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FORMULATION DEVELOPMENT AND EVALUATION FOR POORLY WATER-SOLUBLE DRUG CEFADROXIL

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ABSTRACT

Cefadroxil is a broad-spectrum antibiotic of the cephalosporin type, effective in gram-positive and gram-negative bacterial infections. It is a bactericidal antibiotic. Cefadroxil, a first-generation cephalosporin antibiotic, is used to treat urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. In the present study an attempt has been made to enhance the dissolution rate of a poorly water soluble drug Cefadroxil through the use of super disintegrants. Three super disintegrants, namely, croscarmellose sodium, crospovidone and sodium starch glycolate indifferent concentrations (2, 4, 6 and 8 percent) were employed. The drug selected for present work is Cefadroxil, drug which in the form of hard gelatine capsule. Cefadroxil showed maximum absorption at 278.0 nm and obeyed Beer's law in concentration range of 10-80 µg/ml. Results of analysis were validated statistically and by recovery studies. The proposed method is new, simple, eco-friendly, economic, and accurate and can be utilized in routine analysis of cefadroxil tablets.

Keywords: Hydrotrophy, Spectrophotometry, Dissolution Studies, Croscarmellose Sodium and Cros-povidone as Dispersants

INTRODUCTION

Solubility can be defined as the property of a substance solid, liquid, or gaseous chemic al in nature called solute to dissolve in a solvent solid, liquid, or gaseous in nature to form a homogeneous solution of the solute in the solvent. The solubility of a substance depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and the pH of the solution. The extent of the solubility of

a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begin to precipitate the excess amount of solute.

Most often, the solvent is a liquid, which can be a pure substance or a mixture. One may also speak of solid solution, but rarely of solution in a gas **[1]**.

Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs **[2]**.

The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive pi (π) orbital **[3]**.

MATERIAL AND METHODS

Preformulation Study

Preformulation is the first step in the rational development of dosage form of cefadroxil and it is defined as an investigation of physical chemical properties of cefadroxil alone and when combined with excipients.

Determination Of λ max

Test Solution:

Weigh accurately 20 mg of sample and dissolve in and dilute to 100 ml of the methanol.'

Standard Solution:

Weigh accurately 20 mg of Cefadroxil and dissolve in and dilute to 100 ml of the

methanol. The solution was kept in cuvette of fused silica cell and UV light absorption of the spectrum in the range of 200 nm to 400 nm and compare for the maxima and minima. The spectrum obtained from the test solution should be concordant with the spectrum obtained from standard solution.

Calibration Curve Uv-Visible Spectrophotometry:

Standard Curve of Cefadroxil in Methanol At λ max 278 nm

Cefadroxil was weighed approximately 100mg and dissolved in 100 ml of methanol and volume was made up to 100 ml using methanol. This resulted in preparation of stock solution of 1000 µg/ml. From this stock solution 10 ml was withdrawn and transferred in to 100 ml volumetric flask volume was made up with methanol in order to get standard stock solution containing 100 µg/ml. withdrawn.0.5, 0.1, 1.5, 2.0, 2.5ml of sample separately and further diluted up to 10 ml with methanol. Respectively to prepare aliquot's from conc. 5-25µg/ml The solution was scanned in visible range λmax of 278.0 nm. And standard curve was plotted between conc. µg/ml on x-axis and absorbance on y-axis.

Absorbance and concentration for determination of partition coefficient

FT-IR Study Fourier transform spectrophotometers used polychromatic radiation reaction & calculate the spectrum in frequency domain from the original data by fourier transformation.

Preparation of standard

Weighed approximately 0.001 g of cefadroxil & 0.1 g of KBr.

Preparation of sample

Weighed approximately 0.001 g of cefadroxil & 0.1 g of KBr.

IR spectroscopy was performed using FT/IR Spectrometer and the curve found between the % transmittance and frequency (cm^{-1}) which is nearly similar with the reference spectrum of Cefadroxil.

