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Formulation of Alternative Dosage Form for Cephalosporin (CEFDINIR)

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Abstract

Recent advancements in technology provide viable dosage alternatives for patients having difficulty in swallowing the tablets.

In the present study Mouth Dissolving Tablets (MDT) of Cefdinir were prepared using two techniques: Sublimation method and Effervescent technique. The Effervescent agents used here were citric acid and Sodium bicarbonate. The subliming agents used here was camphor. Six batches of MDT were prepared using each technology by direct compression method.

The evaluation of MDT of Cefdinir were preformed mainly for their Preformulation, Physical evaluation and also for their Weight variation and Release studies. All the MDT formulations were found to be within the standard limits.

MDTs prepared by sublimation method showed comparatively low in vitro dispersion time (10sec). The formulation having camphor mannitol ratio 1:4 (MCS4) was found to be satisfactory one. This is because MCS4 exhibiting hardness of 1.67kg/cm2, friability of 0.92%, maximum moisture uptake of 2.92mg/tab, in vitro drug release of 94.77% at the end of 8 minutes and maximum drug release of 98.52% at end of 20minutes in simulated saliva.

On the other hand, MCE4 was found to be satisfactory one among all batches of MDTs prepared by effervescent method. The formulations with higher content of sodium bicarbonate showed extremely less hardness and dispersion time while more friability and moisture gain.

Among both the methods, MCE4 was selected as optimized batch for ex vivo permeability study due to its satisfactory hardness and friability as compare to MCS4.Selected formulation of Cefdinir MDT (MCE4) was evaluated for Ex-vivo permeability studies as per the procedure. Results showed that more than 60% of the drug was permeated within 6 hours in the MCE4 whereas the pure drug fail to permeate even after 6 hours (29.24+0.12%).93.48% drug permeated in case of MCE4 within 12 hours of study. Thus, in formulation MCE4, the permeability of Cefdinir was enhanced in comparison to pure drug.

Keywords: Cefdinir, Cephalosporin, & Mouth Dissolving Tablets

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1. INTRODUCTION

Antibiotics are lifesaving medicines and most of them come in parenteral forms for immediate administration in case of emergency. The activity of new drug as well as drug profile is evaluated by making parenteral dosage form. Large no. of new parenteral antibiotics is producing day by day for treatment of drug resistant bacteria. Parenteral describes the introduction of nutrition, a medication, or other substance into the body via a route other than the gastro-intestinal tract, especially via infusion, injection or implantation and should be sterile, pyrogen free and free from any physical, chemical and biological contamination.

1.1. Oral alternatives of antibiotics: A need

Antibiotics are the molecules that inhibit microbial growth or kill the microbes .The word "antibiotic" means a chemical substance originate from microorganisms or produced by chemical synthesis that kills or inhibits microorganisms. Antibiotics that act by killing bacteria are called "bactericidal" and those that act by stopping the growth of bacteria are called "bacteriostatic".

Antibiotics are usually classified on basis of their mechanism of action:

1.1. Criteria for Mouth dissolving

Drug Delivery System:

The mouth dissolving tablets should [1]

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment's at low cost.
- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims,
- bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pre gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

1.2. Advantages of Mouth Dissolving Tablets

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as paediatric, geriatric & psychiatric patients [2].
- Achieve increased bioavailability/ rapid absorption through pre gastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travellers and busy people, who do not always have access to water [3].
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patients [2].
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety [3,4]
- Rapid drug therapy intervention.

1.3. Disadvantages of Mouth Dissolving Tablets

- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- It is also show the fragile, effervesces granules property [3].
- FDT requires special packaging for properly stabilization & safety of stable product [4].

1.4. Important criteria for excipients used in the formulation of MDTs [1]

- It must be able to disintegrate quickly.
- It should not have any interaction with the drug and other ingredients

or excipients such as agents used for taste masking of bitter drug.

- It should not interfere in the efficacy and organoleptic properties of the product.
- The concentration of the binder must be in adequate range and the binder should not affect the final integrity means disintegration and stability of the product.
- The properties of all the ingredients should not affect the MDTs.
- The excipients used to formulate MDTs should have melting point in range of 30-35oC. [5]

2. Objectives

The objective of this work is to formulate Mouth dissolving tablets by different methods.

These tablets should have quick onset of action and should not require water for swallowing of tablet, which is a usual inconvenience with conventional tablets especially during traveling. It should have less disintegration and dissolution time hence fast in action, reduce wastage of drug, shows action in small interval of time after administration that is faster relief to the patient can be provided. To eliminate the rough texture in mouth, we attempted to prepare high porosity rapidly mouth dissolving tablets of Cefdinir by using water soluble material. Keeping all these factors in mind, it was considered appropriate to formulate MDT of Cefdinir. The literature survey reveals that MDT of Cefdinir has not been prepared so far. Hence an attempt was made to formulate and evaluate the MDT of Cefdinir using various techniques with the following objectives.

To improve the patient compliance.

To develop dosage form convenient for use by geriatric and pediatric patients.

To enhance the dissolution of drug for fast drug release

More convenient dosage forms.

Quick onset of action

2.1 Selection of drug

Cefdinir, a third generation cephalosporin antibiotic[6,7], has oral bioavailability of about 16-21 % (dose dependent) due to poor aqueous solubility and dissolution rate. Cefdinir is available in only two dosage forms: capsules and suspension forms. Owing to its crystalline nature, Cefdinir has compressibility problem due to which it is not formulated easily in tablet form. The permeability of drug being the rate limiting step in its absorption, hence selected as suitable candidate to improve its solubility along with its permeability for formulating its mouth dissolving tablets.

3. Experimental

3.1 Preformulation study

Characterization of drug

UV Spectroscopy: UV absorption spectroscopy of cefdinir was carried out using UV-VIS scanning spectrophotometer (Shimadzu UV-1800, Japan). UV absorption spectra were recorded using pure drugs (conc. of 20 µg/ml in 0.1N HCl, simulated saliva) and absorption peaks were recorded.

Fourier-Transform Infrared (FTIR) Spectroscopy: An FTIR spectrum of pure drug was recorded by suspending in liquid paraffin and placing in sodium chloride cell on FTIR spectrophotometer (IR Affinity, Shimadzu, Japan).

Differential Scanning Calorimetry (DSC) : Pure drug (5-10 mg) was heated in hermetically sealed aluminium pans with heating rate of 100C/min under nitrogen atmosphere (flow rate 20ml/min) and thermograph was recorded using differential scanning calorimeter (Perkin-Elmer DSC7, USA).

Scanning Electron Microscopy: Pure drug was mounted on a double faced adhesive tape and sputtered with thin gold- palladium layer using sputter coater unit and surface topography was analyzed with scanning electron microscope (JEOL 457V, Japan).

Solubility

The solubility of drug is an important physicochemical property because it affects the bioavailability of drug, rate of release and hence therapeutic efficacy of pharmaceutical product. The solubility of a material is usually determined by equilibrium solubility method, in which a saturated solution of the material obtained by stirring an excess of material in solvent for prolonged period, until equilibrium is achieved. For determination of pH solubility of drug, shake flask method was utilized.

The solubility was determined in the following media: Distilled water, Ethanol, 0.1N HCl, pH 6.8 phosphate buffer.

Method: An excess quantity of drug was added in 50ml volumetric flasks containing

25 ml of different solvents (distilled water, ethanol, 0.1 N HCl and phosphate buffer, pH 6.8) and saturated solutions were prepared. The flasks were sealed and shaken in mechanical shaker. On completion of study period, flasks were removed and solution was passed through Whatmann Filter Paper. The solutions obtained were suitably diluted and solubility was determined by measuring the absorbance spectrophotometrically.

