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Original Research Article

Physicochemical characterization and solubility enhancement studies of Felodipin solid dispersions

Mali Audumbar*, Nalavade Sachin and Bathe Ritesh

Department of Pharmaceutics, Sahyadri College of Pharmacy, Methwade, Sangola- 413307, Solapur, Maharashtra, India.

***Correspondence Info:**
Mr. Audumbar Mali
Department of Pharmaceutics,
Sahyadri College of Pharmacy, Methwade,
Sangola-413307, Solapur, Maharashtra, India
E-mail: maliaudu442@gmail.com

Abstract

The aim of present work is to develope fast dissolving tablets of Felodipine by first preparing solid dispersion with PEG 6000 and PVP K30 in ratio 1:1, 1:3 by direct compression method using different superdisintegrant such as crospovidone (CP), croscarmellose sodium (CCS). The prepared tablets were evaluated for pre-compression parameters such as angle of repose, bulk density, compressibility index, hausner's ratio and post-compression parameters such as thickness, hardness, friability, drug content, weight variation, wetting time, water absorption ratio, In-Vitro disintegration time, in-vitro dissolution studies and stability studies. All the parameters showed good results. The study reveals that formulations prepared by direct compression F5 exhibits highest dissolution using croscarmellose sodium & showed faster drug release 99.89% over the period of 21 min. F5 batch disintigrate in 55 sec. show good disintegration comparison to other formulations of Felodipine.

Keywords: Fast dissolving tablets, Felodipine, solvent evaporation method,direct compression, croscarmellose sodium

1. Introduction

In last three decades drug discovery and medicinal chemistry moved from wet chemistry to combinatorial chemistry and high throughput screening which resulted into an increase of poorly water soluble drugs. In this paradigm, around 70% of new drug candidates have shown poor aqueous solubility in drug discovery. [1,2] Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble.[3] Solid dispersions, defined as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to improve dissolution of poorly water soluble drugs to enhance their bioavailability.[4]

Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents includes enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs.[5] Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Lipophillic molecules especially those belonging to the Biopharmaceutics Classification System (BCS) Class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability etc . Many solubilization techniques have been described that either change the nature of the solvent environment (cosolvent system, emulsion, micellization) or the chemical identity of the dissolved solute (salt formation, complexation, prodrugs). Alteration of the solid state at the particle or molecular level involves a physical change in the

drug and is an attractive option for improving drug solubility.[6,7]

1.1 Objectives

The following objectives are to be considered:

1. To study different methods of solid dispersion.
2. To study the evaluation parameter of solid dispersion.
3. To enhance solubility and bioavailability.

2. Materials and Methods

2.1 Materials

Felodipine was obtained as a gift sample from gift sample from Wockhardt Ltd, Mumbai, polyethylene glycol, polyvinylpyrrolidone, crospovidone, crosscarmellose sodium, lactose, microcrystalline cellulose, mannitol, talc, magnesium stearate, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium lauryl sulfate were purchased from S.D Fine Chemicals, Mumbai.

2.2 Methods

2.2.1 Preparation of the Solid dispersion[8]:

Solid dispersions of Felodipine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in Methanol and then carrier polyvinylpyrrolidone K30 (PVP) & Polyethylene Glycol 6000 (PEG) was added in ratio of 1:1, 1:3. Separately was evaporated at room temperature and dried in hot air oven at 50^{o}C for 4 hours. The resultant mass was passed through sieve No. 60 and stored in dessicator.

Table No. 1:- Preparation of the Solid dispersion of Felodipine

Polyethylene Glycol 6000 (PEG)				Polyvinyl pyrrolidone K30 (PVP)			
1:1		1:3		1:1		1:3	
Felodipine (mg)	(PEG) (mg)	Felodipine (mg)	(PEG) (mg)	Felodipine (mg)	(PVP) (mg)	Felodipine (mg)	(PVP) (mg)
100	100	100	300	100	100	100	300

2.2.2 Preparation of tablets containing Solid dispersion of Felodipine[9]**:-**

The solid dispersions equivalent to 2.5 mg of drug was taken. Then it mixed with directly compressible diluents and superdisintegrant in a plastic container. Microcrystalline cellulose was used as a direct compressible material. Superdisintegrants like croscarmellose sodium and crospovidone were used then magnesium stearate and talc were added. All the ingredients were passed through sieve no. 60. The formulations were compressed with a tablet punching machine using 8 mm diameter round concave punch (Karnavati, mini press). Before tablet preparation, the mixture blend subjected for compatibility studies FT-IR spectroscopy (Model: Synthesis Monitoring System) and precompression parameters like angle of repose, bulk density, tapped density, percent compressibility & Hausner's ratio.