The IR spectrum of the sample is Concordant with the spectrum of working standard

Drug-Excipient Interactions Studies By IR

Method- An accurately weighed quantity of KBr was dried in Hot air oven at 600-700 ^{0} C. dried KBr crushed & put in assembly for finding the background. After it 95% of KBr & 5% of the mixture of drug and excipient was mixed. Mixture was placed in assembly and then an IR spectrum was obtained which is given below.

Formulation of Cefadroxil Capsules:

Cefadroxil was passed through sieve No. 80 followed by other additives and super-disintegrants. The lubricants magnesium stearate and colloidal silicon dioxide were passed through sieve No. 100. Weight

approximately 500mg cefadroxil and additives were transferred to a cylindrical tumbling mixer and mixed for 10 minutes at 15 rpm. The blend was filled (650 mg) in a hard gelatin capsule 'zero' size.

Drug Content Estimation of Cefadroxil Capsules:

The contents of the capsule were emptied and a weight of the powder equivalent 50 mg drug was dissolved in water in a 50 ml volumetric flask. The solution was filtered through Whatmann No. 1 filter paper into another 50 ml volumetric flask and more solvent was passed through the filter to make up to the mark. Further appropriate dilutions were made to give a concentration of approximate 20 mcg/ ml and the absorbance was measured at 278.0 nm using distilled water as blank. The mean percent drug content was calculated as an average of three determinations.

In-Vitro Dissolution Studies:

In-vitro dissolution studies of Cefadroxil capsules were studied in USP XXIII dissolution apparatus-I (Electrolab) employing a basket stirrer, 900 ml of distilled water was used as dissolution medium. The rpm was set to 75 and temperature of the dissolution medium was previously warmed at 37±0.5ºC and was maintained throughout the experiment. One capsule was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of syringe fitted with a pre filter at a known interval. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The samples were analyzed for drug by measuring the absorbance at 278 nm using UV-visible spectrophotometer after suitable dilutions.

Details of in- vitro dissolution studies of Cefadroxil capsules:

Apparatus	**USP**
XXIII tablet dissolution apparatus-I	
Dissolution medium	
Distilled Water	
Dissolution medium volume (ml)	**900**
Temperature (degree)	**37±0.5**
Basket stirrer speed (rpm)	**75**
Sample volume withdrawn (ml)	**5**

RESULTS

Preformulation Study

Results of Preformulation Study can be seen in **Table 1 and 2 below**.

Determination Of λ max

Results of λ max Determination can be seen in **Table 3 and Figure 1, 2 below**.

Calibration Curve Uv-Visible Spectrophotometry:

Results of Calibration Curve Uv-Visible Spectrophotometry and Standard Curve of Cefadroxil in Methanol At λ max 278 nm have been shown in **Figure 3** and **Table 4**.

FT-IR Study

IR spectroscopy was performed using FT/IR Spectrometer and the curve found between the % transmittance and frequency (cm^{-1}) which is nearly similar with the reference spectrum of Cefadroxil **(Figure 4)**.

Table 1: Physical Appearance

S. No.	Properties	Results
1.	Description	Crystalline
2.	Taste	Slightly bitter
3.	Odour	Odourless
4.	Colour	White or almost white powder

Table 2: Solubility Profile of Cefadroxil

S No.	SOLVENTS	OBSERVATION SOLUBILITY
1	Methanol	Freely soluble
2	Alcohol	Soluble
3	Acetone	Soluble
4	PBS	Slightly Soluble
6	Chloroform	Soluble
7	Water	slightly soluble
8	Toluene	very slightly soluble

Table 3: Determination of absorption maxima of Cefadroxil

Wavelength(nm)	Interpretation	Inference
200-400	Scanning range	Drug absorption maxima (λmax) 278.0nm of Cefadroxil
278.0	Highest peak	

