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FORMULATION AND EVALUATION OF FELODIPINE SUSTAINED RELEASE TABLETS BY USING VARIOUS BIODEGRADABLE POLYMERS

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ABSTRACT

In the present research work has been carried out in Formulation and Evaluation of Felodipine Sustained Release Tablets various biodegradable polymers. Recent advances in novel drug delivery systems aims to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is oral sustain release formulation. There are many biodegradable polymer used among these HPMC polymers results of the present study demonstrated that combination of both could be successfully employed for formulating sustained release matrix tablets of Felodipine. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Felodipine.

KEYWORDS

HPMC, Felodipine, Biodegradable polymers and Sustained release tablets.

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INTRODUCTION

The Oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility the enzyme system and its influence on the drug and the dosage form. The majority of oral controlled releases rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the

gastrointestinal milieu. By the following classes of controlled drug delivery system[1,2].

Hydroxypropyl methylcellulose is the polymer most widely used as the gel-forming agent in the formulation agent in the formulation of solid, liquid. Semisolid and even controlled release dosage form. Water penetration, polymer swelling drug dissolution, drug diffusion matrix Erosion from these dosage forms are controlled by a hydration of HMPC, which form a gel barrier through which the drug diffuses. Hydrophilic matrices containing swell able polymer are referred to as hydride matrices, swell able controlled release system or hydrophilic matrix tablet. A number of polymers have been investigated to develop in situ gel forming system, due to the ability of hydrogel to release and entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross linking[3-5].

Among the hydrophilic polymer, cellulose derivative such as methyl cellulose, Hydroxypropyl methylcellulose, are generally considered to be stable and safe as release dosage form. These semi synthetic polymers are quite expensive when compared with natural polymers such as tragacanth and guar gum. The natural polymers are non -toxic and easily available.

Hypertension is sustained elevation of resting systolic BP (> 140mm Hg), diastolic BP (>90 mm Hg) or both. Hypertension with no known cause (Primary, formerly, essential hypertension) is most common. Hypertension with an identified cause (Secondary hypertension) is usually due to a renal disorder. Usually, no symptoms develop unless hypertension is a serve or long-standing. Diagnosis is by sphygmomanometry. Tests may be done determine cause, assess damage, and identify other cardiovascular risk factors[6-8]. The classification of blood pressure in adults based on JNC was given in Table No.1.

The preparation and *in-vitro* release evaluation of sustained release matrix tablets of felodipine are planned to carry out in the following steps. Preparation of mixed blend of drug and excipients. Characterzation Granules; Angel of response, Bulk density, Tapped density, Carr's Index, Hausner's ratio.

Preparation of sustained release matrix tablets of Felodipine by Wet granulation method. Evaluation of matrix tablets, Thickness, Weight variation, Hardness, Friability, Drug content analysis, Determination of *in-vitro* drug release.

MATERIAL AND METHODS

List of materials

Felodipine, Polysorbate 80, MethocelE15 LV, HPMC K100lv cr, HPMCTM E 15, MCC VC 114, Magnesium stearate, Colloidal silicon dioxide, Iron oxide red, Precoat I(HPMC), Mathylene chloride, Isopropyl akcohol, Propylene glycol, All the above drugs and polymers are get from gifted sample of Intermed Pharma Ltd, Chennai.

List of instruments

Electrical balance (V-Tech), Multiple rotary punching machine (Rimek Phase-I), Vernier caliper (Mitutoya), Hardness tester (Monosanto), Friabilator (Nunes), Hydrolic press hardness tester (Dharma scientific products), Dissolution apparatus (Lab India), Sonicator (bath) (Remi equipment Pvt Ltd), Dryer (Techno- Tray dryer), Micro centrifugator (Remi Rsearch Centrifugur), Micro syringe, Hot air ovan (NSW India), Bulk density test apparatus (Konark Instruments), Cyclo mixer (Rapid).

Methods

The method of the research work is to formulate and evaluate the oral sustained drug delivery system containing Felodipine as a model drug by using polymer (HPMC K100LV, HPMC E15LV), Solubulizing agent (Polysorbate 80), microcrystalline cellulose 114, colloidal silicon dioxide, magnesium Stearate. This can be done to achieve better therapeutic success compared to conventional dosage form of the same drug. It has some advantages like, Reduced dosing frequency, Better patient compliance and convenience.

