Formulation And Evaluation Of Fast Dissolving Tablets Of Felodipine

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Abstract

Felodipine fast dissolving tablets (FFDT) were prepared by employing solid dispersions of drug with HP β-CD (1:1), by direct compression method, by employing superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations (5,7.5&10%). The prepared tablets were evaluated for their physical characteristics. Friability of tablets ranged between 0.12-0.34 percent. Drug content of tablets ranged between 99.23-100.15%. FT-IR studies revealed that, there was no incompatibility of the drug with the excipients used. Among all the formulations, promising formulation (F6) appeared to be having the most promising properties. Formulation F6, containing 7.5% w/w crospovidone and 15% w/w avicel. Short-term stability studies on F6 indicated that there was no significant change in drug content and in-vitro dispersion time ($p<0.05$). It was concluded that dissolution rate of felodipine could be enhanced by a combination of HP β-CD and crospovidone.

Key words: Felodipine, Fast dissolving tablets, Direct compression

Introduction

Felodipine (FD), which is used in the present study is a dihydropyridine derivative, that is chemically described as ethyl methyl-4-(2, 3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate and is widely accepted for its excellent antihypertensive and antianginal properties, since it is a calcium antagonist compound (Ca channel blocker). Unfortunately though it has good therapeutic potential, it is poorly water soluble and its dissolution rate is limited by its physicochemical properties[1]. It comes under Class II drugs which have low solubility and high permeability. It was reported that oral bioavailability of felodipine is < 20%.

Disintegration time technique is one popular technique for formulating fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating fast-dissolving tablets by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel[2]. Fast dissolution may be caused by the disintegration time of tablets, because faster disintegration of tablets delivers a fine suspension of drug particles and thus greater dissolution of drug[3] is likely to occur.

Some of the examples of super disintegrants which have been used in FDDS are sodium starch glycolate, cross povidone, cross carmellose, Indion 414, microcrystalline cellulose and low substituted hydroxypropylcellulose.

Most formulations (> 70%) contain excipients at higher concentration than active drug[4]. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately[5]. Hence there is a need to have excipients with multiple characteristics[6].

The reasons for selection of crospovidone are its high capillary activity, pronounced hydration capacity and little tendency to form gels[7]. Sodium starch glycolate was chosen because of its higher swelling capacity[8].

The concept of formulating fast dissolving tablets (FDT) of felodipine direct compression technique, using HP β-CD[9] & superdisintegrants which help to increase the water up take, decrease the wetting time and there by decrease the disintegration time of the tablets is simple and cost effective.

The present investigation aims to study the preparation and evaluation of fast dissolving tablets of felodipine inclusion complexes prepared by direct compression using three super disintegrants. The aim of the present work is to improve the pharmaceutical properties of felodipine like its solubility, dissolution rate and oral bioavailability, which will improve its biological activity.

Materials and methods

Materials:

Felodipine was received as a gift sample from Ranbaxy Lab. Limited (India), HP β-CD, croscarmellose sodium, crospovidone and sodium starch glycolate were obtained as a gift samples from FDC Limited, Mumbai. All other reagents and solvents were of analytical grade and double distilled water was used throughout the study.

Preparation of fast dissolving tablets by direct compression method[10]:

The fast dissolving felodipine tablet formulation was prepared by direct compression of optimized drug and HP β-CD (1:1) solid dispersion, superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations (5, 7.5, and 10%) and Avicel PH 101. All excipients used to formulate tablets according to the Table -1 were passed through sieve # 40, and mixed in geometric dilution until homogeneous blend was obtained. The above blend was lubricated with pre sifted magnesium stearate (1%)

through sieve # 60 and mixed for three minutes in a poly bag. Lubricated blend, whose weight is 100 mg and which is equivalent to 5 mg of drug was compressed on Cadmach rotary 16 station tablet press machine equipped with 6.5 mm standard punches with optimum hardness.