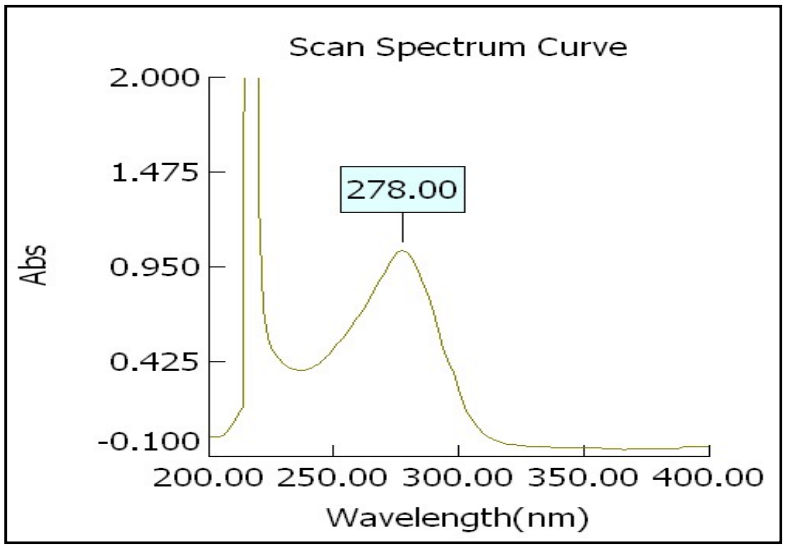

Figure 1: Determination of absorption maxima (λmax) in Methanol

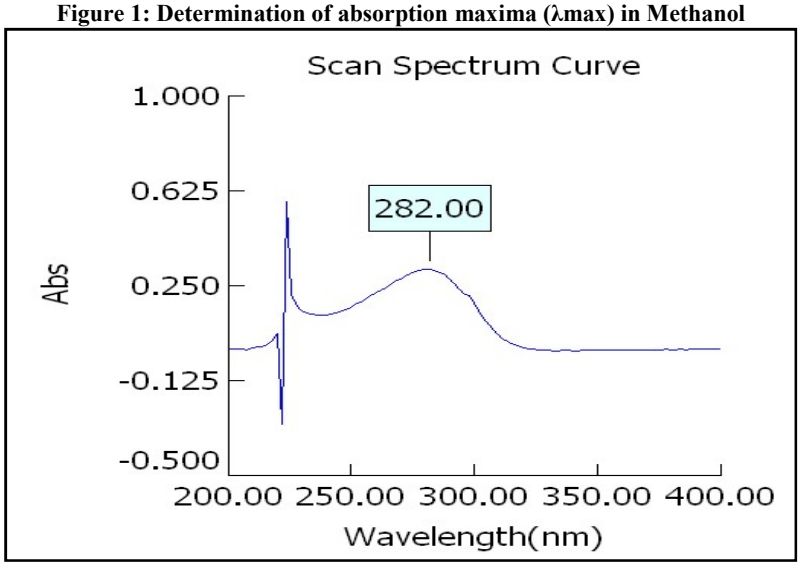

Figure 2: Determination of absorption maxima (λmax) in Water

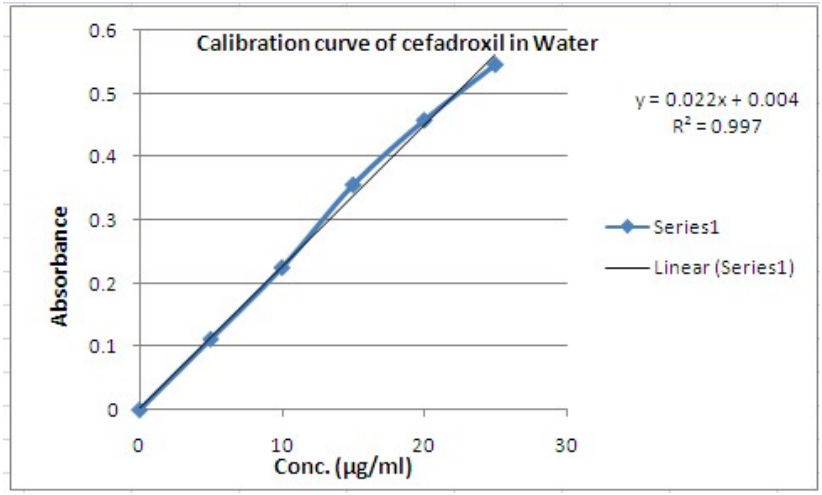

Figure 3: Calibration Curve of Cefadroxil in water
Correlation coefficient (R^2) = 0.997; Equation of regressed line: y = 0.022x + 0.004
Y= value of absorbance; Slope of regressed line= 0.004

Table: 4 Partition coefficient of Cefadroxil

S. No.	Solvent System	Partition coefficient
1.	n-octanol:Water	1.24

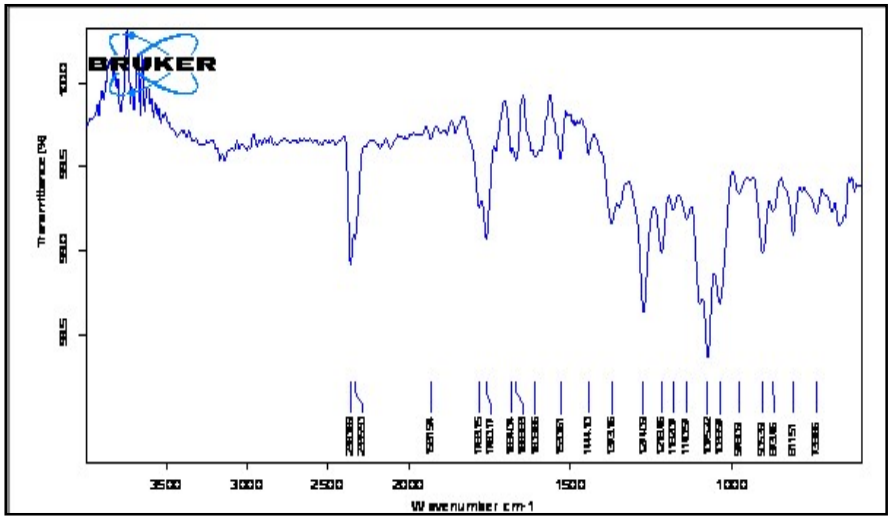

Figure 4: Working standard IR spectrum of Cefadroxil

Drug-Excipient Interactions Studies By IR

Mixture was placed in assembly and then an IR spectrum was obtained which is given below in **Figure 5**.

Formulation of Cefadroxil Capsules:

Cefadroxil was passed through sieve No. 80 followed by other additives and super-disintegrants **(Table 5)**.

Drug Content Estimation of Cefadroxil Capsules:

The mean percent drug content was calculated as an average of three determinations. The results are shown in **Table 6**.

In-Vitro Dissolution Studies

In the present study nine formulations with var iable concentration of dispersants were prepare d by and evaluated the solubility as compared to marketed formulation. The results indicated below **Table 7-10 and Figure 6, 7**.

