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Formulation and characterization of fast disintegrating tablets containing Cefdinir solid dispersion

Sanjay Jain, Sandeep Jain, Ankit Mishra*, Gopal Garg and Rahul Kumar Modi
Faculty of Pharmacy, VNS Group of Institutions, Bhopal, (M.P.) - India

Abstract

The study was carried out with a view to enhance dissolution rate of poorly water-soluble drug by preparing fast disintegrating tablets of solid dispersion of cefdinir, a third generation cephalosporin. Solid dispersion was prepared by using PVP K- 30 and additionally SLS was added as adjuvant which may increase the dissolution rate. Solid dispersion (SD) was prepared by solvent evaporation method using different ratios of cefdinir, polymer and SLS. Optimized SD was incorporated into fast disintegrating tablets (FDT) for a faster release of cefdinir. In vitro dissolution rate of cefdinir from solid dispersion (SD) was significantly higher compared to pure cefdinir. DSC analysis indicated that crystallinity of SD has reduced significantly. FTIR analysis of SD showed no interaction between cefdinir, PVP K-30 and SLS. The dissolution rate of drug was affected by amount of polymer used. The dissolution rate of cefdinir solid dispersion prepared by taking molar ratio of drug: polymer 1:5 and 10% SLS was higher than that of cefdinir solid dispersion prepared by taking molar ratio of drug: polymer 1:6 and 10% SLS. Thus, solid dispersion technique can be successfully used for the improvement of the dissolution profile of cefdinir. FS5 (cefdinir, PVP K-30, SLS) was incorporated into FDTs containing diluents (Microcrystalline cellulose, Lactose) and super-disintegrant (Crospovidone or sodium starch glycolate). FDTs were prepared by direct compression method. Disintegration time, were decreased in the formulations containing Microcrystalline cellulose and Crospovidone, but increased with Lactose and sodium starch glycolate, respectively (36±1.26 to 108±2.89 Sec). The FDT4 batch with disintegration time 36 ± 1.26 Sec was selected as optimized formulation.

Key-Words: Cefdinir, Solid dispersion, Formulation

Introduction

Many patients, particularly children and the elderly population find it inconvenient to ingest conventional solid dosage forms such as tablets and capsules due to an impaired ability to swallow. This leads to patient non-compliance and potentially prolonged duration of treatment. This issue can be addressed through the development of orally disintegrating dosage forms that disperse or dissolve in the saliva and are swallowed without water. Besides improving the acceptability and compliance of patients, FDTs have been investigated for their potential to increase the bioavailability through the enhancement of the dissolution rate. Additionally, pharmaceutical companies have another reason for the development of FDTs [1, 2]. Commercially available FDTs are prepared by various techniques, mainly lyophilisation, moulding and direct compression; thus, they exhibit different disintegration behaviours.

*** Corresponding Author**
E.mail: mishraaa@gmail.com,
modi_srcem@rediffmail.com
Mob. +91-94065-24256

Therefore, the determination of FDTs disintegration time and behaviour is very essential in the evaluation and the development of this new dosage form. [3, 4]

Cefdinir is a BCS class ivth drug with low solubility and low permeability characteristics. Class ivth drugs slowly dissolve in the aqueous environment of the gastro-intestinal tract after oral administration and result in a poor bioavailability, while increasing the dissolution rate will also improve bioavailability [5, 6].

Application of solid dispersions is one of the strategies to increase the dissolution rate of drugs [7, 8]. Solid dispersions consist of two (or more) component systems in which the drug is dispersed monomolecularly or as small particles in a hydrophilic matrix. Increased dissolution rate can be attributed to a strongly enhanced surface area of the drug for dissolution [9, 10].

Solid dispersion techniques have been extensively used to increase the solubility of a poorly water-soluble drug. Solid dispersion (SD) is a viable and economic method to enhance bioavailability of poorly water-soluble drugs and also it overcomes the limitations of other approaches [11, 12].

Material and Methods

Material:

Cefdinir was a gift sample obtained from Lupin pharmaceutical ltd. (Mandideep, India). D-mannitol, PVP K-30 and Microcrystalline cellulose (MCC) was procured from Lobachemie, Mumbai, India. Magnesium stearate, Lactose was obtained from Triveni interchem pvt. ltd. All other reagents and solvents used were of analytical grade.

Methods:

Solubility study:

An excess quantity of Cefdinir was placed in 20 ml capacity volumetric flasks containing 20 ml of different solutions (distilled water, 0.1 N HCl and phosphate buffer, pH 6.8). After 15 days sample was sonicated for 10 min at room temperature. The solution was then passed through a Whatman Filter Paper (Grade 1) and the amount of the drug dissolved was analyzed spectrophotometrically (Shimadzu PharmaSpec 1700) at 286.0 nm after suitable dilution. Absorbance was recorded after proper dilution. All solubility measurements were performed three times [13, 14].

