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ENHANCEMENT OF CEFPODOXIME PROXETIL DRUG BY USING SOLID DISPERSION METHOD AND POLYMER USING CYCLODEXTRINS

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ABSTRACT

The primary aim of this research was to improve the solubility and Bioavailability of BCS Class-IV drugs because of their low solubility and Low permeability and dissolution rate. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response to be shown. The aim of research work is to prepare oral dispersible tablets using solid dispersion as a core material. Solid dispersions were prepared by kneading method, physical mixture and solvent evaporation method using varied concentrations of hydrophilic polymer (Cyclodextrins). Dissolution profile predicted that solid dispersion prepared with 1:2 % w/w CP and Cyclodextrins by solvent evaporation has shown highest drug release. Powder blend of all formulations was evaluated for pre-compression parameters (FTIR, Hausner's ratio, Carr's index and angle of repose) and it was observed that all excipients were compatible with CP and has excellent flow properties. Dispersible tablets were prepared by direct compression method using different concentration (0, 2.5 and 5 % w/w) of croscarmellose sodium and were evaluated for drug content, weight variation, friability, dispersion time and in vitro drug release studies. Drug content was found to be more than 94 % for all prepared tablets whereas friability and weight variation were below 1 % and 5 % w/w respectively. Tablet formulations containing 5% w/w of croscarmellose sodium showed least dispersion time (2.51 minutes) and highest drug release 96 % in just 30 minutes which was better than marketed formulation (CEFOPROX) as well as pure drug.

KEYWORDS: Cefpodoxime proxetil, Bio-Pharmaceutics System, Bioavailability, Dissolution, Supradisintegrant.

1. INTRODUCTION

Cefpodoxime Proxetil belongs to BCS class IV and is a broad spectrum Cephalosporin antibiotic mainly used in skin infection, upper respiratory tract infection and urinary tract infection. It is prodrug and gets activated in intestine by non specific esterase enzyme but due to its poor aqueous solubility which limits its absorption ultimately bioavailability (47%), it fails to reach the systemic circulation in required concentration and unable to elicit the desired pharmacological action.1 As solubility is the primary requisite for the onset of therapeutic effect of drug by absorbing it from the absorption site.

Solubility

Quantitative it is defined as the concentration of solute in a saturated solution at certain temperature and pressure.

Qualitatively it is defined as the spontaneous interaction between two or more substances to form homogenous or molecular dispersion.[6-7]

According to **United State Pharmacopeia (USP)** solubility is defined as number of millilitres of solvent in which 1g of solute will be dissolved. In **Indian Pharmacopeia** solubility is defined as

Table 1.1: Solubility is defined in Indian Pharmacopeia.[8-9]

Terms	Parts of solvent required to dissolved one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	>10000

Biopharmaceutics Classification System

Fundamental basis of the BCS established by Dr. Gordon Amidon who was presented with a distinguished Science award at 2006 International pharmaceutical federation (FIP) congress in Salvador, Brazil. In the Biopharmaceutics classification system drug development tool that allows estimation of the contribution of three major factors are solubility, dissolution and intestinal permeability. 85% of the most sold drugs in the United States and Europe are orally administered. According to the BCS drug substances can be classified in four classes described as follow:

Table 1.2: Biopharmaceutics Classification System.[21]

Class	Solubility	Permeability	Drugs	Characteristics Features
I	High	High	Propanol, Diltiazem, Verapamil etc.	Well absorption orally.
II	Low	High	Itroconazol, Phenytoin, Nifidipine etc.	Variable absorption due to solubility limitation
III	High	Low	Ranitidine, Ciprofloxacin, Insulin etc.	Variable absorption due to permeability limitation.
IV	Low	Low	Methotrexate, Chlorothiazides, Furosemide etc.	Very small absorption due to solubility and permeability.

Various Techniques For Solubility Enhancement.[22]

Physical modification	Chemical modification	Other methods
Particle size reduction Micro-ionization Nano-suspension Modification of the crystal habit Polymorphs Pseudo polymorphs Complexation Use of complexing agents Solubilisation by surfactants	pH modification Salts Soluble pro-drugs	Co-crystallization Co-solvency Hydro-trophy Solvent deposition Porous-micro-particle technology Nanotechnology approaches

Solid Dispersion

Sekiguchi and obi' first developed the concept of theSolid dispersion. According to this solid dispersion is the most commonly used technique for improving the dissolution and bioavailability, therapeutic effect of poorly soluble drugs in 1961.

'Sekiguchi and obi' defined as dispersion of one or more active ingredients which are dispersed in inert carrier or matrix at solid state. Solid dispersion consisting at least two different components that is hydrophilic matrix and hydrophobic matrix.In this solid dispersion the matrix may be crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles.

In now a day's number of drugs are lipophilic and having a problem of less aqueous solubility. So, to overcome these problems water-soluble carriers are used to enhance solubility and bioavailability.[23]

Types of Solid Dispersion

Solid dispersion consists of hydrophilic matrix and hydrophobic drug. So, matrix can be crystalline or amorphous in nature. A drug can be dispersed molecularly in any of particles.

These are classified on the basis of

- Carrier used
- Molecular arrangement

2. MATERIAL AND METHODS

Preformulation Studies[118-120]

2.1.1 Physical appearance

Physical appearance of pure drug was examined by its various Organoleptic properties like colour, state, odour etc.

2.1.2 Melting point determination

The melting point of the pure drug was determined by capillary fusion method. A capillary sealed at one end was filled with small amount of drug and the capillary was kept inverted i.e. sealed end downwards into the melting point apparatus. The temperature at which the solid drug converts into liquid was noted down with the thermometer provided. The melting point was recorded and compared with literature value and melting point was also determined by DSC.

2.1.3 Determination of absorption maxima (λ_{max})

A 20µg/ml solution of drug cefpodoxime proxetil was scanned on the UV Spectrophotometer between 200–400 nm in order to determine absorption maxima (λ_{max}) of the pure drug.

Preparation of calibration curve in methanol

100 mg of cefpodoxime proxetil was dissolved in 100 ml of methanol and 10 ml of this solution was taken in 100 ml of volumetric flask and diluted to 100 ml again with methanol to get 100µg/ml as stock solution. From this

stock solution, aliquots of 0.1 ml, 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, 1.2 ml,1.4 ml, 1.6 ml, 1.8 ml and 2.0 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with methanol. The absorbance was determined at 235 nm using methanol as blank.

Preparation of calibration curve in phosphate buffer (pH 6.8)

a) Preparation of Phosphate Buffer(pH 6.8)

Dissolved 28.8 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml of phosphate buffer.

b) Preparation of Calibration Curve

100 mg of cefpodoxime proxetil was dissolved in 100 ml of methanol and 10 ml of this solution was taken in 100 ml of volumetric flask and diluted to 100 ml with phosphate buffer to get 100 µg/ml as stock solution. From this stock solution, aliquots of 2 ml, 4ml, 6 ml, 8ml, 10 ml, 12 ml and 14 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with phosphate buffer. The absorbance was determined at 232 nm using phosphate buffer as blank.

Preparation of calibration curve in distilled water

100 mg of cefpodoxime proxetil was dissolved in small amount of methanol and diluted to 100 ml with distilled water. 10 ml of this solution was taken in 100 ml of volumetric flask and diluted to 100 ml with distilled water to get 100µg/ml as stock solution. From this stock solution, aliquots of 0.5ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, and 3.0 ml were withdrawn and transferred to 10 ml volumetric flasks and volume was made up to 10 ml with distilled water. The absorbance was determined at 230.0 nm using distilled water as blank.

Infrared spectral assignment

The main application of FTIR spectrophotometry is the determination of identity of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule. The sample was mounted in FTIR compartment and scan was at wave length 4000cm^{-1} to 400cm^{-1}.

Drug polymer interaction studies

While formulating solid dispersion, it is mandatory to give consideration to compatibility of drug and excipient used within the system. It is therefore necessary to confirm that drug is not interacting with the excipient under experimental conditions (40 ± 2ºC and 75 ± 5% RH) for 4 weeks.Physical mixture and excipients were filled in vials and kept for interaction studies.Vials were examined at regular intervals for discoloration, liquefaction, and clump formation in the mixture. Interaction between drug and excipient was also confirmed by FTIR studies.

Preparation of Physical Mixture of Solid Dispersion of Cefpodoxime Proxetil

Physical mixtures of cefpodoxime proxetil were prepared using β-Cyclodextrin in different ratios. First drug and carrier was passed through a 40 mesh screen, then weighed and mixed physically by blending the two components in geometric proportion in a mortar for 10 minutes. Table no 2.2depicts the composition used for preparing physical mixtures of cefpodoxime proxetil.

Table: 2.2: Composition of physical mixtures of cefpodoxime proxetil.

Formulation code	Ratio	
	Drug (CP)	Carrier (β-cyclodextrin)
PM1	1: 1	
PM2	1: 2	
PM2	1: 3	

Table 4.4: Composition of solid dispersion containing cefpodoxime proxetil and β- Cyclodextrin prepared by kneading method.

