



In Vitro Dissolution Enhancement of Felodipine

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Abstract— Purpose: With the introduction of combinatorial chemistry and high throughput screening, the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity that results in decreasing aqueous solubility. It is not surprising that many drug candidates have poor water solubility since the initial selection of drug candidates are based on activity alone. Other physiochemical and biopharmaceutical properties such as permeability, biopharmaceutics and metabolism are rarely considered during the selection process. The aim of this study was to increase dissolution rate of felodipine poorly soluble drugs from BCS class II by complexation process. Methods: Complexation was prepared using cyclodextrine. Different techniques were employed for preparation of complexation with cyclodextrin like physical mixture, cogrinding, kneading technology, solvent coevaporation. Results and Conclusions: The physical properties of the prepared solid mass of FDP was characterized by in vitro dissolution studies, UV- spectroscopy, Fourior transform infrared spectroscopy, differential scanning calorimetry (DSC) and X-ray powder differaction spectroscopy. Additionally, phase solubility studies were performed to support the in vitro dissolution study. The results of Fourior transform infrared spectroscopy shows the compatibility of drug with cyclodextrin, while differential scanning calorimetry (DSC) and X-ray powder differaction spectroscopy showed the confirmation of complexation of cyclodextrin with felodipine. © 2011 IGJPS. All rights reserved

Keywords : Dissolution Enhancement, Felodipine, Cyclodextrin, BCS Class II Drugs, Insoluble Drug Delivery System, Complexation, Solid Dispersion.

INTRODUCTION

Felodipine is a potent dihydropyridine with almost exclusive action on vascular smooth muscle especially peripheral arterioles. In pharmaceutical science, it is widely accepted for its tolerant antihypertension and antianginal properties since it is a calcium antagonist compound (calcium channel blocker) [1]. Specifically, FEL is a compound with strong lipophilic character appearing as a crystalline powder practically insoluble in aqueous solutions [2-3]. The terminal elimination half life of felodipine is reported to about 11 to 16 hours following oral administration of an immediate release preparation, but longer with a modified release formulation. [4]

Cyclodextrins (CDs) are a group of structurally related cyclic oligosaccharides that are formed by enzymatic cyclization of starch. The three most common naturally occurring CDs are α -cyclodextrin (α CD), β -cyclodextrin (β CD) and γ -cyclodextrin (γ CD) consisting of six, seven and eight (α -1,4)-linked α -D-glucopyranose units, respectively. The CD molecules are cone-shaped with a somewhat hydrophobic central cavity and hydrophilic outer surface. They are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or more frequently, some hydrophobic part of it, into the cavity. [5]

MATERIAL & METHODS

Materials:

Felodipine was kindly supplied by Pramukh pharmaceutical pvt. ltd. (Gujarat, India), Beta Cyclodextrin was supplied by Mepro Pharmaceutical pvt. Ltd(Gujarat, India). All the products and materials used in this study comply with the pharmaceutical and analytical standards, respectively.

Methodology:

Phase solubility study:

Phase solubility study for felodipine was performed as described by Higuchi and Connors. [6] Excess amount of felodipine was added into aqueous solution containing carriers at various concentrations and shaken for 96 h at room temp on a shaker (time period of 96 hr was previously determined for achievement of felodipine equilibrium) and protected from light to equilibrate. After equilibrium, the suspensions were filtered through 0.45 μ m Millipore membrane filters. The first 15% of the filtrate was discarded to avoid any potential loss of the drug, because of absorption by the filter until and the subsequent filtrate was collected. The filtrate was appropriately diluted by methanol and the concentration of the felodipine in the filtrate was determined by UV spectrophotometer (UV-1601PC, Shimadzu) at 362 nm. Earlier experiments showed that the presence of different carrier did not interfere with the assay at the concentration employed. Solubility measurements were performed in triplicate.

Methods of preparation: [7]

Preparation of physical mixture (PM): The physical mixture of FDP with β cyclodextrin was prepared in 1:8, 1:10 and 1:12 geomatrix ratios by means of spatula for 20 minutes and passed through 80 mesh screens.

Preparation of cogrinding product (CG): For co-grinding product, FDP with β cyclodextrin were mixed in 1:8, 1:10 and 1:12 geomatrix ratio and triturated in glass mortar pestle for 20 minutes and passed through 80 mesh screen.

Preparation of kneaded product (KN): The kneaded product was prepared by addition of drug into the paste of cyclodextrin, 1:8, 1:10 and 1:12 geomatrix ratio and triturating the resultant mixture till cracking sound appear. The resultant mass was dried at room temp. and pass through 80 mesh screen.

Preparation of co-evaporated product (CE): For the preparation of co-evaporated product, an aqueous solution of cyclodextrin was added to a methanolic solution of felodipine to get 1:8, 1:10 and 1:12 geomatrix ratios of drug and cyclodextrin. The resulting mixture was stirred for 1 hour and evaporated at 45-50 °c until nearly dry. The resulting mass was allowed to dry at room temp for two consecutive days. These dried mass pulverized and pass through 80 mesh screen.

Characterization:

UV Spectroscopy: UV spectra were obtained on a UV spectrophotometer, Shimadzu (L.M. College of pharmacy, Ahmedabad) with a wavelength range of 200 nm- 400 nm.