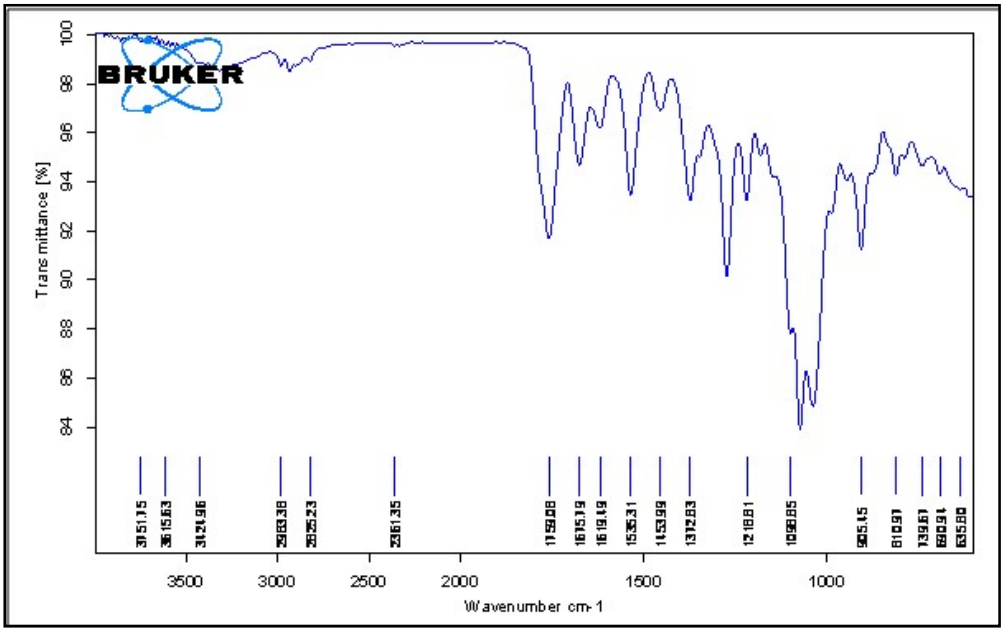

Figure 5: IR spectra of Cefadroxil

Table 5: Formulation codes of Cefadroxil Capsules with Croscarmellose Sodium and Cros-povidone as Dispersants-

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Cefadroxil	500	500	500	500	500	500	500	500	500
2.	Lactose	126	116	108	126	116	108	126	116	108
4.	Croscarmellose sodium	16	24	32	-	-	-			
5.	Cros-povidone	-	-	-	16	24	32			
6.	Sodium starch glycolate	-	-	-	-	-	-	8	12	16
7.	Sodium lauryl sulphate	-	-	-	-	-	-	8	12	16
8.	Magnesium stearate	5	5	5	5	5	5	5	5	5
9.	Colloidal silicon dioxide	5	5	5	5	5	5	5	5	5
10.	Total Weight	650	650	650	650	650	650	650	650	650

Table 6: Average net weight and drug content determination of Formulations

S.No	Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Average net weight* (mg) ±SD	650± 0.001	650± 0.002	650± 0.002	650± 0.002	650± 0.001	649± 0.002	648± 0.002	650± 0.002	650± 0.003
2.	Percent drug content*±SD	99.43± 0.498	98.73 ± 0.410	98.93± 0.410	98.80± 0.163	97.93± 0.249	98.40± 0.163	99.20± 0.326	99.36± 0.543	99.9± 0.312

*** Average of three determinations**

Table 7: Release Kinetics of Cefadroxil Capsules

Time	Formulation Code									Marketed Formulation
	F1	F2	F3	F4	F5	F6	F7	F8	F9	
5	30.22	30.22	35.47	27.14	30.53	34.54	37.93	35.47	38.86	11.25
10	33.62	35.47	38.55	31.15	35.47	44.72	44.72	38.55	40.40	22.12
15	37.32	41.64	41.64	38.55	37.93	52.07	61.99	41.64	44.72	35.56
20	41.64	44.72	47.80	41.02	43.49	60.38	68.78	50.89	66.97	42.23
30	50.89	50.89	50.89	47.80	50.89	78.64	78.95	61.99	75.67	53.26
40	67.85	64.77	64.77	61.07	81.73	84.81	87.90	78.64	85.73	68.89
50	92.83	78.95	82.96	72.79	92.83	95.30	97.15	91.91	99.27	72.25
60	98.38	95.92	99.31	95.61	99.00	98.69	100.23	99.00	100.23	88.56

