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"FORMULATION DEVELOPMENT OF FAST DISPERSIBLE TABLET OF CEFUROXIME AXETIL"

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ABSTRACT
Cefuroxime Axetil is second generation cephalosporin and an orally active drug. Cefuroxime exerts its bactericidal effect by binding to the enzymes involved in bacterial cell wall synthesis. Cefuroxime Axetil is used for upper respiratory tract infection for treatment of sudden allergic attacks. The drug has poor solubility in water and bitter unpleasant taste. Solubility was enhanced with β- CD by Solid dispersion method, before that it was confirmed by Phase solubility study indicated (1:1 molar ratio) Suggested A_l curve linearity with stability constant (416 M^{-1}). Solubility of Cefuroxime axetil was comparatively evaluated with drug solubility without solubilising agent by shaking flask method which was increased. Afterwards Complexes were analysed by UV-VIS spectroscopy and characterized by infrared spectroscopy, DSC and XRPD which confirmed for complex formation. Almost 90% drug was released from the complexes within 60 min. These complex converted in to taste masked resinate by ion exchange resin using indion-235 (1:0.5) ratio with 59.30% drug content and then formulated Fast dispersible tablet by means of SSG (X_1) and Camphor (X_2) as an independent parameter using 3^2 full factorial design. % Friability (Y_1) and DT (Y_2) and % Drug release (Y_3) were selected as dependent variables. A mathematical model was generated for each response parameter. As increase the concentration of SSG, DT was decrease and % Drug release was increased shown in result and discussion. The response surfaces and contour plots for each response parameter are presented for further interpretation of the results.

KEYWORDS: Cefuroxime Axetil, SSG, Camphor, β- Cyclodextrin, Solid Dispersion & Fast Dispersible Tablet.

INTRODUCTION[1-4]
Cefuroxime Axetil is second generation cephalosporin and an orally active drug. Cefuroxime exerts its bactericidal effect by binding to the enzymes involved in bacterial cell wall synthesis.

Cefuroxime axetil tablets are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions like Pharyngitis/Tonsillitis, Acute Bacterial Otitis Media, influenza, Acute Bacterial Maxillary Sinusitis, Exacerbations of Chronic Bronchitis, Skin Infections, Urinary Tract Infections, Gonorrhea, urethral and endocervical Infections. Cefuroxime Axetil is used for upper respiratory tract infection for treatment of sudden allergic attacks. The drug has poor solubility in water and bitter unpleasant taste. Cefuroxime, like penicillins, is a beta-lactam antibiotic, act as a bactericidal agent. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that cefuroxime interferes with an autolysin inhibitor. Cefuroxime Axetil has activity in the presence of some β-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria

OBJECTIVES
- Cefuroxime axetil has extremely bitter taste. Cefuroxime axetil is mostly used for upper respiratory tract infection. It is generally used for pediatric patient and Problem associated with drug is its bitter taste with low aqueous solubility.
- Main poor characteristic of drug is its unpleasant taste and its aqueous poor solubility was overcome by inclusion complex with beta-cyclodextrin.
- Best Complex was turn to ion exchange resin complex (resinate) and it was confirmed by its taste evaluation and by physical characterization and then formulated fast dispersible tablet.
- Number of dry suspension is available in market which having taste, stability and storage problem. Fast dispersible tablet can be used easily for pediatric patient also by dissolve it with warm-cool

water and its taste, stability and storage condition of dry suspension will be overcome by this method.

LIST OF MATERIALS

Table 1: Materials and their sources

Drug/ Excipient	Source
Cefuroxime Axetil	Santurian Lab-Vadodara
β-Cyclodextrin	Balaji Drugs, Vadodara
Hydroxypropyl-β-Cyclodextrin	Balaji Drugs, Vadodara
Indion-204, Indion-234, Indion-414	Ion Exchange (India) Ltd., Mumbai
Microcrystalline Cellulose (pH 102)	Balaji Drugs, Vadodara
Sodium Starch Glycolate	S.D. Fine Chemical ltd., Mumbai, India
Cross Carmellose Sodium	Yarrow Chem Product, Mumbai
Cross Providone	Balaji Drugs, Surat, India
Camphor	Sulabh Chemical, Ahmedabad
Talc	Chemport (India) Pvt. Ltd. Mumbai, India
Sodium Saccharin	Yarrow Chem Product, Mumbai

PREFORMULATION STUDIES OF DRUG[5-9]

FTIR

FTIR spectra for drug alone and with excipients were recorded using a FTIR spectrophotometer with KBR pellets to study drug-excipients and excipient-excipient compatibility. Drug excipient interaction was determined by performing infrared spectroscopy using FTIR (Bruker α , Mumbai). The FTIR studies were carried out by the pressed pellet technique using a KBr press in which the KBr was taken and kept in a hot air oven for two hours for the remo CA any moisture. The above dried KBr was taken for the preparation of pellets of drug, and the selected formulations. The prepared pellet was placed in the sample holder and kept in the instrument to record the FTIR peaks.

Melting Point

Melting point of Cefuroxime Axetil has been carried out using melting point apparatus. Melting point of compounds was taken by open capillary method. A small amount of drug sample was transferred in to capillary tube. Then capillary was placed in melting point test apparatus and noted down the temperature at which the drug started melting and was completely melted

Determination of λ_{max}

- The Standard drug solution of concentration of 10 µg/ml was prepared using following media,
- Distilled Water
- 6.8 pH Phosphate buffer
- 0.1 N HCl
- The solutions were checked it the range of 200 – 400 nm and the λ_{max} found for the Cefuroxime Axetil was between 278-280 nm. And the actual λ_{max} was 280 nm.

CALIBRATION CURVE IN DIFFERENT SOLVENTS

SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF CEFUROXIME AXETIL IN DISTILLED WATER

Aliquots of working standard solution (100 mcg/ml) were suitably diluted with distilled water to get final concentration range of 2-10 mcg/ml. The absorbance of prepared solutions of Cefuroxime Axetil in distilled water measured at 280 nm in Shimadzu-1700 UV spectrophotometer against appropriate blank. The standard calibration curve yields a straight line, which shows that drug obeys beer's law in the concentration range of 2-10 mcg/ml.

SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF CEFUROXIME AXETIL IN PHOSPHATE BUFFER PH 6.8

Aliquots of working standard solution (100 mcg/ml) were suitably diluted with pH 6.8 to get final concentration range of 2-10 mcg/ml. The absorbance of prepared solutions of Cefuroxime Axetil in pH 6.8 measured at 280 nm in Shimadzu-1700 UV spectrophotometer against appropriate blank. The absorbance data for standard calibration curve are given in Table 6.4. The standard calibration curve yields a straight line, which shows that drug obeys beer's law in the concentration range of 2-10 mcg/ml and shown in figure 6.5.

SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF CEFUROXIME AXETIL IN 0.1N HCL

Aliquots of working standard solution (100 mcg/ml) were suitably diluted with 0.1N HCl to get final concentration range of 2-10 mcg/ml. The absorbance of prepared solutions of Cefuroxime Axetil in 0.1N HCl measured at 280 nm in Shimadzu-1700 UV spectrophotometer against appropriate blank. The standard calibration curve yields a straight line, which shows that drug obeys beer's law in the concentration range of 2-10 mcg/ml.