Evaluation:

Precompression parameters such as angle of repose, compressibility index and Hausners ratio were evaluated. The prepared tablets were evaluated for hardness, thickness & diameter, friability, disintegration time, wetting time, uniformity of dispersion, drug content, *in-vitro* dissolution studies and stability studies. Hardness of the tablets was tested by using 'Monsanto' Hardness tester. Five tablets from each batch were tested for hardness. The thickness & diameter of ten tablets (two tablets from each batch) were recorded during the process of compression using calipers.

The friability test was carried out in Roche friabilator. Ten tablets were weighed (W_0) initially and placed in a rotating drum and were subjected to 100 falls of 6 inches height (25 rpm for four minutes). After completion of rotations, the tablets were dedusted by using camel hair brush and weighed (W). The percent loss in weight or friability (f) was calculated by the formula given below.

$$F = [1-W/W_O] \times 100$$

In disintegration time[11] study tablets were put into 100 mL distilled water at 37^0 C. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus. For evaluating the uniformity of weight, twenty tablets were selected at random, weighed together and then individually. The mean and the standard deviation were determined.

Wetting time[12] was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small Petri dish containing 6 ml of simulated saliva of pH 6.2, and the time for complete wetting was measured. Five tablets from each batch were used. In uniformity of dispersion method, 2 tablets were placed in100 ml of water and stirred gently until the tablet dispersed completely. A smooth dispersion must be obtained which passes through a sieve screen with a nominal mesh aperture of 710um (sieve #22).

In drug content study, tablets were weighed individually, pulverized and diluted to 250 mL with sufficient amount of phosphate buffer of pH 6.5 containing 0.1% SLS. After that aliquot of the filtrate was diluted and analyzed spectrophotometrically at 362 nm. Dissolution studies were performed in 500 ml of pH 6.5 phosphate buffer with 0.1% SLS maintained at 37°±0.5°C using USP XXII type II dissolution test apparatus at the speed of 50 rpm. The sample (5 ml) was withdrawn through a filter at different time intervals, and the same was replaced with fresh dissolution medium. The samples were estimated for amount of felodipine dissolved by measuring their absorbance at 362 nm.

Release kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process. To know the mechanism of release from these formulations, the data were treated according to zero-order (cumulative amount of drug released vs time), first-order (log cumulative percentage of drug released vs time), Higuchi's[13] (cumulative percentage of drug released vs square root of time), and Korsmeyer[14] et al's (log cumulative percentage of drug released vs log time) equations.

Stability studies:

Stability study of the tablets was carried out according to ICH guidelines at 40 ± 2^0C/75±5%RH for 3 months by storing the samples in stability chamber.

Characterization of felodipine tablets:

FTIR Studies- IR Spectra for drug, excipients and formulation, F6 were recorded in a Fourier Transform infrared (FTIR) Spectrophotometer with KBr pellets.

Results and Discussion:

The values of pre-compression parameters are given in Table 2 and they indicated good free flowing property. Angle of repose values are in the range of 19-27 indicating that the powder exhibited good flow properties. The values of the compressibility index and the Hausners ratio (9-13 and 1.10-1.17 respectively) also indicated good free flowing properties of the powder.

The data obtained from post-compression parameters such as hardness, thickness, friability, drug content, wetting time, and *in-vitro* disintegration time, are shown in Table-3. In all the formulations, hardness test indicated good mechanical strength, with the results ranging from 3 to 4 kg/cm^2. Thickness of the tablets ranges from 2.54 to 2.85 mm and friability is less than 1%, indicating that the tablets had good mechanical resistance. Drug content was found to be in the range of 99.23 to 100.15%, which is within acceptable limits. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in the presence of a little amount of water and it was found to be in the range of 25 to 108 sec.

In the present study all the tablets disintegrated in ≤ 124 seconds. It was observed that the disintegration time of the tablets decreased as the concentration of superdisintegrants increased. The FFDT made with croscarmellose sodium at 5%, 7.5% and 10% exhibited the disintegration time of 98, 72 and 54 sec respectively, where as crospovidone exhibited 68, 42 and 40 sec respectively at same conditions and sodium starch glycolate made formulations exhibited the disintegration time of 113, 85 and 76 sec respectively at the same concentration.