Formulation code	Ratio	
	Drug (CP)	Carrier (β-CD)
KN 1	1: 1	
KN 2	1: 2	
KN 3	1: 3	

2.2Kneading method: The cefpodoxime proxetil and β-cyclodextrin were triturated in 1:1, 1:2,1:3 ratio using little amount of methanol to give a thick paste, which was kneaded for 30 min and then dried at 40ºC in an oven .The dried mass then pulverized, passed through mesh 40,stored in vacuum desiccators (48 h). The prepared solid dispersion was grounded, sieved through mesh 100 and stored in desiccator for further use.

2.3 Solvent evaporation method: Cefpodoxime proxetil were added in methanol and polymer that is beta Cyclodextrin is added into water. Then mixed both the solution and the solution were vigorously stirred until entire methanol was evaporated to obtain a clear solvent free film. The film was then pulverized and passed through sieve no100.

Table 2.4: Composition of solid dispersion containing cefpodoxime proxetil and β- Cyclodextrin prepared by solvent evaporation method.

Formulation code	Ratio	
	Drug (CP)	Carrier (β-CD)
SE 1	1: 1	
SE 2	1: 2	
SE 3	1: 3	

2.5 Characterization Of Solid Dispersions
The prepared solid dispersions were evaluated for percentage yield, solubility studies and *in vitro* drug release. Best release batch were evaluated for Fourier transform infrared (FTIR), X-ray diffraction (XRD) studies and scanning electron microscopy (SEM).

2.5.1 Percentage yield
Percentage yield of each formulation was determined according to the recoverable final weight of solid dispersion and total weight of drug carrier used.

% yield= 100* Actual yield/ Theoretical yield……..eq(1)

2.5.2 Determination of solubility
Pure cefpodoxime proxetil and solid dispersions equivalent to 10 mg of cefpodoxime proxetil was added to 10 ml of pH 3.0 buffer in 25 ml volumetric flasks. The volumetric flasks was capped properly and shaken at 37± 2˚C in a temperature controlled water bath (Shaking water bath) for 48 h. Resultant samples containing undissolved solid dispersions suspended in the volumetric flasks was filtered through Whatman filter paper no.41, suitably diluted with water and analyzed by UV spectrophotometer at 263 nm.

2.5.3*In-vitro* drug release
The *in vitro* dissolution study was carried out in USP Dissolution test apparatus, type 2(paddle type).900 ml of solution by dissolving 3.03 g of glycine and 3.37 g of sodium chloride in about 500 ml of water, adding cautiously with swirling 0.8 ml of hydrochloric acid, adjusting pH to 3.0 and diluting 1000 ml with water. The temperature of dissolution media was maintained at 37 ± 0.5˚C. The paddle rotation speed was kept at 75 rpm. 1 ml aliquot of sample was withdrawn at 5, 10, 15, 20, 25, 30 min and replaced by 1ml of fresh dissolution media (pH 3.0). The collected samples were analyzed after filtration at 263 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate.

2.5.4 Fourier transforms infrared (FTIR) spectroscopy
Fourier transform infrared (FTIR) spectra of pure drug β-Cyclodextrin and solid dispersion (SE2) were recorded on Bruker (alpha E). The scanning range was 4000 -400 cm^{-1} and the resolution was 4 cm^{-1}.

2.5.5 Scanning electron microscopy (SEM)
The morphology of cefpodoxime proxetil β-cyclodextrin and solid dispersion were determined using a scanning electron microscope (SEM) operated at an accelerating voltage of 3Kv.Sample were prepared by mounting powder on to a brass stub using graphite glue and coated with gold under vacuum before use.

2.6 Preparation of Dispersible Tablet
The tablets containing selected solid dispersion (SE2) were prepared by using single punch machine to produce tablets weighing 500mg. Each tablets contained solid dispersion 300mg equivalent to 100mg of cefpodoxime proxetil. Tablets were prepared with croscarmellose sodium as superdisintegrant. The concentration of superdisintegrant varied from 1-5% in tablet formulations. The mixed blend of drug and excipients was prepared for a total of 20 tablets for each formulation (F1-F5).

Table 2.6: Composition of Tablet.

Ingredients	F1	F2	F3	F4	F5
SE2 (1:2) Dose (100mg)	300	300	300	300	300
CCS	5	10	15	20	25
MCC	65	70	75	80	85
Lactose	90	85	80	75	70
Mg.Stearte	20	20	20	20	20
Talc	20	20	20	20	20

2.7 Evaluation parameter

2.7.1 Precompression parameters [121-122]

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of the blend produced. The characterization of mixed blend was performed to find out the flow property of powders. Bulk density, tapped density, Hausner's ratio, Compressibility index and angle of repose have also been determined.

2.7.2 Bulk density

Bulk density is defined as the mass of blend in the measuring cylinder divided by the bulk volume and is expressed as g/cm^3. Apparent bulk densitywas determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho_b = \frac{M}{V_b} \quad \text{.....eq (2)}$$

2.7.3 Tapped density

Tapped density can be defined as mass of blend in the measuring cylinder divided by its tapped volume. The measuring cylinder containing a known mass of blend was tapped 100 times using density apparatus. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula.

$$\rho_t = \frac{M}{V_t} \quad \text{.....eq (3)}$$

2.7.4Compressibility index

The simplest way for measurement of flow of powder is its compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows.

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100 \quad \text{.....eq (4)}$$

Where, ρ_t = Tapped density, ρ_b= Bulk density

Table: 2.7 Compressibility index as an indication of powder flowProperties.

Carr's Index (%)	Type of flow
<12	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

2.7.4 Hausner's ratio

Hausner's ratio (H_r) is an indirect index of ease of powder flow. It is calculated by the following formula

$$Hr = \frac{\rho t}{\rho b} \quad \text{.....eq(5)}$$

Where, ρ_t is tapped density and ρ_b is bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (> 1.25).

2.7.5 Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula.

$$\tan\theta = \frac{h}{r};$$

Therefore;

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{.....eq (6)}$$

Table 2.8: Angle of repose as an indication of powder flow properties.

Angle of repose(^{o})	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

4.8 Post compression parameter [123-126]

After compression of powder, the tablets were evaluated for organoleptic characteristics like odor, color, taste, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time and dissolution studies.

2.8.1 General appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. This includes tablets size, shape, colour, presence or absence of an odour, surface texture, physical flaws, consistency and legibility of any identifying marking.

2.8.2 Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer (Mityato, Japan).

2.8.3 Uniformity of weight

As per IP, twenty tablets were taken and weighed individually and collectively using digital balance. The average weight of one tablet was calculated. The weight

variation test would be satisfactory method of determining the drug content uniformity.

Table: 2.9 Weight variation limits for tablets as per IP.

Average of Tablets (mg)	Maximum % difference allowed
80 or less	10
80-250	7.5
More than 250	5

2.8.4 Tablet hardness

It can be defined as the force required per unit area to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage transformation and handling before usage depends on its hardness. Hardness of the tablets was determined by using Pfizer tester.

2.8.5 Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping the tablets at a height of 6 inches in each revolution. Reweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were redusted using a soft muslin cloth and reweighed. The friability (%F) is determined by the formula.

$$\%F = (1 - \frac{W}{W_0}) \times 100 \ldots\ldots\ldots\ldots \text{eq(7)}$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

2.8.6 Disintegration test

Modified method: Disintegration of dispersible tablets is achieved by the action of the media in which tablet is put before administration. No tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets.

A cylindrical vessel was used in which 10-meshscreen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of distilled water was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

2.8.7 *In- vitro* dissolution study

The *in vitro* dissolution study was carried out in USP Dissolution test apparatus, type 2(paddle type).900 ml of solution by dissolving 3.03 g of glycine and 3.37 g of sodium chloride in about 500 ml of water, adding cautiously with swirling 0.8 ml of hydrochloric acid, adjusting pH to 3.0 and diluting 1000 ml with water.The temperature of dissolution media was maintained at 37 ± 0.5˚C. The paddle rotation speed was kept at 75 rpm. 1 ml aliquot of sample was withdrawn at 5, 10, 15, 20, 25, 30 min and replaced by 1ml of fresh dissolution media (pH 3.0). The collected samples were analyzed after filtration at 263 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate.

2.9 Comparision With Marketed Tablets

Various parameters like thickness, hardness, average weight, disintegration time, drug content were determined and compared with conventional marketed tablets.

2.9.1 In-*vitro* drug release of selected batch and comparison with marketed tablets

The comparison of the dissolution release of the selected optimized batch tablets and the marketed tablets (xyz) was determined using modified dissolution method. The in vitro dissolution study was carried out in USP Dissolution test apparatus, type 2(paddle type). 900 ml of pH 3.0 buffer was used as dissolution medium. The temperature of dissolution media was maintained at 37 ± 0.5˚C. The paddle rotation speed was kept at 75 rpm. 1 ml aliquot of sample was withdrawn at 5, 10, 15, 20, 25, 30 min and replaced by 1ml of fresh dissolution media (pH 3.0). The collected samples were analyzed after filtration at 263 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate and cumulative percentage drug release was calculated.