Preparation of solid dispersion:

The SD was prepared by solvent evaporation method. Different SD formulations were prepared with varying ratios of drug to PVP K-30 from 1:1 to 1:6 (F-1 to F-6) and drug to PVP K-30 from 1:1 to 1:6 with 10% sodium lauryl sulfate (FS1 to FS). Formulations were dissolved in sufficient amount of ethanol and sonicate for 15 min and evaporated ethanol at 40°C by magnetic stirrer leaving solid residue. The material was further dried with a lyophilizer for 6 hr. The solid mass was milled and passed through 70 mesh sieve and refrigerated at 2–4°C until further analysis. Physical mixtures were also prepared by trituration of Cefdinir and PVP K-30 or Cefdinir, PVP K-30 combination with Sodium lauryl sulfate (SLS), in a mortar and pestle.

Differential scanning calorimetry:

Differential scanning calorimetry thermograms (DSC) of Cefdinir, PVP K-30, SLS, physical mixtures and SD formulations were studied. DSC (JADE DSC-V1-12, PYRIS 6 DSC) was used to study the thermal behavior of the samples. The experiments were performed in a dry nitrogen atmosphere. The samples were heated at a rate of 10 °C min^{-1} from ambient temperature to the melting point. Empty iridium pan was used as a reference.

Fourier transform infrared spectroscopy:

FTIR (Fourier transform infrared spectroscopy) spectra of pure components, their physical mixture were performed. The spectrum was recorded in the range of 4000–400 cm^{-1}. The procedure consisted of dispersing a sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 0.15 $cm^{-1}$and scan speed was 20 scan/s.

Drug content: Exactly Weight amount of solid dispersions, each sample equivalent to 10 mg of drug were dissolved in 6.8 pH phosphate buffer, and were sonicated for 15 min. The solution was suitably diluted with freshly prepared PBS 6.8 pH, and was assayed by a UV-VIS spectrophotometer (SHIMADZU Corporation, Japan) for drug content at 286 nm using the following expression [15].

Percent drug content = (Practical drug content in solid dispersion/ Theoretical drug content in solid dispersions) x100

***In-vitro* dissolution studies of solid dispersion**:-

For the dissolution of solid dispersions, physical mixture and pure cefdinir, they were compressed as tablet by rotary press (Shakti Mechanicals, India). Direct compression method was selected for tabulating [16].

Dissolution rate studies were performed in phosphate buffer (pH 6.8) at 37±0.5 °C using USP II rotating paddle apparatus (VEEGO, India) at 50 rpm. Each tablet containing equivalent to 50 mg of Cefdinir was subjected to dissolution. At predetermined time intervals for 1 h, sample was withdrawn, filtered through Whatman Filter Paper (Grade 1) and spectrophotometrically assayed for drug content at 286 nm. Fresh corresponding medium was replaced into the dissolution medium. Each test was performed in triplicate.

Preparation of fast disintegrating tablets of optimized solid dispersion:

Cefdinir Fast disintegrating tablets were prepared according to the formula given in Table 2. All ingredients were sieved individually through sieve no. 60 and mixed in pestle-mortar and finally magnesium stearate was added as lubricant and again mixed for 5 minutes. The mixed blend was direct compressed using Multi station tablet press to obtained 600 mg weight of each tablet.

Before tablet preparation, the mixture blend of all the formulations were subjected to pre-compression parameters like angle of repose, bulk density, tapped density, % compressibility and flow ability. The fast disintegrating tablets prepared subjected to post-compression parameters like, content uniformity, hardness, friability, weight variation, dissolution and in vitro disintegration. Batches were prepared by direct compression method [17].

Drug Content: Finely powdered tablet was added in to a 100 ml of 6.8pH PBS. Sonicated for 15 min in bath

sonicator (Dolphin, India), filtered, suitably diluted with PBS; 6.8 pH, and Spectrophtometrically (SHIMADZU Corporation, Japan) evaluated at 286 nm.

***In-vitro* dissolution studies:** In-vitro dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 0.1 N HCl (900 ml) maintained at 37 ± 0.5°C. Aliquots of dissolution media were withdrawn at different intervals and content of Cefdinir was measured by determining absorbance at 286 nm spectrophotmetrically (SHIMADZU Corporation, Japan). The dissolution experiments were conducted in triplicate [18].

Statistical analysis: Statistical analysis was performed using 'Sigma Stat' statistical software. One way repeated measures analysis of variance was used to analyze statistical significance of means from two groups. Tukey's test was used to determine specifically the different formulation following ANOVA analysis. All results were considered statistically significant when $p < 0.05$, unless otherwise specified.

