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SOLUBILITY ENHANCEMENT OF CEFIXIME THROUGH SOLID DISPERSION TECHNIQUE

S. K. Sadia*[1], Dr. M. Dhanalakshmi[2] and B. Nageswar Rao[3]

[1,3]Department of Pharmaceutics, KLR Pharmacy College, New Paloncha, TS.

[2]Department of Pharmaceutical Analysis, KLR Pharmacy College, New Paloncha, TS.

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***Corresponding Author**
S. K. Sadia
Department of Pharmaceutics, KLR Pharmacy College, New Paloncha, TS.

ABSTARCT

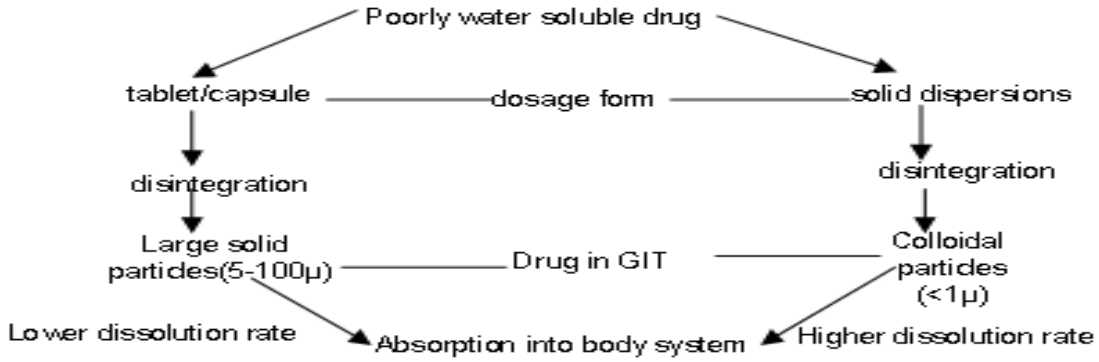
In the present study Cefixime solid dispersions were formulated. The enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. Cefixime was mixed with various proportions of excipients showed no color change at the end of two months, proving no drug-excipient interactions. The pre compression blend of Cefixime solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicates good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers; the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F8 formulation containing, Drug and PEG 6000 in the ratio of 1:4 showed good result that is 97.65% in 60 minutes. As the concentration of polymer increases the drug release was increased. While the formulations containing PEG 4000, 8000 showed less release. Hence from the dissolution data it was evident that F8 formulation is the optimized formulation.

KEYWORDS: Cefixime, PEG 4000, PEG 6000, PEG 8000, Solid Dispersions.

INTRODUCTION

The enhancements of oral bioavailability of poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically

viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs.



Schematic representation of the bioavailability enhancement of poorly Water soluble drug by solid dispersion technique

Fig. 01: Schematic representation of the bioavailability enhancement of poorly water soluble drug by solid dispersion technique.

Methods of Preparation of Solid Dispersions

1. Melting method

The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.[1]

2. Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.[2]

3. Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.[2]

4. Melt extrusion method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w).[38] The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory cutting mill and sieve to exclude particles >355µm.[3]

5. Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.[4]

6. Melt Agglomeration Process

The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the

agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.[5,6]

7. Melt Agglomeration Process

The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.[9,10]

8. Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited If the viscosity increases, the charged jet is dried.[11]

This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.[12]

9. Super Critical Fluid (Scf) Technology

The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids, and supercritical antisolvent. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).[13,14]

Mechanism of Bioavailability Enhancement,[15,16]

Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms

- ✓ Reduction in particle size
- ✓ Improvement in wettability and dispersibility
- ✓ Changing crystalline form of drug to amorphous form
- ✓ Reduction in aggregation and agglomeration of drug particles.

