International Journal of Current Pharmaceutical Research
Vol 2, Issue 3, 2010
ISSN-0975-7066

Research Article

A STUDY ON FORMULATION AND PROCESSING FACTOR INFLUENCING THE RELEASE OF FELODIPINE

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Received 15 Jan 2010, Revised and Accepted 12 Feb 2010

ABSTRACT

In the present investigation, fast dissolving tablets of felodipine were formulated by using super disintegrant croscarmellose sodium and solid dispersion with polyvinyl alcohol (PVA) as a carrier. The tablets were characterized by FTIR study. The formulations were also evaluated for precomressional parameters such as angle of repose, % compressibility and Housness ratio. The post compressional analysis for the parameters such as hardness, friability, in vitro disintegration time, wetting time and in vitro release studies, stability studies were carried out as per ICH guide lines for three months. Tablets prepared by solid dispersion having drug to carrier ratio of 1:4 (A3) yielded the best drug release in terms of dissolution rate. The formulation did not show any change in disintegration time, wetting time and drug content after stability period.

Key words: Fast dissolving tablet, Felodipine, Crosscarmillose sodium, Solid Dispersion, Polyvinyl alcohol.

INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Consideration quality of life , most of these efforts have been focused on medication .among the various dosage forms develop to improve the case of administration , the fast dissolving tablet are the most widely prefer commercial products[1:2]

Now a day's fast dissolving tablets are going more important in the market for treating much disease condition. More is concerned on hypertension, migraine, nausea and vomiting, Parkinson disease, schizophrenia these condition are the widely require the drug to be formulated as fast dissolving tablet. These are most preferable dosage forms over conventional tablet because of ease of administrating, swallowing, pleasant test and availability in several flavors with basic advantage [.3-10]

Felodipine (4RS)-4(2, 3-dichlorophenyl)-2, 6-dimetheyl-1,4-dihydropyridine-3,5-dicarboxylate is a calcium channel blocker used as antihypertensive and antianginal drug. According to biopharmaceutics classification system, felodipine is class II drug, i.e., low solubility and high permeability. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration. Felodipine undergoes extensive first-pass metabolism with a bioavailability of 15%. The major drawbacks in the therapeutics application and efficacy of felodipine as oral dosage form is its low aqueous solubility , which is expressed to be approximately 19.17 mg/L at 25^0 C hence , improvement of its water solubility and dissolution is of therapeutic importance[11-15]. For poorly soluble orally administered drug, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increasing the surface area of available by various methods like micronization, Complexation, solid dispersion etc.[16]. Another pre requisite for the fast dissolution may be the disintegration time of tablets. Because, fast disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug[17].

Hence in the present study fast dissolving tablets of Felodipine were prepared by direct compression method with solid dispersion technique to increase the surface area of the drug and also super Disintegrant has been utilized for faster disintegration. Main advantages of direct compression are low manufacturing cast and high mechanical integrity of the tablets[18].

MATERIALS AND METHODS

Felodipine was gifted from Cipla limited Bangalore, Croscarmellose sodium Gift sample from Maple biotech Pvt. Ltd, Pune. Microcrystalline cellulose, PVA, Talc and Magnesium stearate were purchased from S.D. Fine chemicals Pvt limited, Mumbai and all other materials were of analytical grade.

METHODS

Preparation of solid dispersions of Felodipine with PVA

Solid dispersions of Felodipine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in Ethanol and then carrier (PVA) was added in ratio of 1:1, 1:2, 1:4 and 1:9. The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Preparation of tablets containing solid dispersions of Felodipine by direct compression

The solid dispersions equivalent to 5 mg of drug were taken. Then it mixed with directly compressible diluents and superdisintegrant in a plastic container. Magnesium stearate and aerosil were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend (Table 1).

Drug content of solid dispersion

Accurately weigh solid dispersions equivalent to 5 mg of Felodipine were weighed and transfer to 250 ml volumetric flask. Dissolve in phosphate buffer pH 6.5 containing 0.1% sodium lauryl sulphate (SLS) and the volume was made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically at 362 nm.