Fourier transform infrared (FTIR): Fourier transform infrared (FTIR) spectra were obtained on a spectrophotometer (L.M. college of pharmacy, Ahmedabad) with a resolution of 2 cm⁻¹ from 3500 to 600 cm⁻¹. Pellets were prepared by gently mixing the sample with potassium bromide (1:100 ratio).

Differential scanning calorimetry (DSC): DSC measurements were made on a Pyris- calorimeter (Perkin-Elmer). Approximately 3–5 mg samples were accurately weighed into standard aluminium pans. An empty pan was used as reference. The samples were heated from room temperature to 290 °C with scan rates 5°C/min. All DSC curves were normalized to a sample mass of 1 g. The instrument was calibrated using indium (melting point, 156.61 °C; enthalpy of fusion, 28.71 J, g⁻¹).

X Ray diffraction: The physical state of felodipine in pure drug powder and in optimized mass was evaluated by powder X-ray diffraction. Powder X-ray diffraction (XRD) patterns were determined with an X-ray diffractometer (SICART Mota bazaar, Vallabh Vidyanagar), employing Ni-filtered CuK_α radiation source operating at 30 kVoltage and a current of 40 mA.

In vitro dissolution characterization: In vitro dissolution studies were carried out in 500 ml of 0.1 N hydrochloric acid containing 1 % w/v SLS using USP dissolution apparatus with an aggitation of 100 RPM. SLS was used to maintain sink condition. Powder sample equivalent to 10 mg of drug was filled in empty capsule shell and immersed in the dissolution medium. The dissolution sample (5 ml) withdrawn at different time intervals was filtered through a membrane filter (0.45 μm). This filtered sample was diluted sufficiently by 0.1 N HCL and assayed spectrophotometrically at 362 nm. Fresh medium was added to maintain a constant volume after each sampling. The dissolution were conducted in triplicate and the means of the absorbance were calculated. The cumulative percentage of drug release after 15 min, 30 min, 45 min, 60 min, 120 min as well as time required for 90% drug release is measured.

RESULTS & DISCUSSION

Phase solubility study:

Figure 1 shows that solubility profiles of FDP in 0.1 N HCL influenced by carrier material concentration at room temp. The solubility curve with correlation coefficient squared values (r^2) >0.95 ($r^2=0.95$) was regarded as a straight line (AL type) (Higuchi and Connors, 1965).

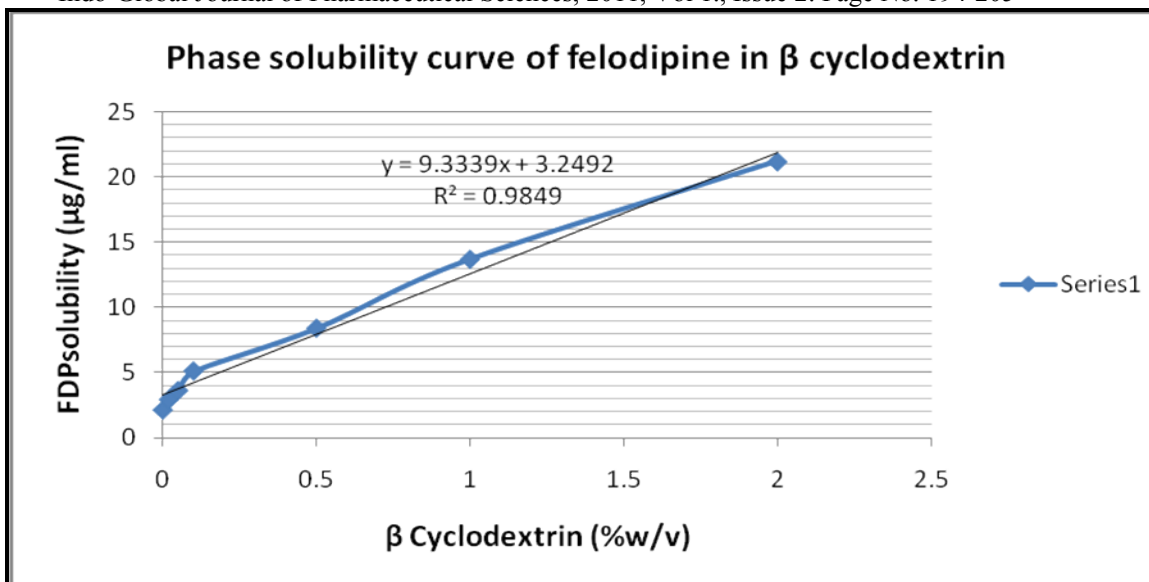


Figure 1: Phase solubility study of felodipine in β cyclodextrin

UV Spectroscopy: Formulation excipients selected on the basis of preliminary tests, which demonstrates no interference of these excipients with the λ_{\max} of FDP. [8] The complex formation with cyclodextrin alters the original UV absorption spectrum of the molecule usually bathochromic shift and or band broadening occurs. The shift of the UV absorption maxima upon complex formation may be explained by a particular shielding of the excitable electrons in the CD cavity. [9] [See Figure 2 and 3]

