Asian Journal of Pharmaceutical and Clinical Research
Vol. 4, Issue 1, 2011 ISSN - 0974-2441

Research Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF FELODIPINE

D SANDEEP KUMAR*[1], B ASHISH REDDY[1], AMIT KUMAR TIWARI[1], B SWETHA[1] AND SUDDHASATTYA DEY[1]

[1] Guru Nanak Institute of Pharmacy, Ibrahimpatnam, Hyderabad, India.
E-mail: sandeep13.07pharm@gmail.com

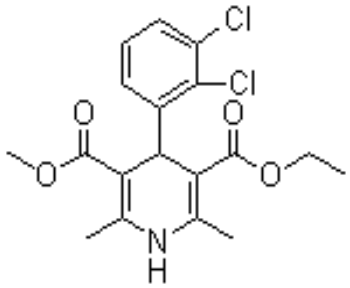
ABSTRACT

Recent advances in Novel Drug Delivery Systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is fast disintegrating/ dispersing tablet formulation. In the present work, fast disintegrating tablets of Felodipine were designed with a view to enhance patient compliance by direct compression method. In the direct compression method, crospovidone (2-10% w/w) was used as super-disintegrant along with microcrystalline cellulose (5-20%w/w) as disintegrant and directly compressible mannitol to enhance mouth feel. Estimation of Felodipine in the prepared tablet formulations was carried out by extracting the drug with methanol and measuring the absorbance at 360nm. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and *in vitro* dispersion time. Based on *in vitro* dispersion time (approximately 8-14 s), one promising formulation was tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer) and drug excipient interaction (IR spectroscopy). Among all the formulations, promising formulation (DCF_3) the formulation prepared by direct compression method (containing 2% w/w crospovidone and 15% w/w microcrystalline cellulose) emerged as the overall best formulation.

Key words: Felodipine, Directly compressible mannitol, Fast disintegrating tablets, Crospovidone.

INTRODUCTION

Felodipine is chemically 3-ethyl 5-methyl 4-(2, 3-dichlorophenyl)-2, 6-dimethyl1-1, 4-dihydropyidine-3,5-dicarboxylate.



Molecular formula of Felodipine is C18H19Cl2NO4. It is a member of dihydropyridine class of calcium channel antagonists and it blocks voltage dependent calcium channels, hence it reduces blood pressure. It is used in the treatment of hypertension. Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent Ca++ currents in vascular smooth muscle and cultured rabbit atrial cells, and blocks potassium-induced contracture of the rat portal vein.

MATERIALS AND METHODS

Materials required

Chemicals and Drugs

Felodipine: Aurbindo-pharma limited.
Mannitol (Pearlitol SD 200): Aurbindo-pharma limited
MCC (PH 102): Aurbindo-pharma limited
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Sodium stearyl fumarate: Aurbindo-pharma limited
Talc: SD fine chemicals.
Aspartame: Aurbindo-pharma limited
Pineapple flavor: Aurbindo-pharma limited
Potassium dihydrogen orthophosphate: SD fine chemicals.

Instruments

UV-spectrophotometer: T60 UV-Visible Spectrophotometer.
Digital Balance: BL-220H, Shimadzu.
Digital pH meter: Motex 152- R.
Dissolution apparatus: Sisco Mumbai.
IR spectroscopy: Perkin Elmer FTIR Series model-1615 Spectrometer.
Hot air oven: Sisco, Mumbai.
Hardness tester: Pfizer.
Friability Test Apparatus: Sisco, Mumbai.
Tablet compression machine: Cadmach, 16 stations.

METHODS

Preparation of standard calibration curve of felodipine in methanol and phosphate buffer solution (6.8ph)

25mg of Felodipine was accurately weighed and dissolved in 25ml of water and phosphate buffer into a volumetric flask (1000 mcg/ml) respectively. 1 ml of this solution was taken and made up to 100 ml with water and phosphate buffer solution, which gives 10 mcg/ml concentrations (stock solution). From this stock solution, concentration of 10, 20, 30, 40,50mcg/ml in water and phosphate buffer solution were prepared. The absorbance of the diluted solution was measured at 360 and 364 nm respectively and a standard plot was drawn using the data obtained. The correlation coefficient was calculated by linear regression analysis. The absorbances of the above concentration are shown in table-1 and table-2.