Characterization of Solid Dispresion[17]

Various characterization methods to assess the solid dispersion are as follows

- ❖ **Drug -carrier miscibility**
- ❖ **Hot stage microscopy**
- ❖ **Differential scanning calorimetry**
- ❖ **Powder X-ray diffraction**
- ❖ **Spectroscopic methods like raman spectroscopy, FT-IR spectroscopy**
- ❖ **Physical Structure**
- ❖ **Amorphous content**
- ❖ **Stability**
- ❖ **Dissolution enhancement**

Mechanism of Drug Release From Solid Dispersion[19]

- When solid dispersions are isolated in water, the carriers often soften or absorb water quickly due to their hydrophilic property and form concentrated carrier layer or gel layer in some cases. If the drug liquefies in this layer and the viscosity of this layer is high sufficient to prevent the diffusion of the drug during it, the rate-limiting step will be the diffusion of the carrier into the bulk phase and this method is carrier-controlled release.
- If the drug is unsolvable or sparingly soluble in the concentrated layer, it can be released intact to contact with water and the dissolution outline will rely on the belongings of drug particles (polymorphic state, particle size, drug solubility). In fact, these two methods often occur simultaneously because the drug may be partly soluble or deceived in the concentrated carrier layer.
- On the other hand, these methods said to explain the different release behaviours of solid dispersions and figure out the way to enhance the dissolution profile of solid dispersions. Copious researches showed the perfection of drug dissolution profile when the ratio of carriers in solid dispersions was increased because the drug was dispersed better and the drug crystallinity diminished.
- In these solid dispersions, the main release mechanism is drugcontrolled release. In compare, other researchers established the decrease in drug dissolution rate when the ratio of the carrier in solid dispersions was improved. This can be clarifying by the carrier-controlled mechanism in which the gel or concentrated carrier layer is formed and performs as a diffusion barrier to delay drug release.
- The release mechanism may also be exaggerated by the ratio of drug–carrier in solid dispersions. Karavas et al. prepared felodipine solid dispersions by using diverse types of PVP, PEG as carriers and accomplished that the percentage of the drug in solid dispersions resolute the mechanism of drug release which was drug diffusion (through the polymer layer)-controlled at low drug contents and drug dissolution-controlled at high drug contents.

Materials Used in the Work

Cefixime, PEG4000, PEG 6000, PEG 8000, Explotab, Magnesium stearate, Aerosil, Mannitol

METHODOLOGY

Determination of Wavelength

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

Formulation Development

Formulation development for solid dispersion

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Cefixime and Water soluble polymers such as PEG 4000, PEG 600, PEG 800. Swere selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart (Table). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of super disintegrates, diluents, lubricant and glidant (shown in Table 01). The blend was evaluated for precompression parameters.

Table 01: Formulation of solid dispersion showing various compositions (Ratios only).

Ingredients	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9	SD10	SD11	SD12
Drug	1	1	1	1	1	1	1	1	1	1	1	1
PEG 4000	1	2	3	4	-	-	-	-	-	-	-	-
PEG 6000	-	-	-	-	1	2	3	4	-	-	-	-
PEG 8000	-	-	-	-	-	-	-	-	1	2	3	4

Table 02: Formulation of tablet by using solid dispersion.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug Equivalent To (50mg- dose)	SD1 (100)	SD2 (150)	SD3 (200)	SD4 (250)	SD5 (100)	SD6 (150)	SD7 (200)	SD8 (250)	SD9 (100)	SD10 (150)	SD11 (200)	SD12 (250)
Explotab	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	7	7	7	7	7	7	7	7	7	7	7	7
Aerosil	7	7	7	7	7	7	7	7	7	7	7	7
Mannitol	221	171	121	71	221	171	121	71	221	171	121	71
Total weight	350	350	350	350	350	350	350	350	350	350	350	350

Micrometric Properties

Angle of repose

The angle of repose of was determined by fixed funnel method. The accurately weighed physical mixtures were taken in a funnel. The height of the funnel was adjusted to 2cm, the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel into the surface.

Table 03: Angle of repose standard values of powders.

S. No	θ range	Flow character
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	>40	Very poor

Bulk Density

Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied was measured.

Tapped density

The measuring cylinder containing weighed mass of powder. The cylinder was then tapped at a constant velocity until a constant volume was obtained.