RESULTS AND DISCUSSION

Pre formulation studies of felodipine

Before reformulation of drug substance in to dosage forms, it is essential that it should be chemically and physically characterized studies give the formulation needed to define the nature of the drug substance and provide a frame work combination with pharmaceutical recipients in the fabrication of dosage forms

Drug - excipient interaction study

In the drug -excipient interaction study it was found that felodipine was having compatibility with all the excipients used in the formulation .active drug blended with individual excipient taken in 1:1 ratio. It was filled in closed vials and placed in stability chambers at as 25°C ± 2°C/ 60% +/ 5% RH, 35°C +2°C RH/; 65%+/ 5% RH and 40°C+ 2°C / 75%+ /5% RH. The compatibility studies were done samples were observed by physical changes at the end of 1^{st},2^{nd} 4^{th} and 6^{th} weeks thus the chosen the exipients for the formulation were found to be compatible with the active ingredient and having low physical interaction with the active pharmaceutical ingredient also there was no change in the physical appearance of the blend.

Compression of Tablets

The mixed granules were compressed in to tablets using 6mmmm round concave shape punches. Wet granulation is a widely employed method for the production of compressed tablet. The polymer is gradually to isopropyl alcohol while the solvent is continuously migrated a portion of the methylene chloride is this suspension, to solubulize the polymer. And the reminder of the methyline chloride is added to obtain the proper volume finally film coated.

EVALUATION OF GRANULES AND TABLETS

The prepared granules were evaluated by following test bulk density, Angle of repose, tapped density, Compressibility index /Carr's index, Hausner ratio and the results are given in Table No.2.

Bulk density

It is the ratio between a given mass of powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Total weight of the powder}}$$

A given quantity of the powder is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (v) and it includes the true volume of the powder and void space among the powder particles.

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. Tan $\theta = h/r$

$\theta = \tan^{-1}(h/r)$ Where, h= height of the pile, r= radius of the pile

Tapped density

Tapped density is defined as the ratio between weight of the sample powder taken and the tapped volume. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface height of 10cm at 2- Second intervals. The tapping was continued until no further range in volume was noted.

Tapped density (ρt) = M/V_f

Where, M = weight of sample powder taken

V_f= tapped volume

Compressibility index /Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility index of the powder was determined by using the following formula.

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

Hausner ratio

By calculating tapped density and bulk density, the Hausner ratio can be calculated.

Hausner ratio = ρ_t / ρ_o

Where, ρt = tapped density

ρ_o = bulk density

EVALUATION OF TABLETS

All the formulated felodipine SR matrix tablets were subjected to the following by control tests. Weight variation, drug content, friability, hardness, dissolution.

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The Weight Variation of tables are within limit.

Drug content

The tablets were assayed individually by extracting the drug from the tablets using 1% Polysorbate 80 solutions. The drug samples were analyzed by measuring the absorption at 254nm by using HPLC.

Hardness

It is determined to get perfect compactness during shipping, coating and packaging and to get proper shape and design. Hardness was measured by using hardness tester. (Pfizer hardness tester) For each batch six tablets were tested. The force required to break the tablet is recorded by the unit is kg/cm^2. Observation: the measured hardness of tablets of each batch was ranged from 8 - 16kg/cm^2.

Friability

Twenty tablets were weighed and placed in the Roche fribilator and apparatus vs. Rotated at 25 rpm or 4 minutes. The percentage friability of all the formulated batches were found under acceptable limit 1-0.6 as specified in IP.

In-vitro evaluation studies

Drug release study was carried out in USP II basket-type dissolution test apparatus dissolution medium was 1% (w/v) Polysorbate 80 in water volume of dissolution medium was 500ml, and bath temperature was maintained at 37+ 1°C throughout the study. Basket speed was adjusted to 100rpm. After 1, 2, 4, 6, 8, 10, 12 hours, 5ml of sample was a withdrawn and analyzed for content by HPLC at 254nm. The release studies were conducted in triplicane (6 tablets in each set), and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility pf the results. The results are tabulated in Table No.3 and graphical representation in Figure No.1. The dissolution medium is 0.5% Polysorbate 80 in water and Temperature maintained at 37°C and Time of sample withdrawal in 1, 2, 4, 6, 8, 10, 12 hours, RPM was maintained at 100.