Table No. 2:- Formulation used in the preparation of tablets using PVP& PEG SD.

Ingredients (mg/tablet)	Polyethylene Glycol 6000 (PEG)				polyvinylpyrrolidone K30 (PVP)			
	F1	F2	F3	F5	F6	F7	F8	F9
Felodipine (Equivalent to 2.5 mg of drug)	5	10	5	10	5	10	5	10
Lactose	110	105	110	105	110	105	110	105
Croscarmellose Sodium	6	6	-	-	6	6	-	-
Crosspovidone	-	-	6	6	-	-	6	6
Micro crystalline cellulose	20	20	20	20	20	20	20	20
Mannitol	6	6	6	6	6	6	6	6
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

3. Analytical Methods

3.1 Preparation of Phosphate Buffer (pH 6.5) [10]:

Dissolve 60.5 g of disodium hydrogen phosphate and 46 g of potassium dihydrogen phosphate in water, add 100 ml of 0.02 M disodium edetate and 20 mg of mercuric chloride and dilute with water to produce 1000 ml.

3.2 Preparation of Felodipine standard stock solution (100µg/ml) in phosphate buffer (pH 6.5) solution[11,12]

Accurately weighed 100 mg of Felodipine in phosphate buffer (pH 6.5) solution in a 100 ml volumetric flask and the volume was made up to 100 ml by using phosphate buffer (pH 6.5) solution containing 0.1% SLS to obtain a primary stock solution of 1000 µg/ml. 1ml of primary stock solution was further diluted to 100 ml phosphate buffer (pH

6.5) to obtain a secondary stock solution of 100µg/ml.

3.3 Preformulation Studies[13,14]

3.3.1 FT-IR Studies

The pure drug, drug-polymers combinations and formulations were subjected to FT-IR spectroscopy (Model: Synthesis Monitoring System) studies. Potassium bromide, pure drug and the polymers were heated to 105^0C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and polymer in 9:1 ratio. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm^{-1} to 1000 cm^{-1} wave number. FT-IR spectrum of Felodipine was compared with FT-IR spectrum of Felodipine with polymer.

3.3.2 Differential scanning calorimetry (DSC) Studies

DSC analysis (Model: Diamond DSC) scans of about 10 mg, accurately weighed Felodipine and solid dispersion prepared with PVP K30 in ratio 1:3 were performed by using an automatic thermal analyzer system. All the samples were run at a scanning rate of 10 °C/min from 50-350°C.

3.4 Solubility Studies

Solubility of Felodipine was determined and it is freely soluble in methanol, acetone, methylene chloride and anhydrous ethanol. Insoluble in water. Solubility studies were performed by taking 1gm Diltiazem hydrochloride in 10ml different solvents.

4. Evaluation of Tablets

4.1 Precompression Parameters[15,16,17,18]

4.1.1 Micromeritic properties

a) Angle of repose (θ):-Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose

h is height of the powder cone

r is radius of the powder cone

Method

The angle of repose values for tablet blends were determined by funnel method (Reposogram). The accurately weighed tablet blend was taken in funnel. The height of funnel was adjusted in such way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using above equation.

Table No.3:- Relationship between angle of repose (θ) and flow properties.

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

b) Bulk density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.

Method

Accurately weighed sample taken in a 25 ml measuring cylinder and measured volume of packing and tapped 100 times on a plane hard wooden surface and tapped volume of packing recorded and LBD and TBD were calculated using following formula;

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}}$$

c) Percent Compressibility

Percent Compressibility of powder mixture was determined by Carr's compressibility index calculated by following formula.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

d) Hausner's ratio

Hausner's ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

4.2 Postcompression Parameters[19,20,21,22]

1) Uniformity of thickness

The thickness of the tablet was measured by using Vernier caliper and expressed in mm. The limit specified was average thickness ± 5% deviation.

2) Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

3) Friability test

The friability of tablets was determined by using Friabilator. It is expressed in percentage (%).Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

4) Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The USP allows a little variation in the weight of a tablet.

Table No.4:- Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight was more than130mg and less than 324 mg, hence 7.5% maximum differences allow.

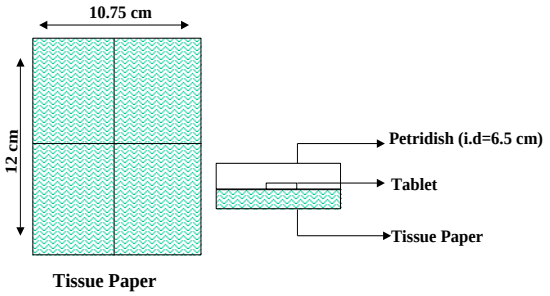
5) Drug content uniformity

Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 100 mg of drug transferred in 100 ml methanol. Its concentration 1000 µg/ml. 10 ml from this stock solution taken and diluted to 100 ml methanol, it makes 100µg/ml. Then 20µg/ml solution prepared by taking 2 ml from stock solution and diluted to 10 ml. Absorbance measure at 362 nm.

6) Wetting time

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish containing 10 ml of water, a tablet was placed on the paper and the time for complete wetting was measured.

Figure 1: Simple methods for the measurement of wetting time of a tablet.



7) Water absorption ratio:-

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$R = 100 (W_a - W_b)/ W_b$

Where, W_b – weight of tablet before absorption,

W_a – weight of tablet after absorption

8) *In- vitro* disintegration time

In that test first place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using phosphate buffer (ph 6.5) containing 0.1% SLS. Maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.5 containing 0.1% SLS maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

9) *In- vitro* dissolution studies

In-vitro drug release was studied by using USP type-II apparatus (USP Type-2 Model, Electrolab) at 50 rpm using 900 ml of phosphate buffer pH 6.5 containing 0.1% SLS as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, 5 ml of the sample from dissolution medium was withdrawn at every 3 min interval, filtered and from filtrate 1 ml was taken and diluted to 10 ml with phosphate buffer. The absorbance of sample was measured by UV spectrophotometric method at 362 nm and concentration of the drug was determined from standard calibration curve.

5. Result and Discussion

5.1 Preformulation Studies

Figure 2: Standard Calibration Curve of Felodipine in phosphate buffer (pH6.5).

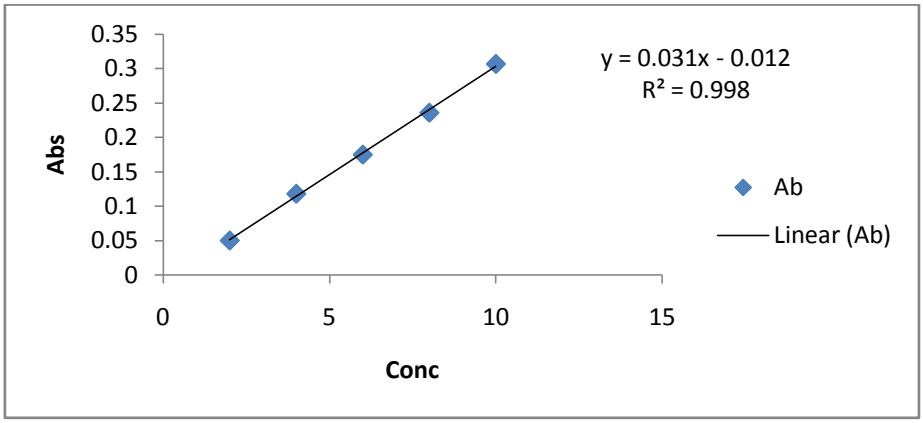


Fig.No.3:- IR spectra of Felodipine.