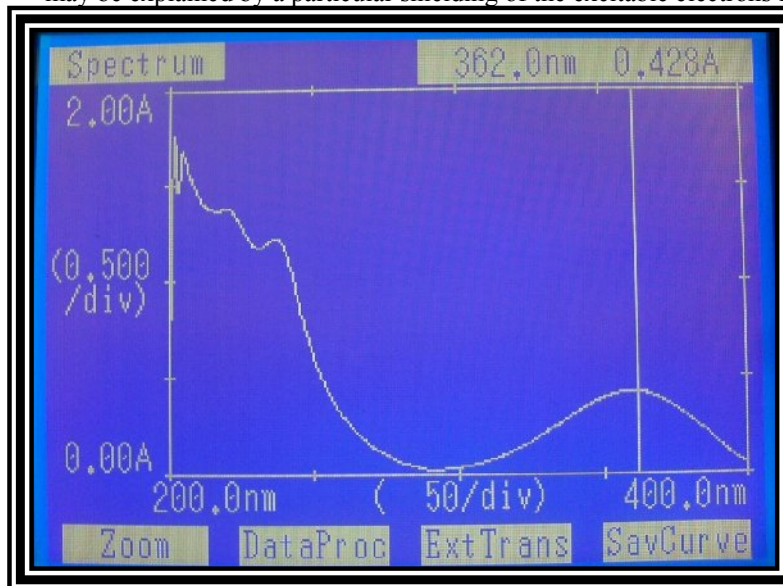


Figure 2: Photographic image showing λ_{\max} of felodipine



Figure 3: Photographic image showing λ_{\max} of felodipine after complexation (Figure 2 and 3 directly indicated increase in absorption maxima and bathochromic shift in λ_{\max})