LIQUID CHROMATOGRAPHIC CONDITIONS

Stationary: C18 (150*4.6cm, 5.0µ, 100A)

Phase: Buffer: Acetonitrile: Methanol (2:2:1) Buffer (6.9g Sodium of dihydrogen phosphate, 8ml of 1M O-Phosporic acid, 1000ml with Water)

Elution mode: 40:40:20(v/v)

Flow rate: 1.0ml/minute

Injection volume: 20µl

Detection: Ambient

The mobile phase was filtered through a 0.22µ membrane and degassed using ultra sonicator. The experiments were carried out at 20°C. The percentage of the labeled amount of felodipine dissolved at the times specified conform to acceptance.

Table No.1: The classification of blood pressure in adults based on JNC

S.No	BP Classification	SBP mm Hg	DBP mm Hg
1	Normal	<120	And <80
2	Prehypertension	120-139	Or 80-89
3	Stage 1 Hypertension	140-159	Or 90-99
4	Stage 2 Hypertension	>160	Or >100

JNC = Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

Table No.2: Angle of response, bulk density, tapped density, carr's compressibility index and Hausner's compressibility

S.No	Property	F1	F2	F3	F4	F5
1	Angel of Response (°)	43.05	28.39	29.05	29.74	29.74
2	Bulk Density (gm/cm3)	0.47	0.48	0.47	0.45	0.47
3	Tapped Density	0.58	0.56	0.56	0.56	0.56
4	Carr's Compressibility Ratio	18.96	14.28	16.07	19.64	19.96
5	Hausner's Compressibility Ratio	1.26	1.16	1.19	1.24	1.23
6	Flow Property	Good	Good	Good	Good	Good

Table No.3: *In-vitro* release profile of felodipine F1-F5 SR tablets

S.No	Time in Hrs	Cumulative percentage release of felodipine				
		F1	F2	F3	F4	F5
1	1	4.26	5.56	6.4	4.5	15.9
2	2	9.82	11.12	16.71	21.02	32.79
3	4	14.63	19.36	25.54	29.83	43.69
4	6	26.14	26.32	34.65	39.5	65.5
5	8	32.71	37.33	41.96	61.59	78.89
6	10	43.53	45.49	53.99	73.9	89.4
7	12	56.88	52.87	74.2	78.89	97.9

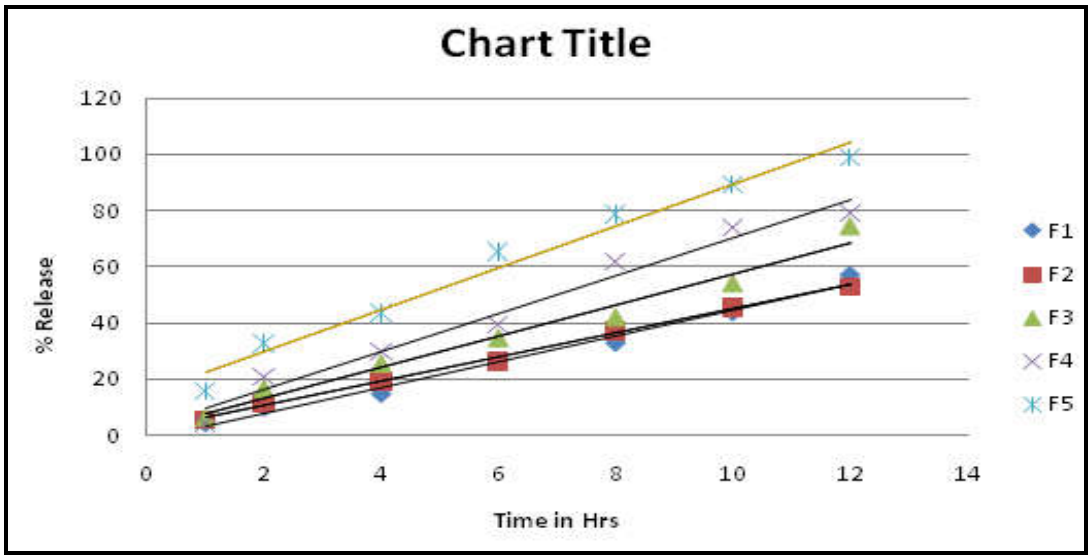

Figure No.1: *In-vitro* %drug release of formulation F1 to F5

CONCLUSION

Recent advances in novel drug delivery systems aims to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is oral sustain release formulation.

Results of the present study demonstrated that combination of both Methocel E15LV, HPMC K100lv cr polymers could be successfully employed for formulating sustained release matrix tablets of Felodipine. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Felodipine.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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