2.10 Stability Studies

The optimized cefpodoxime proxetil dispersible tablet were packed in wide mouth air tight glass container and stored at (40 ± 2 ˚C and 75 ± 5 % RH) for a period of 3 months.

Then tablets were checked for its release properties.

RESULT AND DISCUSSION

3 .1 Preformulation Studies

3.1.1 Physical Appearance

Physical appearance was found to be in agreement with pure drug of cefpodoxime proxetil given in the literature.

Table 3.1: Physical Appearance.

Color	A pale yellow color
Odour	Faint in odor
Taste	Bitter
Physical form	Powder

3.1.2 Melting Point Determination

The melting point of cefpodoxime proxetil determined by capillary fusion method was in the range of 111-113^{0}C as given in table5.2.

Table 3.2 Melting Point Determination.

DRUG	EXPERIMENTAL VALUE	LITERATURE VALUE
CEFPODOXIME PROXETIL	109-112^{0}C	111-113^{0}C

3.1.2 Absoption Maxima (λ_{max}) Of Pure Drug

(a) Determination of absorption maxima (λ_{max}) in methanol

The absorption maximum (λ_{max}) of cefpodoxime proxetil in methanol was found to be 235 nm and spectrum has been shown (Fig 5.1), which is in the close vicinity of maxima reported in literature.

Fig. 3.1: Scan graph of cefpodoxime proxetil in methanol.

3.1.4 a) Determination of absorption maxima (λ_{max}) in phosphate buffer (6.8)

The absorption maximum (λ_{max}) of cefpodoxime proxetil in phosphate buffer (6.8) was found to be 232 nm and spectrum has been shown (Fig 5.2), which is in the close vicinity of maxima reported in literature.

Fig. 3.2: Scan graph of cefpodoxime proxetil in phosphate buffer 6.8.

3.1.4 b) Determination of absorption maxima (λ_{max}) in pH 3.0 buffer

The absorption maximum (λ_{max}) of cefpodoxime proxetil in pH 3.0 was found to be 263 nm and spectrum has been shown (Fig3.3), which is in the close vicinity of maxima reported in literature.

Fig. 3.3: Scan graph of cefpodoxime proxetil in pH 3.0 buffer.

3.1.4 c) Determination of absorption maxima (λ_{max}) in distilled water

The absorption maximum (λ_{max}) of cefpodoxime proxetil in distilled water was found to be 230 nm and spectrum has been shown (Fig 5.4), which is in the close vicinity of maxima reported in literature.

Fig. 3.4: Scan graph of cefpodoxime proxetil in distilled water.

3.1.5 Preparation of Calibration Curves

The calibration curve of cefpodoxime proxetil was found to be linear in the concentration range of 2-20µg/ml in methanol. The absorbance of cefpodoxime proxetil is shown in table and graph is represented in figure respectively.

Table 3.3 Calibration data of cefpodoxime proxetil in methanol.

Concentration (µg/ml)	Mean Absorbance± SD
0	0
2	0.286± 0.036
4	0.423± 0.032
6	0.450± 0.021
8	0.529± 0.025
10	0.612± 0.025
12	0.699± 0.024
14	0.757± 0.045
16	0.849± 0.015
18	0.892±0.023
20	0.995±0.024

Data expressed as mean ±SD (n=3)

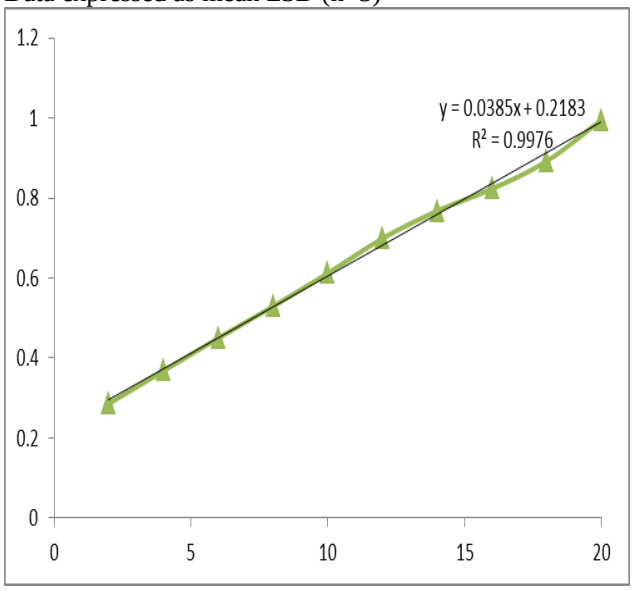

Fig. 3.5: Standard curve of cefpodoxime proxetil in methanol.

Table 3.4 Calibration data of cefpodoxime proxetil in phosphate buffer (pH 6.8).

Concentration (µg/ml)	Mean absorbance ± SD
0	0
20	0.156± 0.023
40	0.286± 0.040
60	0.484± 0.016
80	0.579± 0.011
100	0.707± 0.021
120	0.816± 0.011
140	0.962± 0.011

Data expressed as mean±SD (n=3)

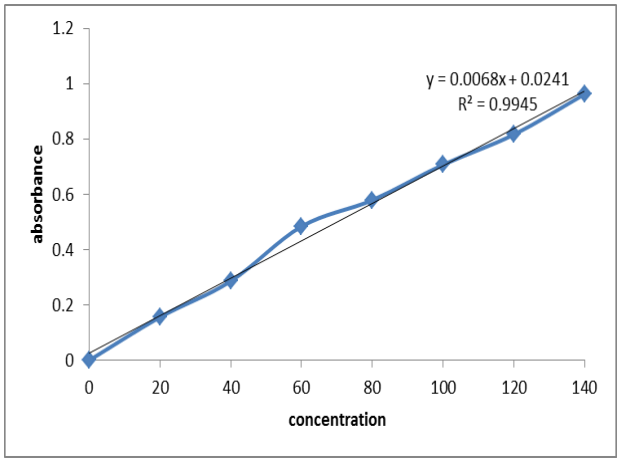

Fig. 3.6: Standard curve of cefpodoxime proxetil in phosphate buffer (pH 6.8)

Table 5.5 Calibration data cefpodoxime proxetil in distilled water.

Concentration	Mean absorbance± SD
5	0.145 ± 0.012
10	0.262± 0.012
15	0.458 ± 0.010
20	0.594 ± 0.016
25	0.723 ± 0.006
30	0.823 ± 0.015

Data expressed as mean ±SD of three experiments

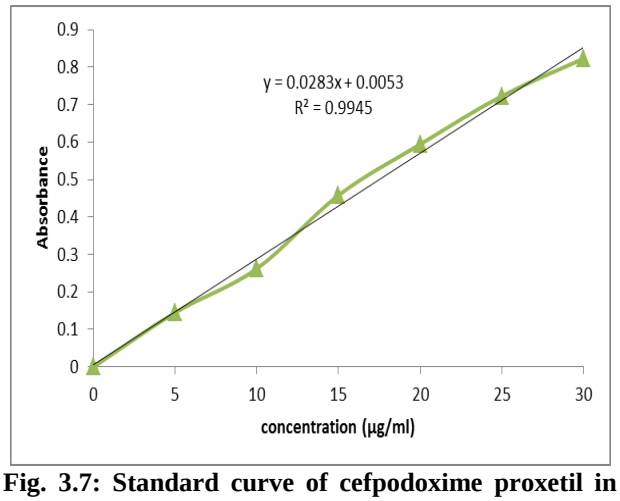

Fig. 3.7: Standard curve of cefpodoxime proxetil in distilled water.

Table 3.6 Calibration data of cefpodoxime proxetil in pH 3.0.

Concentration (µg/ml)	Mean Absorbance± SD
0	0
2	0.130± 0.036
4	0.220± 0.032
6	0.349± 0.021
8	0.436± 0.025
10	0.543± 0.025
12	0.642± 0.024
14	0.739± 0.045
16	0.823± 0.015
18	0.923±0.023
20	0.975±0.024

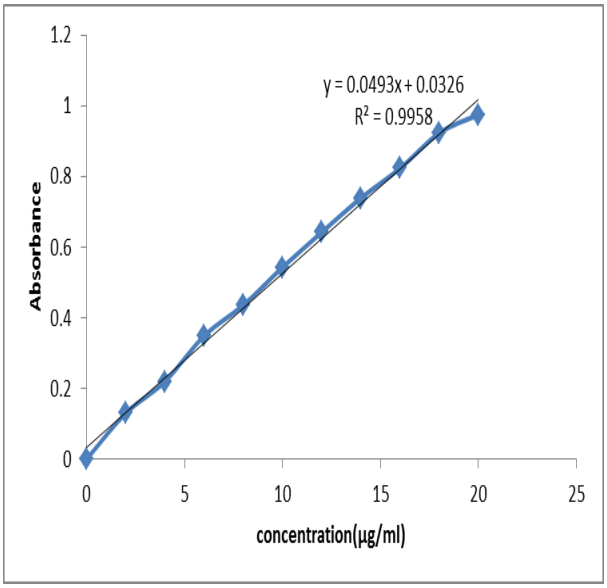

Fig. 5.8: Standard curve of cefpodoxime proxetil in pH 3.0.