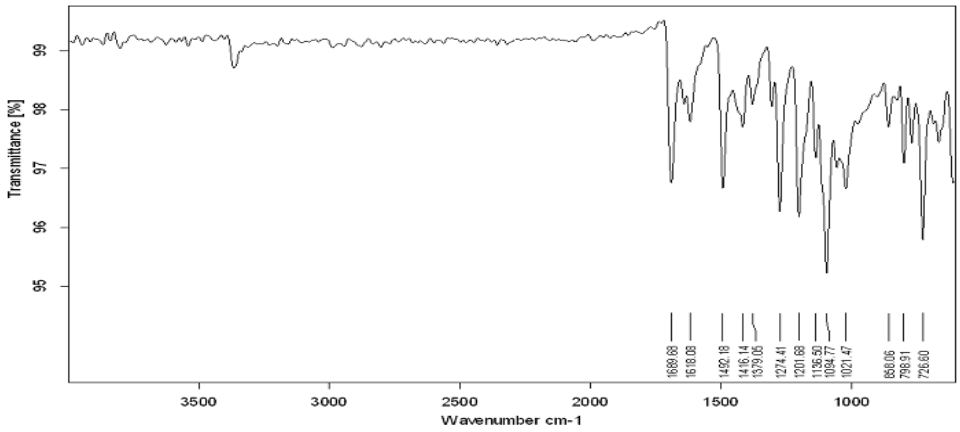


Fig.No.4:- IR spectra of Drug and poly vinyl pyrrolidone K30 (PVP)- I

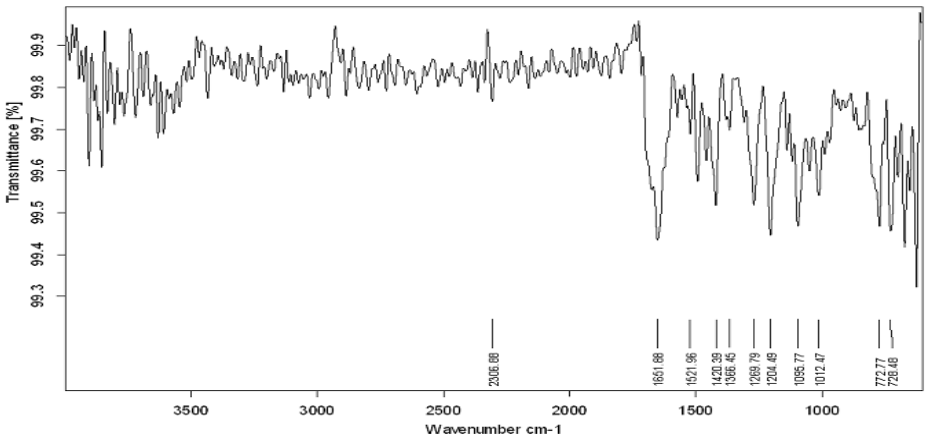


Fig.No.5:- IR spectra of Drug and poly vinyl pyrrolidone K30 (PVP)- III

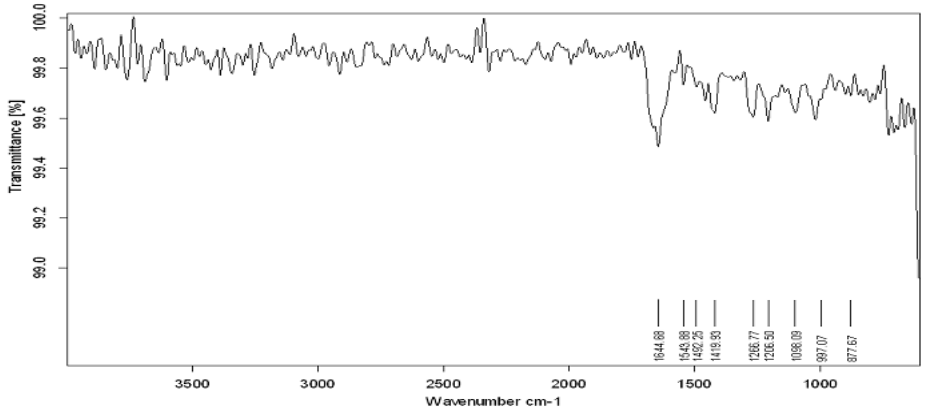


Figure 6: DSC of solid dispersion with PVPK 30 I

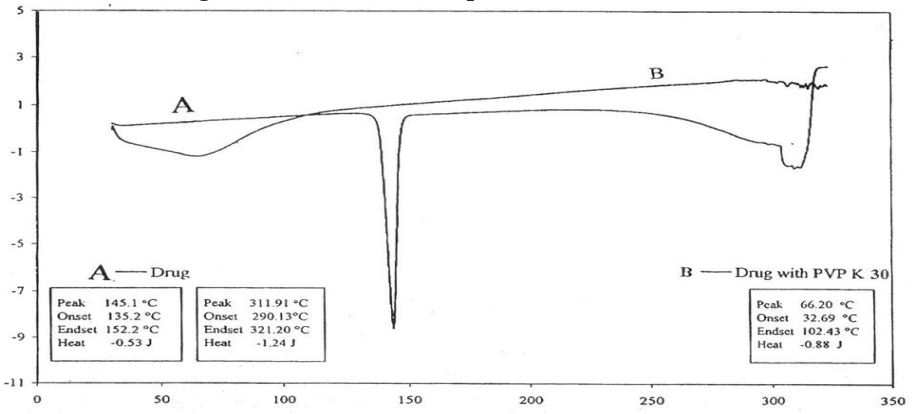


Table No.5:- Drug content of Solid dispersion.

Solvent	Polyethylene Glycol 6000 (PEG)		Polyvinyl pyrrolidone K30 (PVP)	
	1:1	1:3	1:1	1:3
Water	0.08 x 10^3 =0.0158	0.14 x 10^3 = 0.01	0.16 x 10^3 = 0.01	0.10 x 10^3 = 0.158
Methanol	0.10 x 10^3 =0.012	0.17 x 10^3 = 0.1	0.19 x 10^3 =0.0158	0.13 x 10^3 =0.0071

Table No. 6:- Determination of the yield.

Polyethylene Glycol 6000 (PEG)		polyvinylpyrrolidone K30 (PVP)	
I	III	I	III
99 %	99.5 %	98 %	97.5 %

5.2 Precompression Parameter

Table No.7:- Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Carr's Compressibility Index and Hausner's ratio.

Formulation Code	Angle of Repose(θ)	Loose Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm$^{3)}$	Compressibility Index %	Hausner's ratio
F1	22.78	0.42	0.52	19.23	1.32