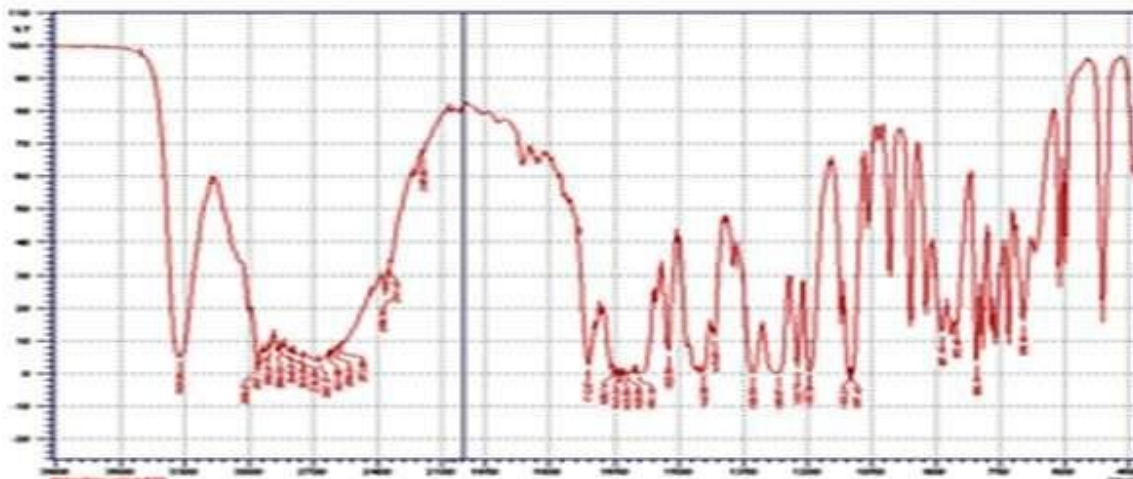


Figure 4: Fourier transforms infrared spectroscopy of felodipine

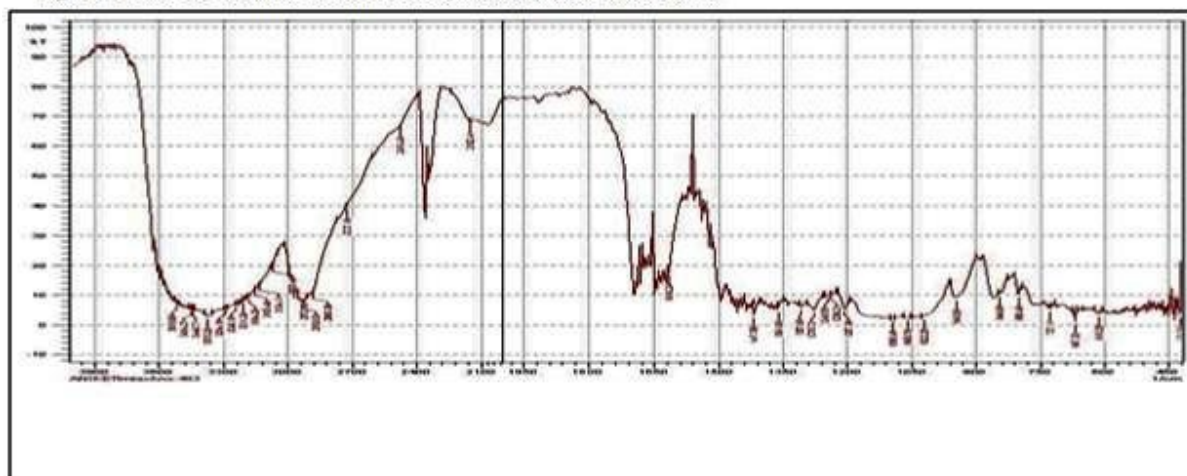


Figure 5: Fourier transforms infrared spectroscopy of felodipine PM

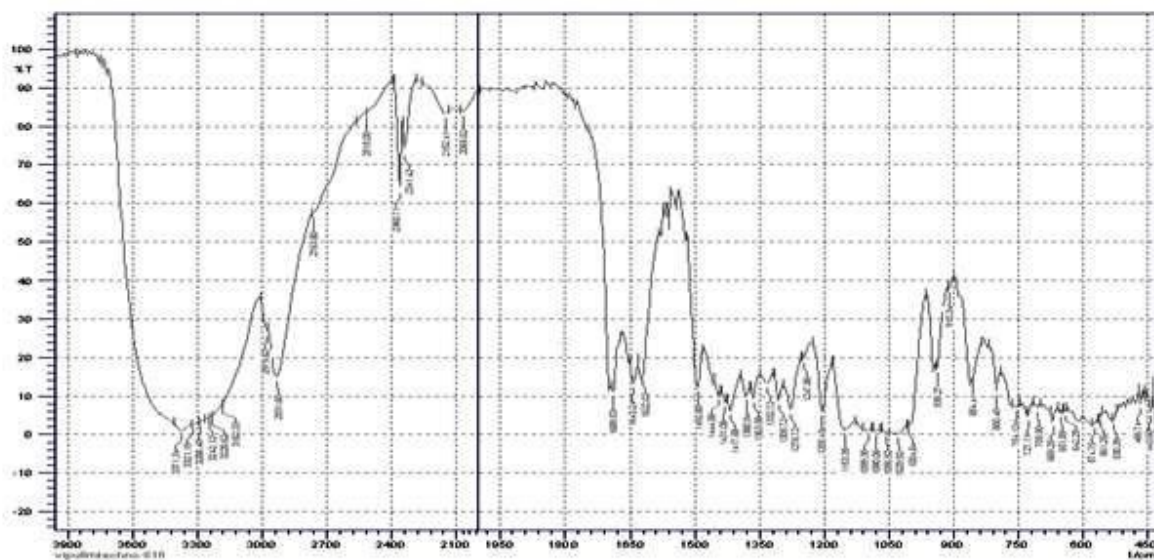


Figure 6: Fourier transforms infrared spectroscopy of kneaded product felodipine

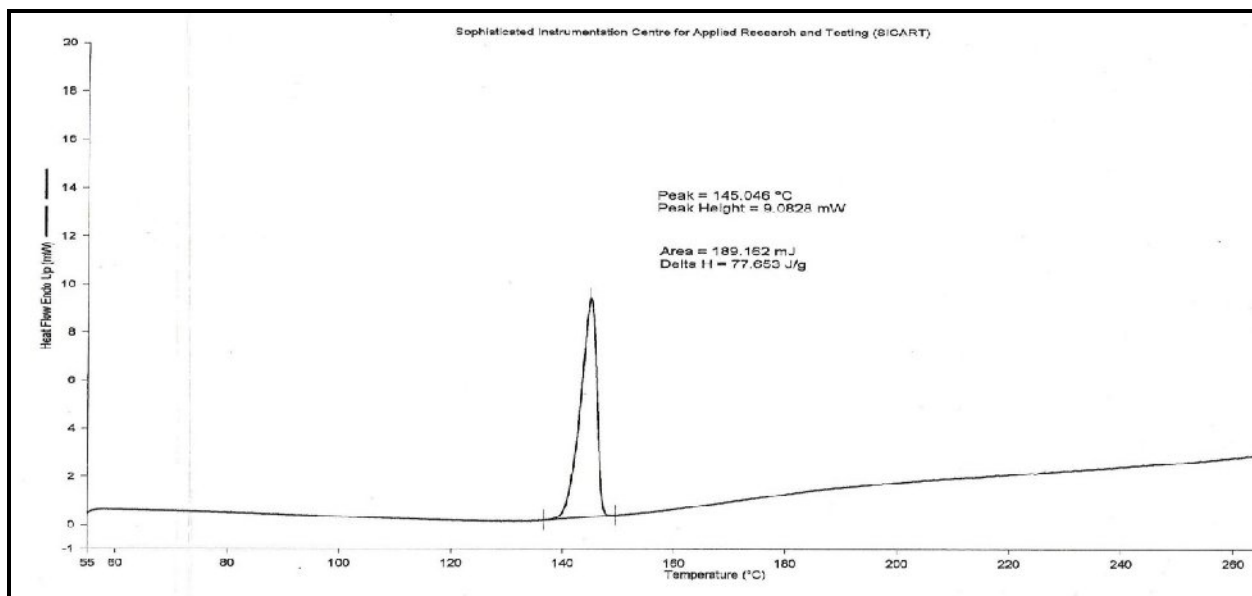