Characterization of complex

Solid dispersion of drug with polymer was characterized to assess any possible interaction by following methods:

Differential Scanning Calorimetry (DSC): Samples (5-10 mg) was heated in hermetically sealed aluminium pans with heating rate of 100C/min under nitrogen atmosphere (flow rate 20ml/min) and thermograph were recorded using differential scanning calorimeter (Perkin-Elmer DSC7, USA).

Fourier-Transform Infrared (FTIR) Spectroscopy: FTIR spectra of samples were recorded by suspending in liquid paraffin and placing in sodium chloride cell on FTIR spectrophotometer (IR Affinity, Shimadzu, Japan). Any changes in peaks were analyzed.

Scanning Electron Microscopy: Samples were

mounted on a double faced adhesive tape and sputtered with thin gold- palladium layer using sputter coater unit and surface topography was analyzed with scanning electron microscope (JEOL 457V, Japan). The SEM of sample was compared with pure drug and any change in cystallinity was determined.

Phase Solubility Studies

Known excess of drug (cefdinir) solid dispersion in different ratios was added in 30ml of simulated gastric fluid (0.1N HCl) in series of 100ml volumetric flask. The flasks were placed overnight in water bath incubator shaker. After 24 hours, the flasks were kept aside for equilibrium to achieve followed by filtration of solution through micro-syringe filter. The filtered samples were diluted and studied by UV-VIS Spectroscopic method at 286nm. The whole phase solubility study was also carried out in simulated saliva.

Characterization of granules

The pure drug (Cefdinir) has compressibility problem due to its crystalline nature, therefore prepared granules before compression were characterized for evaluating powder flow ability by following evaluation parameters[8, 9]:

Angle of Repose (θ): The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. Angle of repose is calculated by using eq. no.1 as given below:

Tan θ = h/r Therefore **θ = Tan-1 h/r (**1)

Where θ = Angle of repose, h = height of the cone, r= Radius of the cone base.

S.NO.	Angle of Repose(degree)	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>40	Very poor

Table 3.1: Angle of repose as an indication of powder flow properties

Bulk Density (Db): It is the ratio of total mass of powder (M) to the bulk volume (Vb). Apparent bulk density was determined by pouring presieved drug excipient [10] blend into a graduated cylinder and measuring the volume and weight. Bulk density (expressed in gm/ml) was calculated according to formula mentioned in eq. no. 2:

Db = M/ Vb (2) Where, M = Mass of the Powder, Vb= Bulk volume of the powder.

Tapped Density (Dt): It is the ratio of total mass of powder to the taped volume of powder. Tapped density (expressed in gm/ml) was calculated according to formula mentioned in eq. no. 3:

Dt = M/Vt (3)

Where, M = Mass of the Powder Vt = Tapped volume of the powder.

Carr's index (Carr's Consolidation Index): It indicates the powder flow properties. It is expressed in percentage and is given by eq. no. 4:

Percentage compressibility (I) = $Dt - \frac{Db}{Dt} * 100$

S.NO.	% Compressibility	Flowability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair passable
4	22-35	Poor
5	35-38	Very Poor
6	<40	Very Very Poor

Table 3.2: Relationship between % compressibility and Flowability

Hausner's Ratio: Hausner's ratio is the ratio of tapped density (calculated using V2500 i.e., volume after 2500 tapping's) to bulk density. Lower the value of Hausner's ratio (>1.25) better is the flow property and is calculated using the formula:

Hausner's Ratio:= Dt/Db

3.1.2 Determination of λ Max and Preparation of Calibration Curve of Cefdinir

Preparation of stock solute

Accurately weighed 100mg of Cefdinir was dissolved in small amount of 0.1 N HCl and volume make up was done by 0.1 N HCl in 100ml calibrated volumetric flask and fill up to the mark to get a concentration of 1mg/ ml (stock I). The stock – I solution was further diluted to get a solution of concentration 500 µg / ml (stock – II).

Spectrophotometric scanning of Cefdinir

1 ml of the stock – II was suitably diluted to get solution of concentration 10 µg / ml. UV at 286 nm. This absorption maxima was used for further studies.

Preparation of calibration curve of Cefdinir

From the stock – II, a series of dilutions were prepared-five concentrations from 2-14 µg/ml. Absorbance of these dilutions were taken at

286 nm in UV spectrophotometer by using 0.1N HCl as blank. Graph was plotted Concentration vs. Absorbance to obtain the standard calibration curve. The same procedure was repeated to prepare calibration curve of drug in simulated saliva.

Preparation of Reagents

Preparation of 0.1 N HCL Solution:

Dissolve 8.5 ml of Hydrochloric acid solution in distilled water and diluted the volume to 1000 ml with distilled water.

Composition of simulated saliva [11]:

Ingredients	Concentration (amount)
KH_2PO_4	12 mm (1.6 g)
Nacl	40 mm (2.3 g)
$CaCl_2$	1.5mM (0.17 g)
NaoH	To pH 6.8

Table 3.3: Composition table of simulated saliva

3.1.3 Formulation of Mouth Dissolving tablets of Cefdinir

3.1.3.1Preparation of Solid Dispersion

Cefdinir was mixed with water soluble polymer (D-Mannitol) to formulate the mouth dissolving tablet of Cefdinir.

Ethanol was added into the mixture to make smooth solid dispersion. The dispersion poured down into the marked petridishes with different ratios and then the petridishes were put into the hot air oven to evaporate the solvent and a temperature not above

600c. The dried dispersion was scratched out carefully to obtain the dispersion in required quantity. Cefdinir and water soluble polymer (D-Mannitol) solid dispersion was used in formulating mouth dissolving tablets as this ratio was optimized from observations of phase solubility studies.

3.1.3.2 Preparation of Mouth dissolving tablets

Tablet preparation by sublimation method

Cefdinir and water soluble polymer (D-Mannitol)[12] solid dispersion along with a sublimation agent (DL-Camphor) used to formulate the mouth dissolving tablet of Cefdinir. DL-Camphor was powdered using pestle mortar and sieves. The tablet weight was adjusted so as to contain 125mg of Cefdinir (normal dose) in each tablet.

Batch No.	Solid Dispersion * (mg)	Manni tol (mg)	Camph or (mg)
MCS1	375	225	0
MCS2	375	215	10
MCS3	375	205	20
MCS4	375	195	30
MCS5	375	185	40
MCS6	**375**	**175**	**50**

Table 3.4: Formula for cefdinivir sublimation tablets

*Solid dispersion of drug (375mg of S.D equivalent to 125mg of drug), average weight is 600 mg

The drug with excipients [13] including lubricant was mixed in mixer. The mixture was compressed using 8mm punch diameter with 12 stations R&D rotary compression machine. The compressed tablets were then subjected for sublimation using vacuum oven.