Results and Discussion

Solubility study: The solubility of Cefdinir in water, 0.1 N HCl and phosphate buffer (pH 6.8) are shown in Table 4. The solubility of Cefdinir in water at 37 ± 1°C was found to be 0.23 ± 0.061 mg/ml, which is in agreement with the previous article. The solubility values of cefdinir in 0.1 N HCl and phosphate buffer (pH 6.8) were observed to be approximately 0.11 ±0.046 mg/ml and 1.651 ±0.63 mg/ml respectively. The pH of solution had a significant effect on the solubility of cefdinir.

Solid dispersion characterization:

Determination of percent drug content: Exactly Weight amount of solid dispersions, each sample equivalent to 10 mg of drug were dissolved in 6.8 pH Phosphate buffer, and were sonicated for 15 min. The solution was suitably diluted with PBS 6.8 pH, and was assayed by a UV-VIS spectrophotometer (SHIMADZU Corporation, Japan) for drug content at 286 nm.

***In-vitro* dissolution studies:** Rate of release from different formulation of solid dispersion (Fig no. 10-11) were observed initially fast but after some time release become slower. The pure drug showed a release of 41.80 % at the end of 1 h, while SD showed 85.22% drug release in 1 h. The percent drug dissolution increased with an increase in the ratio. Physical mixtures (PM) showed less improved dissolution rate which is not significant. By solid dispersion the dissolution rate was 2.03 times higher than the pure drug.

The enhancement of rate of drug dissolution could be because of the dispersion of drug in pores of PVP K-30 and increased wettability. The dissolution rate of the drug increased up to the ratio of 1:5, but at higher ratios it decreased. This might be due to the firm adsorption of the drug on PVP K-30, which hinders the dissolution of the drug. Incorporation of SLS in the solid dispersion, results was increase dissolution rate by an effective prevention of Drug crystallization during dissolution. This was clearly showed in DSC analysis of solid dispersion (Fig no.-4) of 1:5 ratio cefdinir and PVP K-30 with 10% SLS. Endothemic peak of Cefdinir is moved down compare to pure cefdinir and physical mixture of Cefdinir, PVP K-30 and SLS, which indicate that the drug was converted to amorphous form, from crystalline form.

On application of one way repeated measures analysis of variance significant differences in the release rates were found between the formulations FS4-pure drug, FS4-Physical mixture, FS4-FS1, FS6-Pure drug, FS6-Physical mixture, FS5-Pure drug, FS5-Physical mixture, FS3-Pure drug, FS3- Physical mixture, FS2-Pure drug (Level of significance $P<0.05$).

Tablets were prepared by direct compression method. From the results, it can be concluded that the tablets containing crospovidone (batch S4 and S6) exhibit quick disintegration time and drug release (Fig 12) followed by tablets containing sodium starch glycolate. The probable reason for delayed the disintegration time of the tablet might be slow water uptake or more gelling tendency of sodium starch glycolate than crospovidone [19].

The tablet blend of all the batches were evaluated for different derived properties viz.-angle of repose (between 25 and 27), Bulk density (between 0.52 and 0.54 gm/cm3), Tapped Density (0.59–0.64 gm/cm3), Compressibility index (between 11 and 15, and flow ability (good). The results of Angle of repose and compressibility indicated that the flow ability of blend is significantly good. FDTs were prepared in batches FD1–FDT6 and evaluated for tablet properties like, weight variation, hardness, friability, wetting time, water absorption ratio, content uniformity, disintegration time and dissolution. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness were shown in the range of 4.2 ±0.20–4.76 ± 0.17 kg/ cm^2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of FDTs. The values were found to be in the range of 36

±1.26-108 ± 2.89. The percentage drug content of all the tablets was found to be between 95.75 ±1.07-98.56 ±1.16 of Cefdinir which was within acceptable limit. All the tablets prepared were subjected for 1release profile. Drug release was found between 87.035 ±0.52-98.18 ±0.38. Among Six Batches, Batch FDT4 is selected as optimized batch because of its lowest disintegration time and highest drug release [20].

On application of one way repeated measures analysis of variance significant differences in the release rates of Fast disintegrating tablets were found between the formulations FDT4-FDT1, FDT4-FDT2, FDT4-FDT6, FDT4-FDT5, FDT4-FDT3, FDT3-FDT1, FDT5-FDT1, FDT6-FDT1, FDT2- FDT1. Who's P value was found to be less than 0.05 ($P<0.05$) [21-23].

Conclusion

A total number of seven formulations were prepared by direct compression technique. The solid dispersion of Cefdinir with PVP K-30 and SLS greatly enhanced its dissolution rate. Molecular properties of drug and polymer were studied using DSC and FT-IR, both suggested complexation between drug and polymer. The change in crystalline form of drug to amorphous form due to monomolecular dispersion was suggested by DSC studies. The complexes were successfully formulated into fast disintegrating tablets. Two superdisintegrants were used in formulation of FDTs, among two crospovidone was most effectible.

