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PREPARATION AND CHARACTERIZATION OF COMBINED DOSAGE FORM OF ATENOLOL AND INDAPAMIDE TABLETS

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ABSTRACT

The control of blood pressure is required in patients with hypertension to produce the maximum reduction in clinical cardiovascular end points, especially in patients with co-morbidities like diabetes mellitus where more aggressive blood pressure lowering might be beneficial. Recent clinical trials suggest that the approach of using drugs combined therapy for Hypertension gives significant contribution to the global health for the control of hypertension. In the present study we have formulated (f1 to f 6) matrix tablets of atenolol and Indapamide for the management of hypertension. As in studies we found that these drugs show confined release in combined formulated product. The formulation of SR matrix tablet was done by using different concentration of delayed release agent. Preformulation studies were performed prior to compression. The compressed SR matrix tablets were evaluated for weight variation, hardness, friability, drug content release for drugs in 24 hours respectively. The stability studies were carried out for the optimized batch for one months and it showed satisfactory results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows Zero order rate which is a sustained drug delivery system.

KEYWORDS: Hypertension, Preformulation, friability, drug content, matrix.

INTRODUCTION

Hypertension (HTN) or high blood pressure sometimes called arterial hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Hypertension, elevated blood pressure, is a noteworthy public health concern worldwide due to its significant contribution to the global health burden and its role as a prominent risk factor for the development of a number of disease processes. In the year 2001, high blood pressure accounted for "54% of stroke, 47% of ischemic heart disease, 75% of hypertensive disease, and 25% of other cardiovascular disease worldwide". The negative impact of hypertension on health status is clear, especially taking into account the disability, decreased quality of life, and mortality associated with stroke and cardiovascular disease. In 2001, 7.6 million deaths (13.5% of all deaths) and 92 million disability life-years (6% of total) were attributable to systolic blood pressure greater than 115 mm Hg.[1] For hypertension β-blockers are presently most important class of drug[1]. The first therapeutic drug shown to possess and ability to membrane-stabilising properties is Atenolol [(4-2–hydroxy-3–isopropyl-aminopropoxy) phenylacetamide] a cardioselective β-blocker. It may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin and α-methyldopa. 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] Whereas Indapamide (thiazide-type diuretics) is indoline derivatives of chlorosulphonamide (4-Chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide having antihypertensive effect is associated with an improvement in arterial compliance and a reduction in total and arteriolar peripheral resistance. It has two properties beyond diuresis. First, there is added vasodilation second unusual properties a high concentration class I and III antiarrhythmic effect. Indapamide has a terminal half-life of 14 to 16 hours and effectively lowers the blood pressure over 24 hours.[6-9] Hence in the present study combined formulation is prepared of sustained release matrix tablet using Atenolol and Indapamide with different polymers. The formulation is developed and drug release for extended duration is seen.

MATERIALS AND METHODS

Xanthum gum, guar gum, Glyceryl behenate, Glyceryl monostearate and Stearic acid Magnesium starate, Talc, all the ingredients used were of analytical grade. Formulation chart of Tablet is given in Table No: 1.

Preformulation Studies[10-12]

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

Organoleptic characteristics

The colour, odour, and taste of the drug were characterized and recorded.

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.

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.

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 -1 in Perkin – elemer FT-IR spectrophotometer.

Fabrication of tablets

Preparation of Atenolol and indapamide matrix tablet was done by dry granulation method. All the ingredients such as xanthum gum, guar gum, Glyceryl behenate, Glyceryl monostearate mixed thoroughly, after this materials were sieved through 22 and 44 meshes, lastly talc and magnesium stearate were added. Finally the tablets were compressed using single punch machine.

Evaluation of Pre-formulation parameters of granules[12-14]

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.

Hausner's Ratio =Tapped density/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.

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

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.

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.

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. The percentage friability was determined by using following formula.

% friability = initial weight- final weight⁄ initial weight x 100

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

Thickness

20 tablets were taken randomly for this purpose, the tablet thickness were determined individually with the aid of a vernier caliper.

Content uniformity

In this test, 30 tablets 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.

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.

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 having 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.

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 99.50 ±1.04 % of Atenolol and 99.90±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. A total number of six formulations were 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.

Table No. 1: Formulae 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
Xanthum gum	60	60	60	60	60	60
Gaur gum	60	60	60	60	60	60
Glyceryl behenate	18	18		36		
Glyceryl monostearate	18		18		36	
Stearic acid		18	18			36
Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5
Total	200	200	200	200	200	200

Table No. 2: Organoleptic properties.

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

Table No. 3: Result of solubility analysis

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

Table No. 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	0.485	0.566	14.28	1.10	20 ±0.01
2.	F2	0.487	0.562	14.61	1.15	21± 0.02
3.	F3	0.477	0.550	12.72	1.16	21±0.03
4.	F4	0.475	0.565	15.09	1.18	24 ±0.02
5.	F5	0.476	0.558	14.84	1.17	19 ±0.09
6.	F6	0.480	0.577	15.43	1.18	19±0.08

Table No 5: Result of post-formulation parameters of Matrix Tablet.

S. No.	Hardness	Thickness	Friability	Drug content	Weight uniformity
F1	4.6	4.6	0.05	99.91	500 ± 1.1
F2	4.7	4.6	0.06	99.88	500 ±0.09
F3	4.5	4.7	0.08	98.88	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	5.0	4.6	0.06	96.75	500 ± 0.08

Table No.6: Release profile of formulation F1 to F6

Formula	Zero order		First order		Higuchi plot		Korsmayer Peppas plot			
	Atn	Ind	Atn	Ind	Atn	Ind	Atn	Ind	Atn	Ind
	R^2	R^2	R^2	R^2	R^2	R^2	N	R^2	N	R^2
F1	0.999	0.999	0.993	0.995	0.960	0.956	1.211	0.888	1.192	0.880
F2	0.999	0.999	0.990	0.996	0.961	0.962	1.209	0.899	1.210	0.892
F3	0.999	0.999	0.995	0.996	0.967	0.967	1.215	0.897	1.225	0.905
F4	0.999	0.999	0.996	0.995	0.968	0.965	1.221	0.905	1.236	0.917
F5	0.999	0.999	0.992	0.991	0.969	0.968	1.230	0.916	1.256	0.927
F6	0.999	0.999	0.992	0.990	0.970	0.969	1.239	0.922	1.266	0.935

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 xanthum gum, guar gum, Glyceryl behenate, Glyceryl monostearate as retarding agent. The dry granules of different formulae were prepared and evaluated, So we found out angle of repose which ranged from 19±0.08 to 24 ±0.02, bulk density of dry granules ranged from 0.475- 0.487 and the drug content of weight amount of dry granules of all formulation were found to be in a ranged from 40 ± 0.65 to 80 ±1.03. Then after preparation the thickness of tablet was carried out for all batches were found consistent. The tablets of various batches were evaluated for test such as hardness, friability and drug content, thickness, uniformity of weight. The result of the dissolution study indicating that most of formulations released 7.88-5.60 of drugs release at the end of 2hrs and 88.50, 79.72 at end of 24hrs respectively, but formulation containing Glyceryl behenate shows drug release 20.48 at the end of 2 hrs and 99.98 at the end of 24 hrs. which indicate that the drug– polymer ratio released the drug from matrix and this ratio fits for the matrix sustained released tablet of combined dosage form of atenolol and indapamide in that respected polymer. he average percentage deviation of all tablet formulation was found to be within the pharmacopoeia 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 of 24 hours and this was obtained from SR matrix tablets of F1, F2 where the drug shows Zero order kinetics.

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