2. Tablet preparation by effervescent method

D-Mannitol was grinded in motor and pestle to powder and pass through sieve. Cefdinir and Mannitol were mixed together and then mixture was divided in two equal portions. Citric acid was added in one portion and sodium bicarbonate was added in another portion. Both portions were mixed together and lubricant was added in mixture.[14]

Formulation code	Average weight of one tablet (mg)		
	Initial weight	After 6 hours	After 8 hours
MCS1	603.0 +0.2	602.0+0.4	601.1+0.6
MCS2	602.3 +0.4	597.2+0.3	592.3+0.71
MCS3	603.1+0.21	594.3+0.62	582.1+0.57
MCS4	599.3+0.32	585.2+0.6	567.0+0.66
MCS5	598.2+0.30	576.2+0.58	557.1+0.75
MCS6	597.3+0.35	569.3+0.64	545.5+0.71

Table 3.4 (b): Data of sublimation

*Tablet in vacuum oven at 700mm Hg at 450C for sublimation

Batch No.	Solid Disper sion* (mg)	Citric Acid (mg)	Ma nnit ol (mg)	Sodium Bicarbo nate (mg)
MCE 1	375	35	190. 00	0.00
MCE 2	375	35	177. 50	12.50
MCE 3	375	35	165. 00	25.00
MCE 4	375	35	152. 50	37.50
MCE 5	375	35	140. 00	50.00
MCE 6	375	35	127. 50	62.50

Table 3.5: Formula of cefdinivir effervescent tablet

*Solid dispersion of drug (375mg of S.D equivalent to 125mg of drug)

The mixed blend was compressed using rotary compression machine to obtained 600mg weight of each tablet. Tablets made were vacuum dried to remove all moistures present within them

3.1.4 Evaluation of Mouth Dissolving tablets of Cefdinir

3.1.4.1 Physical Evaluation [15]

a) Thickness of tablets

Organoleptic properties of all tablets were measured using varnier calipers. The extent to

which the thickness of each tablet deviated from + 5% of standard value was determined.

b) Hardness and Friability of tablets Hardness of tablets was determined by Monsanto Hardness Tester. It is expressed in Kg/cm2 or pound. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. A pointer rides along a gauge in the barrel to indicate the force. The force of facture is recorded and the zero reading is deducted from it. Six tablets from each batch were selected and evaluated and average value with standard deviation was recorded. Friability of Tablets was performed in a Roche Friabilator. It consists of a plastic chamber that revolves at 25 rpm. About 10 tablets were weight together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablet drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed.

c) Moisture uptake by tablets

Ten tablets from each formulation were kept in a desiccator, over calcium carbonate at 37o C for 24 hours. The tablets were then weighed and exposed to 75% RH, at room temperature for two weeks in the desiccator. Require humidity was achieved by keeping saturated chloride solution at the bottom of the desiccator for three days. Tablets were re-weighed and percentage increase in weight was recorded in each days.

3.2.4.2 Weight variation and release studies

a) Weight variation [15]

Twenty tablets were weighed individually and the average weight was calculated. From the average weight of the prepared tablets, the standard deviation and individual deviation were determined by individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

b) In vitro dispersion time

A tablet was put into 10 ml of simulated saliva solution at 37 + 0.5◦C. Time required for complete dispersion of a tablet was recorded. This test was performed for six tablets and average time taken for dispersion with standard deviation was recorded.

c) In vitro dissolution study

In vitro drug release studies were carried out in two different medium. To study the drug release behavior in mouth, dissolution studies were carried out in 50ml simulated saliva taken in 100ml beaker (table). All the formulations were also studied at pH 1.2 (USP XXII type II Electro lab, Mumbai, India). Samples were withdrawn at different intervals, diluted suitably and analyzed at 286 nm for cumulative drug release using an ultraviolet visible spectrophotometer (Shimadzu, Kyoto, Japan)

Parameter	Simulated Saliva	At Gastric pH
Method	Modified	USP XXII type II
Dissolution medium	50 ml of Simulated Saliva in 100ml beaker	500 ml of 0.1N HCl
Temperature	37°C±1°C	37°C±1°C
RPM	50	100
Sample taken	0.5 ml	5 ml
Dilution factor	200 times	20 times
Λ max	286 nm	286 nm

Table 3.6: Tablet dissolution apparatus parameters

***d) Ex vivo* intestinal permeation studies:**

Ex-vivo intestinal permeation study of pure drug and finalized batch were carried out using non-everted gut sac technique (approved from Institutional Animal Ethics Committee), the small intestine of freshly sacrificed rats was removed by cutting across the upper end of duodenum and the lower end of ileum. The small intestine was washed out carefully with oxygenated saline solution using syringe equipped with blunt end. The clean intestinal tract was prepared into 6±0.2cm long sacs. Each sac was filled with 1ml of pure drug and formulation MCE4 (equivalent to 10mg of cefdinir suspended in 0.1N HCl) via a blunt needle, and the two sides of the intestine were tied tightly with thread. Each non- everted intestinal sac was placed in a glass conical flask containing 50 ml of Krebs Ringer phosphate buffer saline solution. The entire system was maintained at 37oC±1oC in a shaking water bath operating at 50 rpm and aerated with oxygen (10– 15 bubble/min). Samples were taken at different intervals and analyzed at λ max 286nm using a UV–visible spectrophotometer (Shimadzu, Kyoto, Japan).

4. RESULTS

4.1 Preformulation study

4.1.1 Characterization of drug

The model drug (Cefdinir) was characterized for various parameters as shown in the table given below:

Properties	Specifications	Observations
Appearance	White to light yellow powder	White powder
Physical form	Crystalline powder	Crystalline powder
Melting point	152-155°C	154°C

Table 4.1: Characterization of Cefdinir

4.1.1.1 UV Specroscopy

Observations:

The UV Spectrophotometric method used to check the purity of drug and after scanning it give absorption maxima at 286 nm after scan near the reported peak in US Pharmacopeia which describes that the drug was pure. Cefdinir shows UV Absorption spectra at 286nm in simulated saliva and almost same peak at 281nm was observed in 0.1N HCl.

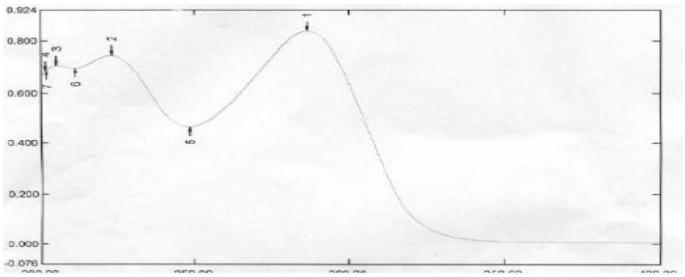

Figure 4.1: UV absorption spectra of cefdinivir in simulated saliva solution

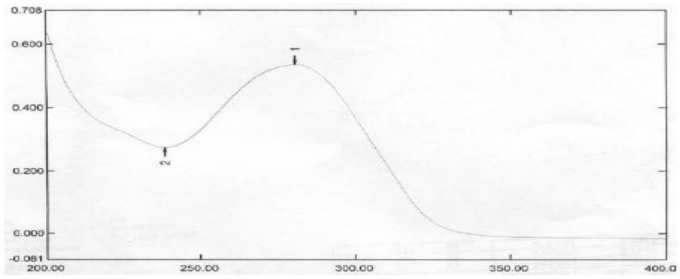

Figure 4.2: UV absorption spectra of cefdinivir in 0.1N HCl

4.1.1.2 Fourier-Transform Infrared (FTIR) Spectroscopy

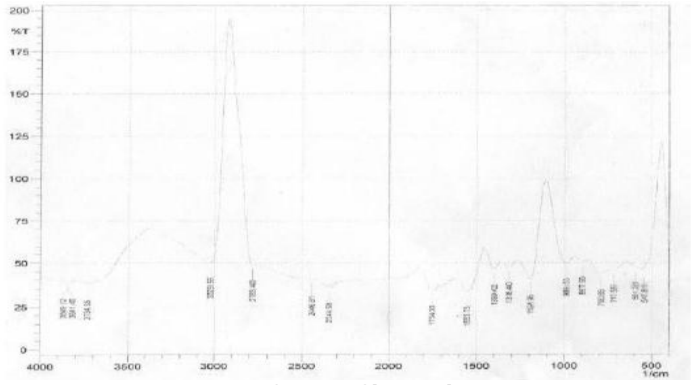

Figure 4.3: FTIR spectra of pure cefdinivir drug

S. No.	Function al group	Report ed peak	Observed peak
1	CS stretch	Below 1100 cm-1	989 cm-1
2	C=Ostretch (carbonyl)	1900-1650 cm-1	1700 cm-1
3	Aromatic carbon	3000-2500 cm-1	3023 cm-1
4	N-OH (Nitro)	1375-1275 cm-1	1318 cm-1

Observations:

The peaks observed indicate same functional group as present in structure of drug indicating purity of drug.