Acknowledgement

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Table 1: Formula table for different solid dispersions

Sr. No.	Formulation	PVP K-30	Cefdinir	Sodium lauryl sulfate
1	F1	50	50	-
2	F2	100	50	-
3	F3	150	50	-
4	F4	200	50	-
5	F5	250	50	-
6	F6	300	50	-
7	FS1	50	50	10%
8	FS2	100	50	10%
9	FS3	150	50	10%
10	FS4	200	50	10%
11	FS5	20	50	10%
12	FS6	300	50	10%

a. Quantities of PVP K-30 and Cefdinir is given in mg/ formulation
b. Quantity of SLS is taken as % of total tablet contain

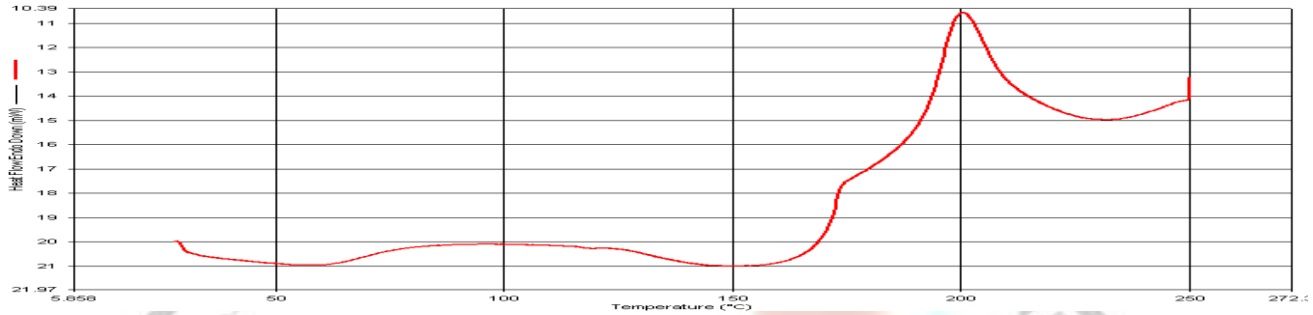

Fig. 1: DSC of Cefdinir