3.1.6 Ft-Ir Spectrum Of Pure Drug

Cefpodoxime proxetil identified by infra –red spectra which were compared with its standard IR. The IR spectra as shown in fig that the peaks obtained in the test spectrum were similar to that given in standard spectra.

The IR spectrum of cefpodoxime proxetil revealed the presence of characteristic peak at 3420 cm^{-1}due to N-H stretching while peaks at 2943cm^{-1} is due to alkyl stretching. Strong absorption peak absorbed at 1675cm^{-1} was assigned due to carbonyl stretching. A peak at 1534 and 1034cm^{-1} indicates the sulphonyl group and alkene group.

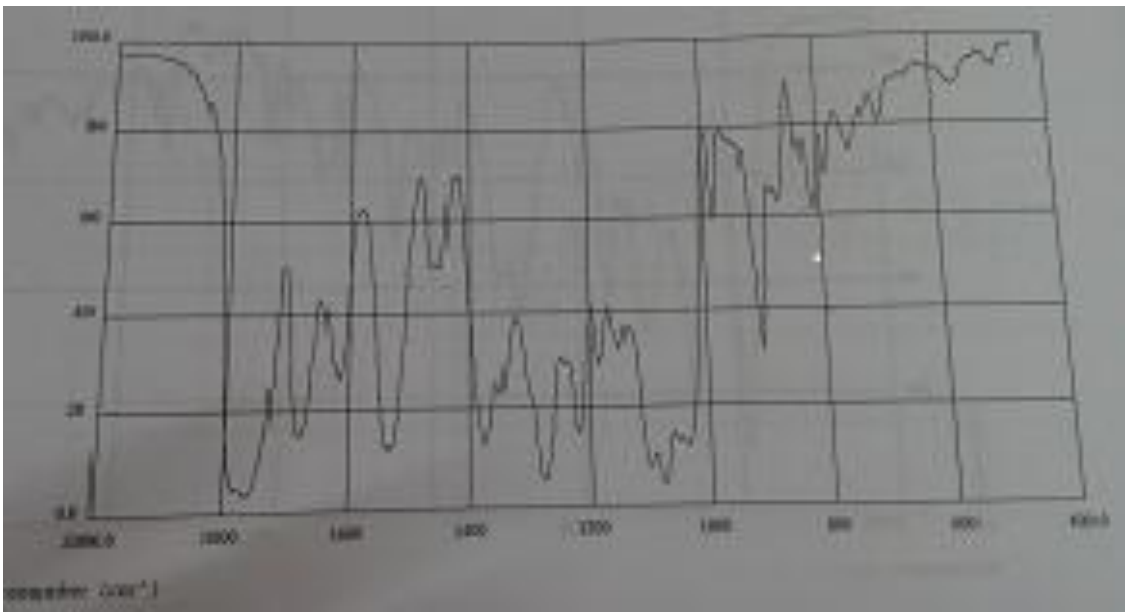

Fig. 3.9: Official FTIR spectra of cefpodoxime proxetil in IP 2010.

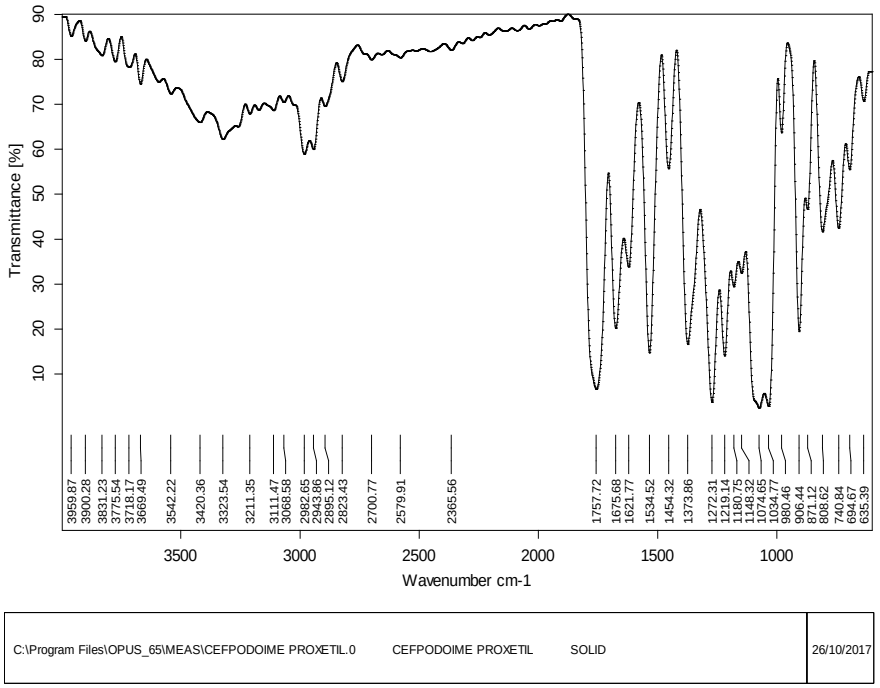

Fig. 3.10: FTIR of cefpodoxime proxetil.

Table 3.7 Peak value of cefpodoxime proxetil from FTIR.

Peak assignment	**Cefpodoxime proxetil (cm^{-1})**
N-H stretching	3420
C-H (alkene) aromatic Stretching	1534
C-N stretching	1219
C=O	1675
-CH_3stretching	2943
C-S-C stretching	1034

3.1.7 Drug –Excipient Compatibility Studies

No discoloration, liquification and clump formation was observed in the physical mixture of drug and excipient. This clarifies that there is no interaction between cefpodoxime proxetil and β-cyclodextrin. FTIR studies also proved no interaction between drug and β-cyclodextrin because all the major peaks of pure drug and β-cyclodextrin were retained in the physical mixture of highest ratio (1:2) as shown in figure 3.11.

Table 3.8 Drug–polymer compatibility studies.

Drug/ Drug +polymer	**Observed Physical Appearance**					**FTIR (cm^{-1})**
	0 Week	**1 Week**	**2 Week**	**3 Week**	**4 Week**	
	1:2	1:2	1:2	1:2	1:2	1677, 2942, 1219, 1534, 1036, 3320
Drug	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder	
Drug+polymer	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder	Pale yellow powder	1674, 2933, 1219, 1534, 1029, 3326

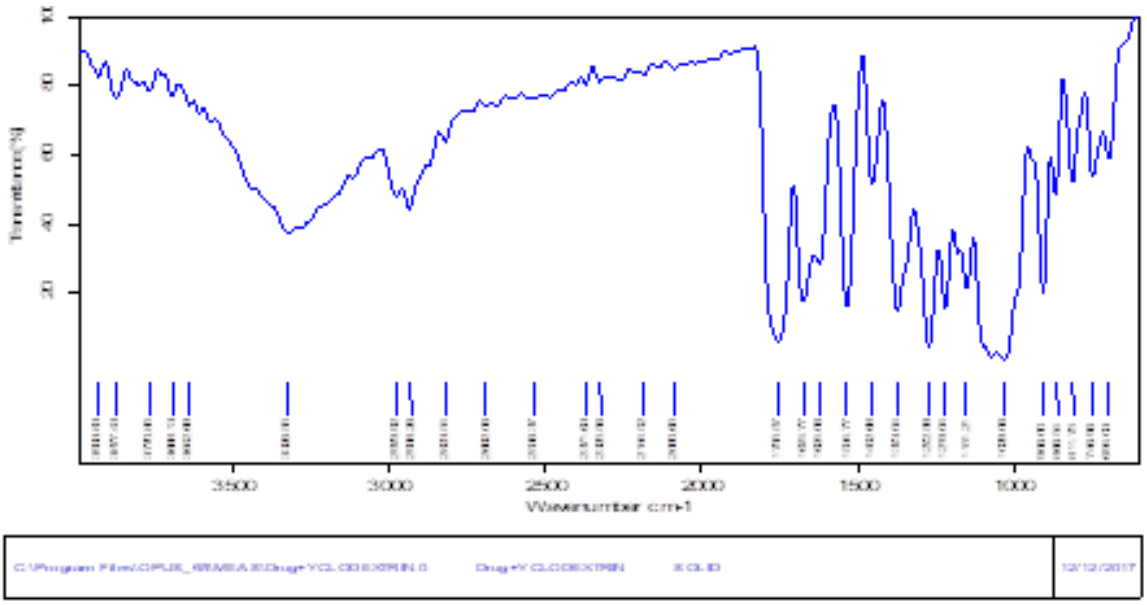

Fig. 5.11: FTIR spectra of drug and polymer.

3.2 Characterization of Solid Dispersion

3.2.1 Percentage Yield

The percentage yield and percent drug content of all solid dispersions prepared by physical mixture, kneading method and solvent evaporation methods were determined. The results of % drug content were shown in table5.9Respectively**.**

Table: 3.9 Percentage yield and drug content of solid dispersions of physical mixture.

Formulation code	Percentage(%) yield	% Drug content
PM1	85±0.123	70± 0.212
PM2	88 ±0.147	83±0.215
PM3	90±0.176	90±0.221

Table: 3.10 Percentage yield and drug content of solid dispersions of kneading method.