Formulation of fast disintegrating tablets

Direct compression[2, 3]:

Fast disintegrating tablets of Felodipine were prepared by direct compression according to the formulae given in table-3.

- All the ingredients were passed through 60 mesh sieve separately.
- The drug and MCC was mixed by small portion of both each time and blending it to get a uniform mixture and kept aside.
- Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 7 mm size to get a tablet of 120 mg weight using a Rotary Clit 10 station compression machine. The tablets were prepared according to the formulae shown in table-3.

Evaluation of tablets

Weight variation[4, 5]:

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. The results are shown in table-5.

Hardness and Friability[7, 8]:

Friability of the tablets was checked by using Roche Friabilator. This device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. The results are shown in table-5

Content uniformity test[9]:

Ten tablets were weighed and powdered, a quantity of powder equivalent to 1 mg of Felodipine was transferred to a 50 ml volumetric flask and 40 ml water is added. The drug is extracted into the methanol by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to 50 ml with water and the liquid is filtered. The Rizatryptan benzoate content was determined by measuring the absorbance at 234 nm after appropriate dilution with water. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. The results are shown in table-5

Wetting time and Water absorption ratio[7]:

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting is measured (figure-4). The wetted tablet was then weighed. The results were shown in table-5.

Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \left(\frac{W_a - W_b}{W_a}\right)$$

Where, Wa is weight of tablet after water absorption and

Wb is weight of tablet before water absorption.

***In-vitro* dispersion time[1, 10]**

Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5ºC. Time required for complete dispersion of a tablet was measured. The results were shown in table-5 and figure-3.

Dissolution study[11]

In vitro dissolution of a Felodipine fast disintegrating tablet was studied in USP type-II dissolution apparatus (Sisco) employing a paddle stirrer. 900 ml of phosphate buffer pH 6.8 was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37±0.5ºC and was maintained throughout the experiment. One tablet was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 364nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Felodipine released was calculated and plotted against time.

Drug-Carrier interaction studies[10, 12]:

While developing a new formulation, it is necessary to check the drug compatibility with the carrier or excipient used and that the drug has not undergone any degradation when it passes through the various processes. Suitable evidential experiments are conducted to justify and prove the intactness of the drug in the formulations. Various methods available for characterizing the products are: TLC, IR spectra, X-ray diffraction, scanning electron microscopy, diffuse reflectance spectroscopy and differential scanning calorimetry.

Infrared Spectroscopy[13, 14, 15]:

Infrared spectroscopy is one of most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of a formulation. IR spectra of Felodipine and its formulations were obtained by KBr pellet method using Perkin Elmer FTIR series model-1615 spectrometer in order to rule out drug-carrier interaction occurring during the formulation process.

RESULTS AND DISCUSSION

In direct compression method the formulations were prepared using super-disintegrants such as Crospovidone (CP), along with microcrystalline cellulose (MCC) (PH. 102) in different ratios. The hardness of the tablet formulations made by the direct compression method was found to be in the range of 2.20 to 2.70Kg/cm, indicating good, mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, friability value was found to be less than 1%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits. The percent drug content of all the tablets was found to be in the range of 102.24 to 106.19 of the expected Felodipine content, which was within the acceptable limits (tables-5). In vitro dispersion time, wetting time and water absorption ratio for all the Felodipine tablet formulations prepared by direct compression method were determined and the results are shown in (table-5). Among the tablets prepared by direct compression method using crospovidone (CP) and microcrystalline cellulose (MCC) as disintegrants, formulation DCF_3 containing 2% w/w crospovidone and 15% w/w microcrystalline cellulose was found to be promising and has shown in vitro dispersion time of10.02, wetting time of 11.55 s and water absorption ratio of 70.55% .

***In-vitro* dissolution study**

In vitro dissolution studies were performed in phosphate buffer of pH 6.8, on the above promising formulations, namely DCF_3, The results are shown in (table-6). From the above data it is evident that among the promising formulations, DCF_3 (prepared by direct compression method), released 98.75% and 89% drug in 10 minutes (pH 6.8 phosphate buffer).