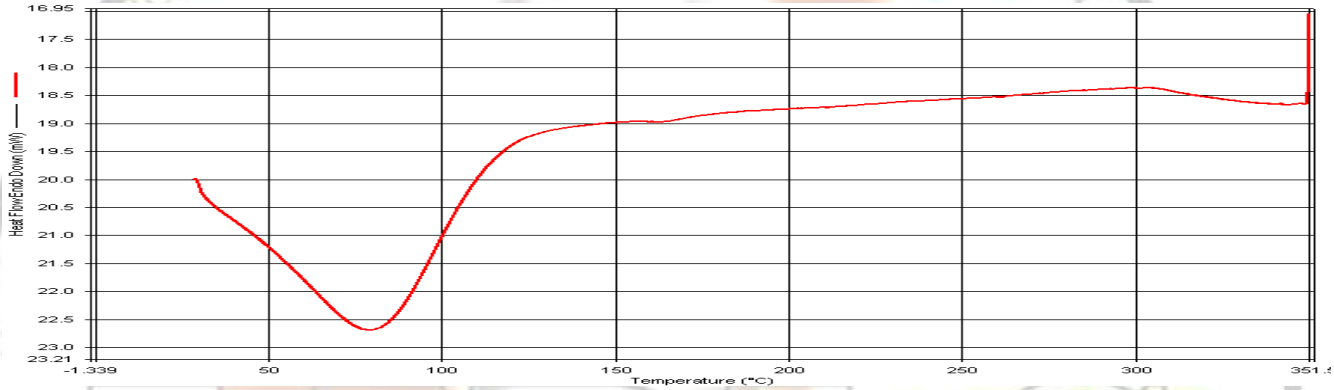

Fig. 2: DSC of PVP K-30

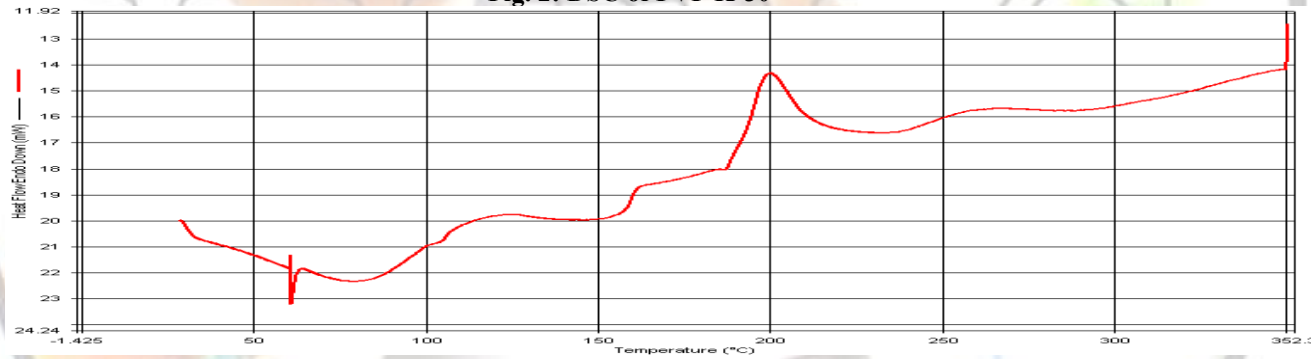

Fig. 3: DSC of Physical mixture of Cefdinir and PVP K-30

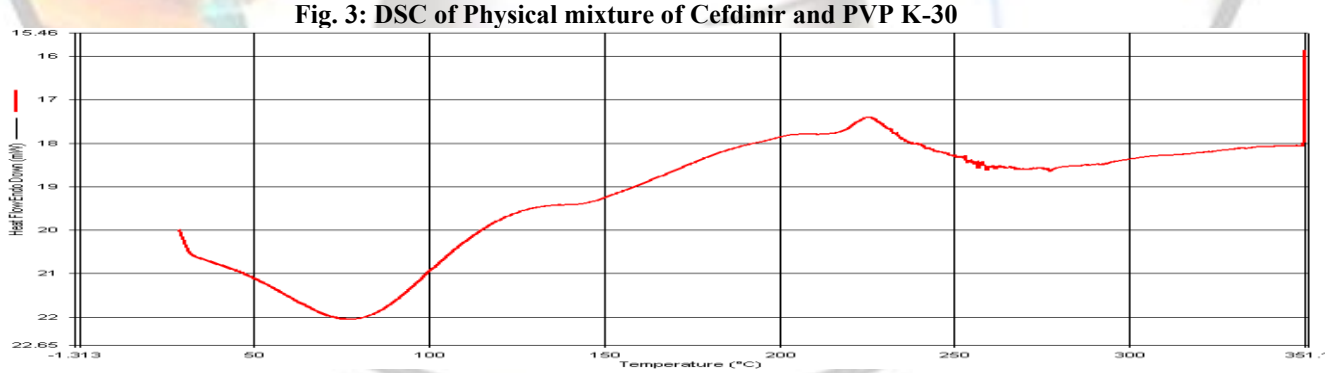

Fig. 4: DSC of formulation of solid dispersion

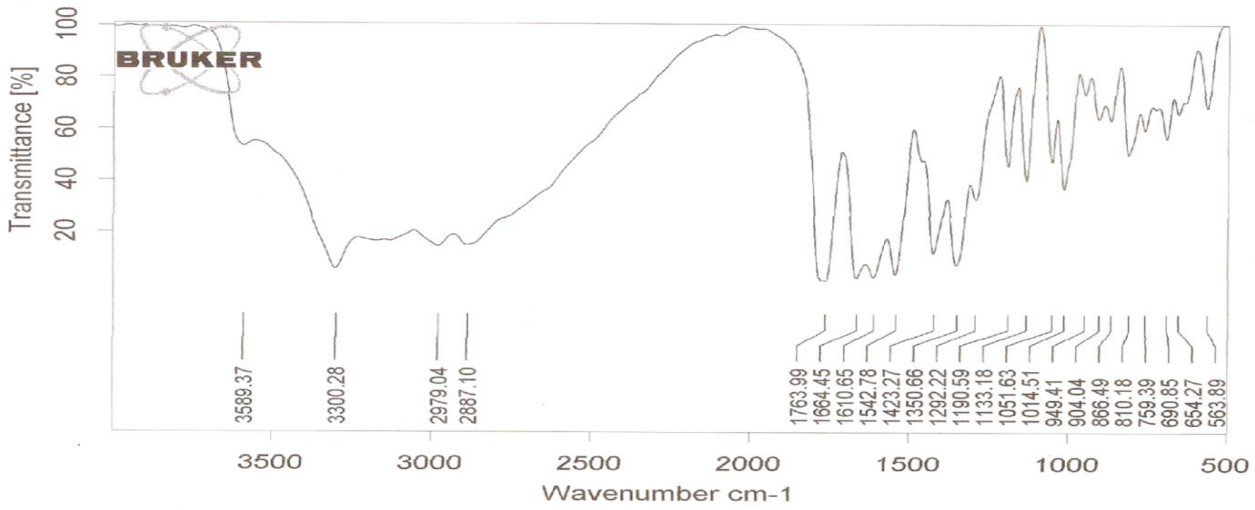

Fig. 5: FT-IR Spectrum of Cefdinir

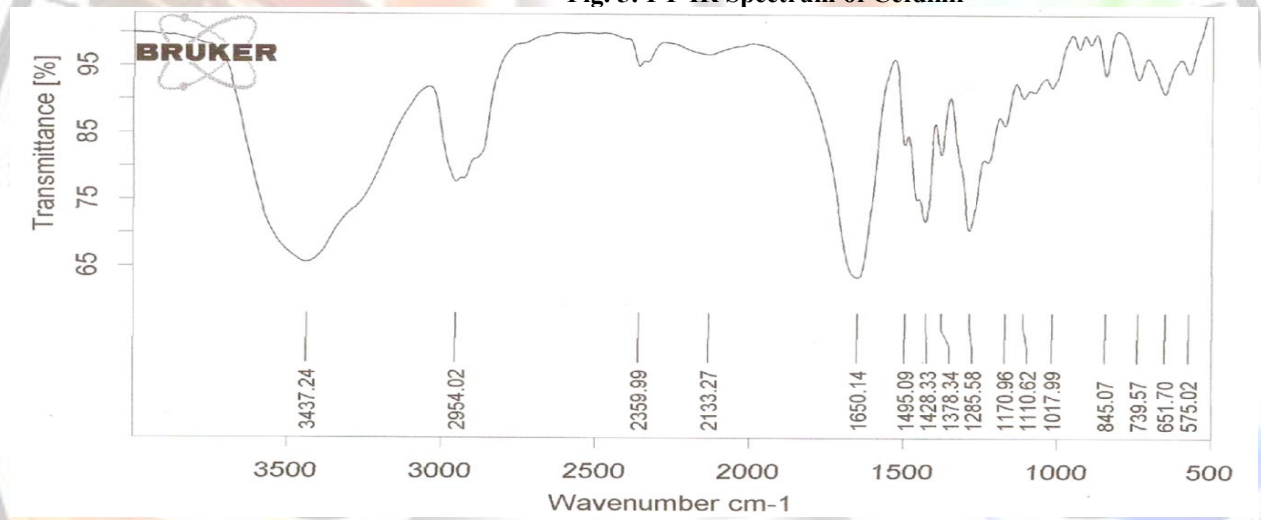

Fig. 6: FT-IR Spectrum of PVP K-30

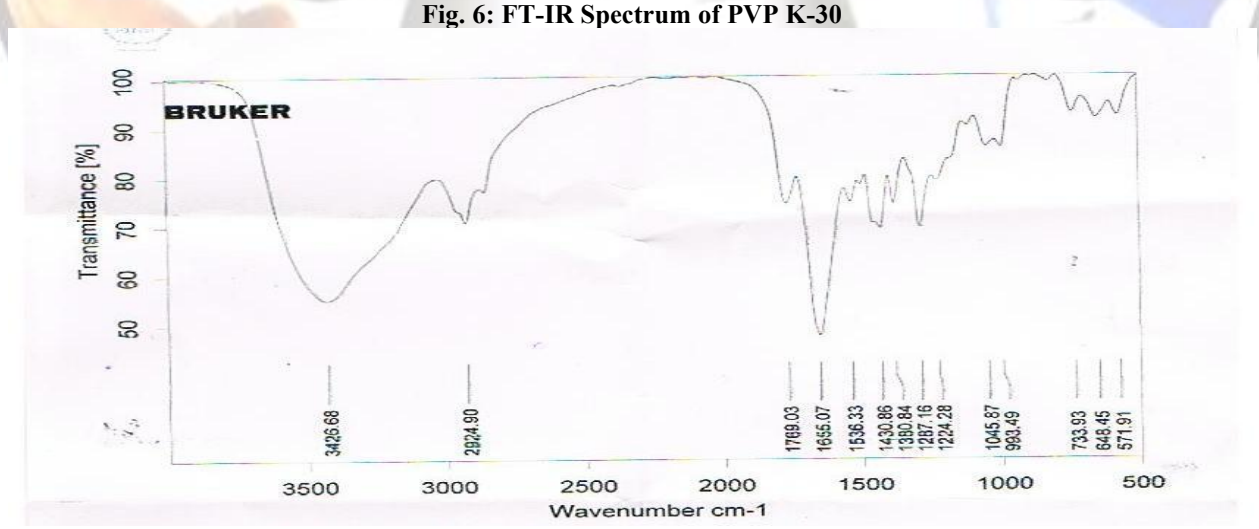

Fig. 7: FT-IR Spectrum of formulation of SD (FS5)

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Table 2: Formula used for preparation of fast disintegrating tablets

Ingredients	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Solid Dispersion(Equivalent to 50 mg Drug)	387.5	387.5	387.5	387.5	387.5	387.5
Microcrystalline Cellulose	-	70.25	140.5	140.5	70.25	-
Lactose	140.5	70.25	-	-	70.25	140.5
Sodium starch glycolate	60	60	60	-	-	-
Crospovidone	-	-	-	60	60	60
Manitol	6	6	6	6	6	6
Magnesium Stearate	6	6	6	6	6	6
Total Weight	600mg	600mg	600mg	600mg	600mg	600mg

Table 3: Quantitative Solubility studies of cefdinir in selected media at 37°C ±1 °C