Carr's Index (%)

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these influence the compressibility index.

Table 04: Carr's Index Values.

S.no	CI(%) range	Flow character
1	5- 15	Excellent
2	12-16	Good
3	18-20	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner Ratio

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

Hausner's Ratio=Tapped density / Bulk density

Table 05: Hausener's Ratio Values.

S.no	Hausner ratio range	Flow characteristic
1	< 1.25	Good flow
2	1.25- 1.5	Moderate flow
3	> 1.5	Poor flow

Evaluation Tests

Average weight

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Thickness

The thickness of Cefixime tablets was determined by using digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness

The hardness of the tablets was determined by using Monsanto hardness tester. Six individual tablets from each batch were taken and results averaged.

Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets Apparatus was run for 10 minutes and the basket was lift from the fluid and observed for disintegration of tablets.

Content of uniformity

The tablets were individually weighed and crushed. The quantity of powder equivalent to mass of the one tablet was extracted in 10ml of methanol and then made up 100ml with phosphate buffer pH 6.8, shaken for 30mins. The solution was filtered through whattmen filter paper. The drug content was determined by UV spectrometer at respective wavelength for Cefixime after suitable dilution with phosphate buffer pH 6.8.

***In vitro* Dissolution Study**

Drug release from formulated Cefixime tablets was determined by using USP dissolution test apparatus II (Paddle apparatus). The tablets were place in 900 ml of dissolution medium as phosphate buffer pH 6.8 maintained at 37 ± 0.5°C and 50 rpm. At appropriate intervals (5, 10, 15, 30, 45 and 60) 5ml of the samples were taken and the dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were then analyzed at respective wavelength by UV-spectrophotometer. The concentration was calculated by using calibration curve.

Fourier Transform Infrared (FTIR) spectroscopy

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the Pure drug and optimized formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

RESULTS AND DISCUSSION

1. Analytical Method Development

Table 06: Calibration curve of Cefixime in phosphate buffer pH 6.8.

Concentration (µg/mL)	Absorbance
0	0
5	0.128
10	0.247
15	0.355
20	0.476
25	0.612

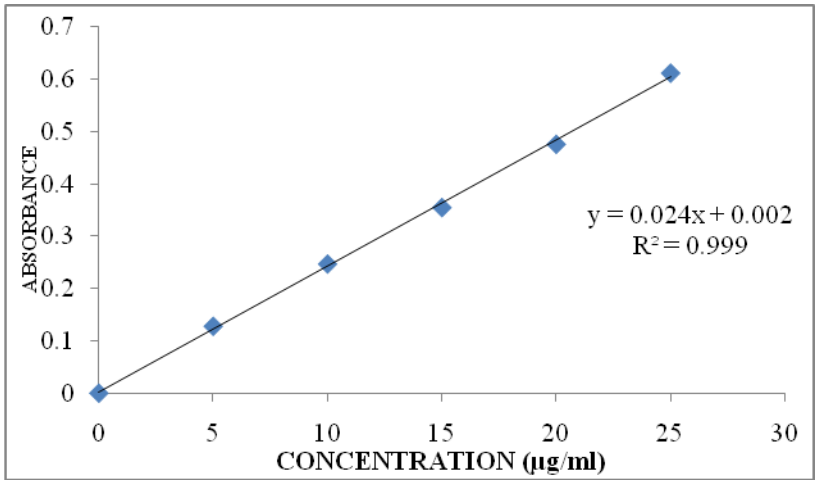


Fig. 02: Calibration curve of Cefixime in phosphate buffer pH 6.8.

2. Micromeritic properties

Table 07: Evaluation of pre compression parameters of solid dispersion blend.