Figure 7: DSC curve of felodipine

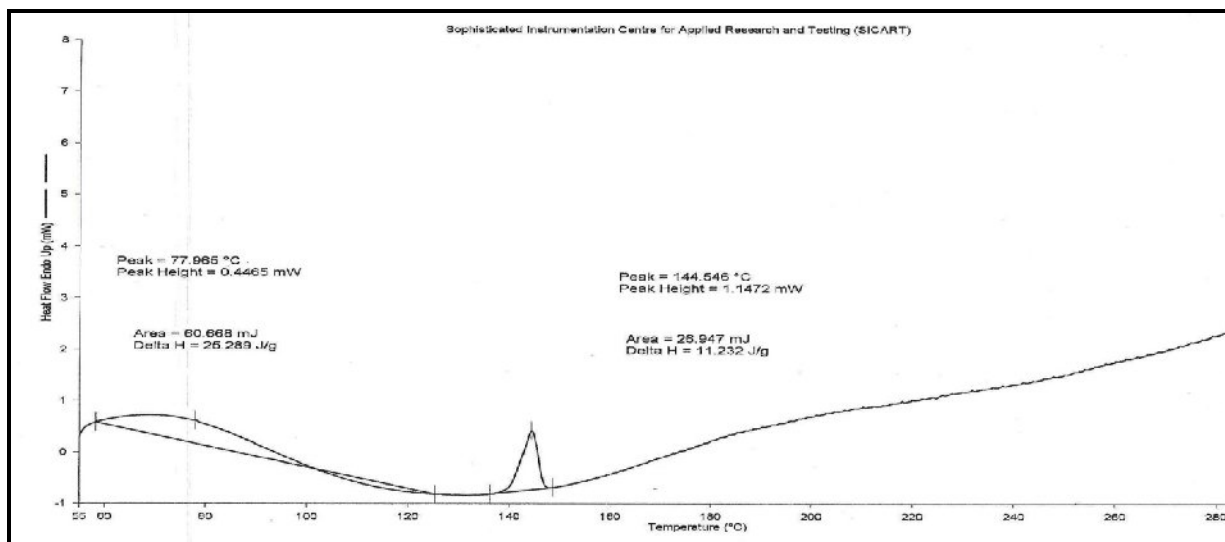


Figure 8: DSC curve of felodipine PM

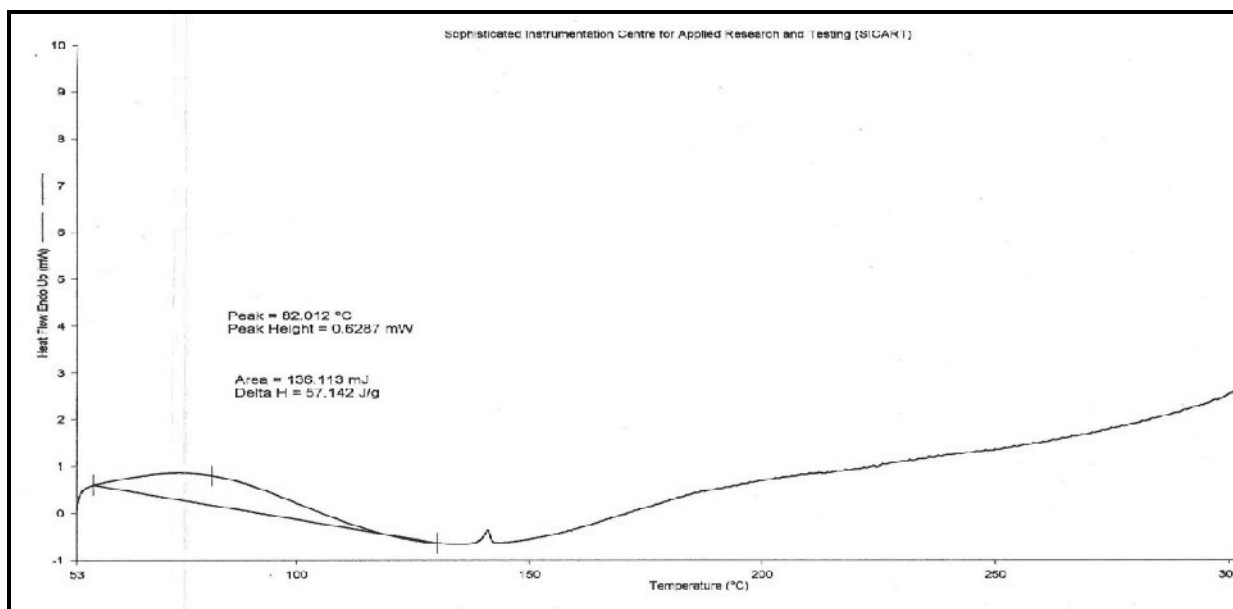


Figure 9: DSC curve of felodipine kneaded product

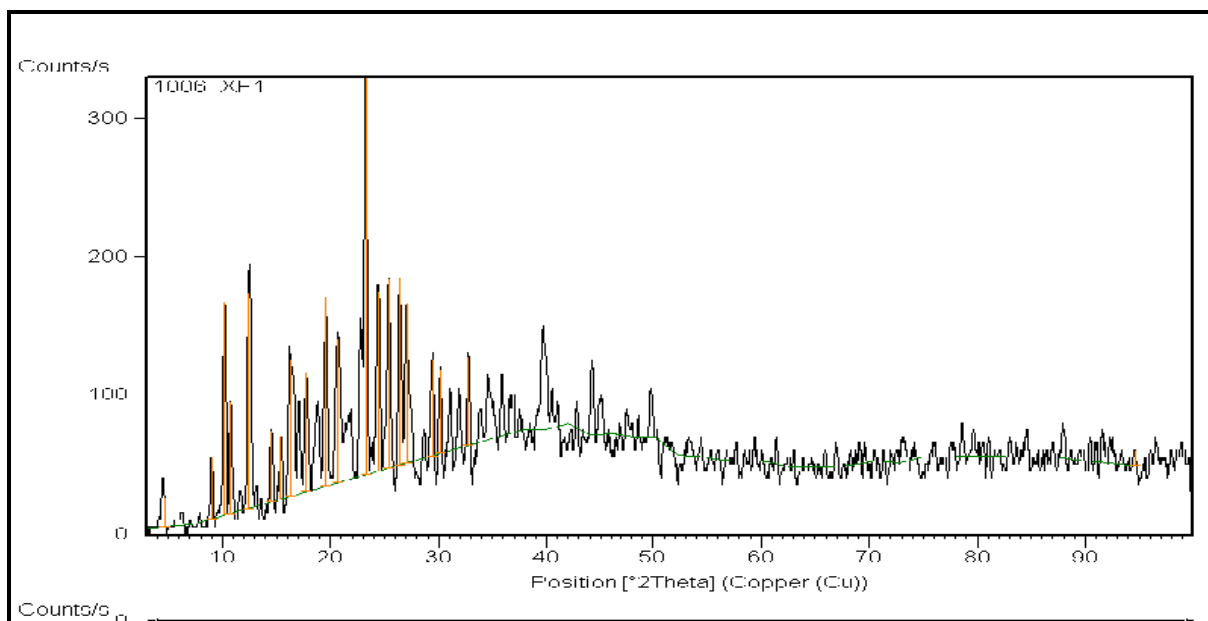


Figure 10: XRD patterns of pure felodipine

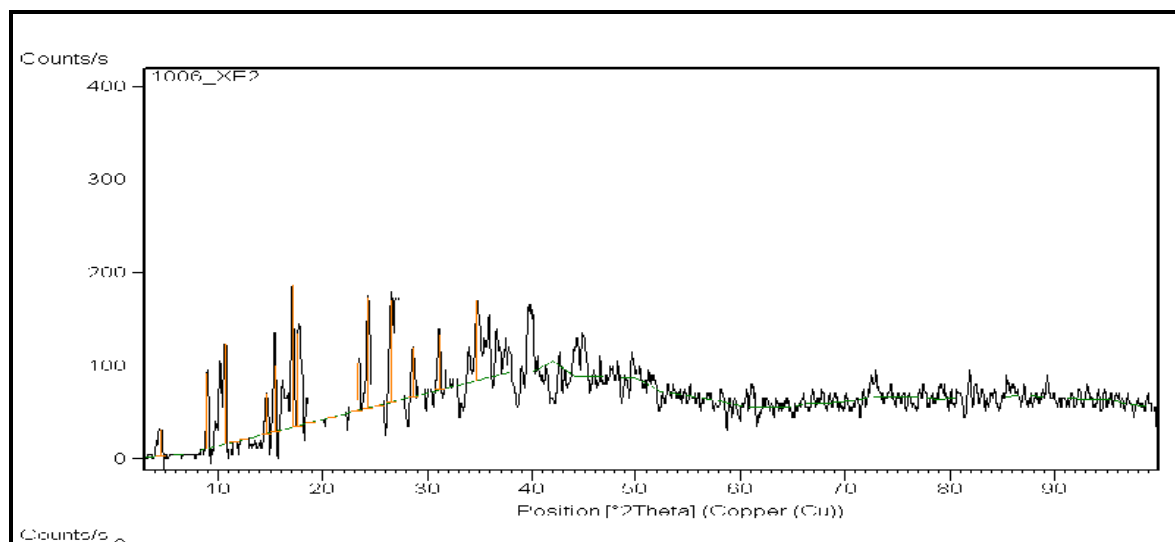


Figure 11: XRD patterns of inclusion complex of felodipine

Table 1: FORMULATION BATCHES FOR FDP- BETA CYCLODEXTRIN COMPLEXATION

Time (Minutes)	F0	F1	F2	F3	F4	F5	F6
DP ₁₅	8.6	11.8	14.6	16.3	11.8	14.9	16.5
DP ₃₀	17.2	20.6	29.8	32.5	21.2	30.1	32.5
DP ₄₅	21.6	34.8	37.4	41.3	34.9	39.0	44.3
DP ₆₀	30.2	42.5	46.2	50.6	45.6	48.4	52.8
DP ₉₀	41.4	55.9	58.3	62.8	56.0	60.1	65.2
DP ₁₂₀	49.5	67.6	70.0	76.3	69.1	70.5	79.6
t ₉₀	4 hr	3.30 hr	2.45 hr	2.3 hr	3.30 hr	2.45 hr	2.3 hr