S.No.	Solvent	Solubility of cefdinir(mg/ml)
1	Distilled water	0.23±0.061
2	0.1 N HCl	0.11±0.046
3	6.8 pH phosphate buffer	1.615±0.63

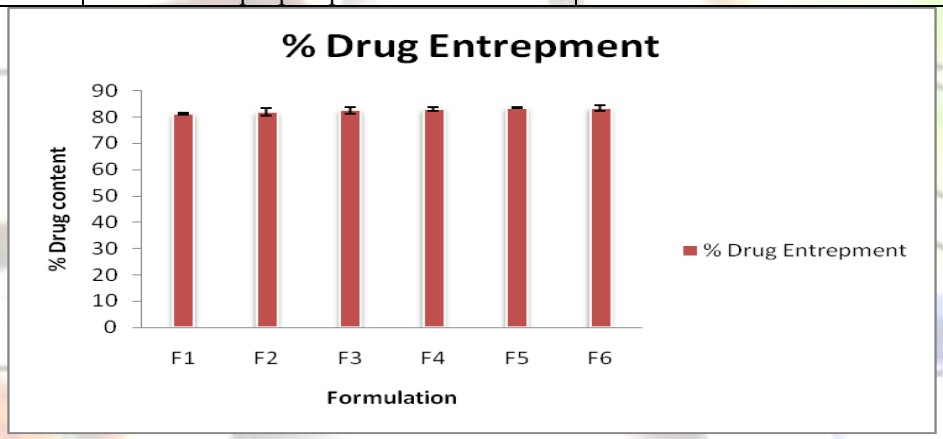


Fig. 8: Percent Drug content of different formulation of Solid Dispersion

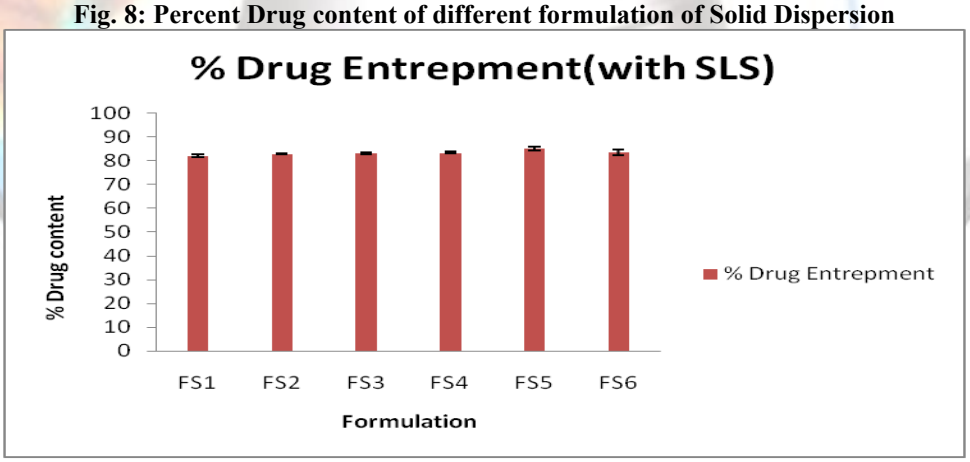


Fig. 9: Percent Drug Content of different formulation of Solid Dispersion with PVP K-30 and SLS

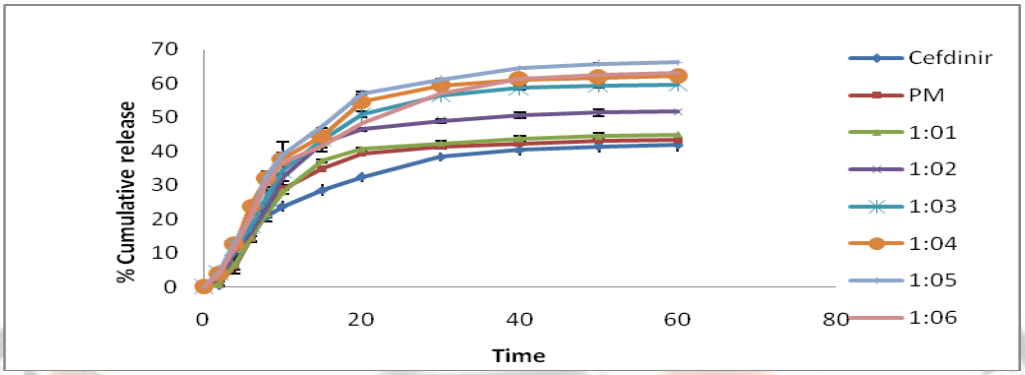
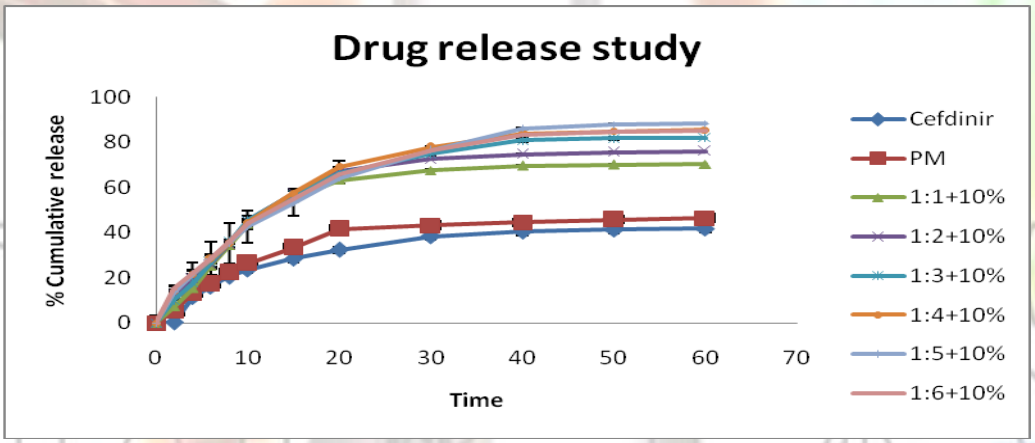