SOLUBILITY STUDIES

SOLUBILITY STUDY AT VARIOUS PH

Excess amount of Cefuroxime Axetil Drug was added to screw caped conical flask containing 25 ml of different pH buffer solution like 1.2 pH buffer, 6.8 pH buffer and 7.4 pH buffer, distilled water separately and placed on an Orbital shaker and agitated at room temperature for 24 hours. The solutions were filtered and analyzed at respective λ_{max} as described in calibration curve by using UV-visible spectrophotometer. The study was performed in triplicates. Saturation solubility was calculated for different pH medium.

PHASE SOLUBILITY STUDIES

The most widely used approach to study inclusion complexation is phase solubility.

Method described by Higuchi and Connors.

Phase solubility of Cefuroxime Axetil with β -Cyclodextrin (β-CD)

Procedure: For phase solubility studies of Cefuroxime Axetil, an excess of drug (10 mg) was added to 10 ml portions of distilled water, each containing variable amount of β-Cyclodextrin such as 5,10,15,20 and 25 x 10^{-3} moles/liter. All the above solutions with variable amount of β-Cyclodextrin were shaken for 24 hours. After shaking, the solutions were filtered and their absorbance was noted at 280 nm. The solubility of the Cefuroxime Axetil in every β-Cyclodextrin solution was calculated and phase solubility diagram was drawn between the solubility of Cefuroxime Axetil and different concentrations of β-Cyclodextrin. The stability constant of Cefuroxime Axetil: β -Cyclodextrin complex was calculated using Higuchi and Connor's equation.

Kc (1:1) = Slope/Intercept (1 – slope)

S0 = Solubility of Cefuroxime Axetil in aqueous complexation media (distilled water) without β – Cyclodextrin.

"Slope" was calculated from phase solubility diagram.

Phase Solubility of Cefuroxime Axetil With Hydroxypropyl β –Cyclodextrin (HP- β-CD)

Procedure: For phase solubility studies of Cefuroxime Axetil complexes, an excess of drug (10 mg) was added to 10 ml portions of distilled water, each containing variable amount of hydroxypropyl β-Cyclodextrin (HP β-CD) such as 5,10,15,20 and 25x10^{-3} moles/liter. All the above solutions with variable amount of HP β-CD were shaken for 24 hours. After shaking, the solutions were filtered and their absorbance was noted at 280 nm. The solubility of the Cefuroxime Axetil in every HP β-CD solutions was calculated and phase solubility diagram were drawn between the solubility of Cefuroxime Axetil and different concentrations of HP β-CD. The stability constant of Cefuroxime Axetil: HP β-CD complex was calculated using Higuchi and Connor's equation.

Kc (1:1) = Slope/Intercept (1-slope)

S0 = Solubility of Cefuroxime Axetil in aqueous complexation media without HP-β-CD

"Slope" was calculated from phase solubility diagram.

SOLUBILITY ENHANCEMENT OF CEFUROXIME AXETIL

Solid Dispersion (Kneading):

Materials Used for the Solud Dispersion (Kneading): Cefuroxime Axetil Drug, β- Cycledextrin, Hydrodypropyl- β- Cyclodextrin, water.

Procedure: Drug was weighed accurately in their molar ratio and poured in porcelain dish, β-CD and HP β-CD were also weighed inj their molar ratio and poured in that porcelain dish. Then lable it with CA:β-CD (1:1), And, CA:HP-β-CD (1:1) respectively. then in each porcelain dish, little amount of water was added to prepare the dough mass, and then that dough mass was dried in oven at 30^0C. after drying of it the complex was scrapped & passed through sieve no 80. The complexes were packed in Zip lock bag with appropriate label. & the % practical yield was calculated.

Table 2: Drug: Carrier Ratio in Solid Dispersion (Kneading)

Method	Drug: Carrier	Drug:Carrier Ratio	Molar Concentration	Code
Solid Dispersion (Kneading)	CA: β –CD	1:1	510.5:1135	$CBSD_1$
	CA: HP- β –CD	1:1	510.5:1541	$CHSD_1$

PHYSICAL EVALUATION OF SOLUBILITY IMPROVISED COMPLEX

Micromeritic Properties

There are different micromeritics properties which are used for the flow property of the drug, & polymer. which are Angle of repose, Bulk density, Tapped density, Carr's compressibility index, Hausner's ratio.

- **Angle of repose:** It is the maximum angle possible between tip of pile and horizontal plane and it was measured by fixed funnel method. It was measured by following formula:

$\tan\theta = h/r$

Table 3: Reference Values for Angle of Repose as per USP

Flow Property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate,vibrate	46-55
Very poor	56-65
Very,very poor	>66

- **Bulk density:** It is the ratio of mass of the blend to bulk volume. It was measured by pouring powder in measuring cylinder and measuring the volume occupied by powder.

- **Tapped density:** It is the ratio of mass of the blend to tapped volume. It was measured by digital tap

densitometer by measuring the volume occupied by powder after 100 standard tapping.

- **Carr's index:** It was measured by below formula

$$\% \text{ compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 4: Reference Values For Carr's Compressibility index as per USP

Flow Property	Carr's Compressibility Index (%)
Excellent	<10
Good	11-15
Fair	16-20
Passable	21-25
Poor	26-31
Very Poor	32-37
Very Very Poor	>38

- **Hausner's ratio:** It was measured by formula given below:

$$H.R = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 5: Reference values For Hausner's Ratio as per USP

Flow Property	Hausner's Ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very Poor	1.46-1.59
Very Very Poor	>1.60

Saturation Solubility Study

The saturation solubility studies were carried out to determine the solubility of solid dispersions. Weighed amount of solid dispersions were added to 250 ml conical flasks containing 15 ml of 0.1N HCl. The sealed flasks were shaken for 24 hrs at 37±0.5ºC. Then aliquots were filtered through whatmann filter paper. The concentration of Cefuroxime Axetil was determined by UV spectrophotometer at 280 nm.

% Practical yield

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

% Drug content

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of Distilled water. The solution was filtered, diluted suitably and drug content was analyzed at 280 nm by UV spectrophotometer. Each sample analyzed in triplicate. Actual drug content was calculated for all batches using the equation as follows in solid dispersion Actual Cefuroxime Axetil content in weight**.**

$$\%\text{Drug Content} = \frac{\text{Quantity of solid dispersion}}{\text{Theoretical amount of Cefuroxime Axetil}} \times 100$$

***In-vitro* dissolution studies**

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in-vivo* behavior. *in-vitro* release profile for each solid dispersion as well as pure drug was performed using USP Type II dissolution apparatus. Sample equivalent to 250 mg of Cefuroxime Axetil was added to 900ml of 0.1 N HCl at 37+ 0 .5°C and stirred at 100 rpm aliquot of 5 ml was withdrawn at time intervals of 10,20,30,40,50 & 60 min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 280 nm after suitable dilution if necessary, using appropriate blank.

XRD of Complex

- **Instrument Name**-X-Ray Diffractrometer (XRD)
- **Make/Model**: Philips Holland/X'Pert MPD

Procedure: With the help of a spatula place the finely ground powder on to an open hole aluminum holder and fill it. With the help of a microscopic slide press the sample gently to prepare an absolutely flat diffracting surface. Place the sample plate (ready for analysis) in the sample holder of the instrument. Set the required conditions and start analysis to collect the diffractogram.

Differential Scanning Calorimetery (DSC)

Procedure: Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC TA- 60WS) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug and complex were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10^0C/min over a temperature range of 25^0C to 150^0C. DSC study was performed for Cefuroxime Axetil and complex of drug.