4.1.1.3 Differential Scanning calorimetry (DSC)

a) Cefdinir was given a sharp endothermic peak at 154.23oC. The melting point of Cefdinir was in the reported range 152-155oC.

b) The intensity of the peak was sharp it describes that Cefdinir was crystalline in nature.

c) DSC of mannitol was revealed that it gives the single sharp peak at 171.21^{0}C.

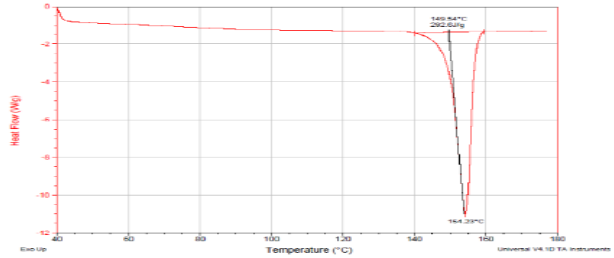

Figure 4.4: DSC of Cefdinivir

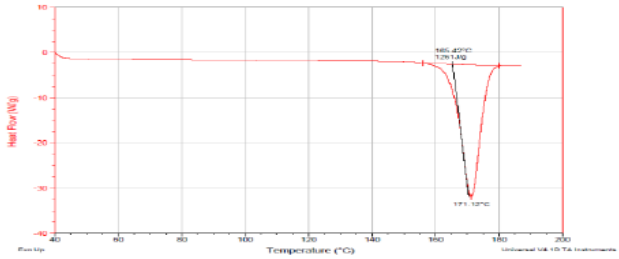

Figure 4.5: DSC of mannitol

Scanning electron microscopy (SEM)

The SEM of the cefdinir drug was described its nature as crystalline. Cefdinir, Mannitol SEM figures were taking on 1000 magnification to define surface morphology and nature of both compounds.

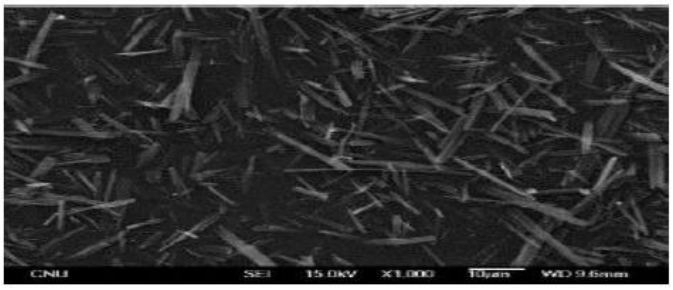

Figure 4.6: SEM of Cefdinivir 1000X

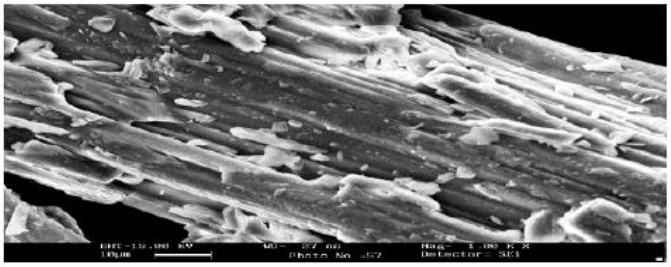

Figure 4.7: SEM of mannitol 1000X

Observations:

a) SEM of Cefdinir describes that it is crystalline in

nature so to enhance its solubility apply some attempts to be taken. b) The mannitol was crystalline in nature as shown in SEM (Figure No. 4.7) but it creates pores for water penetration.

4.1.2 Solubility Study

The solubility profile of drug is shown in the following table:

S.No.	Solvents	Solubility±S.D* (mg/ml)
1	Distilled water	0.10±0.01
2	Ethanol	0.19±0.01
3	0.1N HCl	0.59±0.01
4	6.8 pH phosphate buffer	0.73±0.02

Table 4.2: Solubility profile of cefdinivir (N=3)

Observations:

As shown in table drug has solubility of 0.10±0.01mg/ml in distilled water and 0.19±0.01mg/ml in ethanol indicating insolubility of drug in both solvents and solubility of 0.59±0.01mg/ml in 0.1N HCl and 0.73±0.02mg/ml in 6.8 phosphate buffer indicating drug was slightly soluble in both solvents which meets the standard specifications as given in drug profile.

4.1.3 Characerization of complexes

4.1.3.1 Fourier transform infrared spectroscopy

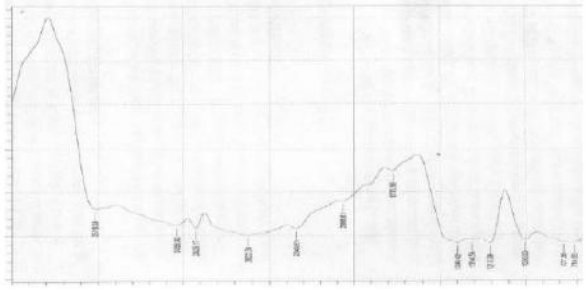

Figure 4.8: FTIR Spectroscopy of Mannitol

S. No.	Functional group	Reported peak	Observed peak
1	Free OH group	3500-3200 cm-1	3516 cm-1
2	C-O stretch (primary alcohol)	1320-1050 cm-1	1314 cm-1
3	C-H stretch	2960-2850 cm-1	2924.17 cm-1

Observations

The peaks observed in FTIR of mannitol indicate same functional group as present in structure of mannitol indicating purity of mannitol.

FTIR of solid dispersion of drug with Mannitol

Observations:

All the peaks in FTIR of solid dispersion were well defined and appeared clearly in the spectrum. Nomissing of the peaks take place indicating no interactions between drug and polymer were seen.

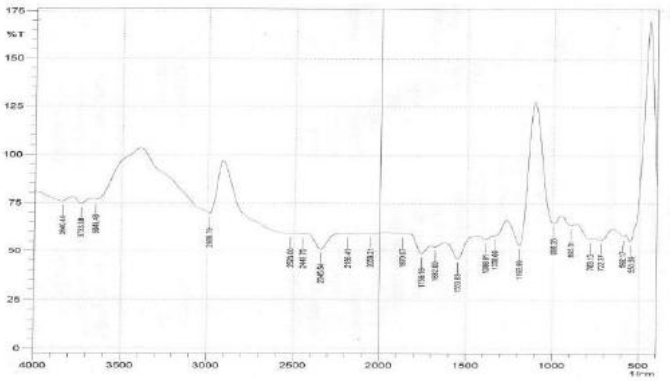

Figure 4.9: FTIR Spectroscopy of Cefdinir with Mannitol solid dispersion

S. No.	Functional group	Reported peak	Observed peak
1	CS stretch	Below 1100 cm-1	996 cm-1
2	C=O stretch (carbon yl)	1900-1650 cm-1	1759.1 6 cm-1
3	Aromatic carbon	3000-2500 cm-1	2989.79 cm-1
4	N-OH (Nitro)	1375-1275 cm-1	1338 cm-1

4.1.3.2 Differential scanning calorimetry (DSC)

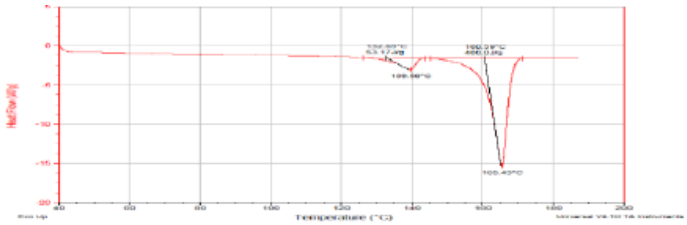

Figure 4.10: Differential scanning calorimetry of cefdinir and Mannitol

Observations:

a) The pure Cefdinir was given a sharp endothermic peak at 154.23oC and mannitol sharp peak was at 171.21oC. The thermogram of solid dispersion revealed broadening of melting endotherm of drug along with significant decrease in enthalpy of fusion.

b) The shallow in endotherm of cefdinir was observed at 139.50oC indicating presence of residual crystallinity.