Fig.10: Dissolution studies of Cefdinir, Physical mixture, and solid dispersion at different cefdinir/PVP K-30 ratios. Each point represents the mean ± S.D. (n=3)



a. Each point represents the mean ± S.D. (n=3)

Fig. 11: Effect of 10% SLS on the Dissolution profile of Cefdinir, Physical mixture, and solid dispersion at different cefdinir/PVP K-30 ratios

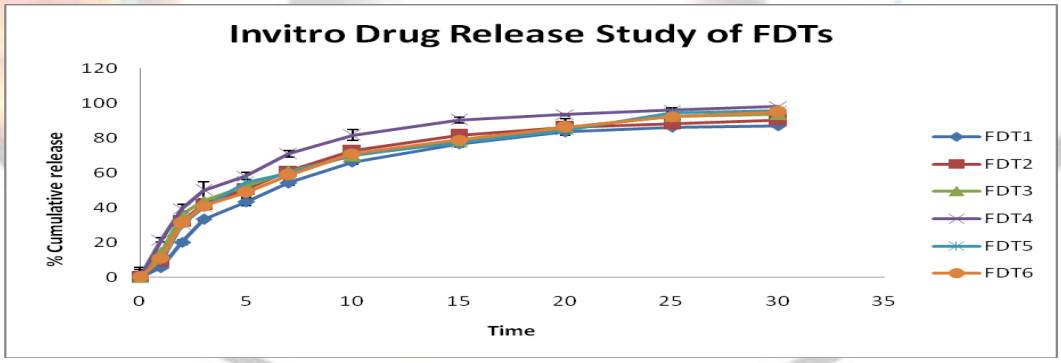


Fig. 12: Dissolution profile of different formulation of Fast disintegrating tablets

Table 4: Characterizations of mixed blend

Property	Formulation					
	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Angle of repose	25.52 ± 0.70	25.67 ± 0.65	26.12 ± 0.41	26.41 ± 0.43	26.72 ± 0.54	26.32 ± 0.47
Bulk density (gm/ cm3)	0.54 ± 0.12	0.52 ±.18	0.53 ± 0.11	0.53 ± 0.13	0.54 ±.16	0.52 ± 0.18
Tapped density (gm/cm3)	0.63 ± 0.14	0.60±.23	0.61 ± 0.19	0.59 ± 0 .11	0.64 ±.13	0.60 ± 0.23
% Compressibility	14.2% ± 0.5	13.3%±.95	12.6% ± 1.1	11.3 ±0.85	15.6 ± 0.93	13.3% ± 0.95
Flow ability	Good	Good	Good	Excellent	Good	Good

Table 5: Characterizations of fast disintegrating tablets

Parameter	Formulation					
	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Weight variation	Passes	Passes	Passes	Passes	Passes	Passes
Hardness kg/sq cm	4.63 ±. 20	4.40 ±0.17	4.53 ±0.30	4.23 ±0.15	4.73 ±0.20	4.76 ±0.17
Friability %	0.62%	0.71%	0.76%	0.99%	1.55%	1.39%
Disintegration time (s)	108 ±2.89	98.16 ±2.92	74.66 ±3.26	36 ±1.26	45 ±1.37	51 ±1.47
Content uniformity	96.21 ±1.21	97.34 ±1.02	98.10 ±1.16	98.56 ±1.16	95.75 ±1.07	97.56 ±1.37
Wetting time (s)	53.33 ±7.57	47.33 ±4.16	39.66 ±1.52	24.33 ±3.05	31.33 ±5.03	34.56 ±1.32
% Water absorption ratio	85.25 ±3.18	87.26 ±1.46	91.15 ±0.77	95.04 ±0.44	79.46 ±1.61	72 ±2.35