DRUG-ION EXCHANGE RESINATE COMPLEX

Preparation of Drug Resin Complexes

The drug resin complexes were prepared by batch process. An accurately weighed Eq weight of 1 gm of Cefuroxime Axetil cyclodextrin complex was taken and dissolved in 100 ml distilled water. Then equal amount of ion exchange resin (Indion-234) was added to the drug solution and stirred on magnetic stirrer. Time to reach

equilibrium was determined by periodically measuring concentration of drug solution. It was found that 5-8 hours is optimum period for attainment of loading equilibrium. Resinate thus formed was filtered and washed with an excess amount of demonized water. The drug content in the final filtrate was analyzed by UV-spectroscopy. The amount of drug adsorbed was determined by the difference between amount of drug present in stock solution and amount remaining in filtrate at the end of equilibrium. Resinates were dried overnight in a hot air oven at 50^0C and then stored in tightly closed in desiccators.

A series of solutions containing Equivalent weight of 1 gm of Cefuroxime Axetil cyclodextrin complex was prepared. pH of these solutions were adjusted to 3, 4, 5, 6, 7, 8, 9 ion exchange resin was added to each beaker and stirred for 5-8 hours on magnetic stirrer. Resinate thus formed was filtered and washed with an excess amount of deionized water. The drug content in the final filtrate was analyzed by UV-spectroscopy.

Selection of drug resin ratio

Three batches were prepared containing β-CD complex–Indion-234 in the ratio of 1:0.5, 1:1 and 1:1.5. The pH of solution was maintained at pH 7.0. The slurry was stirred for 5 hours. Resinates obtained were separated by filtration, washed with copious quantity of deionized water and drug contents was determined.

Determination of Drug Content

Resinate equivalent to dose was placed in 1N HCl (900ml) and stirred at 100 rpm for one hour. The solution was filtered and analyzed for content of Cefuroxime Axetil. Stability of complexes was determined by placing weighed quantity of complex in deionized water for 24 hours and analyzed for drug content.

***In-vitro* drug release profile**

The following conditions were employed to study *in-vitro* dissolution

USP Dissolution Apparatus : Type II.
Volume of Dissolution medium : 900 ml.
Speed of paddle rotation : 100 rpm.
Temperature : 37°C ± 0.5°C.
Dissolution Medium : 0.1 N HCl.
Test time : 60 min
Sample size : Resinate equivalent to dose

At 5 min. interval aliquots of medium (10ml) were taken, filtered and absorbance was measured by UV spectrophotometrically.

FORMULATION OF FAST DISPERSIBLE TABLETS OF CEFUROXIME AXETIL COMPLEX BY WET GRANULATION TECHNIQUE

Formulation of Taste Masked Complex

The taste masked complex equivalent to drug dose is taken and formulated in to fast dispersible tablets. The formulation was optimized using 3^2 factorial design.

Preliminary Studies of Fast Dispersible Tablet

During pre-optimization studies, three sublimating agent viz. camphor, menthol were investigated for formulating Fast Dispersible Tablet. Cross carmellose sodium, crospovidone and sodium starch glycolate was used as superdisintegrants in formulation along with camphor as a sublimating agent in various ratios to obtain good results.

Later, depending upon the results obtained camphor and cross carmellose sodium, cross providone & SSG were selected for further investigation. The initial study to screen suitable subliming agent i.e. camphor and superdisintegrants of each blend was carried out using the formula shown in following table 6.

Table 6: Formulation of Fast dispersible tablets (600 mg) of Cefuroxime Axeil resinate as a trial batch

Ingredient	Concentration (mg)
Resinate (Eq-to 250 mg)	432.83
Super disintegrant (X_1)	30-50
Subliming agent (X_2)	25-45
MCC pH-102	Q.S
Magnesium Stearate	4
Talc	4
Sodium saccharine	Q.S

Table 7: Fast Dispersible Tablets (600 Mg) of Cefuroxime Axetil Resinate.

Formula	DRC	SSG	CCS	CP	Camphor	MCC pH-102	Magnesi-um Stearate	Talc	Sodium Saccharin
F1	432.83	-	30	-	45	84.17	4	4	0.07
F2	432.83	-	40	-	45	74.17	4	4	0.07
F3	432.83	-	50	-	45	64.17	4	4	0.07
F4	432.83	-	30	-	35	94.17	4	4	0.07
F5	432.83	-	40	-	35	84.17	4	4	0.07
F6	432.83	-	50	-	35	74.17	4	4	0.07
F7	432.83	-	30	-	25	104.17	4	4	0.07
F8	432.83	-	40	-	25	94.17	4	4	0.07
F9	432.83	-	50	-	25	84.17	4	4	0.07
F10	432.83	-	-	30	45	84.17	4	4	0.07
F11	432.83	-	-	40	45	74.17	4	4	0.07
F12	432.83	-	-	50	45	64.17	4	4	0.07

F13	432.83	-	-	30	35	94.17	4	4	0.07
F14	432.83	-	-	40	35	84.17	4	4	0.07
F15	432.83	-	-	50	35	74.17	4	4	0.07
F16	432.83	-	-	30	25	104.17	4	4	0.07
F17	432.83	-	-	40	25	94.17	4	4	0.07
F18	432.83	-	-	50	25	84.17	4	4	0.07
F19	432.83	30	-	-	45	84.17	4	4	0.07
F20	432.83	40	-	-	45	74.17	4	4	0.07
F21	432.83	50	-	-	45	64.17	4	4	0.07
F22	432.83	30	-	-	35	94.17	4	4	0.07
F23	432.83	40	-	-	35	84.17	4	4	0.07
F24	432.83	50	-	-	35	74.17	4	4	0.07
F25	432.83	30	-	-	25	104.17	4	4	0.07
F26	432.83	40	-	-	25	94.17	4	4	0.07
F27	432.83	50	-	-	25	84.17	4	4	0.07

DRC- DRUG RESINATE COMPLEX, SSG- SODIUM STARCH GLYCOLATE, CCS-CROSS CARMELLOSE SODIUM, CP- CROSPOVIDONE, MCC- MICROCRYSTALLINE CELLULOSE

EVALUATION OF FAST DISPERSIBLE TABLETS

Weight Variation

Twenty tablets were taken at random from each formulation and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight.

Hardness

Tablets were taken at random from each formulation and hardness was checked using Monsanto Hardness Tester.

Friability

Pre-weighed sample of tablets was placed in the Roche Friabilator tester, which was then operated for 100 revolutions. Tablets were dedusted and reweighed. % Friability was calculated.

Content Uniformity Test

Drug content of all the batches was determined. For this purpose ten tablets were weighed and crushed in a small glass mortar with pestle. The fine powder was weighed to get 250 mg equivalent resinate of Cefuroxime axetil, and transferred to 250 ml conical flask containing 100 ml of 0.1N HCl and stirred for 4 hours on magnetic stirrer. Dispersion was filtered and the filtrates obtained were analyzed spectrophotometrically at 280 nm and drug content was determined.

In-vitro Dissolution study

The following conditions were employed to study *in-vitro* dissolution

USP Dissolution Apparatus : Type II.
Volume of Dissolution medium : 900 ml.
Speed of paddle rotation : 100 rpm.
Temperature : 37°C ± 0.5°C.
Dissolution Medium : 0.1 N HCl.
Test time : 60 min

At 2 min. interval aliquots of medium (10ml) were taken, filtered and absorbance was measured by UV spectrophotometer.