Results:

The DSC studies revealed that there was change in the melting endothermic peaks in solid dispersion represent the increase in solubility of Cefdinir.

4.1.3.3 Scanning electron microscopy (SEM)

Observations:

a) Mannitol enhances the solubility of Cefdinir by recrystallize itself and makes dispersion (Figure No. 4.11).

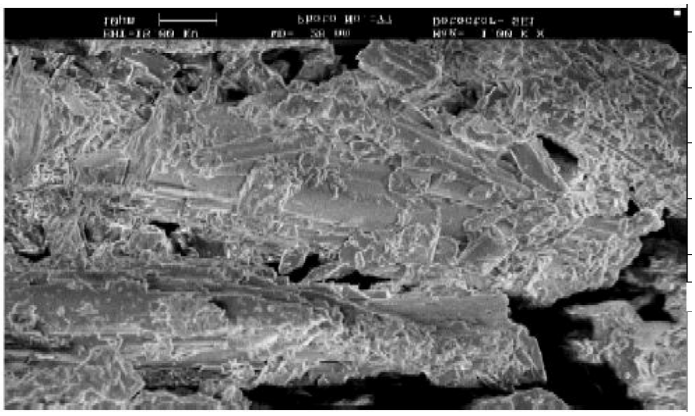

Figure 4.11: Scanning electron microscopy of cefdinir with mannitol at 1000X

b) The orientation of the cefdinir was changed due to which the elongated crystals of cefdinir were seemed to be small means leads to decrease the particle size. Then increment in surface area make drug more soluble. Taste is the essential requirement in Mouth Dissolving tablets. Taste is modified or masked by solid dispersion and mannitol incorporated in it provides sweet taste in the formulation.

4.1.4 Phase solubility study

Drug:Polymer (w/w)	Solubility of Physical Mixture ± S.D. *	Solubility of Solid Dispersion ± S.D. *
1:0	592± 1.1	592± 1.1
1:1	634±1.2	957±2.0
1:2	657±2.0	1246±0.6
1:3	784±0.6	1903±1.3
1:4	957±2.0	2465±2.0

Table 4.3: Phase solubility studies of Cefdinir and its complexes in 0.1N HCl

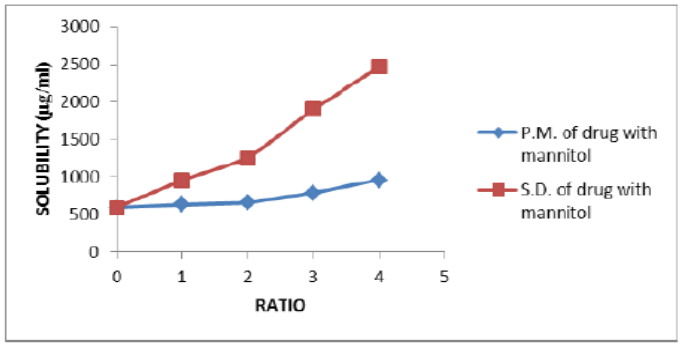

Figure 4.12: Phase solubility graph of cefdinir and its complexes in 0.1N HCl

Phase solubility in Simulated Saliva: The results of phase solubility study of drug and its complexes in saliva was given in table
4.4 and graph 4.13

Observations:

As compare to physical mixtures, solid dispersions of drug with mannitol increases solubility of drug (Cefdinir) linearly with mannitol concentration (2465±2mcg/ml in 0.1N HCl, 3434±2.6mcg/ml in simulated saliva in ratio 1:4). For preparing tablets,
1:3 ratio was used as above this ratio tablet weight get increased above 600mg and tablets can become patient inconvenient.

Drug:Polymer (w/w)	Solubility of Physical Mixture±S.D.*	Solubility of Solid Dispersion±S.D.*
1:0	734±0.6	734±0.6
1:1	834±0.6	1619±1.3
1:2	980±1.3	2153±0.7
1:3	1065±0.6	2673±0.6
1:4	1111±3.3	3434±2.6

Table 4.4: Phase solubility studies of Cefdinir and its complexes in Simulated Saliva (N=3)

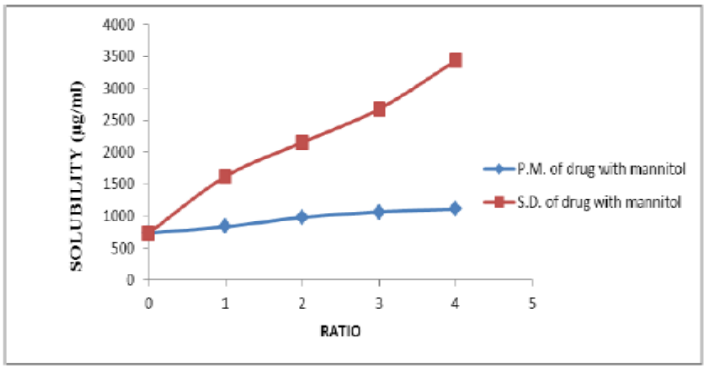

Figure 4.13: Phase solubility graph of cefdinir and its complexes in simulated saliva

4.1.5: Characterization of granules

Observations:

a) As shown in table pure drug has Carr's index-29.62 as well as angle of repose more than 40 o which indicates poor flowability of drug.

b) The Carr's index of powder blends was found between (13.79-14.81%) which indicates good flowbility of the powder blend as shown in table 4.9. The good flowability of the powder blend was also evidenced with Hausner ratio (1.16-1.17) and angle of repose in the range of (22.98-24.64o) which indicating good flow properties of the granules.

4.2 Preparation of Standard Plot: Graph was plotted between Concentration Vs Absorbance to obtain the standard calibration curve. (Fig. 4.16 & 4.17.)

Concentration (µg/ml)	Absorbance ± S.D.*
2	0.129±0.03
4	0.272±0.04
6	0.402±0.05
8	0.532±0.04
10	0.646±0.06
12	0.769±0.05
14	0.907±0.04

Table 4.6: Standard Plot Observations of Cefdinir in 0.1 N HCl (N=3)

S.No.	Parameters	Pure Drug	MCE1	MCE2	MCE3	MCE4	MCE5	MCE6
1	Bulk density (gm/cm³)	0.19	0.50	0.46	0.47	0.50	0.48	0.46
2	Tapped density (gm/cm³)	0.27	0.58	0.54	0.55	0.58	0.56	0.54
3	Hausner ratio	1.42	1.16	1.17	1.17	1.16	1.16	1.17
4	Carr's inde x (%)	29.62	13.79	14.81	14.54	13.79	14.28	14.81
5	Angle of repose	40.250	23.580	22.980	24.520	24.640	23.520	23.960