Drug-Excipient interaction studies (by FT-IR)

The IR spectrum of the pure drug shows characteristic peaks at 3267cm^{-1} and 1693 cm^{-1} due to –NH and Carboxyl groups respectively. Formulations DCF_3 exhibited similar peaks at 3267 and 1693 cm⁻respectively for the above groups. This confirms undisturbed structure of the drug in the formulations. Hence, there are no drug-excipient interactions.

Table -1: Standard graph of felodipine in Methanol(λ_{max}360nm)

S. No.	Concentration (mcg/ ml)	Absorbance			Mean
		I	II	III	
1.	0.00	0.000	0.000	0.000	0.000
2.	10.0	0.171	0.174	0.176	0.173
3.	20.0	0.362	0.358	0.361	0.360
4.	30.0	0.620	0.624	0.622	0.622
5.	40.0	0.757	0.756	0.753	0.755
6.	50.0	0.951	0.950	0.948	0.949

Table -2: Standard graph of felodipine in pH 6.8 Phosphate Buffer (λ_{max} 364 nm)

S. No.	Concentration (mcg/ ml)	Absorbance			Mean
		I	II	III	
1	00	0.000	0.000	0.000	0.000
2	10	0.218	0.214	0.216	0.216
3	20	0.422	0.420	0.426	0.422
4	30	0.649	0.645	0.648	0.647
5	40	0.831	0.834	0.832	0.832
6	50	1.203	1.202	1.206	1.203

a=–0.0014; b=0.122; r=0.999

Table -3: Formulations chart of felodipine fast disintegrating tablets prepared by direct compression method

Ingredients (mg/Tablet)	Formulation Code					
	DCF_1	DCF_2	DCF_3	DCF_4	DCF_5	DCF_6
Felodipine	1.00	1.00	1.00	1.00	1.00	1.00
Crospovidone	2.40	2.40	2.40	6.00	6.00	6.00
Microcrystalline cellulose (PH 102)	6.00	12.00	18.00	6.00	12.00	18.00
Aspartame	1.20	1.20	1.20	1.20	1.20	1.20
Talc	2.40	2.40	2.40	2.40	2.40	2.40
Sodium stearyl fumarate	1.20	1.20	1.20	1.20	1.20	1.20
Flavor (pineapple)	1.20	1.20	1.20	1.20	1.20	1.20
Mannitol (SD 200)	104.60	98.60	92.60	101.00	95.00	89.00
Total	120.00	120.00	120.00	120.00	120.00	120.00

Table -4: Pre-compression parameters of formulations prepared by Direct Compression Method

Parameters	Formulation code					
	DCF_1	DCF_2	DCF_3	DCF_4	DCF_5	DCF_6
Angle of repose (º)	29.26	30.12	28.66	30.45	29.23	27.56
Bulk density (gm/cc)	0.449	0.460	0.465	0.450	0.480	0.455
Tapped density (gm/cc)	0.526	0.536	0.525	0.548	0.590	0.552
Carr's Index (%)	16.72	16.67	15.79	14.79	19.00	16.45
Hausner's ratio	0.82	0.85	0.82	0.84	0.80	0.82

Table -5: Post compression parameters of formulations prepared by direct compression method

Parameters	Formulation code					
	DCF_1	DCF_2	DCF_3	DCF_4	DCF_5	DCF_6
Hardness* (kg/cm^2)± SD	2.23± 0.09	2.66±0.11	2.26± 0.12	2.56± 0.07	2.40±0.16	2.23± 0.15
Thickness (mm)	3.10	3.30	3.20	3.30	3.20	3.10
Friability (%)	0.521	0.424	0.420	0.516	0.432	0.409
In vitro dispersion time*(sec) ±SD	16.39± 0.69	12.6± 0.32	10.02±0.15	11.12± 0.09	8.24± 0.13	6.23± 0.19
Wetting time*(sec) ± SD	14.23± 0.39	12.45± 0.36	11.55± 0.32	12.22± 0.59	10.42±0.21	09.55±0.18
Water absorption ratio* (%) ± SD	52.55± 0.42	60.22± 0.41	70.55± 0.44	67.68± 0.39	55.49± 0.40	75.26±0.42
Drug content* (%) ± SD	106.19 ±0.27	104.25±0.96	103.08±1.89	105.13±1.02	102.24±1.15	103.47±2.23
Weight variation	119-126 mg within the IP limits of ± 7.5%.					