Table 8: Zero Order Release Kinetics of Optimized Formulation F9

S.NO.	Time (Min.)	% CDR
1	5	38.86
2	10	40.40
3	15	44.72
4	20	53.97
5	30	57.67
6	40	81.73
7	50	99.27
8	60	100.23

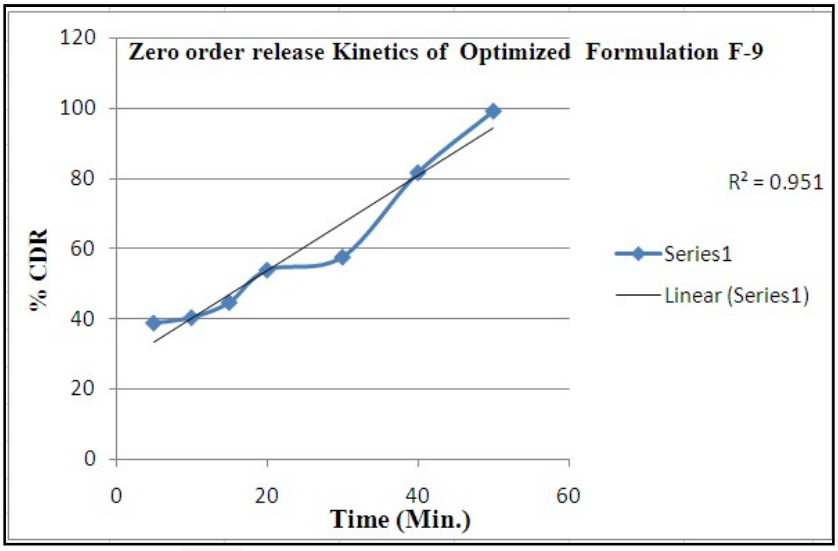

Fig 6: Zero order release kinetics of cefadroxil

Table 9: First order Release kinetics of Optimized formulation F9

S.NO.	Time (Min.)	Log % CDR
1	5	1.589501
2	10	1.606401
3	15	1.650498
4	20	1.732168
5	30	1.760972
6	40	1.912376
7	50	1.996814
8	60	2.001014

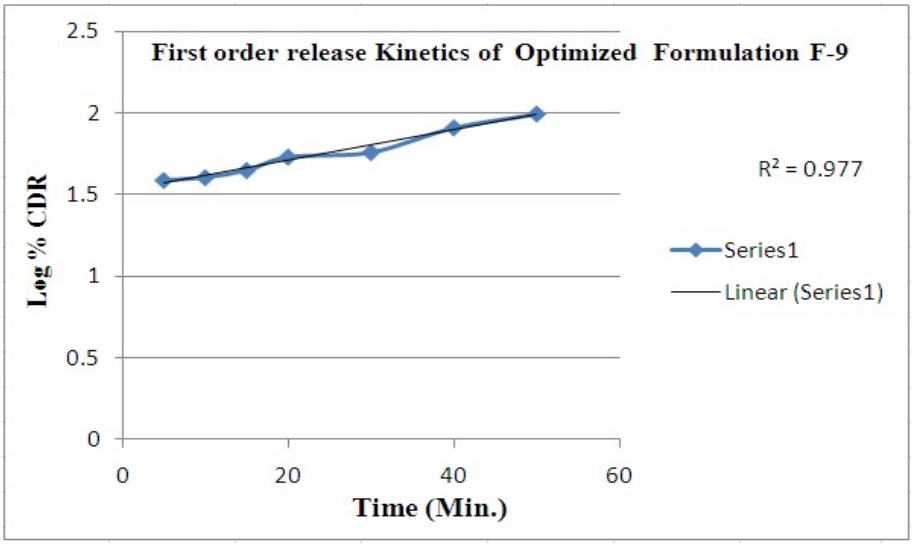

Figure 7: First order release kinetics of cefadroxil

Table 10: Comparative study of regression coefficient for selection of optimized Formulation F-9

Zero order		First order
r2	0.951	0.977

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry because of their dissolution rate limited absorption, which influences their oral bioavailability.