Formulation Code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio
F1	27.02	0.48	0.57	18.75	1.08
F2	27.69	0.32	0.46	28.91	1.44
F3	27.34	0.32	0.46	29.13	1.45
F4	26.04	0.35	0.50	29.62	1.42
F5	27.34	0.35	0.49	28.71	1.40
F6	27.69	0.34	0.48	28.65	1.40
F7	27.69	0.35	0.48	27.83	1.38
F8	27.66	0.33	0.49	28.57	1.46
F9	28.34	0.33	0.47	28.72	1.40
F10	27.69	0.35	0.50	29.68	1.42
F11	26.34	0.33	0.50	28.09	1.49
F12	26.01	0.39	0.55	28.62	1.40

3. Post compression parameters

Table 08: Evaluation of post compression parameters of solid dispersion tablet.

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disintegration time (sec)	Content uniformity (%)
F1	350.1	4.02±0.20	3.63±0.05	0.34±0.06	37±0.01	98.2±0.21
F2	349.2	4.01±0.54	3.52±0.03	0.64±0.01	45±0.24	100.3±0.4
F3	348.7	4.03±0.63	3.65±0.02	0.25±0.02	52±1.5	99.1±0.36
F4	349.6	4.04±0.45	3.45±0.01	0.49±0.03	34±0.02	95.2±0.20
F5	347.5	4.00±0.35	3.65±0.02	0.50±0.02	55±0.47	95.9±0.85
F6	349.8	4.01±0.63	3.65±0.01	0.35±0.04	46±0.04	98.6±0.35
F7	350.2	4.08±0.63	3.60±0.03	0.18±0.008	34±0.22	99.3±0.45
F8	348.9	4.02±0.47	3.75±0.01	0.29±0.09	28±0.10	100.2±0.41

F9	3491	4.09±0.42	3.53±0.03	0.36±0.04	44±0.03	99.33±0.37
F10	349.3	4.02±0.45	3.60±0.14	0.47±0.03	35±0.05	98.6±0.23
F11	348.6	4.04±0.47	3.70±0.03	0.54±0.01	43±0.04	99.4±0.01
F12	347.4	4.06±0.63	3.65±0.024	0.41±0.07	58±0.03	97.25±0.20

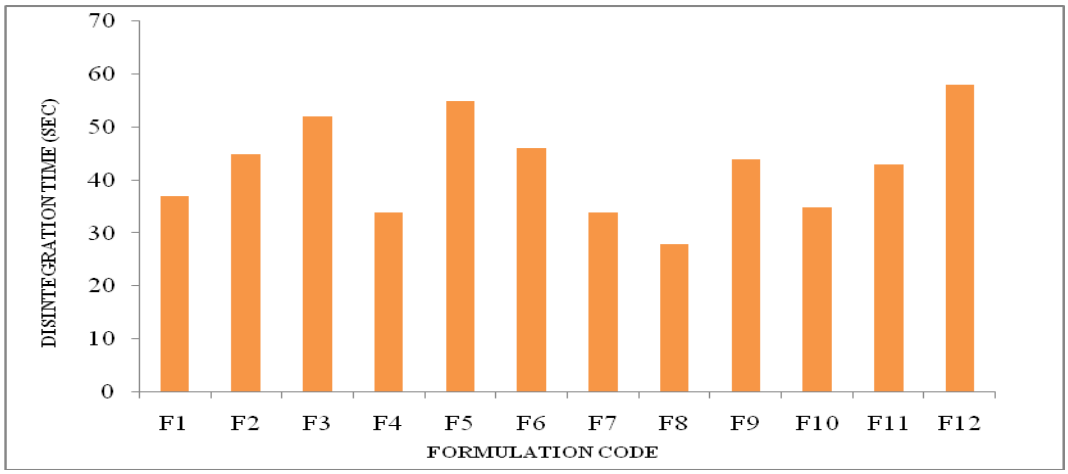


Fig. 03: Disintegration Time.