* Average of three determinations

Table -6: In-vitro dissolution data of tablet formulations of Felodipine and Formulation in pH 6.8 Phosphate Buffer

Time (min)	Cumulative Percent Drug Released					
	DC_1	DCF_2	DCF_3	DCF_4	DCF_5	DCF_6
2	50.49±0.62	53.96±0.67	63.02±1.11	55.90±0.62	64.09±0.89	61.09±0.73
4	65.98±0.78	65.92±1.10	71.20±1.73	65.69±1.21	73.21±1.19	59.29±0.96
6	75.29±0.98	78.56±0.89	82.18±0.76	72.29±0.83	84.21±1.11	66.20±1.13
8	78.12±0.79	83.89±1.23	91.21±2.14	87.30±1.19	92.91±1.89	78.15±2.08
10	83.62±0.21	87.98±0.65	98.75±1.42	93.20±0.69	99.29±1.34	92.13±2.49
15	87.21±0.74	90.96±1.69	_	95.21±0.96	_	_
30	91.22±1.09	_	_	_	_	_

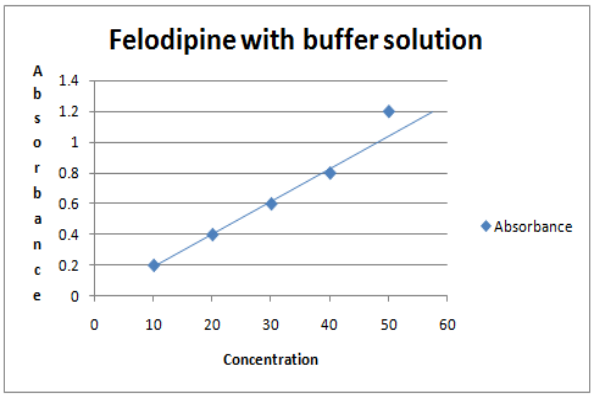


Figure -1: Standard Graph of Felodipine in Methanol (λ_{max} 360 nm)

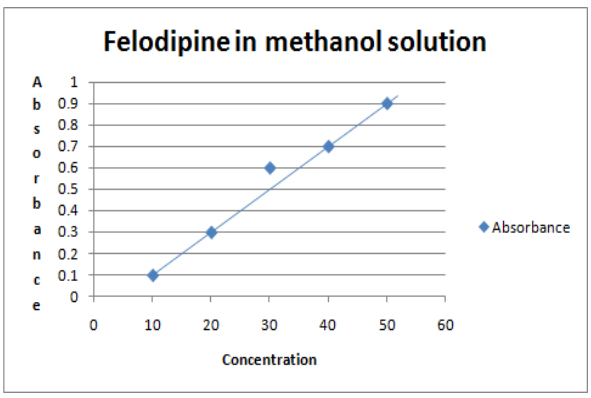


Figure 2: Standard Graph of Felodipine in pH 6.8 Phosphate Buffer (λ_{max} 364 nm)