Table 4.5: Physical characteristics of powder blends

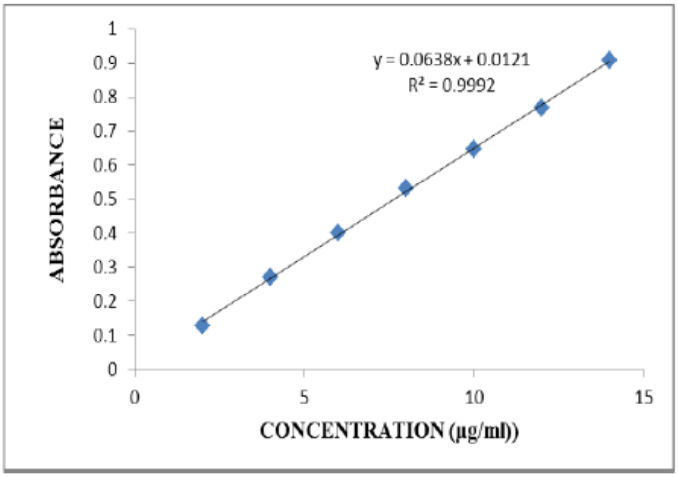

Figure 4.14: Calibration curve of Absorbance Vs Concentraion of drug in 0.1N HCl

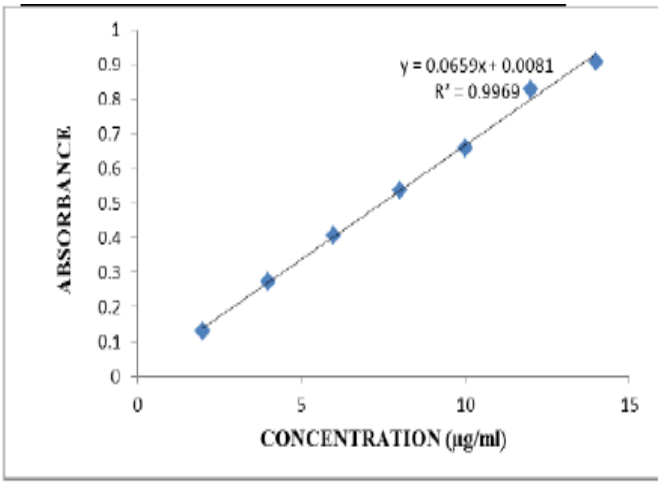

Figure 4.15: Calibration curve of Absorbance Vs Concentration of drug in simulated saliva

Observations:

a) Linearity was seen within the various prepared dilutions.

b) R2 value was 0.999 which is near to unity.

c) Slope = 0.063 and Intercept = 0.0121

Concentration (µg/ml)	Absorbance±S.D.*
2	0.132±0.06
4	0.275±0.08
6	0.406±0.05
8	0.539±0.06
10	0.659±0.07
12	0.829±0.05
14	0.909±0.06

Table 4.7: Standard Plot Observations of Cefdinir in Simulated Saliva

Observations:

a) Linearity was seen within the various prepared dilutions.

b) R2 value was 0.998 which is near to unity.

c) Slope = 0.068 and Intercept = 0.0037.

4.3 Evaluation of mouth dissolving tablets of cefdinir

4.3.1 Physical Evaluation

a) Thickness of Tablets

Thickness of tablet was measured by Vernier calipers using the procedure described in Experimental Section 4.2.4.

S. No.	Formulation code#	Thickness* in mm ±S.D.
1	MCE1	2.90±0.02
2	MCE2	2.82±0.08
3	MCE3	2.84±0.06
4	MCE4	2.82±0.06
5	MCE5	2.89±0.05
6	MCE6	2.83± 0.01
7	MCS1	2.79±0.08
8	MCS2	2.80±0.06
9	MCS3	2.81±0.04
10	MCS4	2.79±0.07
11	MCS5	2.80±0.03
12	MCS6	2.84± 0.06

Table 4.8: Result of Evaluation of Thickness of MDT Formulation of Cefdinir (N=3)
#Note: - MCE: Effervescent Tablets, **MCS**: Sublimation tablet

Observations:
The thickness of these tablets was found to be in between 2.79±0.07 to 2.90±0.02 mm which was within the pharmacopoeial limits.

b) Hardness and Friability of Tablets
The crushing strength (Kg/cm2) of prepared tablets was measured by using Monsanto tablet hardness tester and friability was measured by using Roche Friabilator. The hardness and friability of tablets are shown in Table 4.9

Observations:
The hardness of Sublimation Method is lower, because that technique makes the tablets more porous which make them less hard and more friable. The hardness for MCE1 (4.56 kg/ cm2) was found to be highest and for MCS6 (1.10 kg/ cm2) was found to be least. Maximum friability was 1.03% and minimum friability 0.39 % observed for MCS6 and MCE1 respectively.

Formulation code*	Hardness (Kg/cm2) + S.D	Friability# % + S.D
MCE1	4.56±0.7	0.39+0.04
MCE2	4.23±0.2	0.53+0.07
MCE3	4.09±0.5	0.56+0.04
MCE4	4.00±0.6	0.62+0.06
MCE5	3.95±0.5	0.69+0.07
MCE6	3.87±0.7	0.76+0.04
MCS1	3.44±0.4	0.57+0.04
MCS2	2.83±1.0	0.74+0.07
MCS3	2.05±0.4	0.80+0.05
MCS4	1.67±0.6	0.92+0.03
MCS5	1.25±0.4	0.99+0.04
MCS6	1.10±0.8	1.03+0.06

Table 4.9: Results of Hardness and Friability of MDT Tablet of Cefdinir
MCE: Effervescent Tablets, MCS: Sublimation tablet # (for 10 tablets)

c) Moisture Uptake by Tablets
All the formulation was evaluated for the moisture uptake using the procedure in the Experimental section 3.2.4

Formulation code*	Moisture gain (mg/tab)				
	1day	da	7 day	15 day 30 day	
MCE1	0.34	0.60	1.38	1.64	3.88
MCE2	0.57	1.29	2.46	2.54	4.04
MCE3	0.68	1.59	2.75	3.60	6.16
MCE4	0.81	2.28	3.72	4.07	7.27
MCE5	0.92	2.09	3.81	4.27	7.76
MCE6	0.74	1.87	3.48	4.76	8.00
MCS1	0.00	0.00	0.31	0.86	1.19
MCS2	0.00	0.31	0.89	1.24	2.19
MCS3	0.00	0.66	1.67	2.20	2.76
MCS4	0.00	0.89	1.91	2.73	2.92
MCS5	0.00	0.11	2.46	2.62	2.81
MCS6	0.00	0.15	3.84	2.21	2.39

Table 4.10: Result of Evaluation of Moisture Uptake of MDT tablets of Cefdinir **MCE:-** Effervescent Tablets, **MCS**:- Sublimation tablet

Observations:
The moisture uptake of these tablets was found to be in between 1.19 to 8.0 mg/tab by MCS1 and MCE6 after 30 days.

4.3.2 Weight variation and Release studies

a) Weight variation

S.No.	Formulation code*	Average weight of one tablet (mg) #+ S.D	Formulation code *	Average weight of one tablet (mg) + S.D
1	MCS1	601.1 + 0.6	MCE 1	600.4 + 1.17
2	MCS2	592.3 + 0.71	MCE 2	599.3 + 0.60
3	MCS3	582.1 + 0.57	MCE 3	601.1 + 0.66
4	MCS4	567.0 + 0.66	MCE 4	598.5 + 1.11
5	MCS5	557.1 + 0.75	MCE 5	602.3 + 1.26
6	MCS6	544.5 + 0.71	MCE 6	598.9 + 0.75

Table 4.11: Result of Evaluation for Weight Variation of MDT tablets of Cefdinir
Average weight of formulation after sublimation
MCE:- Effervescent Tablets, MCS:- Sublimation tablet

Observations:

As shown in the table 4.11, the average weight of the prepared tablets was within the Pharmacopoeial limit i.e. (±5%).

b) In vitro Dispersion Time

All the formulations were evaluated for in vitro dispersion time as per the procedure described in Experimental Section. 4.2.4

S.No.	Formulation code #	*In vitro* D. T (sec)*+SD	Formulation code*	*Invitro* D. T (sec)* + SD
1	MCS1	174+1.3	MCE1	172+1.3
2	MCS2	124+0.6	MCE2	130+0.6
3	MCS3	70+0.6	MCE3	92+1.3
4	MCS4	34+1.5	MCE4	45+0.6
5	MCS5	17+0.6	MCE5	31+0.6
6	MCS6	10+1.1	MCE6	22+1.1