Disintegration Time

The disintegration time was measured using a modified disintegration method (n=3). For this purpose, a petri dish 10cm (in diameter) was filled with 10ml of water. The tablet was carefully put in the centre of the petri dish and the time for the tablet to completely disintegrate into fine packets was noted.

Stability Studies

Stability studies on the optimized formulation batches were carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions.

The tablets were stored in an aluminum foil and subjected to –

- Elevated temperature and humidity conditions of 40 ± 2^{o}C/ 75 ± 5% RH
- A control Sample was placed at an ambient condition.

Both test and control samples were withdrawn at the end of short time stability test for 30 days and evaluated for –

- Active drug content.
- Disintegration Time.
- *in-vitro* drug release.

RESULT AND DISCUSSION

FTIR

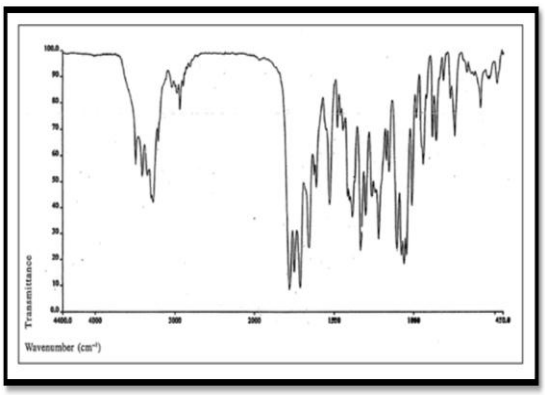

Figure 1: Reference Spectra for FT-IR of Cefuroxime Axetil Pure Drug

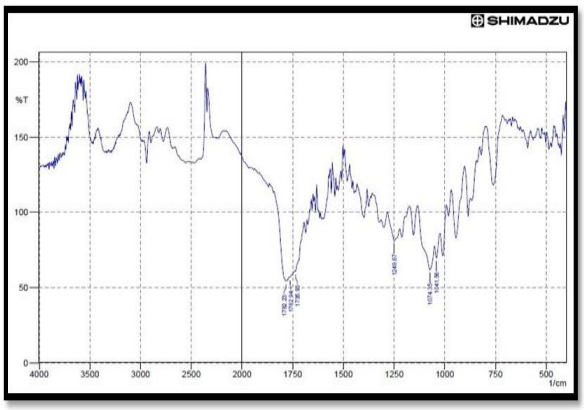

Figure 2: FT-IR of Cefuroxime Axetil Pure Drug

DETERMINATION OF λ_{max} (280 nm)

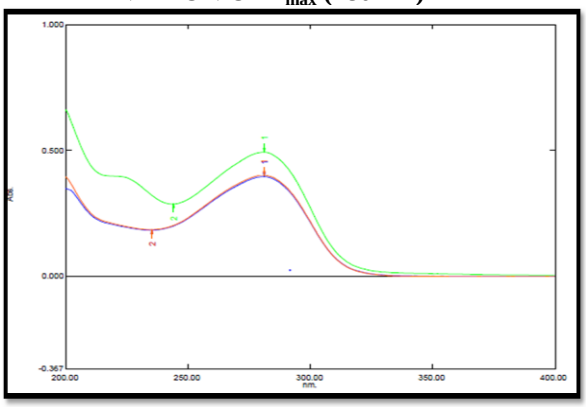

Figure 3: Overlay spectra of Cefuroxime Axetil in different Solvents.

From the above overlay graph of the Cefuroxime Axetil in different solvents like 0.1N HCl, Phosphate Buffer pH 6.8, & Distilled Water, the λ_{max} of Cefuroxime Axetil selected to be is 280nm.

CALIBRATION CURVE IN DIFFERENT SOLVENTS

SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF CEFUROXIME AXETIL IN DISTILLED WATER

A standard curve of Cefuroxime Axetil in distilled water was analyzed in the range of 2-10 µg/ml. The selected range of CA was found to be linear. A regression coefficient (R^2) at 280 nm was found to be 0.989. This standard concentration method obeys Beers law and found to be suitable for the determination of drug content and *in-vitro* drug release study.

Table 8: Standard Calibration Curve of Cefuroxime Axetil in Distilled Water

Concentration (µg/ml)	Absorbance Distilled Water
2	0.098±0.004
4	0.171±0.005
6	0.265±0.007
8	0.362±0.009
10	0.492±0.012

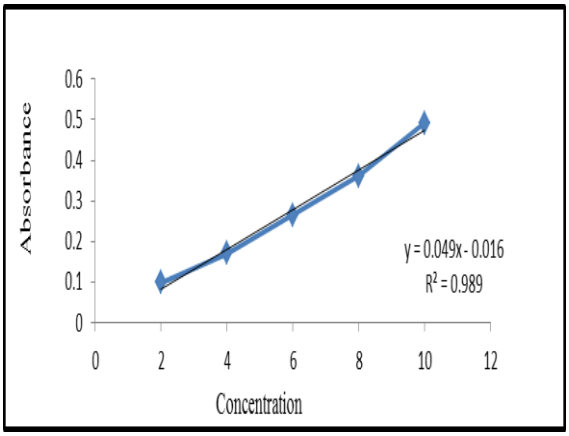

Figure 4: Calibration Curve of Cefuroxime Axetil in Distilled Water,R^2= 0.989.

Spectrophotometric Method for Estimation for CA in pH 6.8

A standard curve of Cefuroxime Axetil in pH 6.8 was analyzed in the range of 2-10 µg/ml. The selected range of CA was found to be linear. A regression coefficient (R^2) at 280 nm was found to be 0.998. This standard concentration method obeys Beers law and found to be suitable for the determination of drug content and In vitro drug release study.

Table 9: Standard calibration curve of Cefuroxime Axetil in phosphate buffer pH 6.8.

Concentration (µg /ml)	Absorbance Phosphate Buffer pH 6.8
2	0.091±0.002
4	0.163±0.004
6	0.237±0.005
8	0.329±0.005
10	0.401±0.007

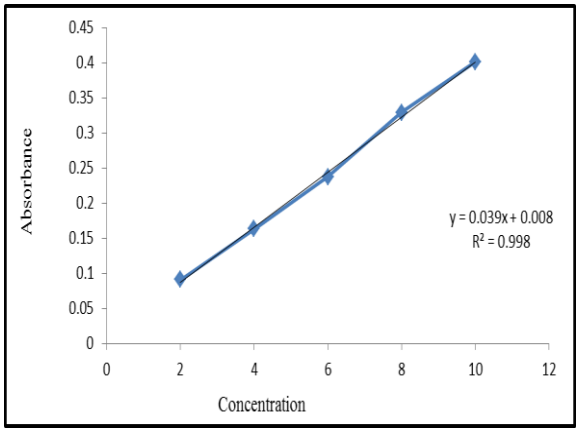

Figure 5: Calibration Curve of Cefuroxime Axetil in pH 6.8, R^2 = 0.998

Spectrophotometric Method For Estimation of Cefuroxime Axetil in 0.1N HCl

Standard curve of Cefuroxime Axetil in 0.1N HCl was analysed in the range of 2-10 µg/ml. The selected range of CA was found to be linear. A regression coefficient (R^2) at 280 nm was found to be 0.998. This standard concentration method obeys Beers law and found to be suitable for the determination of drug content and *in-vitro* drug release study.