In the present study an attempt has been made to enhance the dissolution rate of a poorly water soluble drug Cefadroxil through the use of super disintegrants. Three super disintegrants, namely, croscarmellose sodium, crospovidone and sodium starch glycolate indifferent concentrations (2, 4, 6 and 8 percent) were employed.

DISCUSSION

The drug selected for present work is Cefadroxil, drug which in the form of hard gelatine capsule.

- The drug sample was firstly identified spectrophotometrically by UV, FTIR and the result showed the authenticity and purity of drug sample.
- The maximum absorbance of drug was determined by UV-3000+ Labindia spectrophotometer and was found to be at 278.0 nm which was in accordance with the standard.
- Qualitative solubility of drug was checked in various solvent and found that the drug was freely soluble in methanol, soluble in acetone, alcohol, sparingly soluble in isopropanol, chloroform, slightly soluble in phosphate buffer saline, water, very slightly soluble in toluene and which shows that the drug is lipophillic.
- Partition coefficient of the drug was determined in n-octanol:distilled water The value of partition coefficient was found to be 1.24.
- Melting point of drug was determined by capillary melting point apparatus. The melting point was found to be in the range of 197-199°C which was matched with standard melting point.
- Drug-excipient interaction was determined by IR spectrophotometer which shows no interaction between drug and excipient.

Drug content uniformity studies:

All the formulations were found to be white, fine and free flowing powders. The drug content estimated in various formulations are given in the tables-7.2 were found to be within ±2.5% range of the expected percent drug content values in majority of the cases. The low values of the standard deviation and coefficient of variation (<2%) indicate uniform distribution of the drug within the prepared formulations.

In Vitro Dissolution study:

The data from the dissolution studies of Cefadroxil in pure form and from various formulations are given in **Table 7-10 and** the dissolution profiles are shown in **Figure 6, 7**.

The formulation containing 2% croscarmellose sodium and SLS (F-9) showed a marked increase in the dissolution rate of Cefadroxil (100% in 60 minutes). No significant increase in the dissolution was observed with further increase in the concentration of croscarmellose sodium.

The efficiency of the excipient inenhancing the dissolution rate of Cefadroxil can be attributed to excellent swelling property of the croscarmellose sodium and increased effective surface area of the drug. From this data it can be clearly seen that croscarmellose sodium gave a very fast drug release when compared to other dispersants.

Drug Release Kinetics:

The in vitro drug release data obtained from all formulations were fitted into two popular models of data treatment.

• Cumulative percent drug release versus time plots (zero-order).

• Log cumulative percent drug remained versus time plots (first-order).

When the data was plotted as log cumulative percent drug remaining versus time, the plots obtained were linear indicating first order release kinetics.

Statistical analysis of the data by the method of least squares gives correlation coefficient values in the range of –0.951 to –0.977 for most of the formulations.

CONCLUSION

From the present study, the following conclusions can be drawn:

- The formulations prepared using super-disintegrants were found tobe white, fine and free flowing with uniform drug content.
- IR spectroscopic studies indicated that there are no drug-excipient interaction.
- In vitro dissolution studies indicated that there is an increase in the dissolution rate with addition of super disintegrants.
- The drug release from all the formulations displayed nearly first order release kinetics.
- Formulation containing 2% croscarmellose sodium showed promising results in enhancing the dissolution rate of cefadroxil (99.27% release in 50 min.). This formulation (F9) has displayed a two-fold increase when compared to the commercial formulation. Thus, it can be concluded that the superdisintegrant croscarmellose sodium can be used for enhancing the in vitro dissolution rate

of poorly water soluble drug cefadroxil, providing nearly first order drug release.

- The efficiency of various super-disintegrants in enhancing the dissolution rate of cefadroxil.

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