F2	23.74	0.40	0.53	24.52	1.33
F3	20.80	0.43	0.49	12.24	1.35
F4	22.29	0.43	0.53	23.25	1.32
F5	23.74	0.42	0.51	17.64	1.35
F6	24.22	0.40	0.52	23.07	1.28
F7	20.30	0.45	0.54	16.66	1.34
F8	21.30	0.40	0.51	21.56	1.24

5.3 Post compression parameter

Table No. 8:- Uniformity of Thickness, Hardness and Friability.

Formulation Code	Uniformity of Thickness* (n=3) (mm)	Hardness* (n=3) (Kg/cm^2)	Friability* % (n=10)
F1	365±0.05	3.2±0.18	0.4±0.05
F2	3.48±0.06	3.1±0.12	0.6±0.06
F3	3.42±0.03	3.3±0.35	0.5±0.07
F4	3.75±0.10	3.0±0.33	0.5±0.05
F5	3.80±0.06	3.4±0.19	0.7±0.04
F6	3.84±0.06	3.0±0.22	0.4±0.06
F7	3.66±0.07	3.1±0.12	0.3±0.07
F8	3.88±0.05	3.0±0.14	0.3±0.05

Table No.9:- Drug Content, Uniformity of Weight and In Vitro Disintegration Time.

Formulation Code	Drug Content* (n=3) (%)	Uniformity of Weight* (n=10) (mg)	Disintegration Time* (sec)
F1	94.76±0.6	148.20±07	56±0.53
F2	96.02±0.8	149.23±06	53±0.41
F3	97.41±0.7	148.51±04	41±0.59
F4	93.53±0.6	149.63±08	58±0.46
F5	95.17±0.4	147.92±09	55±0.38
F6	96.44±0.9	149.64±02	49±0.61
F7	92.57±0.9	148.86±04	59±0.93
F8	94.61±0.3	PASS	53±0.87

Table No. 10:- Wetting Time, Water Absorption Ratio.