The wetting times are comparatively lower for tablets were with cross povidone than cross carmellose sodium. Comparatively, the wetting times of tablets were in the order of, cross povidone < cross carmellose sodium< sodium starch glycolate.

Comparatively, the disintegration times of tablets were in the order of cross povidone < cross carmellose sodium < sodium starch glycolate. The disintegration time of tablets containing cross povidone are comparatively lower than the tablets with cross carmellose sodium. The faster disintegration of tablets with cross povidone may be attributed to its rapid capillary activity and pronounced hydration. Thus the results show that disintegration times can be decreased by using cross povidone as super disintegrant.

Dissolution Studies

The dissolution of felodipine from the tablets is shown in figures 1, 2&3. The formulation without superdisintegrant (F1) showed 100% drug release at the end of 45 minutes. As it is a fast dissolving formulations more than 80% of the drug should be released within 10 min, hence to enhance the initial stage release, superdisintegrants such as cross carmellose sodium, crospovidone and sodium starch glycolate were included in the formulation. From the results it was observed that the formulation F4 and F6 showed positive results with more than 80% of the drug release in 10 min. Even though the dissolution rate was enhanced with sodium starch glycolate, it's not showed up to the acceptable limits shown in figure-3. Comparison of dissolution profile of optimized FFDT with pure drug is shown in figure-4.Dissolution parameters such as time required to release 50% of the drug (T_{50}), % dissolution efficiency (DE), % of drug dissolved at 10 min (D_{10}) are given in figures -5&6).

Rate order kinetics:

The dissolution data was fitted into kinetic parameters and their linear regression plots i.e zero order, first order, Higuchi plot, Hixson crowell plot and Peppas plot were drawn. Values of correlation coefficients ('r' values) of release kinetics of all the formulations are shown in Table 4. The dissolution from the tablets followed first order rate kinetics with non Fickian diffusion mechanism

In Figure 7 shows the IR spectrum of pure drug and formulation F6, it is observed that there is no appreciable change in the position of absorption band. It may be concluded that there is no chemical interaction between the drug and the polymer.

Conclusion:

The results of the present study indicate the formulation containing cross povidone showed good disintegration and drug release characteristics. Fast dissolving tablets of felodipine, F6, disintegrated within 42 seconds and more than 90% of the drug release within 10 minutes.

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TABLES

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Felodipine – HP BCD complex	23.32	23.32	23.32	23.32	23.32	23.32	23.32	23.32	23.32	23.32
Croscarmellose sodium	-	5	7.5	10	-	-	-	-	-	-
Crospovidone	-	-	-	-	5	7.5	10	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	5	7.5	10
Microcrystalline cellulose (Avicel PH 101)	75.78	70.78	68.28	65.78	70.78	68.28	65.78	70.78	68.28	65.78
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	100	100	100	100	100	100	100	100	100	100

Table-1 Formulae for the preparation of FFDT

Properties	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Angle of repose	27.13	25.20	24.56	22.33	21.12	20.19	19.87	26.32	24.12	22.88
Carr's index	13.24	12.77	11.87	10.88	12.80	10.93	9.65	13.11	12.98	11.51
Hausners ratio	1.17	1.13	1.12	1.10	1.14	1.12	1.11	1.16	1.14	1.13

Table -2: Comparison of flow properties of different tablet blends

Formulation code	Weight variation* (mg)	Drug content** (%)	Hardness ⅄ (Kg/cm^2)	Friability* (%)	Disintegration time⅄⅄ (with water)	Wetting time⅄⅄	Uniformity of dispersion⅄ (particles remaining on sieve no 22)
F1	100±0.87	99.23±0.75	3-4	0.12	124	108	No
F2	99±0.96	100.12±0.45	3-4	0.23	98	83	No
F3	101±0.35	99.67±0.86	3-4	0.31	72	58	No
F4	100±0.87	100.09±0.87	3-4	0.25	54	46	No
F5	100±0.75	99.56±0.65	3-4	0.19	68	57	No
F6	99±0.86	99.36±0.88	3-4	0.12	42	26	No
F7	98±0.34	99.82±0.82	3-4	0.11	40	25	No
F8	99±0.73	100.15±0.63	3-4	0.34	113	94	No
F9	101±0.39	99.27±0.27	3-4	0.32	85	71	No
F10	100±0.83	99.66±086	3-4	0.29	76	64	No