Table 4.12: Result of in vitro Dispersion time of MDT Formulation of Cefdinir (*N=3) **MCE:** Effervescent Tablets, **MCS**: Sublimation tablet

Observation:

The average dispersion time for all the formulation comes in range of 10 to 174 seconds. So dispersion time of tablet was within the Pharmacopeial limits.

c) In vitro Dissolution Studies In simulated saliva

Time (minutes)	Formulation codes % Cumulative Drug Release+ S.D*				
MCS1	MCS2	MCS3	MCS4	MCS5	MCS6
1	8.00±0.6	11.59±0.5	29.93±0.5	34.04±0.6	64.15±0.5
4	21.99±0.7	44.39±0.4	68.74±1.5	79.61±0.4	91.08±0.6
8	41.40±0.6	64.29±0.6	77.67±0.8	94.77±0.7	97.57±0.8
12	52.88±0.6	77.02±0.6	89.31±0.7	97.63±0.8	98.21±0.5
16	60.72±0.7	84.19±0.7	93.61±0.4	98.20±0.1	98.66±0.15
20	70.98±0.8	92.40±0.6	96.02±0.3	98.52±0.5	98.66±0.3
1	8.00±0.6	11.59±0.5	29.93±0.5	34.04±0.6	64.15±0.5

Table 4.13: In vitro drug release of MDT by Sublimation method in simulated saliva (*N=3)

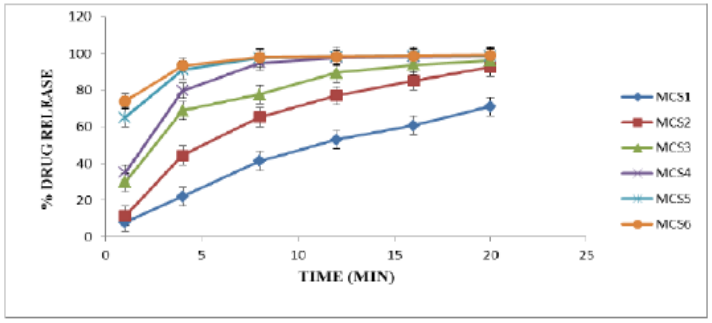

Figure 4.16: In Vitro Drug Release Profile of Formulated Tablets by Sublimation in Simulated Saliva

Observation:

As shown in the table the highest dissolution rate and drug release at the end of 8 minutes was shown by MCS6 (97.81%) followed by MCS5 (97.57%) and MCS4 (94.77%).

Time (minutes)	Formulation codes % Cumulative Drug Release± S.D*					
	MCE_1	MCE_2	MCE_3	MCE_4	MCE_5	MCE_6
1	8.03±0.6	9.59±0.4	12.93±0.2	33.44±0.4	62.15±0.5	76.29±0.6
4	22.34±0.5	49.21±0.6	56.56±0.4	80.03±0.5	88.97±0.6	92.84±0.7
8	41.49±0.7	75.57±0.6	77.67±0.6	90.84±0.7	93.54±0.4	96.57±0.5
12	53.48±0.6	87.02±0.5	92.81±0.7	95.57±0.8	96.28±0.5	98.2 ± 0.2
16	62.92±0.8	92.09±0.4	96.90±0.5	98.2±0.6	98.21±0.2	98.66±0.3
20	71.05±0.5	95.21±0.7	98.02±0.4	98.61±0.5	98.66±0.3	98.66±0.3

* n=3

Table 4.14: In vitro drug release of MDT by Effervescent method in simulated saliva

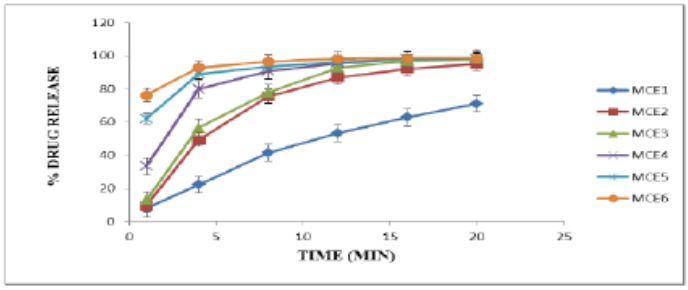

Figure 4.17: In Vitro Drug Release Profile of Formulated Tablets by Effervescent Technique in Simulated Saliva

Observation:

As shown in the table the highest dissolution rate and drug release at the end of 8 minutes was shown by MCE6 (96.57%) followed by, MCE5 (93.54%) and MCE4 (90.84%).

Time (minutes)	Formulation codes % Cumulative Drug Release± S.D*					
	MCS_1	MCS_2	MCS_3	MCS_4	MCS_5	MCS_6
1	8.30±0.5	10.53±0.4	25.44±0.5	36.10±0.5	64.22±0.4	79.15±0.4
4	25.58±0.5	52.31±0.8	57.73±0.8	81.59±0.6	90.04±0.6	93.46±0.5
8	47.82±0.7	77.02±0.6	86.22±0.6	93.47±0.4	95.08±0.3	96.19±0.6
12	65.52±0.6	88.27±0.6	94.26±0.2	96.42±0.4	97.76±0.5	98.34±0.3
16	72.28±0.4	93.75±0.5	96.64±0.7	97.32±0.5	98.21±0.2	98.66±0.3
20	81.02±0.6	96.19±0.7	97.71±0.7	98.21±0.6	98.66±0.3	99.01±0.1

* n=3

Table 4.15: In vitro drug release of MDT by Sublimation method in 0.1 N HCl

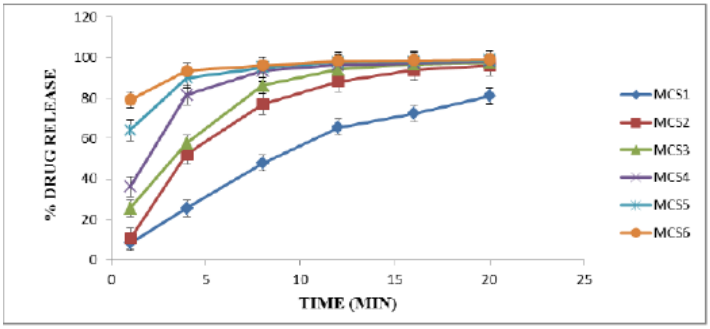

Figure 4.17: In Vitro Drug Release Profile of Formulated Tablets by Sublimation Technique in 0.1N HCl

Observations:

As shown in the table, highest dissolution rate and drug release at the end of 8 minutes was shown by MCS6 (96.19%) followed by MCS5 (94.08%) and MCS4 (93.47%).

Time (minutes)	Formulation codes % Cumulative Drug Release± S.D*					
	MCE_1	MCE_2	MCE_3	MCE_4	MCE_5	MCE_6
1	8.25±0.5	9.62±0.4	13.54±0.5	34.56±0.4	63.82±0.4	77.06±0.6
4	25.46±0.4	50.27±0.7	57.42±0.4	80.08±0.6	89.11±0.6	92.94±0.5
8	47.75±0.6	76.44±0.6	84.37±0.8	90.82±0.7	93.49±0.5	96.04±0.3
12	64.92±0.7	87.38±0.8	93.76±0.7	94.64±0.6	96.87±0.5	97.9±0.4
16	71.84±0.6	93.05±0.7	96.76±0.3	96.43±0.6	97.79±0.4	98.21±0.2
20	80.05±0.5	95.89±0.6	97.63±0.7	97.99±0.4	98.66±0.3	98.66±0.3

*n=3

Table 4.16: In vitro drug release of MDT by Effervescent method in 0.1 N HCl

Observations:

As shown in the table highest dissolution rate and drug release at the end of 8 minutes was shown by MCE6 (96.04%) followed by, MCE5 (93.49%) and MCE4 (90.82%).