Table 10: Standard Calibration Curve of Cefuroxime Axetil in 0.1N HCl

Concentration (µg /ml)	Absorbance 0.1N HCl
2	0.074±0.013
4	0.155±0.021
6	0.244±0.028
8	0.327±0.031
10	0.395±0.016

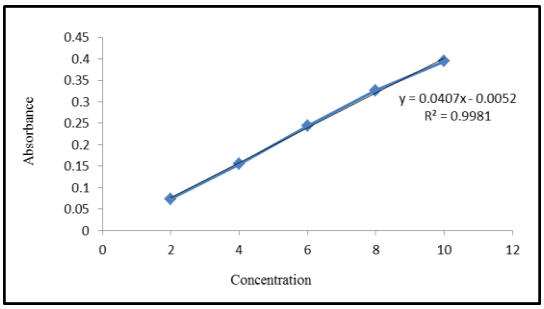

Figure 6: Calibration curve of Cefuroxime Axetil in 0.1N HCl, R^2 = 0.998

SOLUBILITY STUDIES

Solubility Study at various pH

Table 11: Solubility of Cefuroxime Axetil in different pH Medium

Sr.No.	Solubility	Reported solubility(µg /ml)	Performed solubility(µg/ml)
1	Distiled water	0.567± 0.91	0.632± 0.026
2	1.2 pH buffer	0.116± 0.97	0.588± 0.013
3	6.8 pH buffer	0.304± 0.66	0.740± 0.014
4	7.4 pH buffer	0.598± 0.83	0.776± 0.008

Phase Solubility Study With β-Cyclodextrin & Hydroxypropyl - β –Cyclodextrin.

Table 12: Stability Constant of Complex

Sr. no	Complex	Stability Constant(Kc) M^{-1}
1	CA: β-CD complex	416M^{-1}
2.	CA: HP- β-CD complex	290 M^{-1}

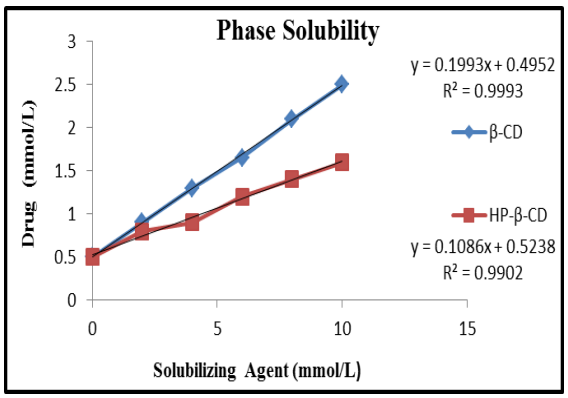

Figure 7: Phase Solubility Study of CA: β-CD & CA:HP-β- CD Complex.

For Improve the Solubility Inclusion Complex with β-Cyclodextrin is Used. The Phase Solubility Diagram for Cefuroxime Axetil And β-CD System in Distilled Water Suggest that The Molar Ratio of the Complex is 1:1. The Stability Constant (Kc) of CA:β-CD 1:1M Inclusion Complex was found to be 416M^{-1}.

FT-IR STUDY of complex

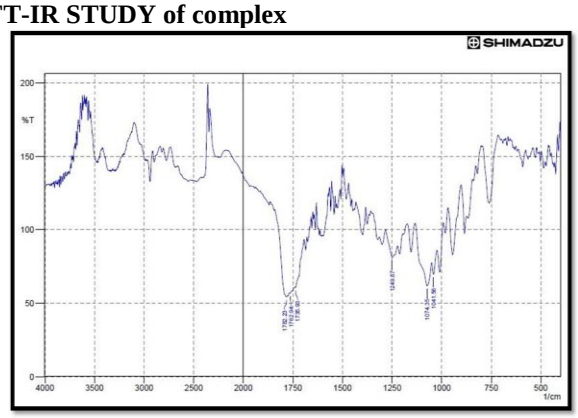

Figure 8: FT-IR Spectrum of Pure Cefuroxime Axetil

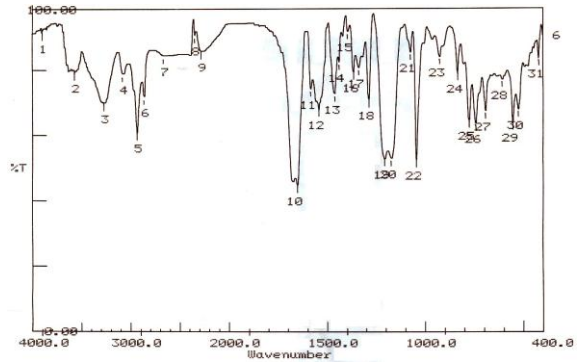

Figure 9: FT-IR Spectrum of β-Cyclodextrin

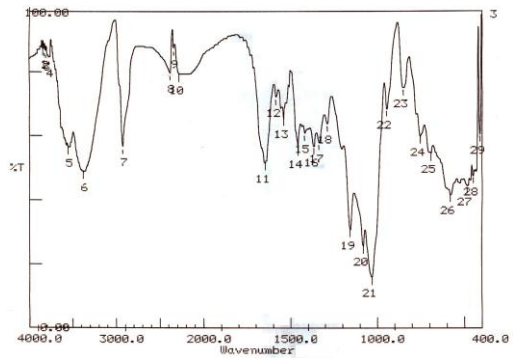

Figure 10: FT-IR Spectrum of Formulation – CSD_1

Functional group of Cefuroxime axetil is remaining stable in Solid dispersion complexes and its confirm that there is no interaction of drug with excipient.

XRD of Drug and Complex

The XRPD patterns of Cefuroxime Axetil:β-CD systems are represented in figure 11 to 13. The diffractograms of Cefuroxime Axetil and β-CD exhibited a series of intense peaks, which is an indicative of their crystalline nature. X-RD pattern of Solid dispersion (CSD_1) is simply the superimposition of each component indicating no formation of new structure. This indicates that the inclusion complex prepared by Solid dispersion contains crystalline peak.