Evaluation of Felodipine tablets

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time, drug content and stability studies.Pfizer hardness tester was used for the determination of the hardness of the tablets. The tablet was placed in contact between the plungers and the handle was pressed,the force of the fracture was recorded .The thickness of tablets were recorded during the process of compression using Calipers(Mitotoyo;Japan) .The friability of the tablets was determined using a Roche Friabilator (Electrolab,EF-2 Friabilator) by taking two tablets from each batch and accurately weighed and placed in the Friabilator then operated for 100 revolutions .Then the tablets were dedusted and reweighed .Percentage friability was calculated using the formula,$F= (1-w_o/w)*100$. In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1 litre beaker containing 900 ml of

phosphate buffer pH 6.5 containing 0.1% SLS and time of disintegration was recorded at 37±2º C. In the wetting time study, a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For drug content analysis a total 10 tablets were weighed and powdered .The powder equivalent to 5mg of Felodipine was taken and dissolved in phosphate buffer pH 6.5 containing 0.1% SLS .After that an aliquot of the filtrate was diluted and analysed spectrophotometrically (UV 1700 Shimadzu Corporation. Japan) at 362 nm . The stability study of the tablets was carried out according to ICH guidelines .The formulations were stored at 40 ±2ºC / 75 ±5%RH for 4 weeks in a stability chamber (Labcare ,Mumbai,India)

In vitro release studies

The invitro dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 6.5 containing 0.1% SLS) was taken in vessel and the temperature was maintained at 37 ± 0.5ºC. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with Phosphate buffer pH 6.5 containing 0.1%SLS prior to analysis in the UV Spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 362 nm.

Characterization of Felodipine tablets

FT-IR analysis

The IR spectra for drug, PVA and SD were recorded in a Fourier transform infrared (FTIR) spectrophotometry (FTIR1615, Perkin Elmer, USA) with KBr pellets.

RESULTS AND DISCUSSIONS

The values of pre–compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Results are shown in Table 2. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, t_{50}%, t_{90}% and drug content are shown in Table 3.

In all the formulations, the hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥ 102.50 %) and uniform in all the formulations.

Table 1: Formula used in the preparation of tablets using PVA solid dispersion

Ingredients (mg)	A1	A2	A3	A4
Amount of solid Dispersion equivalent to 5 mg of drug	9.10	16..52	27.12	51
Lactose	110.40	102.98	92.38	68.50
MCC	20	20	20	20
Croscarmellose Sodium	6	6	6	6
Magnesium Stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5
Tablet Weight	150	150	150	150

Table 2: Precompressional parameters

Formulation	Angle of repose(θ) (±SD), n=3	Compressibility (%) (±SD), n=3	Hausner's Ratio (±SD), n=3
A1	20.28 ±1.22	25.75 ±1.12	1.32 ±0.04
A2	22.78 ±0.55	24.55 ±0.92	1.24 ±0.07
A3	24.12 ±1.55	21.92 ±2.20	1.22 ±0.09
A4	20.72 ±0.92	25.12 ±1.55	1.37 ±0.06

Table 3: Post compression parameters, disintegration time, wetting times, dissolution parameters and drug content of tablets

Formulation	Hardness test (kg/cm²) ±SD, n=6	Friability (%) ±SD, n=10	Thickness (mm) ±SD, n=4	Disintegration time (sec) ±SD, n=6	Wetting time (sec) ±SD, n=6	$t_{50\%}$ (min) ±SD, n=4	$t_{90\%}$ (min) ±SD, n=4	Drug content (%) ±SD, n=6
A1	3.12±0.20	0.28 ± 0.05	3.50± 0.05	45± 1.50	60±4.20	2.50± 0.20	9.40±0.55	101.55±1.52
A2	3.20±0.21	0.32 ±0.04	3.42±0.07	42±1.22	56 ±3.20	2.12±0.40	8.55 ± 0.24	102.20±2.20
A3	3.30± 0.18	0.33±0.07	3.47 ± 0.04	40±3.12	52±1.50	2.00±0.12	7.52±0.32	100.00± 2.24
A4	3.65± 0.31	0.35± 0.00	3.50±0.09	35±2.75	49± 3.10	1.20± 0.37	5.32± 0.42	102.50±1.92

Table 4: Tablet parameters after stability studies

Formulation	Disintegration Time(sec) (±SD), n=6	Thickness (mm) (±SD), n=4	Drug content (%) (±SD), n=6
A1	46.00±2.20	3.50±0.060	101.20 ±1.20
A2	42.00±3.20	3.41±0.09	102.50±1.55
A3	41.00±4.40	3.48±0.06	100.00±0.95
A4	35.00±3.00	3.51±0.08	101.95±1.00