Formulation code	Percentage(%) yield	% Drug content
KN1	80 ±0.176	73±0.167
KN2	82 ±0.188	87±0.235
KN3	85±0.193	92±0.165

Table: 3.11Percentage yield and drug content of solid dispersions of solvent evaporation method.

Formulation code	Percentage(%) yield	% Drug content
SE1	82 ±0.182	75±0.321
SE2	86±0.180	88±0.236
SE3	89±0.185	93±0.321

The % yield of solid dispersions was found to be promising approx. 90% for all batches. This showed that physical mixture, kneading method and solvent evaporation methods are efficient for the preparation of solid dispersions. The % drug content of cefpodoxime proxetil prepared by kneading and solvent evaporation lies between 85%-90% and low value of standard deviation in the % drug content indicated the uniform distribution of drug in all the solid dispersions.

3.2.3 Saturation solubility studies

Solubility data of pure drug and solid dispersion in distilled water at 37±2^{O}C is shown in table respectively and graph is represented in figure 3.12-3.15.

Table: 3.12 Solubility data of pure drug and solid dispersions of physical mixture in pH 3.0 buffer at 37±2 ^{O}C.

Formulation code	Solubility(mg/ml)
Pure	0.00494±0.001
PM1	0.040±0.003
PM2	0.170±0.005
PM3	0.123±0.006

Data expressed as mean±SD (n=3)

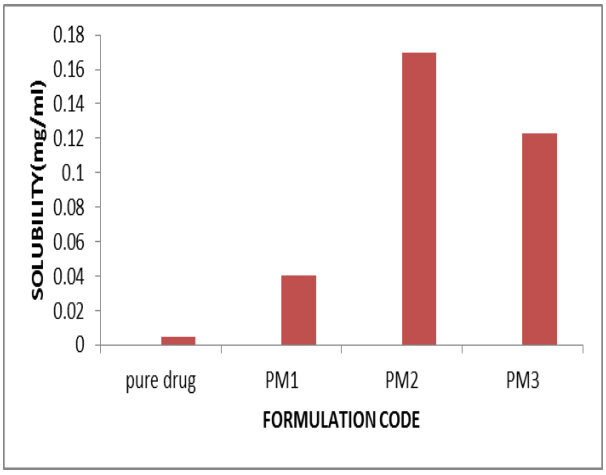

Fig: 3.12 Solubility plot of different of physical mixtures of cefpodoxime proxetil.

Table: 3.13 Solubility data of pure drug and solid dispersions of kneading method in pH 3.0 buffer at 37±2 ^{O}C

Formulation code	Solubility(mg/ml)
Pure	0.00494±0.001
KN1	0.064±0.006
KN2	0.179±0.005
KN3	0.164±0.006

Data expressed as mean ±SD (n=3)

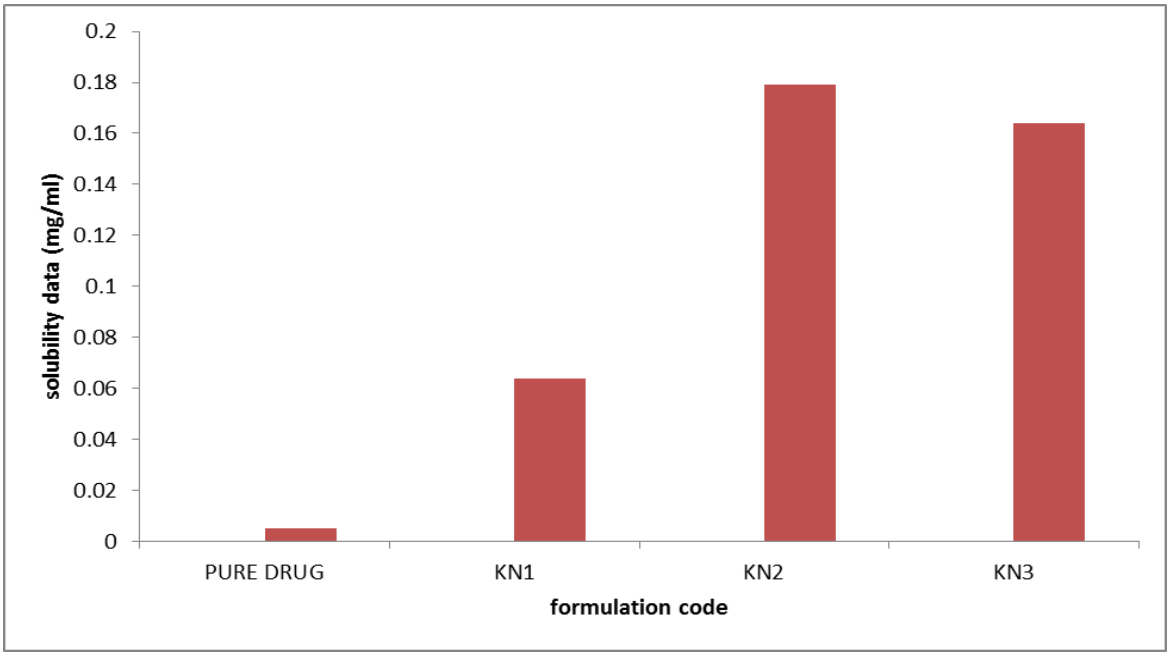

Fig: 3.13 Solubility plot of cefpodoxime proxetil and solid dispersion prepared by kneading method

Table: 3.14 Solubility data of pure drug and solid dispersions of solvent evaporation method in pH 3.0 buffer at 37±2 ^{O}C.

Formulation code	Solubility(mg/ml)
Pure	0.00494±0.001
SE1	0.093±0.004
SE2	0.210±0.007
SE3	0.192±0.008

Data expressed as mean ±SD (n=3)

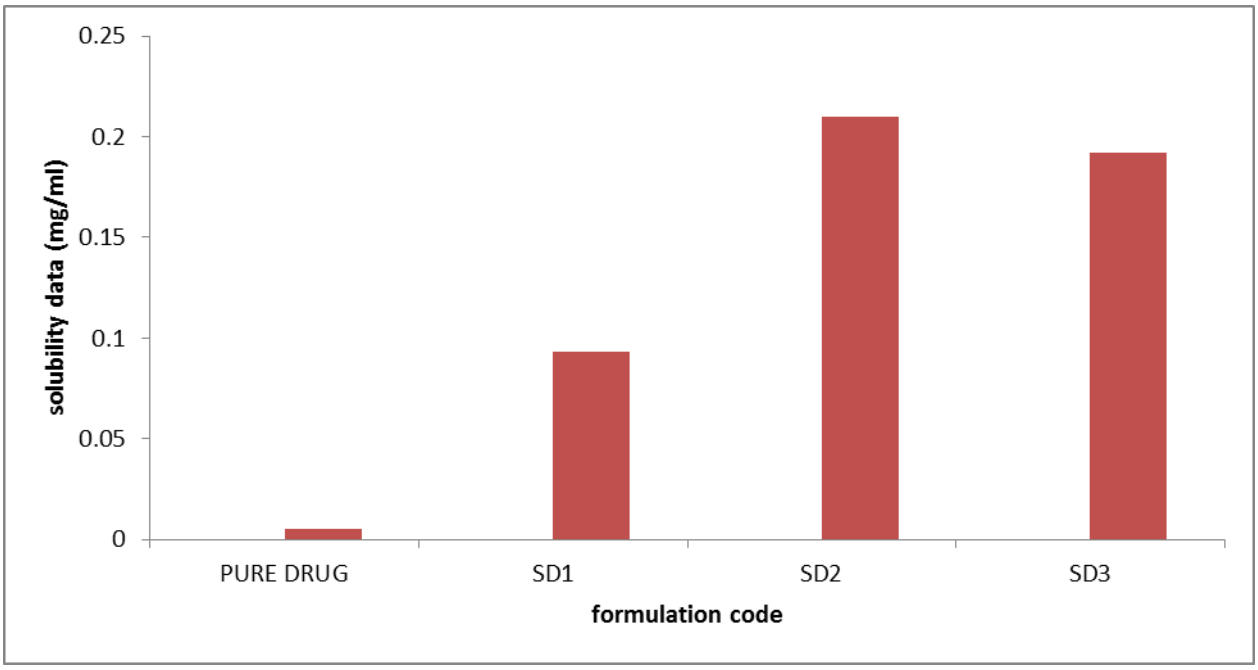

Fig: 3.15 Solubility plots of cefpodoxime proxetil and solid dispersion prepared by solvent evaporation method

3.2.3 Dissolution Release Profile

The dissolution profile of pure drug and solid dispersions were carried out in pH 3.0 buffer. Dissolution release values are shown in table3 .15- 3.17. From the data, it is evident that the onset of dissolution of pure drug was very low. The dissolution release from pure drug was only 36% in 60 min. Therefore, this release suggested a strong need to enhance the solubility of pure drug. The presence of β- Cyclodextrinincreases the solubility of pure drug as well as dissolution from the solid dispersion, which increases the dissolution rate as shown in figure. This is clear from the dissolution studies that the solid dispersion (1:2) of cefpodoxime proxetil: β-Cyclodextringives fastest dissolution of drug as compared to other formulations. The release profile showed two different phases of drug release. An initial rapid phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process medium by β-Cyclodextrin. Solid dispersion technique has improved the dissolution rate of cefpodoxime proxetil to greater extent.

