result of solubility analysis

S. No.	Solvent	Solubility
1.	Methanol	Freely soluble
2.	Water	Soluble
3.	Ethanol	Soluble
4.	Acetone	Slightly soluble

Compatibility Studies (Drug-Excipients compatibility studies)

The IR spectra of drug with polymers were

compared with the standard IR spectrum of the pure drugs. In this technique 3 mg of sample and 300 mg of potassium bromide was finely ground using mortar and pestle. A small amount of mixture was placed under a hydraulic press compressed at 10 Kg/cm2 to form a transparent pellet. The pellet was kept in the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Perkin-elemer FT-IR spectrophotometer. [13]

Formulation of tablets: Formation of Atenolol and idapamide matrix tablet was prepared by wet granulation method. For these all the powders were passed through 80 mesh8. Drug and polymer were mixed thoroughly with including granulating agent, after mass of cohesive material was sieved through 22 and 44 mesh9. Afterwards the granules dried at $40^{O}C$ for 6-12 hrs, then talc and magnesium starate were added. Finally the tablets were compressed using single punch machine, tablet compression machine 11mm punch were used[10].

Evaluation of Pre-formulation parameters of granules [10,12]

Determination of Bulk Density and Tapped Density

20g of the mix blend (W) was introduced into a 100ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density was calculated using the following formulae.

- **Bulk density=W/ VO**
- **Tapped density=W/ VF**

Where,

W= weight of the granules**,**

VO = initial volume of the granules**.**

VF = final volume of the granules**.**

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h / r$$

Where, h and r are the height and radius of the powder cone respectively.

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Compressibility index (Carr's Index)

Compressibility index is an important

measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is material having values of less than 20% has good flow property given in table 4.

$$CI = \frac{\text{Tapped density–Bulk density}}{\text{Tapped density}} X\ 100$$

Evaluation Parameter of tablets[10, 12]

General Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc[10] .

Size & Shape:It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Organoleptic properties: Colour distribution must be uniform with no mottling. For visual colour comparison compare the colour of sample against standard colour.

Weight variation: All prepared matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated[10,12].

Friability: 20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of a soft brush. Tablet samples were weighed accurately and placed in Roche friabilator. After the given number of rotations (100 rotations) loose dust was removed from the tablets as before and the finally tablets weight determined. The lost in weight indicate the ability of the tablets to withstand stress of handling and transportation [10,12]. The percentage friability was determined by using following formula:

$$\% \text{ friability} = \frac{\text{initial wt.- final wt.}}{\text{initial wt.}} X\ 100$$

Hardness: The hardness of the tablets was determined by diametric compression

Table 4: Result of pre-formulation parameters of granules

S. No.	Formulations	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
1.	F1	0.486	0.567	14.28	1.16	22 ± 0.02
2.	F2	0.479	0.561	14.61	1.17	19 ±0.01
3.	F3	0.487	0.558	12.72	1.14	22 ±0.03
4.	F4	0.478	0.563	15.09	1.15	23 ±0.02
5.	F5	0.476	0.559	14.84	1.17	21 ±0.09
6.	F6	0.482	0.570	15.43	1.18	20 ±0.08

using a Hardness testing apparatus (Monsanto tester). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate[10,12].

Thickness: 20 tablets were taken randomly for this purpose, the tablet thickness were determined individually with the aid of a vernier caliper. [10,12]

Uniformity of content of active ingredient

Content uniformity: In this test, 30 tablet are randomly selected for the sample and at least 10 of them are assayed individually. Nine of the 10 tablet must contain not less than 85% and more than 115% of the label drug content. The 10 tablet may not less than 75% or more than 125% of the labeled content, if these condition not met then remaining tablet from the 30 must be assayed individually, and none may fall outside of the 85% to 115% range. In evaluating a particular lot of tablet, several sample of tablet should be taken from various part of production run to satisfy statistical procedure[10,12].

Disintegration test: Sustained released matrix tablets are not expected to disintegrate like convectional tablets. Disintegration time was measured by using 6 tablets from each formulation, i.e. one tablet per disintegrating basket.[10,12]

Dissolution test (In-vitro dissolution study):

The release rate of Atenolol and Indapamide SR matrix tablet was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The in vitro release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. At every interval 10 ml of the solution was withdrawn from the dissolution apparatus at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours and samples were replaced with fresh dissolution medium to maintain the constant volume. The samples were filtered through a filter and absorbance of these solutions was measured at 225.0 nm (Atenolol) and 240.0 nm (Indapamide) using Elico SL 210 UV/V is double beam spectrophotometer[10,12] shown in Table 5.