The tablets were subjected for evaluation of invitro disintegration time and it was observed that all the formulations disintegrated rapidly. This may be due to disintntigration property of filler MCC, which leads to faster water uptake hence it facilitates swelling action of cross carmellose sodium in bringing about the faster disintegration. The dissolution of Felodipine from the formulations is shown in Fig. 2 .The results were compiled in Table 3. The dissolution rate of tablets prepared with solid dispersion in the

ratio1:1, 1:2, 1:4 1:9 (A1, A2, A3, A4) with PVA increased significantly (P< 0.05) . This may be due to the use of Croscarmellose sodium, which causes swelling to 4-8 folds in 10 seconds[19], also due to disintegration properties of filler MCC and due to particle size reduction and improved wettability[20]. In addition to micronization, conversion of drug to amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions[21]

FT-IR analysis

The IR spectrums of pure drug Felodipine, carrier PVA and Felodipine SD with PVA used in the present study shows characteristics absorption band are shown in the following IR region (Fig. 3)

FELODIPINE IR (KBR) cm^{-1}

3370(NH Stretching)

3069(Aromatic CH stretching)

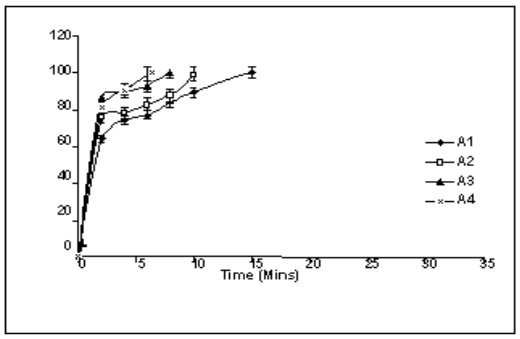

Fig.1: Dissolution profiles of formulations containing PVA solid dispersion

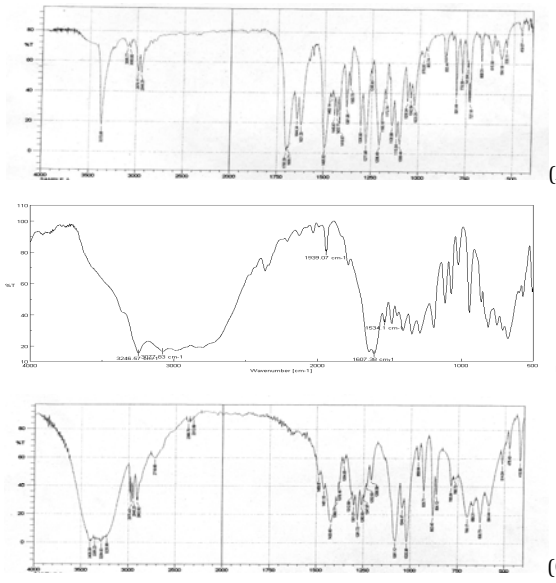

Fig. 2: FTIR spectrum of pure Felodipine (A),PVA (B), Felodipine SD with PVA(C)

The spectrum contains very broad peaks in the range 3200 to 3500 and a very sharp peak at 3370 indicating the presence of OH of PVA and NH of Felodipine. The spectrum shows the presence of carbonyl group of the drug at 1700 and 1688, NH bending 1643 and C═C ring stretching at 1617, 1496 and 1443. Since all the major peaks of the pure drug and PVA are present without any change in their position

2840, 2948(Ch stretching of CH2 and CH3 groups)

1700, 1688 (C═O stretching)

1644(NH bending)

1621, 1495, 1460(C═C ring stretching)

1099(C O C stretching)

727,801(Substituted benzene ring)

564 (Cl stretching)

PVA IR (KBR) cm^{-1}

Broad pick at 3077 to 3246 may be due to the hydrogen bonded OH groups.

1607 to1939 CH stretching.

1534 CH bending

in the spectrum of the SD. It can be concluded that the drug and carrier have retained their identity without losing their properties and not going in to a chemical interaction with each other. Thus the conclusion from the IR spectra of the drug and formulation is that there is no interaction between drug and carrier.

The stability study for all the formulations were carried out according to the ICH guidelines at 40 ± 2º C / 75 ±5% RH for 4 weeks, by storing the tablets in a stability chamber (Labcare, Mumbai, India) . No change was observed in the disintegration time of all the formulations. No significant change in the thickness was observed in all the formulations and drug content of all formulations was within the acceptable limits. Results are shown in Table 4.

CONCLUSION

The major problem of Felodipine is its very low solubility in biological fluids. The results revealed that it is possible to enhance the dissolution rate of Felodipine by increasing the surface area of the drug by solid dispersion method. Tablets prepared by PVA solid dispersion of ratio 1:9 (A4) yielded best results in terms of dissolution rate.

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