Table: 3.15 Dissolution release profile of pure drug and from solid dispersion of physical mixture

Time	Pure Drug	PM1	PM2	PM3
0	0	0	0	0
5	9.10±0.40	27.98±0.20	50.67±0.12	50.12±0.26
10	10.24±0.14	34.35±0.38	52.68±0.18	53.63±0.56
15	12.62±0.35	42.53±0.68	55.06±0.23	56.64±0.63
20	13.35±0.72	49.62±0.73	57.07±0.20	59.04±0.45
25	15.54±0.16	52.31±0.67	61.46±0.43	63.65±0.38
30	19.57±0.38	55.77±0.58	64.02±0.48	66.03±0.14
35	20.48±0.23	56.72±0.23	66.22±0.73	69.9±0.16
40	21.58±0.79	58.7±0.16	71.15±0.34	70.13±0.25
45	22.86±0.18	60±0.19	77.01±0.28	74.62±0.26
50	24.87±0.63	61.46±0.56	78.65±0.13	77.6±0.18
55	29.45±0.48	63.46±0.32	83.41±0.12	80.02±0.23
60	36.21±0.20	64.39±0.16	86.34±0.06	84.65±0.09

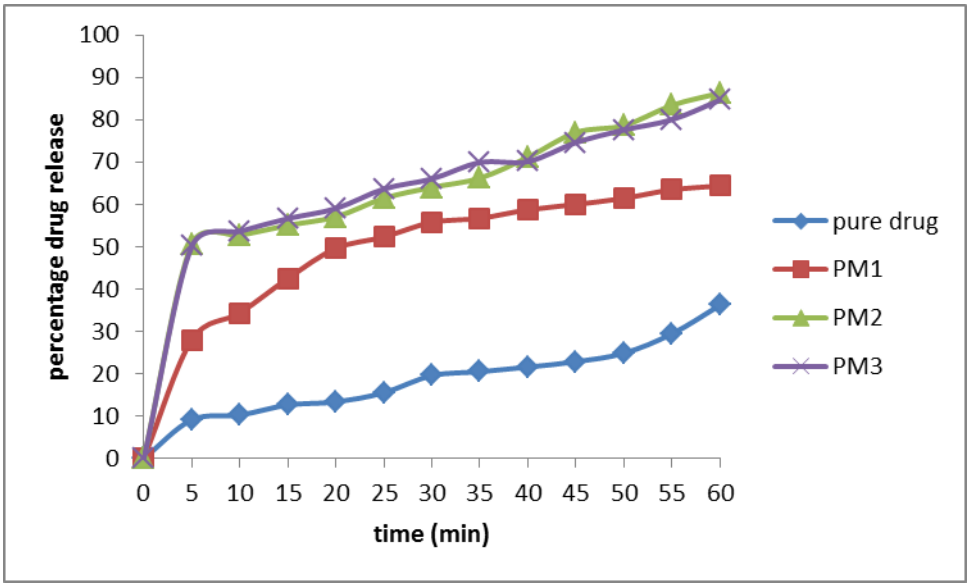

Figure: 3.15 Percent release of pure drug and solid dispersion of physical mixture method.

Table: 3.16 Dissolution release profile of pure drug and from solid dispersion of kneading method.

Time	Pure drug	KN1	KN2	KN3
0	0	0	0	0
5	9.10 ±0.40	11.6±0.48	15.38±0.38	18.32±0.19
10	10.24±0.14	15.36±0.26	17.23±0.25	22.54±0.64
15	12.62±0.35	18.63±0.78	22.43±0.16	28.75±0.52
20	13.35±0.72	20.54±0.34	26.5±0.73	34.09±0.23
25	15.54±0.16	23.54±0.32	30.53±0.18	40.08±0.18
30	19.57±0.38	26.62±0.62	34.2±0.82	46.77±0.32
35	20.48±0.23	30.64±0.32	42.54±0.56	51.23±0.76
40	21.58±0.79	36.5±0.23	48.76±0.23	57.32±0.13
45	22.86±0.18	40.74±0.40	51.47±1.28	62.3±0.53
50	24.87±0.63	46.57±0.11	58.43±0.28	66.39±1.21
55	29.45±0.48	51.3±0.84	65.54±0.20	68.23±0.86
60	36.21±0.20	58.03±0.16	72.54±0.06	70.31±0.20

Data expressed as mean±SD (n=3)

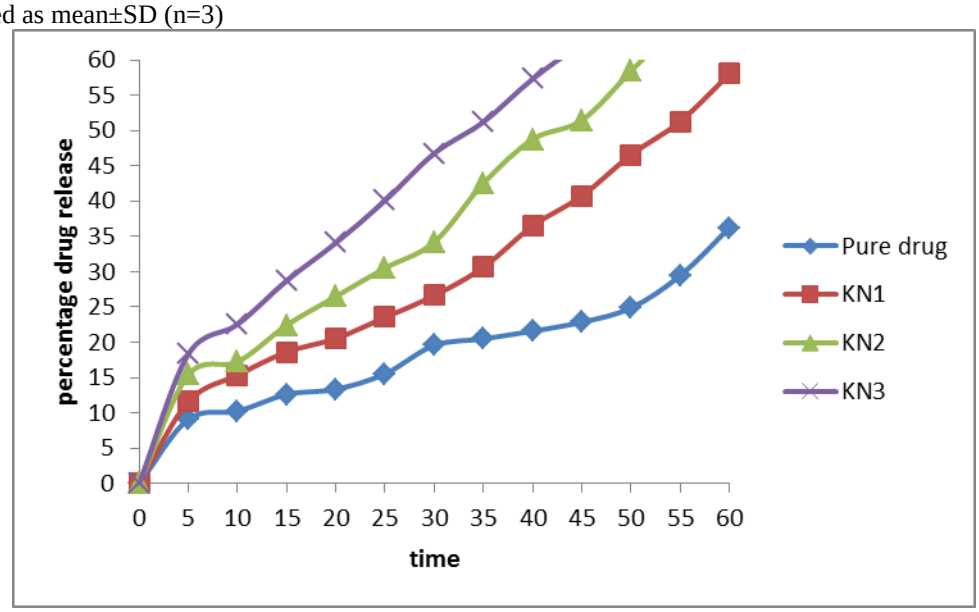

Figure: 3.16 Percent release of pure drug and solid dispersion of kneading method.

Table: 3.17 Dissolution release profile of pure drug and from solid dispersion of Solvent evaporation method.

Time	Pure drug	SE1	SE2	SE3
0	0	0	0	0
5	9.10 ±0.40	12.42±0.32	15.34±0.23	18.56±0.40
10	10.24±0.14	14.34±0.43	17.56±0.22	22.57±1.30
15	12.62±0.35	18.67±0.32	25.65±0.15	27.65±0.12
20	13.35±0.72	24.42±0.40	29.45±0.13	32.45±0.45
25	15.54±0.16	33.56±0.25	34.56±0.12	39.76±0.32
30	19.57±0.38	38.57±0.23	39.57±0.32	46.5±0.18
35	20.48±0.23	47.65±0.32	48.65±0.14	52.34±0.32
40	21.58±0.79	58.56±0.30	59.65±0.17	60.34±0.28
45	22.86±0.18	62.34±0.66	64.56±0.55	63.54±0.26
50	24.87±0.63	66.76±0.80	75.54±0.20	72.35±0.46
55	29.45±0.48	70.34±0.14	84.34±0.18	80.09±0.86
60	36.21±0.20	74.34±0.12	90±0.06	86.52±0.20

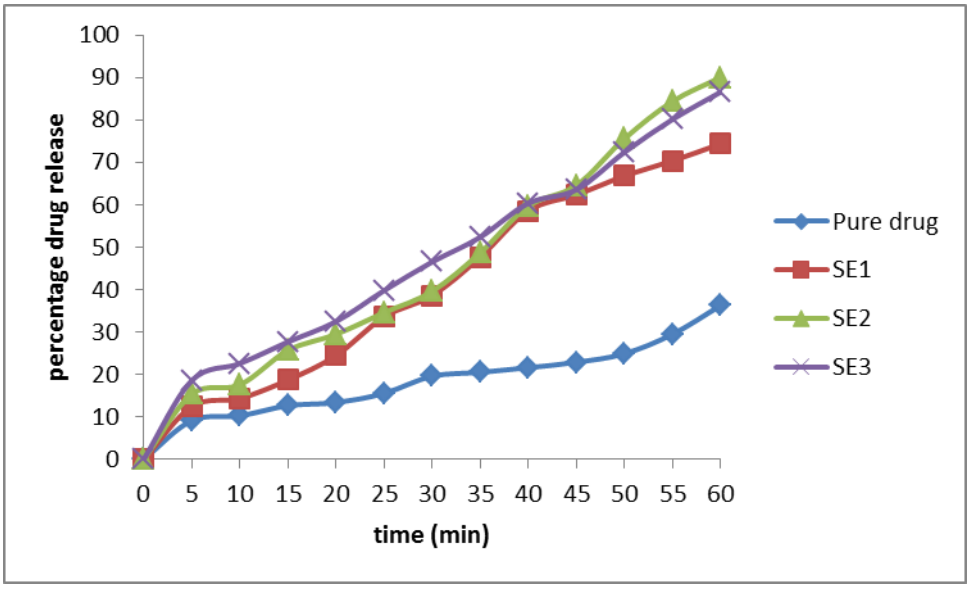

Figure: 3.17 Percent release of pure drug and solid dispersion of solvent evaporation method.