*: mean ± s.d. (n=20) ; **: mean ± s.d. (n=10); ⅄ n=5 ; ⅄⅄ n= 3

Table 3: Physical characterization of FFDT

Formulation	Zero order		First order		Higuchi	Hixson – Crowell	Peppas	
	Ko	r	K_1	r	r	r	n	r
F1	1.8612	0.7703	0.0631	0.9721	0.9687	0.9683	0.3551	0.9897
F2	2.9077	0.7429	0.2017	0.8404	0.9585	0.9448	0.3364	0.9514
F3	4.4452	0.7828	0.1492	0.9695	0.9623	0.9312	0.2748	0.9948
F4	4.3809	0.7074	0.1902	0.9689	0.9742	0.9548	0.2013	0.9883
F5	4.4728	0.8104	0.1377	0.9713	0.9796	0.9296	0.3093	0.9923
F6	4.2924	0.6364	0.2549	0.9178	0.9793	0.9281	0.1333	0.9423
F7	4.3176	0.6302	0.3270	0.9931	0.9757	0.9712	0.1302	0.9182
F8	2.9976	0.8034	0.1138	0.9778	0.9799	0.9784	0.3804	0.9903
F9	2.9010	0.7316	0.1483	0.9256	0.9583	0.9554	0.2981	0.9762
F10	2.8814	0.7654	0.1426	0.9436	0.9867	0.9797	0.2783	0.9753

Table 4: Correlation coefficient values and release kinetics of FFDT

FIGURES

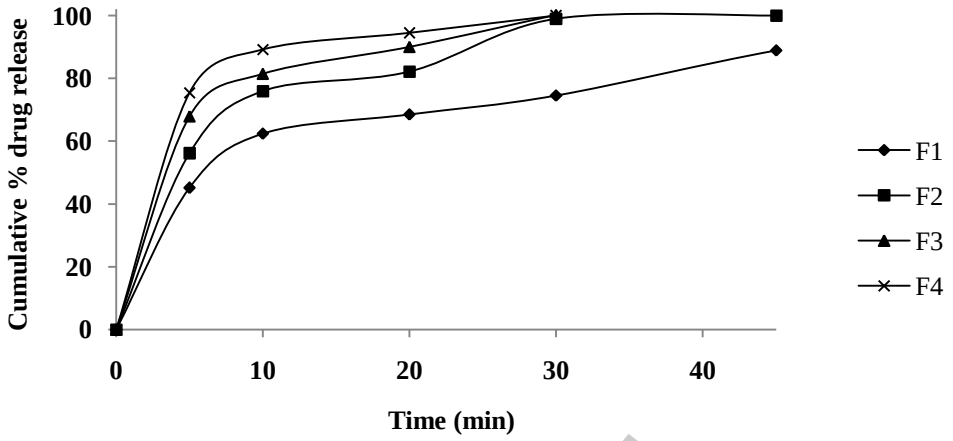

Fig 1: Dissolution profile of FFDT prepared by using various concentrations of croscarmellose sodium.