Formulation Code	WettingTime*(n=3) Mean ±SD(Sec)	Water Absorption Ratio* (n=3) Mean ±SD (%)
F1	56±1.35	79.71±0.19
F2	53±1.62	84.94±0.52
F3	42±1.45	78.20±0.31
F4	58±1.91	76.83±0.20
F5	59±1.53	95.48±0.41
F6	55±1.76	90.62±0.30
F7	47±1.41	76.21±0.79
F8	57±1.68	88.41±0.37

Table No.11:- *In vitro* dissolution Studies.

Formulation code		After 3 min % Release	After 6 min % Release	After 9 min % Release	After 12 min % Release	After 15 min % Release	After 18 min % Release	After19 min % Release
Polyethylene Glycol 6000 (PEG)	F1	28.49	30.54	44.19	57.09	80.98	88.27	97.99
	F2	29.55	31.41	39.49	59.51	74.03	86.68	89.70
	F3	28.44	33.02	36.67	44.19	59.54	76.88	89.47
	F4	28.58	33.65	44.19	63.58	71.58	85.43	88.19
Polyvinyl pyrrolidone K30 (PVP)	F5	29.40	31.83	45.27	62.70	79.93	91.27	99.89
	F6	28.44	32.68	48.40	59.51	71.24	88.47	98.47
	F7	29.72	33.42	48.00	63.15	79.47	90.67	99.21
	F8	29.43	33.02	44.93	59.51	72.23	88.67	96.36

Figure 7: Comparative in Vitro Release Profile of Felodipine Fast dissolving tablets for Formulations F1, F2, F3, F4.

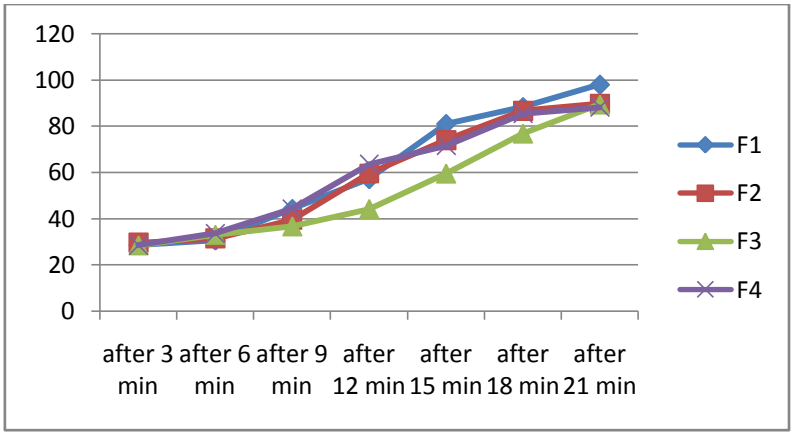
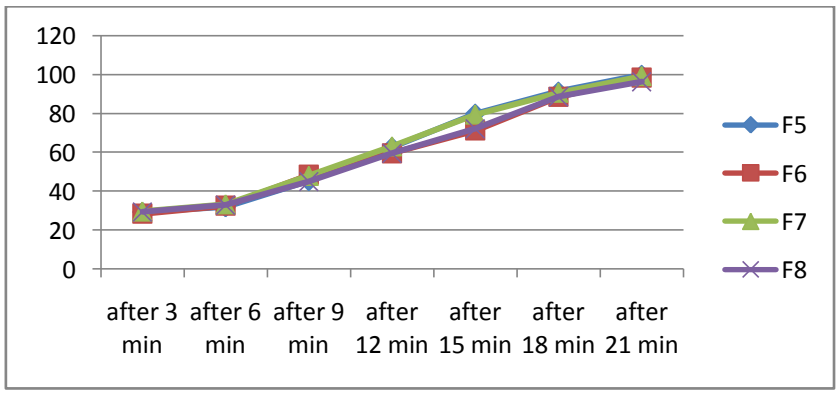


Figure 8: Comparative in Vitro Release Profile of Felodipine Fast dissolving tablets for Formulations F5, F6, F7, F8.