SEM (Scanning electron photomicrograph)

The SEM images for Cefpodoxime proxetil beta-Cyclodextrin and solid dispersion SD are shown in fig. The drug powder consisted of irregular rod like crystals and this rod shaped crystals leads to very poor flow and compression difficulties. The prepared solid dispersion agglomerates were spherical to larger extent and remaining was irregular in shape with smooth surface, which enabled them to flow very easily. In case of solid dispersion SEM images the cefpodoxime proxetil crystals appeared to be incorporated into particles of the beta- Cyclodextrin.

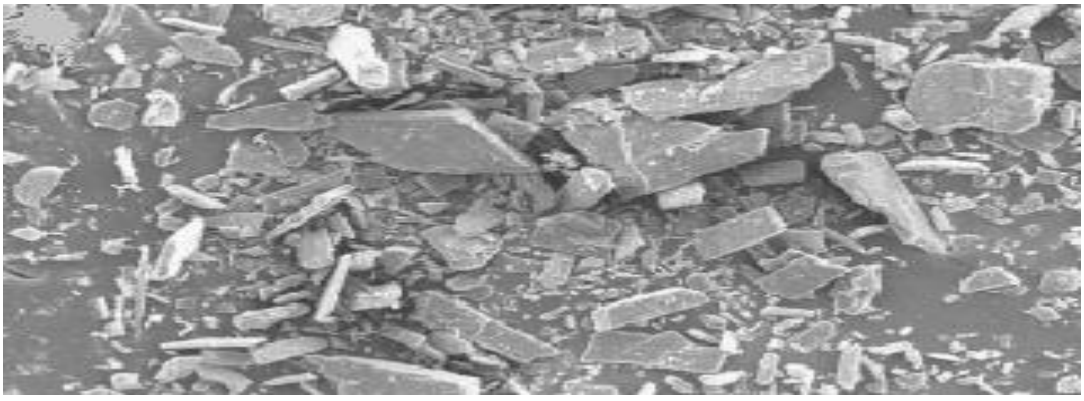

Fig 3.18 SEM images of cefpodoxime proxetil

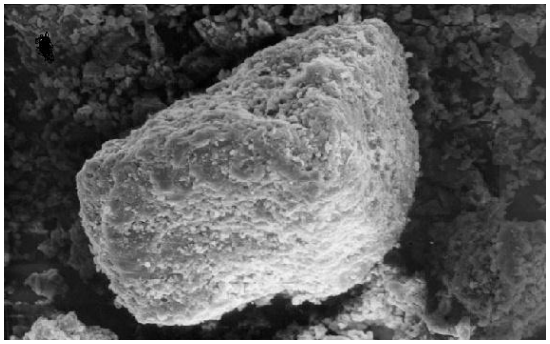

Fig. 3.19 SEM images of beta-Cyclodextrin.

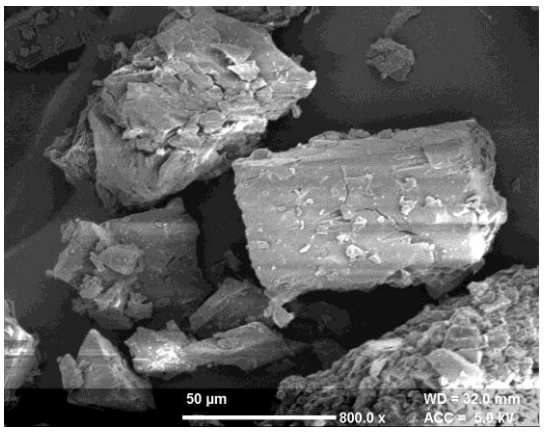

Fig: 3.20 SEM Images of SE(1:2) prepared by solvent evaporation method

Characterization of Blends

Table 3.18: Characterization of blends (Pre-compression parameters).

Formulation codes	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose(°)
F1	0.72±0.009	0.82±0.004	1.02±0.003	14.34±0.068	25.04±0.962
F2	0.74±0.014	0.86±0.009	1.09±0.013	14.09±0.732	24.18±0.432
F3	0.70±0.030	0.84±0.023	1.13±0.019	15.45±1.230	23.09±0.642
F4	0.73±0.012	0.88±0.016	1.15±0.014	16.68±0.765	25.54±0.0698
F5	0.76±0.031	0.90±0.011	1.17±0.018	17.57±0.892	27.72±0.772

Data expressedas mean±SD (n=3)

Table 3.19: Characterization of dispersible tablets (Post-compression parameters).

Formulation Codes	Average Weight(mg)	Thickness(mm)	Hardness(kg/cm^2)	Friability(%)
F1	480.7±0.24	3.60±0.026	2.9±0.05	0.78±0.03
F2	489.3±0.23	3.50±0.36	3.2±0.06	0.80±0.02
F3	500.8±0.32	4.02±0.38	3.5±0.8	0.75±0.04
F4	496.4±0.24	3.63±0.23	3.6±0.03	0.69±0.05
F5	502.8±0.20	3.94±0.34	3.2±0.05	0.82±0.04

Data expressed as mean±SD (n=3)

Table 3.20: Characterization of dispersible tablet.

Formulation Codes	Disintegration Time(sec) pH 3.0 buffer	Drug Content (%)
F1	185.27±0.47	82.14±0.34
F2	170.30±1.25	86.17±0.40
F3	160.23±1.24	88.85±0.93
F4	156.20±0.82	90.14±0.62
F5	90±1.24	96.14±0.83

Data expressed as mean ±SD (n=3)

Table: 3.21 In vitro drug release study.

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	22.34±0.32	24.13±0.20	26.18±0.36	28.16±0.28	30.12±0.56
10	30.56±0.47	32.06±0.24	34.1±0.28	36.13±0.63	42.13±0.65
15	42.06±0.42	44.09±0.28	47.12±0.18	50.09±0.56	55.03±0.23
20	54.09±0.23	56.08±0.32	60.23±0.20	62.14±0.39	66.7±0.58
25	63.19±0.16	66.08±0.20	70.08±0.25	72.07±0.18	78.82±0.78
30	70.23±0.09	76.03±0.011	80.04±0.04	85.43±0.03	96.12±0.002

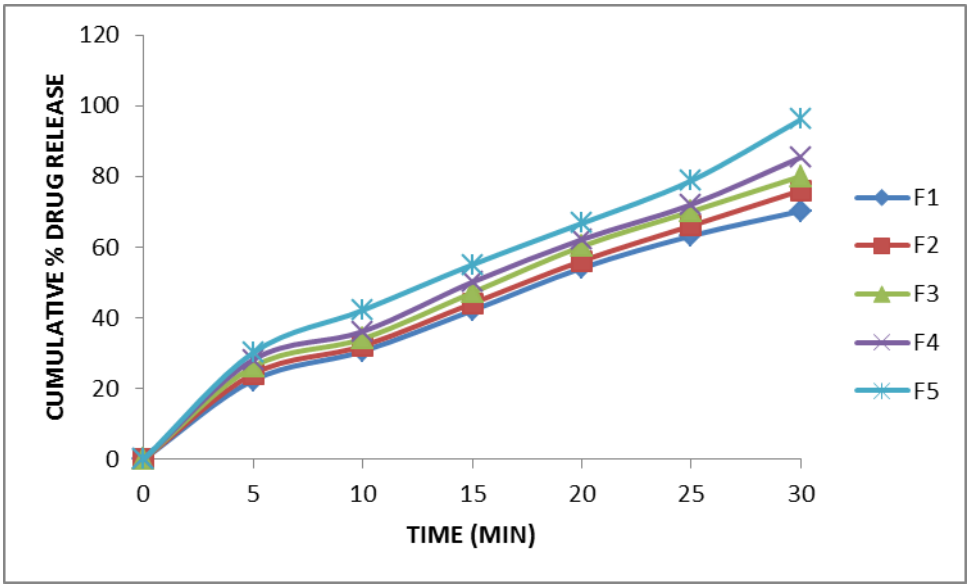

Fig: 5.21 In vitro drug release study

Comparison With Marketed Tablets

Various parameters such as weight variation, thickness, hardness, drug content were determined and compared with conventional marketed tablet-cefpodoxime proxetil dispersible tablets.

Table 3.22: SE2 formulation and marketed formulation.