Table 2: IN VITRO DISSOLUTION PROFILES OF FELODIPINE FROM BATCH F7-F12

Time (Minutes)	F7	F8	F9	F10	F11	F12
DP ₁₅	41.96	43.36	46.23	43.62	43.76	46.40
DP ₃₀	54.34	65.71	69.04	58.07	66.54	71.72
DP ₄₅	66.67	79.79	81.94	67.38	81.29	83.07
DP ₆₀	80.00	91.36	93.02	77.85	94.20	89.60
DP ₉₀	92.57	101.30	99.70	90.96	98.32	96.19
DP ₁₂₀	102.23	102.63	101.16	101.03	97.67	97.53
t ₉₀	90 min	60 min	60 min	90 min	60 min	60 min

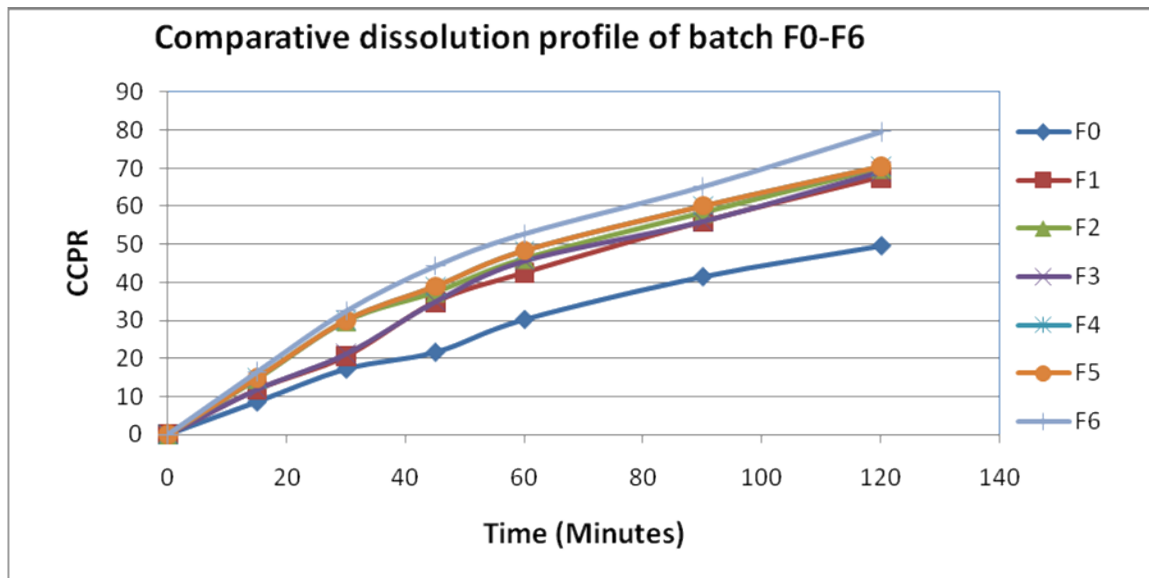


Figure 12: Comparative dissolution profile of batch F0- F6

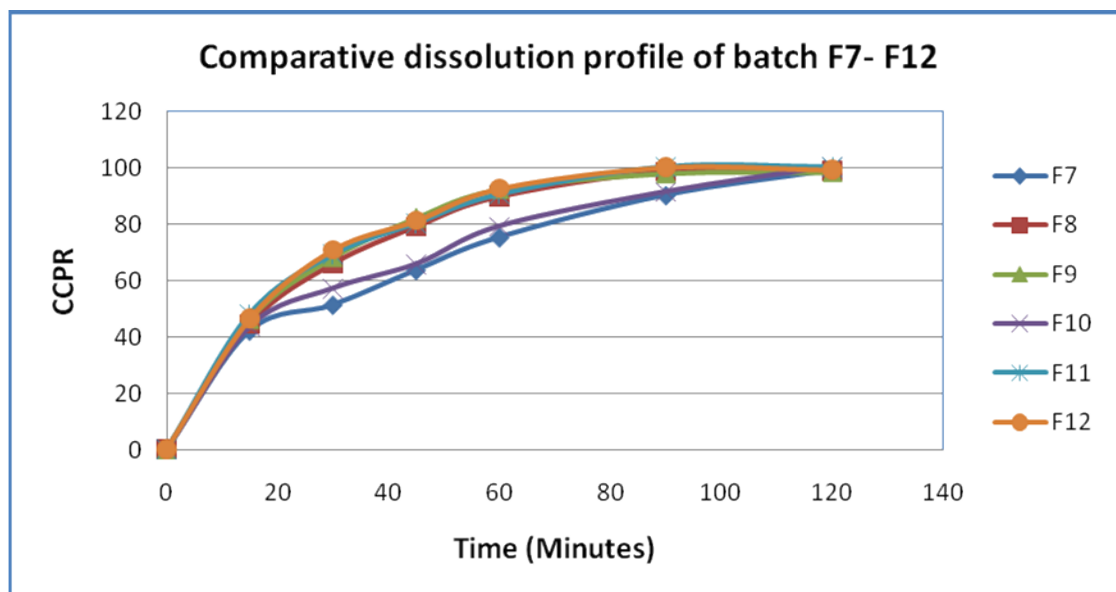


Figure 13: Comparative dissolution profile of batch F7- F12

FTIR:

Complexation process of Felodipine with the beta cyclodextrin has been confirmed by the FT-IR spectroscopy. The FT-IR spectra of the inclusion complexes of the felodipine studied are significantly different from those of the corresponding physical mixtures and of felodipine alone. The PM of 1:1 ratio showed superimposed spectra of FDP and beta cyclodextrin which proves the compatibility of beta cyclodextrin with the FDP. In the FT-IR spectra of the inclusion compounds of Felodipine studied, the bands in the range $3050\text{--}3250\text{ cm}^{-1}$ with a maximum at 3070 cm^{-1} , assigned to the stretching vibrations of the N–H bonds in the dihydropyridine ring are not clearly distinguished. The differences also appear in the band corresponding to the vibrations of carbonyl groups in the ester bonds. In the spectra of the felodipine the band occurs at $1690\text{--}1710\text{ cm}^{-1}$ while in the spectra of the corresponding inclusion complexes it is less broadened and % transmittance reduces. The differences also appear in the band corresponding to the amine group in the pyridine ring. In the spectra of the felodipine the band occurs at $3360\text{--}3380\text{ cm}^{-1}$ while in the spectra of the corresponding inclusion complexes it is much broadened. Some differences are also noted in the range $450\text{--}500\text{ cm}^{-1}$, band corresponding to the chlorine groups of phenyl which in case of inclusion complex shortened to a great extent. From these results, it can be speculated that drug-carrier hydrogen bonding existed in these solid binary system, causing reduced drug recrystallization.[10]

Differential scanning calorimetry (DSC): The DSC thermograms of felodipine, felodipine (PM), and the inclusion complexes of felodipine are illustrated into the Figure 7,8 and 9 respectively. Physical mixture showing almost similar identical melting endotherm and spectra are overlapable which proves the compatibility of used excipients [Figure 8]. The formation of inclusion complexes is indicated by the disappearance of peak or significant change in area of the peak or shift of the endothermic peaks corresponding to the drug melting process [Figure 9]

X Ray diffraction:

The powder X-ray diffraction (PXRD) patterns of pure FDP, and Kneaded complex are shown in Figure 10 and 11. Felodipine presented a crystalline form as demonstrated by various intense diffraction peaks [Figure 10]. The crystalline peaks located at 4.6 °, 8.9 °, 10.1 °, 10.7 °, 12.4 °, 14.5 °, 15.3 °, 16.3 °, 17.7 °, 19.5 °, 20.6 °, 23.2 °, 24.4 °, 25.4 °, 26.4 °, 27 °, 29.4 °, 30.1 °, 32.7 °, and 94.5° (2 θ) corresponding to felodipine crystals were observed. Felodipine had a more intense peak at 10.1 °, 12.4 °, 16.3 °, 19.5 °, 20.6 °, 23.2 °, 24.4 °, 25.4 °, 26.4 ° and 27 ° in addition to relatively less intense peaks at 4.6 °, 8.9 °, 10.7 °, 14.5 °, 15.3 °, 17.7 °, 29.4 °, 30.1 ° and 32.7 °. XRD patterns of kneaded binary systems showed reduced diffraction intensity as indicated in Figure 11. All these factors indicate some degree of amorphization or inclusion complex formation FDP in cavity of cyclodextrin.

From the above figure 12 and 13, it was concluded that pure drug felodipine having very poor solubility and poor dissolution profile. The dissolution profile of F0 batch was suggested that only 49.5 % drug release occur after 2 hr in 0.1 N HCL and time required for 90 % drug dissolution is nearly about 4 hr, which suggests the poor dissolution characteristic of FDP. All the solid binary system prepared from physical mixture methods (F1 to F3) and cogrinding methods (F4 to F6) using β cyclodextrin not showing any significant improvement in dissolution characteristic of FDP. While in contrast other methods like kneading method (F7 to F9) and solvent co-evaporate methods (F10 to F12) produce significant enhancement in dissolution rate of FDP. However, the rate of dissolution enhancement by both kneading methods and solvent co-evaporated methods were nearly identical and showing almost similar dissolution profile. So, due to greater advantage of kneading method over solvent coevaporated method, kneading method was selected for further research work (see the table)

Based on phase solubility study and preliminary study, it was concluded that there was a linear enhancement in dissolution rate of FDP as the conc. of cyclodextrin increased. So, from the all the methods, kneading method was the optimized batch in 1:10 proportion of drug to β cyclodextrin which showing 90 % of drug release within 60 minutes.

CONCLUSION

The aim of this work was to improve the dissolution rate of felodipine which is required for improving the dosage form characteristic and also to reduce fluctuation in dissolution profile as well as for better *in vivo* characterization. Many techniques are known to improve dissolution rate of poorly soluble drugs amongst these preparation of physical mixture, co-grinding techniques, kneading techniques and solvent co-evaporated techniques are selected in this research work because of its ease of preparation, ease of optimization, and reproducibility. Amongst these techniques kneading method and solvent co-evaporated methods found to be more effective than previous two techniques. Now, in industry due to the concept of green formulation, always the formulation without solvent is encourage by industry person because the sometimes presence of solvents creates volatile impurities. With consideration of concentration of cyclodextrin and the concept of green formulation, **Batch F8** was considered to be

the optimised batch showing significant improvement in dissolution profiles that utilized 1:10 ratio of drug and beta cyclodextrin using kneading techniques.

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