4. *In vitro* Dissolution Studies

Table 09: *In vitro* dissolution studies of formulated solid dispersion tablets.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	20.36	24.65	28.12	30.11	18.64	21.79	25.31	32.28	38.94	36.89	29.95	20.15
10	32.25	36.14	34.98	35.48	24.98	27.43	32.56	47.24	55.62	42.31	37.43	26.97
15	41.59	45.20	48.75	42.99	39.67	32.85	46.40	65.83	78.24	49.67	42.26	33.59
20	48.45	58.34	56.89	58.76	45.25	40.15	49.12	79.26	83.40	54.92	50.19	41.67
30	54.94	61.48	65.19	69.27	49.20	46.29	57.99	83.38	88.26	66.36	57.66	48.99
45	60.18	68.15	70.47	74.18	53.12	58.91	64.82	86.17	92.16	75.21	60.98	51.36
60	64.29	71.49	79.8	87.71	56.53	63.13	71.50	97.65	95.59	82.44	65.43	58.68

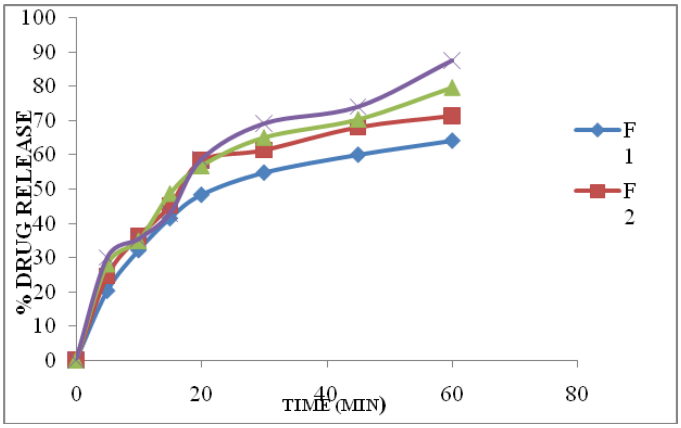


Fig.04: *In vitro* dissolution studies of formulated solid dispersion tablets by using PEG 4000.

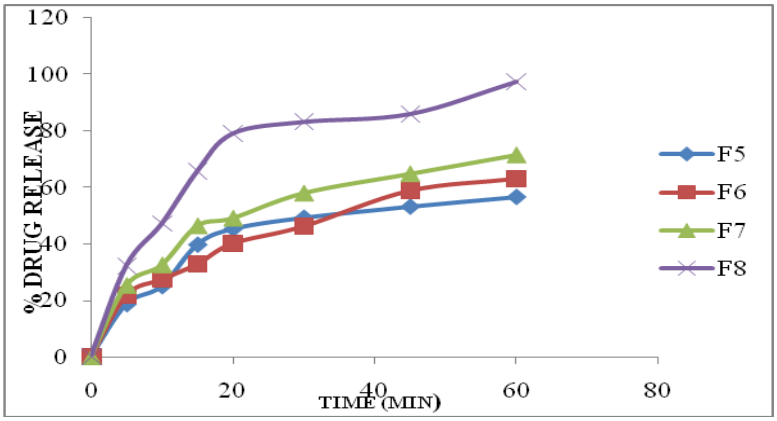


Fig. 05: *In vitro* dissolution studies of formulated solid dispersion tablets by using PEG 6000.

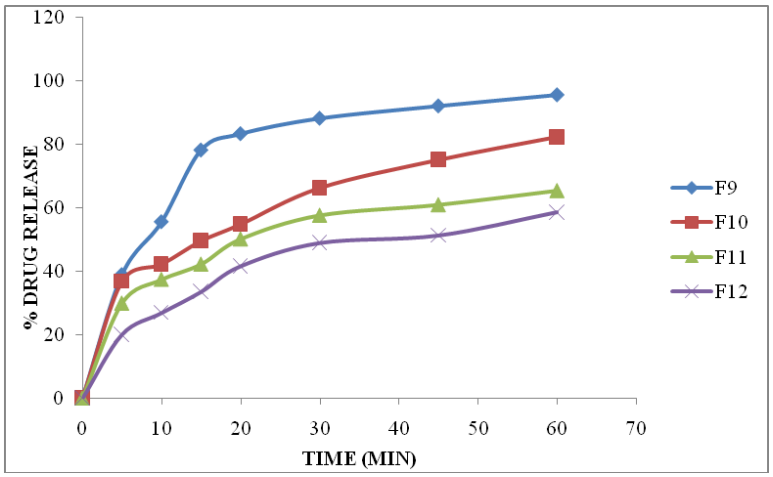


Fig. 06: *In vitro* dissolution studies of formulated solid dispersion tablets by using PEG 8000.