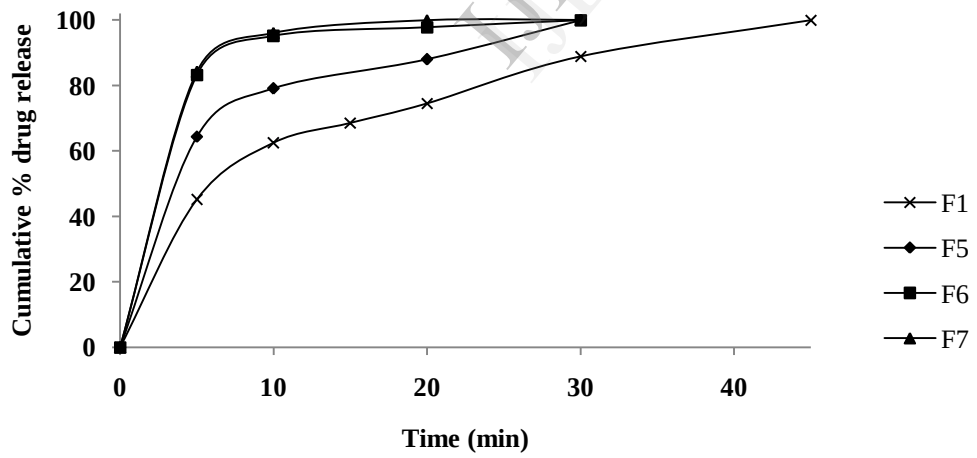

Fig 2: Dissolution profile of FFDT prepared by using various concentrations of crospovidone.

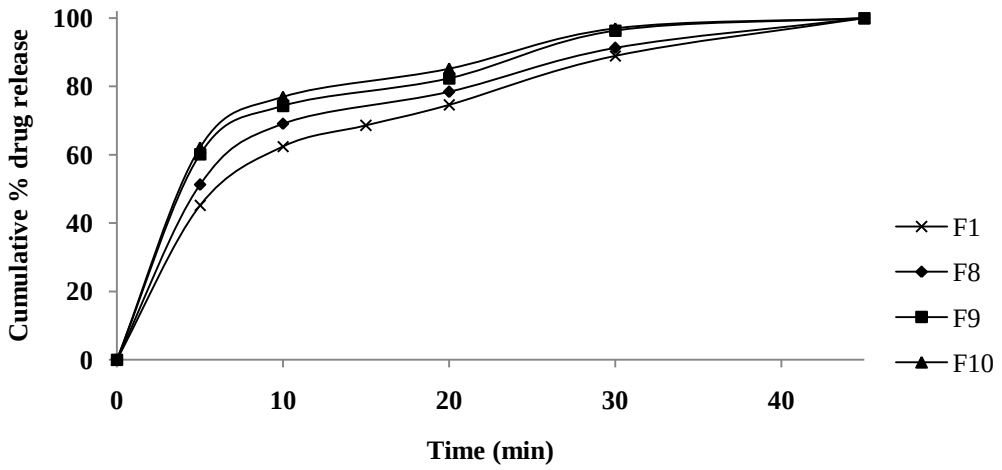

Fig 3: Dissolution profile of FFDT prepared by using various concentrations of sodium starch glycolate.