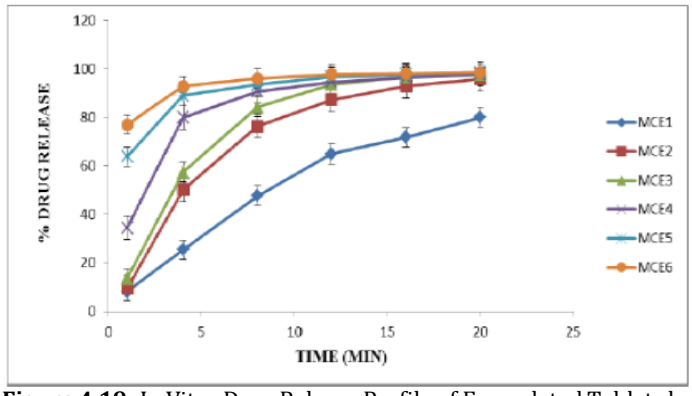

Figure 4.19: In Vitro Drug Release Profile of Formulated Tablets by Effervescent Technique in 0.1 N HCl

d) Ex vivo intestinal permeation studies

Ex vivo intestinal permeation studies were performed as per the procedure described in Experimental Section 4.2.4. The result of ex vivo drug permeated studies of pure drug and optimized batch are shown in table below:

TIME (hours)	Pure Drug % Cumulative Drug Permeated+ S.D	MCE4 % Cumulative Drug Permeated+ S.D
0.5	3.99±0.2	3.99±0.2
1	4.21±0.08	12.92±0.1
1.5	6.71±0.04	19.68±0.09
2	11.97±0.01	24.24±0.08
2.5	14.52±0.06	30.78±0.1
3	19.78±0.03	34.38±0.08
3.5	21.89±0.05	39.96±0.05
4	24.90±0.03	51±0.2
6	29.24±0.12	62.23±0.1
8	34.86±0.09	67.28±0.08
10	46.88±0.15	84.48±0.19
12	58.38±0.17	93.48±0.12

Table 4.17: Ex vivo drug release profile of pure drug and MCE4

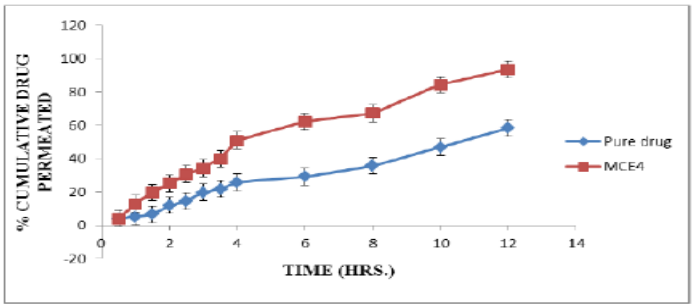

Figure 4.20: Ex Vivo Drug Release Profile of Pure Drug and MCE4

Observations:

In the MCE4 more than 60% of the drug was permeated within 6 hours whereas the pure drug fails to permeate even after 6 hours (29.24+0.12%). This may be due to the poor aqueous solubility of the drug

CONCLUSION

Mouth dissolving tablets are one of the best oral alternatives as compare to traditional tablets as MDT tablets are designed to be dissolving on tongue rather than swallow whole. These tablets dissolve and/or disintegrate rapidly in saliva without the need for water. The basic approaches for developing mouth dissolving tablets include maximizing the porous structure of tablet matrix. Thus we tried to formulate mouth dissolving tablets giving complete dissolution of formulation with minimum residue.

The basic approach followed in this study was to incorporate effervescing agents in optimum concentration and maximize the porous structure of the tablet matrix thorough sublimation technique so as to achieve rapid dispersion and instantaneous dissolution of the tablet along with good mouth feel, taste, and excellent mechanical strength. The Effervescent [16] agents used here were citric acid and Sodium bicarbonate. The evaluation of MDT of Cefdinir were preformed mainly for their pre formulation, Physical evaluation such as Thickness, Hardness, Friability, Moisture uptake etc. and also for their Weight variation and Release studies. In vitro dispersion time and in vitro Dissolution Studies were performed using the official procedures with some modifications. All the MDT formulations were found to be within the standard limits.

We can conclude the following points from the present study:

MDT by Sublimation Method approaches with mannitol and camphor in the ratio of 1:4(MCS4) is the best formulation in that category.

MDT by Effervescent Method approaches with sodium bicarbonate and citric acid in the ratio of 1.5:1(MCE4) is the best formulation in that category.

Higher the concentration of effervescent agent (Sodium bicarbonate and Citric acid) and higher will be the moisture uptake by the tablets.

Higher the concentration of subliming agent (Camphor), higher will be the porosity, rapid dispersion and higher drug release and lower will be the hardness of MDT.

Thus, it may be concluded that the MDT of Cefdinir can be successfully prepared with effervescent technique.

REFERENCES

1. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmaceutics and Pharmacology, 50(4):375–382, 1998.
2. Bradoo, R. Fast Dissolving Drug Delivery Systems. JAMA India, 4 (10): 27- 31, 2001.
3. Chang R, Guo X, Burnside BA, Couch R. Fast-dissolving tablets. Pharm. Tech. 24(6): 52-58, 2000.
4. Reddy LH, Ghosh B, Rajneesh. Fast dissolving drug delivery systems: a review of the literature. Indian J. Pharm. Sci. 64(4): 331-336, 2002.
5. Rowe CR, Sheskey JP, Quinn EM. Handbook of Pharmaceutical Excipients. RPS publishing, Great Britain; 629-633, 2009.
6. Guay DR. Cefdinir: an advanced generation, broad spectrum oral cephalosporin. Clinical Therapeutics. 24(4): 473-489, 2002.
7. Guay DR, Cefdinir: an expanded spectrum oral cephalosporin. Ann Pharmacother. 34(12): 1469-1477, 2000.
8. Anas B, Diana Z. Formulation and evaluation of Aceclofenac fast dissolving tablets using foam granulation technique. Indo global journal of pharmaceutical sciences. 2(4): 342-347, 2012.
9. Chander H, Kumar S, Bhatt B. Formulation and evaluation of fast dissolving tablets of Ramipril. Der Pharmacia Sinica. 2(6): 153-160, 2011.
10. Rowe CR, Sheskey JP, Quinn EM. Handbook of Pharmaceutical Excipients. RPS publishing, Great Britain; 433-435, 2009.
11. Panigrahi R, Behera S, Murthy NP. Formulation and evaluation of fast dissolving tablet of Lisinopril. IJRRPAS. 2(1): 65-81, 2009. 148.
12. Ruan LP, Chen S, Yu BY, Zhu DN, Cordell GA, Qiu SX. Prediction of human absorption of natural compounds by the non-everted rat intestinal sac model. Eur J Med Chem. 41:605–10, 2006.
13. Daoust RG, Lynch MJ, Mannitol in chewable tablets. Drug Cosmet Ind. 93(1):26-28, 1963.
14. Rowe CR, Sheskey JP, Quinn EM. Handbook of Pharmaceutical Excipients. RPS publishing, Great Britain; 181-183, 2009.
15. Yanze, F.M., Duru, C., Jacob, M. A process to produce effervescent tablets: fluidized bed dryer melt granulation. Drug Dev Ind Pharm. 26(11): 1167–1176, 2000.
16. Tablets. The Indian Pharmacopoeia. Government of India and Ministry of Health and Family welfare, I.P Commission, Ghaziabad; 735-737, 1996.
17. Sendall FEJ, Staniforth JN, Rees JE, Leatham MJ. Effervescent tablets. Pharm J. 230: 289–294, 1983.