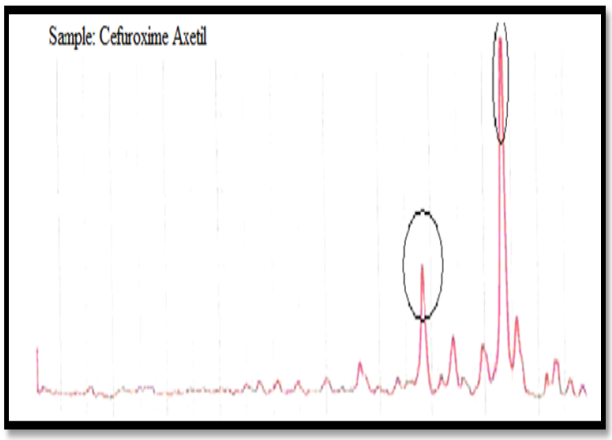

Figure 11: XRPD of Cefuroxime Axetil

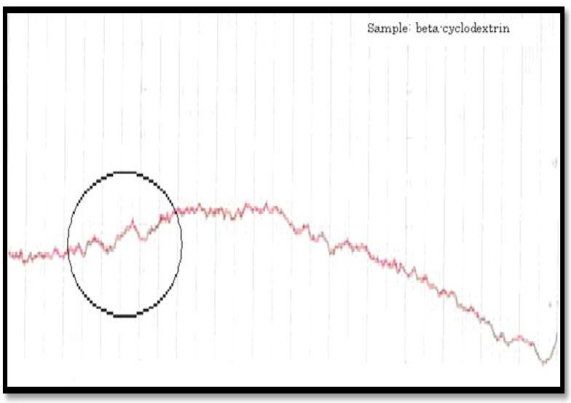

Figure 12: XRPD of beta-cyclodextrin

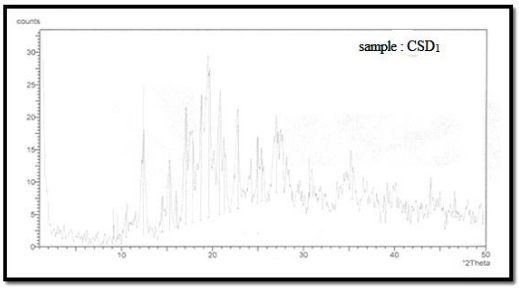

Figure 13: XRPD of CSD_1

DSC of Complex & Pure Drug

The thermal behavior of the Cyclodextrin inclusion complexes was studied using DSC in order to confirm the formation of solid inclusion complexes. When the guest molecules are incorporated in Cyclodextrin cavity or in the crystal lattice, their melting, boiling and sublimation points usually shifted to a different temperature or disappear within the temperature range, where the Cyclodextrin lattice is decomposed. The thermograms of pure Cefuroxime Axetil and β-CD and corresponding cyclodextrin complexes are presented in figure14. The DSC thermogram of Cefuroxime Axetil showed an endothermic peak at 210°C corresponding to its melting point. The thermogram of β-CD showed a very broad endothermic effect, which attained a maximum around 280 to 290°C due to the release of water molecules. The thermograms of Cefuroxime Axetil and β-CD (1:1 M) prepared by Solid dispersion i.e., CSD_1 showed broadened endothermic peaks at 225°C.

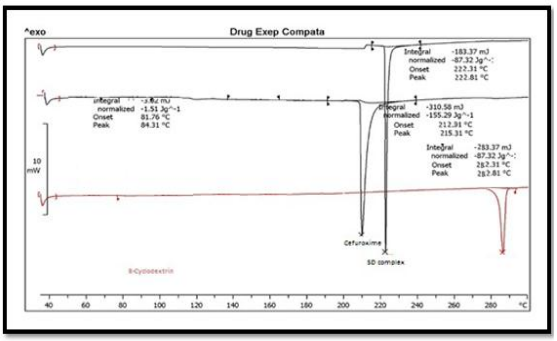

Figure 14: DSC of Pure Cefuroxime Axetil Drug, β-CD & CA: β-CD Complex (Solid Dispersion)

FTIR Studies of Resinate/Resin

The complexation was confirmed by carrying out IR studies on Indion 234, drug and Resinate complex. In the hydroxyl frequency region Cefuroxime Axetil shows a strong band at cm^{-1} and cm^{-1} which was attributed to hydroxyl stretching and carboxylic OH stretching respectively. The resinate of Cefuroxime Axetil –Indion 234 also shows these regions below to Cefuroxime Axetil indicating formation of complex.

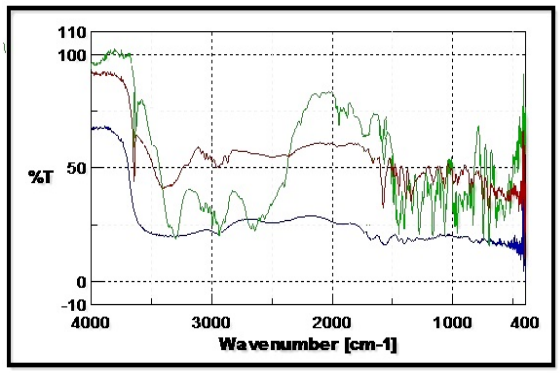

Figure 15: FTIR of Green: - Pure Cefuroxime Axetil, Blue: - Indion 234, Red: - Resinate.

OH-Stretching peak found at 3400.61 in resinate and near same in CA also and other Functional group of Cefuroxime axetil is remaining stable in Resinate complexes and its confirm that there is no interaction of drug with excipient.

Selection of Suitable Experimental Design

In a full factorial design, all the factors were studied at all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation. In the present study, fitting a cubic model is considered to be better as the values of the response surfaces are not known from the previous findings. Hence, 3^2 Factorial design (FD), was chosen for the current formulation optimization study.

Based on the criteria of minimum values of disintegration time (around 9 sec-1 minutes), high percentage release in 60 minutes (70-90%), and percentage friability (less than 1 %), the levels of two ingredients were fixed.

The disintegration time was found to decrease significantly with the increase in the concentration of camphor and sodium starch glycolate. Also, the release after 10 minutes was greatly increased with increase in concentration of both the ingredients. The percentage friability was above 1% with increased concentration of both the ingredients. Based on the results the levels of camphor and sodium starch glycolate is depicted in Table 13.

Table 13: Level of Camphor and SSG

Formula	SSG	CAMPHOR
S1	30	45
S2	40	45
S3	50	45
S4	30	35
S5	40	35
S6	50	35
S7	30	25
S8	40	25
S9	50	25

EVALUATION OF GRANULES

The prepared granules were evaluated for the blend property like bulk density, tapped density, Carr's index, Hausner ratio and angle of repose. Results obtained are shown in Table 14.

Table 14: Blend properties of formulation of Cefuroxime Axetil fast dispersible tablets

Formulations	Bulk density	Tapped Density	Carr's index	Hausner ratio	Angle of repose (in °)
S1	0.332±0.003	0.384±0.001	13.529	1.156	26.32±0.704
S2	0.276±0.001	0.336±0.001	17.938	1.218	25.64±0.480
S3	0.289±0.004	0.348±0.002	16.842	1.202	24.93±0.543
S4	0.303±0.002	0.374±0.003	18.894	1.232	25.50±0.483
S5	0.311±0.001	0.361±0.001	13.665	1.158	25.33±0.522
S6	0.277±0.001	0.322±0.002	13.857	1.160	27.40±0.654
S7	0.284±0.003	0.355±0.002	19.981	1.249	27.17±0.641
S8	0.332±0.002	0.381±0.007	12.838	1.147	26.11±0.222
S9	0.301±0.005	0.358±0.002	15.813	1.187	24.75±0.943

The above result predicts that, the Carr's index was in the range of 10-20% which is considered as excellent to good granulation property. Angle of repose less than 30° gives the good flow property to the granules. All these results indicate that, the granules possess satisfactory flow and compressibility properties.

EVALUATION OF FAST DISPERSIBLE TABLETS

Physical evaluation of tablets

All the tablet preparations were evaluated for various physical parameters and assay before proceeding further. Table 15 includes the values (mean ± SD) of weight variation, hardness and thickness of 9 tablet batches

prepared using different combinations of functional excipients. Tablet weights in all the 9 batches varied between 598 to 600, thickness between 4.53 mm to 4.73 mm and tablet hardness between 4.00 to 4.39 kg/cm^2. Thus, all the physical parameters of the manually compressed tablets were found within controls.