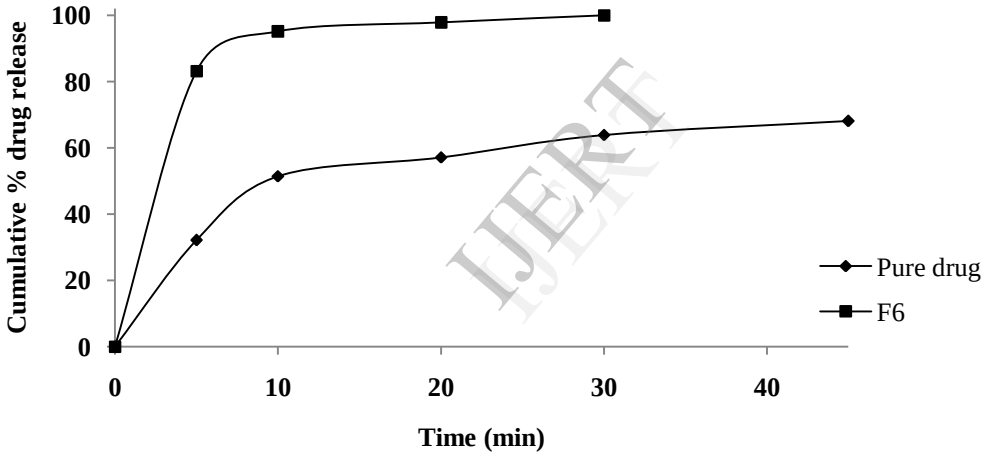

Fig 4: Comparison of dissolution profile of optimized FFDT with pure drug

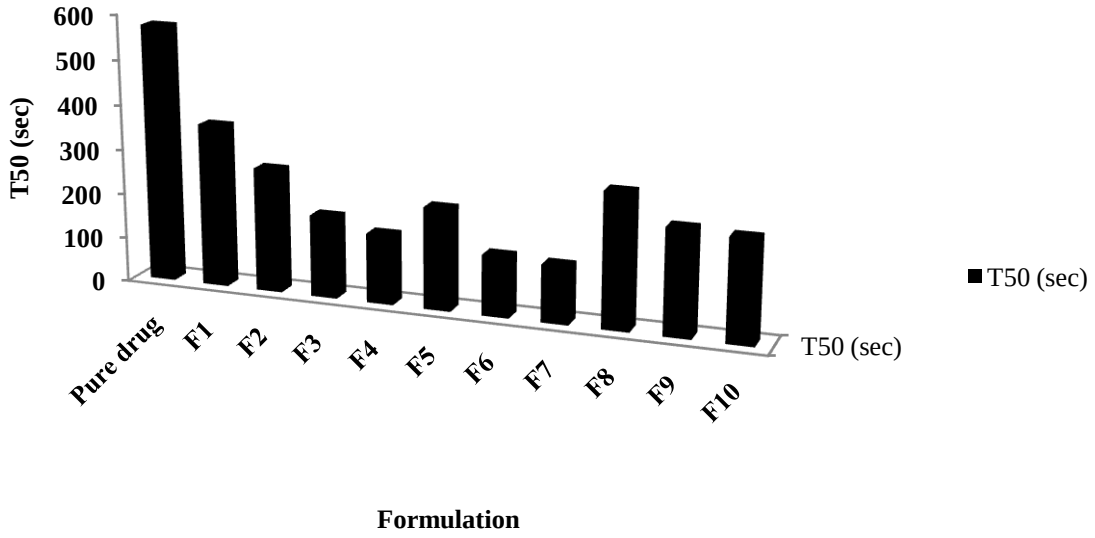

Fig 5: Comparison of T_{50} for different formulations of felodipine