6. Discussion

6.1 Drug-excipients Compatibility Studies:-

a. FTIR Studies: The IR spectra of drug and solid dispersion formed with PVP K30-I show no major changes.

b. Compatibility study by DSC: - DSC analysis (Model: Diamond DSC) were samples heated at the rate of 10^{O} C min in an aluminum cup. There is no considerable change observed in melting endotherm of drug in solid dispersion. It indicates that there is no

interaction between drug and other polymer used in the formulation.

6.2 Evaluation of Tablets

6.2.1 Precompression Evaluation Parameters:-

1) Angle of repose (θ):- All formulations showed the angle of repose within 29^0. It indicates that all formulations showed good flow properties.

2) Bulk density: The loose bulk density and tapped bulk density for all the formulations varied from 0.40 gm/cm^3 to 0.45 gm/cm^3 and 0.49 gm/cm^3 to 0.54 gm/cm^3 respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped density.

3) Percentage compressibility:-The percent compressibility for all the eight formulations lies within the range of 12.24 to 24.52 %. All formulations are showing good compressibility.

4) Hausner's ratio: Hausner's ratio of all the formulations lies within the acceptable range. The Hausner's ratio of all the formulations is in the range of 1.24 to 1.35.

6.2.2 Postcompression Evaluation Parameters:-

1) Thickness: The values are almost uniform in all formulations. Thickness was found in the range from 3.42±0.03 mm to 3.88±0.05 mm respectively.

2) Hardness test: Hardness was maintained to be within 3.0±0.14kg/cm^2 to 3.4±0.19kg/cm^2, as these tablets are mouth dissolving.

3) Friability: Friability was in between 0.3±0.05 to 0.7±0.04 Results revealed that the tablets possess good mechanical strength.

4) Weight variation test: All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±7.5 %.

5) Drug content uniformity: - The drug content of the tablets was found between 92.57±0.9 to 97.41±0.7 of Felodipine. The results indicated that in all the formulations the drug content was uniform.

6) Wetting time: - The wetting time of the tablets was found between 42±1.45 to 59±1.53 sec. The wetting time in all the formulation was very fast. This may be due to ability of swelling and also capacity of absorption of water. Croscarmillose sodium and MCC absorb water in all the formulations and shows fast wetting time. Apart from all the superdisintegrants formulations containing Croscarmillose sodium shows fast wetting time.

7) Water absorption ratio: - The values of formulations found in the range of 76.21±0.79 to95.48±0.41. The water absorption increased due to high swelling property. Croscarmilose sodium shows highest swelling property. So the water absorption ratio value of formulation F5 was high.

8) *In-Vitro* disintegration time: All the formulations show disintegration time less than 58 seconds. Disintegration time was observed in order of Crospovidone < Croscarmellose sodium. Disintegration time of Croscarmellose sodium has high water uptake and swelling which leads to faster disintegration.

9) *In-Vitro* dissolution studies: - The rapid dissolution was observed in formulations F1, F2, F3, F4 releases 97.99%, 89.70%, 89.47%, and 88.19%. of drug respectively, at the end of 15 minutes. Formulations F5, F6, F7 and F8 which shows drug release 99.89%, 98.47%, 99.21%, and 96.36% respectively at the end of 15 min. This rapid dissolution might be due to fast breakdown of particles and rapid absorption of drug. In all the formulations the drug release within 15 minutes. High dissolution may occur due to faster breakdown and due to carrier PVP K30. Best optimized batch was F5 because of lesser disintegration time and highest percentage drug release due to PVP K30 at the end of 15 min among all the formulations.

7. Conclusion

Preformulation studies of Felodipine were performed; the FT-IR and DSC analysis revealed that the superdisintegrants and excipients used were compatible with Felodipine. Solid dispersion prepared with PVP K30 with ratio 1:3 shows maximum drug release as compared with other polymer. Fast dissolving tablets of Felodipine can be prepared by direct compression method using superdisintegrants like crospovidone, croscarmellose sodium. Amongst all the formulations, containing croscarmillose sodium as superdisintgrants is fulfilling all the parameters satisfactorily. It has shown excellent in-vitro disintegration, in-vitro dissolution compared to other superdisintegrants. Apart from all the formulations of F5 formulation showed maximum drug release (99.89%) at the end of 21 min.

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