Table 15: Physical evaluations of 3^2 factorial designs on fast dispersible tablet

Trial No.	Formulation Composition		Physical Evaluation		
	SSG	Camphor	Weight Variation (mg)±SD	Hardness (kg/cm^2) ±SD	Thickness (mm) ±SD
S1	30	45	600.00±1.000	4.36±0.763	4.53±0.057
S2	40	45	599.33±1.154	4.39±0.763	4.66±0.057
S3	50	45	598.33±1.527	4.34±0.763	4.66±0.057
S4	30	35	599.33±0.577	4.31±0.500	4.60±0.100
S5	40	35	600.33±0.577	4.23±0.500	4.56±0.115
S6	50	35	600.00±1.000	4.00±0.288	4.53±0.057
S7	30	25	600.00±1.000	4.28±0.500	4.73±0.057
S8	40	25	599.66±0.577	4.29±0.500	4.73±0.057
S9	50	25	600.33±0.577	4.30±0.288	4.60±0.100
Broad Range			598-600	4.00-4.39	4.53-4.73

Table 16: Physical evaluations of 3^2 factorial designs on fast dispersible tablet

Trial no	% friability	Disintegration time(sec)±SD	% assay	Wetting time.	% Drug Release
S1	0.67±0.010	31.12±1.000	98.30±0.319	41.00±1.000	71.10±1.521
S2	0.68±0.026	30.20±1.527	98.92±0.432	32.33±1.527	97.44±1.528
S3	0.71±0.001	14.32±0.577	99.15±0.411	32.33±1.527	98.13±1.669
S4	0.85±0.015	29.33±1.527	98.65±0.496	22.33±1.154	62.86±1.445
S5	**0.79±0.001**	**15.66±1.527**	**98.61±0.997**	**15.33±1.527**	**99.15±1.004**
S6	0.81±0.010	14.66±1.527	98.19±0.380	19.33±1.527	72.54±1.544
S7	0.97±0.015	28.66±1.527	97.68±1.112	26.66±1.527	68.58±1.005
S8	0.97±0.015	17.66±0.577	99.42±0.444	21.33±1.527	83.82±1.027
S9	0.96±0.015	13±1.000	97.23±0.675	20.33±1.527	72.54±1.227
Range	0.67-0.85	13-31	97.23-99.42	10.33-41	62.86-99.15

***In-vitro* Disintegration Time**

According the European Pharmacopoeia, the Fast Dispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. It was observed that tablets of all the nine formulations had a disintegration time of less than 3 minutes and hence they passed the test for disintegration time.

Also, it was observed that S_1 to S_9 formulation had a disintegration time of less than 32 sec, indicating that concentration of sodium starch glycolate increased and the disintegration time decreased.

Wetting Time

The wetting time of tablets as shown in Table no 16 of all nine formulations was in the range of 9 to 42 seconds. The wetting time is closely related to the disintegration time. There is a direct relationship between the wetting time and disintegration time, i.e., faster the wetting time, faster is the disintegration time.

Tablet Assay

The drug content for tablets of all the formulations was found to be in the range of 97.23 - 99.42%. Thus, the assay of Cefuroxime Axetil was found to be within the range and satisfactory.

Dissolution Studies

The dissolution profiles of all the nine formulations are shown in Fig.16. The release of drug largely depended on the disintegration time. That is, faster the disintegration of tablets, better and faster the release. For formulation S_4 to S_9 the drug release was around 60-90% after 60 minutes.

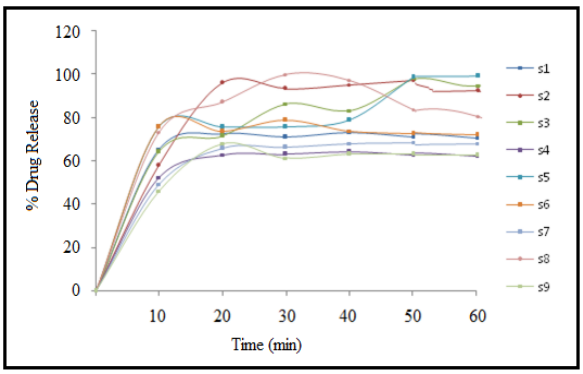

Figure 16: Dissolution Profiles of all the Nine Formulations

Contour plots and response surface analysis

Two-dimensional contour plots and 3-D response surface plots are shown in figure 17 and 18, which are very useful to study the interaction effects of the factors on

the responses. These types of plots are useful in study of the effects of two factors on the response at one time. All the relationships among the two variables are nonlinear, although they exhibit a nearly linear relationship as shown in figure 19.

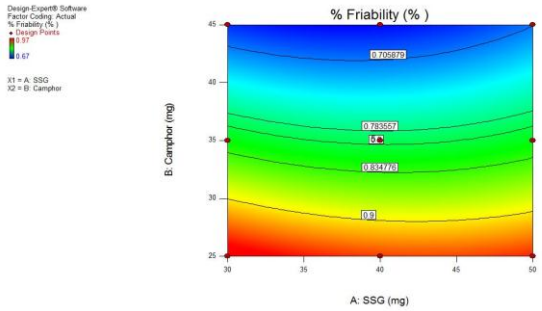

Figure 17: 2D contour plot of Y_1

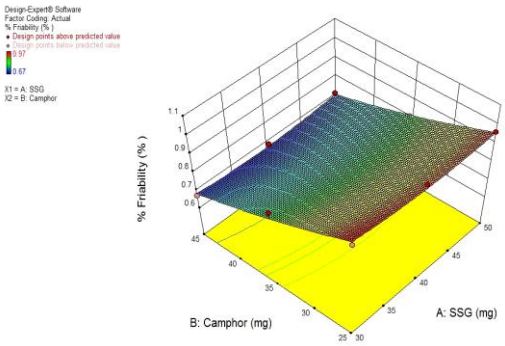

Figure 18: Response surface plot of Y_1 (% Friability)

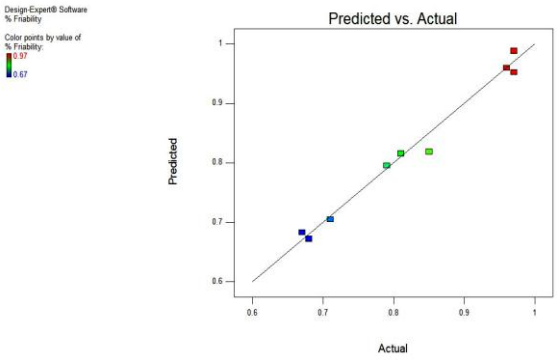

Figure 19: Linear correlation plot of Y_1 (% Friability) between actual and predicted value

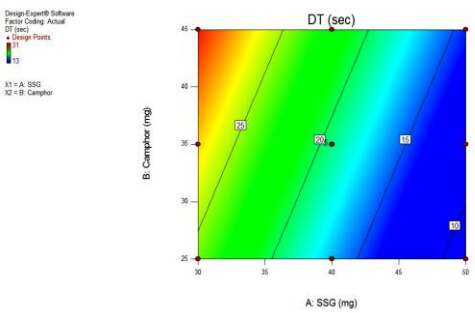

Figure 20: 2D contour plot of Y_2 (Disintegration Time)

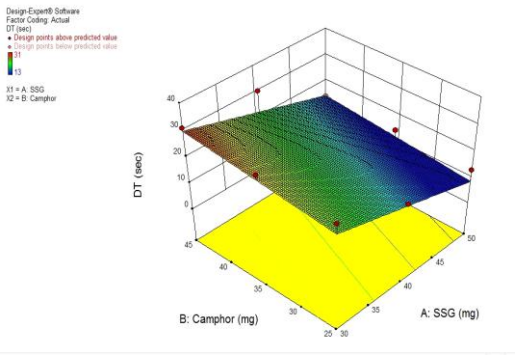

Figure 21: Response surface plot of Y_2 (Disintegration Time)