5. Drug Excipient Interactions

5.1 Fourier Transform infrared (FTIR) spectroscopy studies

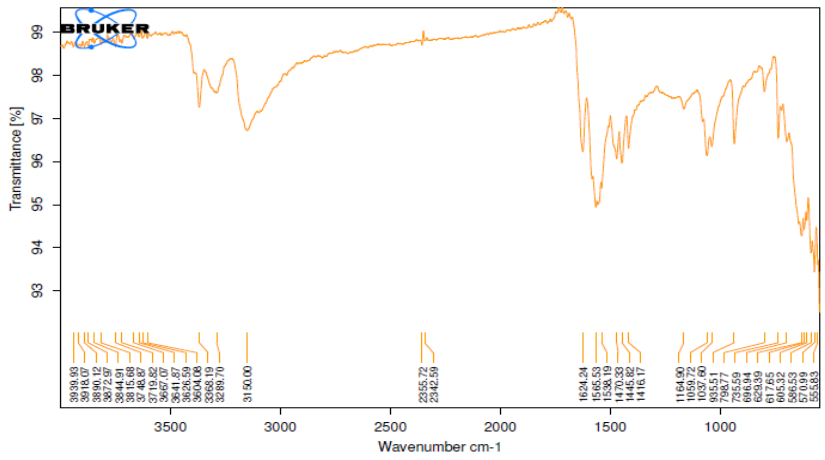


Fig. 07: FT-IR Spectrum of Cefixime pure drug.

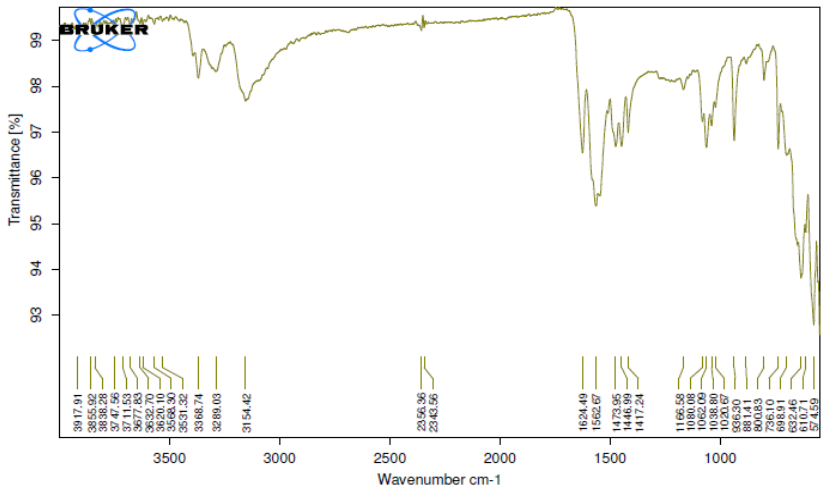


Fig. 08: FT-IR Spectrum of Optimised Formulation.

CONCLUSION

- ✓ Cefixime is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects.
- ✓ The standard curve of Cefixime was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 6.8 phosphate buffer.
- ✓ Cefixime was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.
- ✓ The pre compression blend of Cefixime solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The pre compression blend of all the batches indicating good to fair flowability and compressibility.
- ✓ Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets.
- ✓ The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests.
- ✓ Among all the formulations F8 formulation containing, Drug and Peg 6000 in the ratio of 1:4 showed good result that is 97.65% in 60 minutes. As the concentration of polymer increases the drug release was increased. While the formulations containing PEG 4000, PEG 8000 showed less release compared to formulations containing PEG 6000. Hence from the dissolution data it was evident that F8 formulation is the better formulation.

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