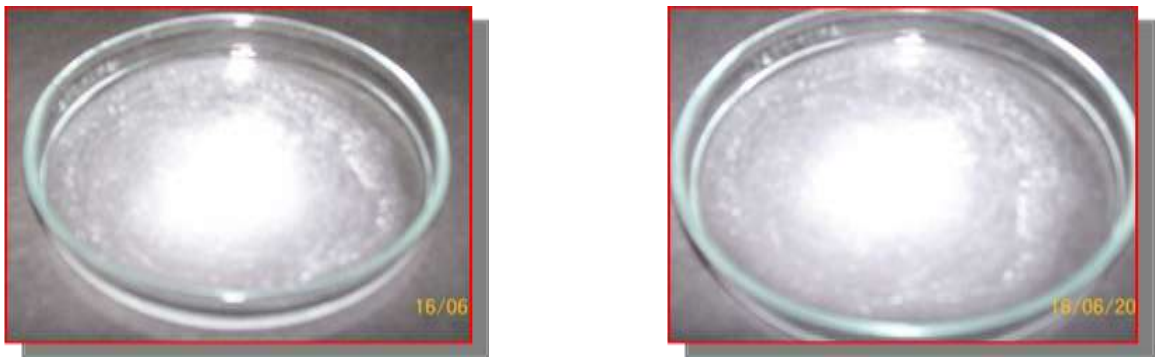


Figure -3: In-vitro dispersion of Tablets prepared by Direct Compression Method

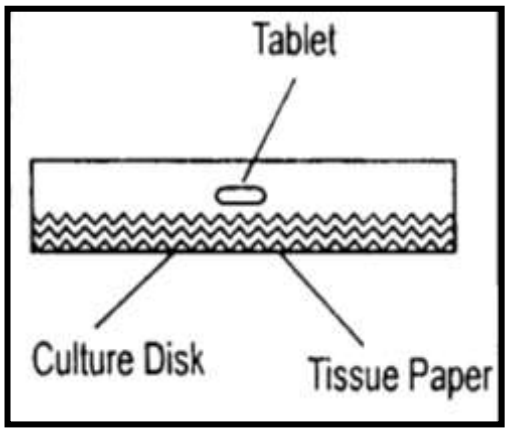
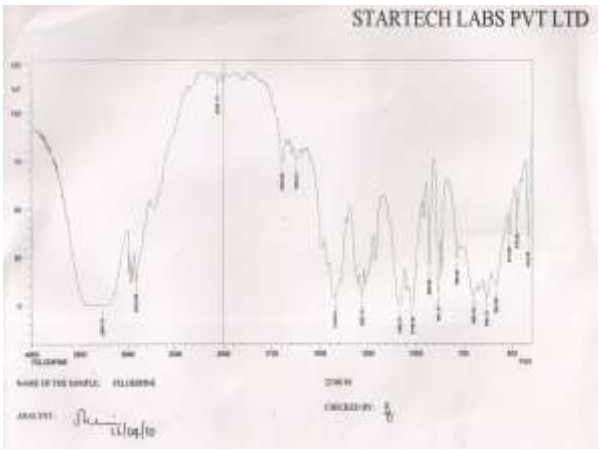


Figure -4: Schematic representation of wetting time/water absorption ratio determination

Figure 5: Wetting time and water absorption ratio of Fast Disintegrating Tablets



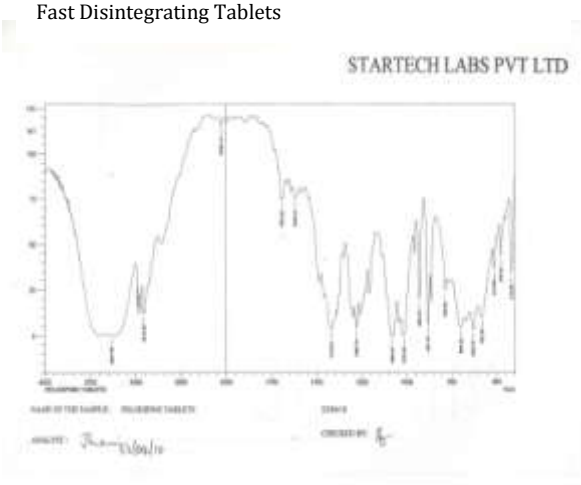


Figure -6: 1) IR Spectra of Felodipine powder 2) IR Spectra of Felodipine tablets

CONCLUSION

All the tablets of Felodipine were subjected to weight variation, drug content-uniformity, hardness, friability, water absorption ratio, wetting time, *in vitro* dispersion time, dissolution and drug-excipient interactions.

Based on the above studies, following conclusions can be drawn:

- Tablets prepared by direct compression technique were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets were found to be in the range of 2.20 to 2.70 Kg/cm^2 for direct compression method The friability value of the prepared batches of tablets were found to be less than 1%.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- The in vitro dispersion time of Felodipine tablets prepared by direct compression found to be in the range of 6-16 s.
- Based on the *in vitro* dispersion time, formulations DCF_3 was found to be promising and displayed a dispersion time of approximately 10.02 s. Wetting time of promising formulations was found to be 11.55 s, which facilities their faster dispersion in the mouth.

- The promising formulations (DCF_3) have displayed good water absorption of about 70.55%, which indicates better and faster swelling ability of the disintegrants in presence of little amount of water.
- IR-spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation.

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