Parameters	SE Formulation	Marketed formulation
Avg. weight (mg)	502±0.20	498.20±0.23
Thickness (mm)	3.94±0.34	3.9±0.5
Hardness (kg/sq.cm)	3.2±0.05	3.2±0.5
Drug content (%)	96.14± 0.83	90.87±0.23
Disintegration time(sec)	90.00±1.24	160±0.43
Friability(%)	0.82±0.04	0.80±0.56

***In-vitro* drug release of SE2 (1:2) formulation and comparison with marketed tablets (cefpodoxime proxetil dispersible tablet**).

Table 3.23: Comparativerelease data with marketed formulation.

Time (min)	% Drug cumulative Released of SD Formulation	% Drug cumulative Released of Marketed Formulation
5	30.12 ±0.56	28.80±0.59
10	42.13±0.65	35.12±0.19
15	55.03±0.23	42.08±0.51
20	66.07±0.52	52.03±0.20
25	78.82±0.78	60.40±0.11
30	96.12±0.002	73.06±0.18

Data expressed as mean ±SD (n=3)

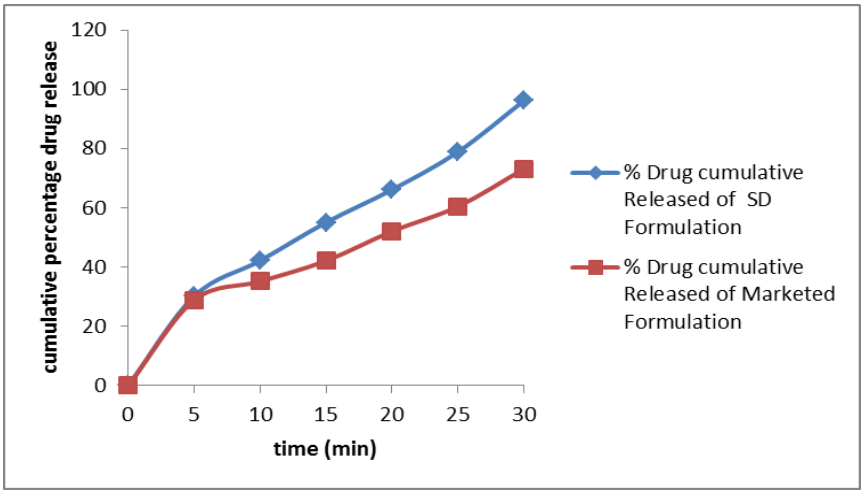

Figure: 3.25 Cumulative Percent drug release curve for optimized tablets and marketed tablets

Stability Studies

Table 3.24: Effect of storage conditions on optimized tablets.

No. of days	Avg. weight (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)	Drug Content (%)
0	502±0.99	3.9±0.1	0.82±0.051	90±1.24	96.14±0.312
15	500±0.76	3.8±0.1	0.80±0.033	92±1.09	96.04±0.017
30	498±0.85	3.9±0.2	0.83±0.072	90±1.55	96.32±0.009
45	499±1.24	3.6±0.2	0.82±0.043	89±1.10	96.20±0.014
60	498±0.31	3.9±0.2	0.81±0.069	90±1.44	96.28±0.021
75	500.03±0.92	3.8±0.3	0.79±0.088	92±1.12	96.10±0.015
90	499±0.38	3.9±0.3	0.82±0.092	90±1.57	96.15±0.008

Data expressed as mean±SD (n=3)

Table: 3.25Comparison of drug release data before and after storage

Time(min)	Percent Drug Released ± S.D.	
	Initial	After stability studies
0	0	0
5	30.12±0.56	29.06±0.40
10	42.13±0.65	41.34±0.73
15	55.03±0.23	53.30±0.36
20	66.07±0.52	64.12±0.48
25	78.82±0.78	77.24±0.65
30	96.12±0.002	94.24±0.34

Data expressed as mean ±SD (n=3)

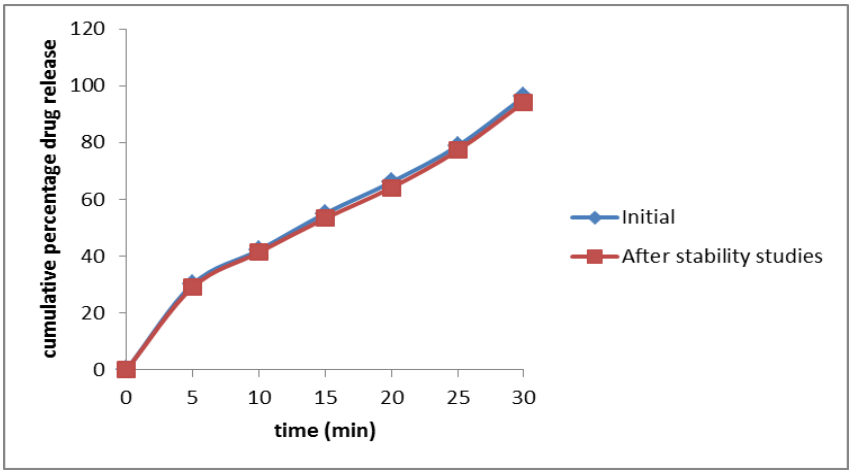

Figure: 3.26 Comparison of drug release before and after stability

CONCLUSION

In this work an attempt was made to increase the solubility of the BCS class IV drugs. There are numbers of drugs which are under BCS IV class having poor solubility with poor permeability, poor dissolution and ultimately which leads to have poor bioavailability. So it is difficult to formulate this type of dosage form because they show maximum side effects and also have therapeutic effects. So, solid dispersion is one of the most widely used techniques to enhance the solubility of poorly water soluble drugs. Various techniques are available for the preparation of solid dispersions like solvent evaporation , melt method, spray drying melt extrusion method , Lyophilization method etc.

Cefpodoxime proxetil is an orally administered broad spectrum third-generation cephalosporin. It is a pro-drug that is de-esterified *to* cefpodoxime, which has potent antibacterial activity. It is generally well tolerated and demonstrates good therapeutic potential in patients with various common bacterial infections. This compound has been used most widely in the management of infections of the respiratory and urinary tracts as well as those of the skin structure, acute otitis media, pharyngitis, tonsillitis etc. cefpodoxime proxetil were selected as the model drugs for the research work because they have poor aqueous solubility. So it is necessary to increase the water solubility of the drug for the therapeutic purpose. Beta –Cyclodextrin was selected as a carrier to improve the solubility and dissolution characteristics of the drug.

In the Preformulation studies, cefpodoxime was characterized by its physicochemical properties such as melting point, UV and FTIR studies. UV spectrophotometric method was established for quantitative estimation of cefpodoxime proxetil in the formulation. The absorption maxima wasfound to be in between 230-263nm range in different media. Drug polymer interaction studies were carried out for 4 weeks at 40± 2^0 C and 75± 5% RH. Samples were evaluated after every week for physical and chemical changes. No physical and chemical change was observed after four weeks. The drug and polymer were found to be compatible and were found to be suitable for dosage form design.

After Preformulation studies, the drug was formulated as solid dispersion with beta- Cyclodextrin as a carrier. Different ratios of solid dispersion were prepared by different methods

1. Physical mixture method (PM) (1:1, 1:2, 1:3)
2. Kneading method (KN) (1:1, 1:2, 1:3)
3. Solvent evaporation method (SE) (1:1, 1:2, 1:3)

Prepared solid dispersions were compared based on solubility parameters. Solvent evaporation solid dispersion show better result with respect to kneaded and physical mixture dispersion.

SE>KN>PM>DRUG

SE2 solid dispersion was found to be better among all the solid dispersion. The prepared solid dispersion were characterized by bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose the drug content was found to be 94%. The solubility was found to be near 90%. Solid dispersion were evaluated for the physical and chemical changes in absorption maxima(λmax), FTIR and SEM. SE2 formulation has been selected for the preparation of tablets.

During the formulation of tablets both pre- compression and post compression studies were carried out. In case of pre- compression studies the drugs were blended with the polymer. The blend was evaluated for their flow properties and mass volume relationship. The results of bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose indicated the good compressibility and flow characteristics of the formulated mixed blends. SE2 solid dispersion was formulated into tablets using direct compression method in which cross carmellose sodium (5%w/w) was used as superdisintegrant. Magnesium stearate and talc were used as glidant and microcrystalline and lactose used as diluent. The prepared tablets were evaluated for organoleptic characteristics like color, odor and physical characteristics like diameter, thickness, hardness, friability, weight variation, disintegration time, and dissolution studies.

The prepared tablets were compared with the marketed formulation (GUDCEF-100/ FDC Pvt. Limited Baddi) in terms of dissolution; disintegration and drug content were found to possess better dissolution efficiency.

No significant changes were observed on physical characteristics, drug content and on drug release of the tablets after keeping the tablets for one month at 40 ±2^0 C and 75 ±5% RH. So, it was concluded that the prepared tablets were stable under these stress conditions.From the above experimental finding, it can be concluded that the solid dispersion increases the solubility of the poorly water soluble drug like cefpodoxime proxetil using Beta- Cyclodextrin as a carrier. The dispersible tablets of cefpodoxime were found to be better dissolution and solubility preparation.

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