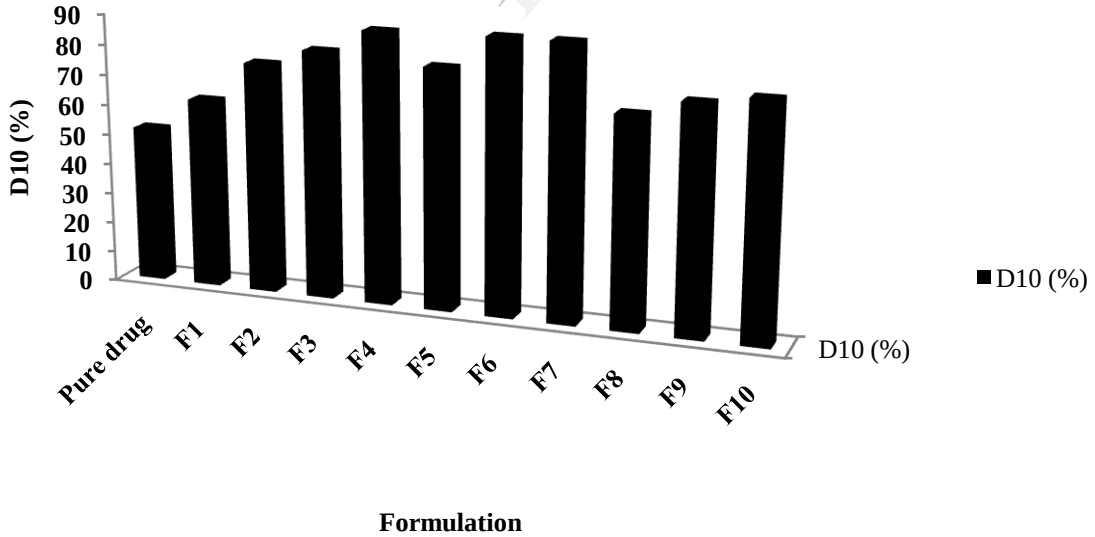

Fig 6: Comparison of D_{10} for different formulations of felodipine

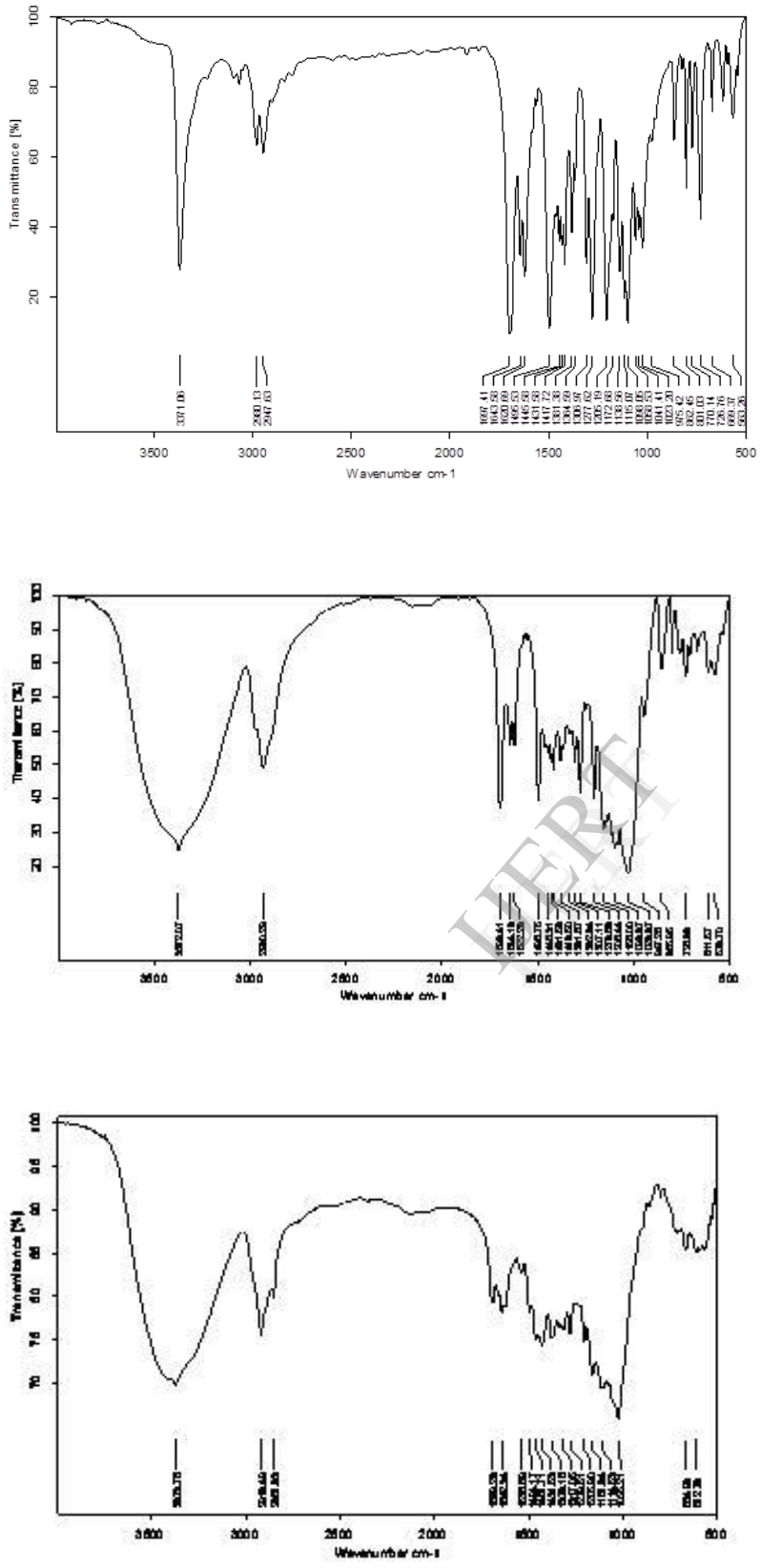

Fig 7: FTIR Spectras a) For pure drug b) For drug & HPβ- CD c) For drug Formulation, F6