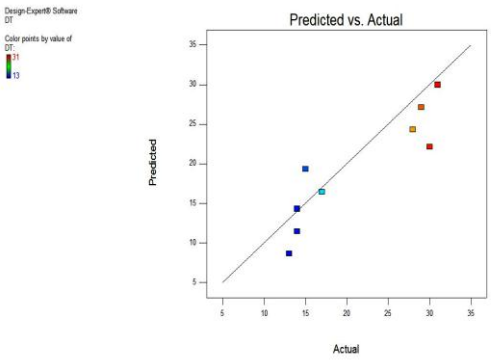

Figure 22: Linear correlation plot of Y_2 (Disintegration Time) between actual and predicted value

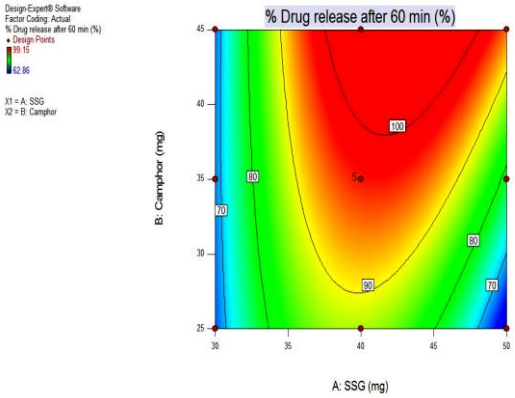

Figure 23: 2D contour plot of Y_3 (% Drug Release)

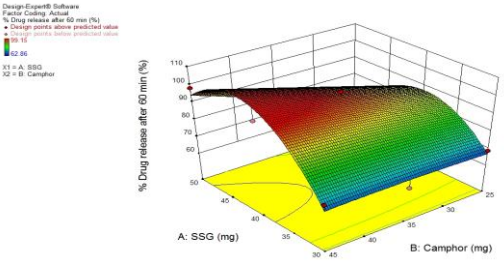

Figure 24: Response surface plot of Y_3 (% Drug Release)

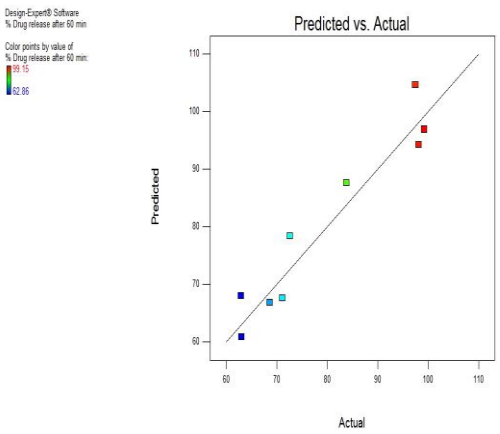

Figure 25: Linear correlation plot of Y_3 (% Drug Release) between actual and predicted value

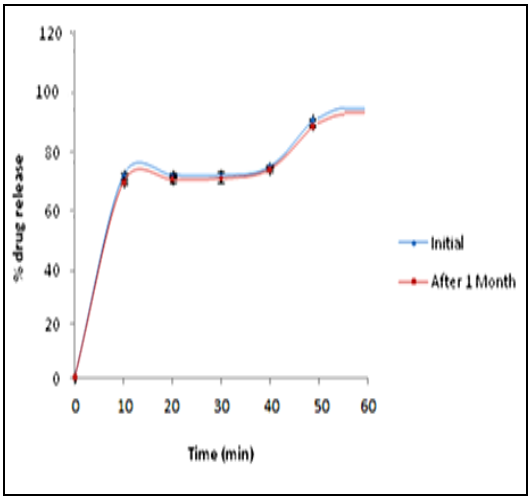

Figure 26: Comparative dissolution profile initial and after 1 month

ACELERATED STABILITY STUDIES OF OPTIMIZED BATCH S5

Table 17: Stability study of Optimized Batch S5 at 40^0C/75RH

PARAMETER	Initial	After 1 month
Hardness (kg/m^2)	4.33±0.500	4.33±0.500
Friability (%)	0.791±0.001	0.830±0.001
In-vitro Disintegration Time (sec)	17.66±1.527	18.33±1.527
Wetting Time (sec)	15.33±1.527	16.33±1.527
Assay	98.61±0.997%	97.64±0.995%

There were no changes observed in the hardness, *in-vitro* disintegration time, wetting time, assay and dissolution of the tablets after 1 month storage at 40^0C/75%RH. The results of stability indicates that the prepared formulations were stable.

SUMMARY AND CONCLUSION

Cefuroxime Axetil is second generation cephalosporin and an orally active drug. Cefuroxime exerts its bactericidal effect by binding to the enzymes involved in bacterial cell wall synthesis. Cefuroxime Axetil is used for upper respiratory tract infection for treatment of sudden allergic attacks. The drug has poor solubility in water and bitter unpleasant taste. Solubility was enhanced with β- CD by Solid dispersion method, before that it was confirmed by Phase solubility study indicated (1:1 molar ratio) Suggested A_l curve linearity with stability constant (416 M^{-1}). Solubility of Cefuroxime axetil was comparatively evaluated with drug solubility without solubilising agent by shaking flask method which was increased. The Phase Solubility Study was confirmed that solubility of Cefuroxime axetil was increased by the addition of β- Cyclodextrin & Stability Constant of CA: β- CD complex was 416 M^{-1}. Then complexes were characterized by FT-IR, DSC & XRPD studies to check the drug-excipients compatibility. In which FT-IR studies shows that there is no any interaction between drug and excipients. Peak of Cefuroxime Axetil was observed in complex form which indicates entrapment of drug in hydrophobic cavity and it confirms complex formation. In DSC indicated that Cefuroxime Axetil, β- CD & Cefuroxime Axetil containing solubilized agent exhibits endothermic peak at 210^0C, 283^0C & 225^0C respectively and thus it confirmed complex formation. In XRD, narrow broad peaks of complex shows the amorphous form and diffraction pattern of Complex was some what change than Cefuroxime Axetil which proves that complexes build in stabilized formed due to β- CD . Solubility of drug was enhanced by Solid dispersion techniques with addition of β- CD as a solubilizing agent was mentioned in result and discussion. % Cumulative Drug Release Studies proved 99.81% within 60 mins in 0.1 N HCl, which confirmed that solubility played its role in dissolution rate. Then selected complex was turned in to Taste masked resinate using indion-234 (1:0.5) ratio. It shows 59.30 % drug content with good taste masking by *in-vivo* & *in-vitro* taste evaluation. Resinate equivalent to 250 mg as a single dose converted in to fast dispersible tablet by Wet Granulation method using SSG, Camphor for prolonged action. 3^2 factorial designs was employed to design fast dispersible tablet according to trial batch S_1 to S_9 Afterward X_1- SSG & X_2- Camphor was selected as an independent variables with % Friability, Disintegration Time & % Drug release as a response parameter. Out of nine optimized formulation, S_5 was existing uniform friability with DT (15sec) & % Drug release (99.15%) in 60 min. From the results of % Cumulative Drug Release. RSM graph confirmed that as concentration of SSG was increased, drug release increased with addition of optimum concentration of Camphor as a subliming agent.

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