RESULTS AND DISCUSSION

The method was successfully used for determination of drugs in a pharmaceutical formulation. Assay results for combined dosage form using proposed method showed 99.30 ±1.04 % of Atenolol and 100.40±1.09% of Indapamide. Six formulations of Atenolol and Indapamide were formulated using different drug delay releasing agent ratio. The Prepared SR matrix tablets of Atenolol and Indapamide met the standard Pharmacopoeial requirements. In the present study SR matrix tablets were prepared by wet granulation process by using ingredients.

Table 5 : Evaluation of Atenolol and idapamide Sustained Release Matrix Tablet

S. No.	Hardness	Thickness	Friability	Drug content	Wt uniformity
F1	4.8	4.6	0.08	97.91	500 ± 1.1
F2	4.7	4.6	0.09	97.88	500 ±0.09
F3	4.2	4.7	0.05	99.88	499 ± 1.21
F4	5.2	4.6	0.07	96.82	500 ± 1.22
F5	5.1	4.6	0.08	96.22	499 ± 1.11
F6	5	4.6	0.06	96.75	500 ± 0.08

prepared. The values of Preformulation parameters evaluated were within prescribed limit and indicated good fine flow property. The data of evaluated tablets such as weight variation, hardness, thickness, friability, content uniformity and In-vitro disintegration time. All the formulation showed very low drug release in 0.1 N HCl (pH 1.2) and complete drug release showed in phosphate buffer at pH 6.8.

CONCLUSION

The study was undertaken with the aim to formulate and evaluate combination therapy of Atenolol and Indapamide SR matrix tablet for treatment of hypertension using Gaur gum, HPMC Pvp , Ethyl cellulose , Xanthan Gum for sustained release film coating as retarding agent. The granules of various formulations were prepared and evaluated for angle of repose, ranged from 22.30 ± 0.01 to 27.63 ± 0.03. The bulk density of granules using pvp 10% alcoholic solution was found to be 13.12-14.84.The drug content of weight amount of granules of all formulation were found to be in a ranged from 38 ± 0.65 to 75 ±1.03. The thickness of tablet was carried out for all batches were found consistent. The tablets of various batches formulated were evaluated for test such as hardness, friability and drug content, thickness, uniformity of weight. The average percentage deviation of all tablet formulation was found to be within the pharmacopoeial limit and hence all formulation passed the evaluation test. Formulation of SR matrix tablets show their slow, controlled and complete release of Atenolol and Indapamide over a period

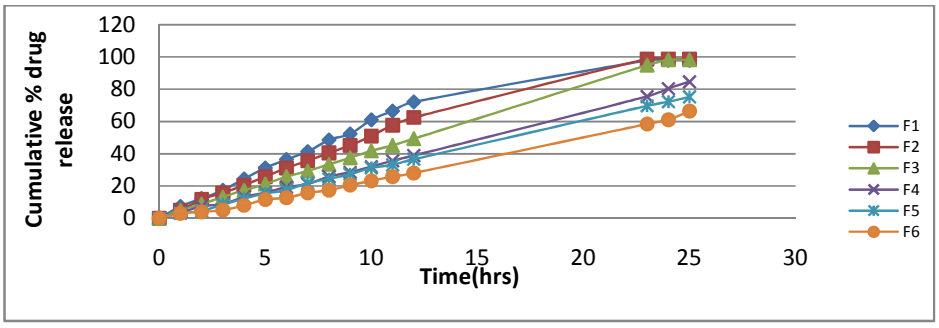

Fig. 1: Plot for cumulative % drug release Vs time (zero order kinetics)

of 24 hours was obtained from SR matrix tablets of F1, F2 formulated and the drug shows Zero order kinetics. The result of the dissolution study indicating that F1, F2, released 9.3, 5.71, of formulation at the end of 2hrs and 84.56, 73.82 at end of 24hrs respectively, But this formulation containing HPMC released 23.48 at the end of 2 hrs and 99.97 at the end of 24 hrs alone this could indicate that the drug–polymer ratio released the drug from matrix and this ratio fits for the matrix sustained released tablet of atenolol and indapamide together. Thus it can be concluded that release of Atenolol and Indapamide from tablets was slow and sustained over longer period of time.

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