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FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLET OF CEFIXIME BASED ON CYCLODEXTRIN BINARY SYSTEMS

B. Radha Madhavi*[1]
Varanasi S N Murthy[1]
A. Prameela Rani[1] and
Y. Mohan Kumar[2]

[1] A. N.U. College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar – 522510, Guntur
[2] Scientist, FRD, IPDO, Dr. Reddys Laboratories, Hyderabad.

ABSTRACT

The purpose of the present study was to formulate and evaluate taste masked oral disintegrating tablets of Cefixime to increase the palatability and bioavailability of the drug. In the present work, an attempt was made to mask the taste by complexation technique, Taste improvement of drug by β-Cyclodextrin was done by simple complexation approach using physical and kneading methods with various ratios. Taste perception study was carried and the optimized taste masking ratio 1:3of kneading mixture was selected based on bitterness score and characterized by Fourier transform infrared spectroscopy (FTIR) to identify the physicochemical interaction between drug and carrier and its effect on dissolution. In-vitro drug release studies for the prepared solid dispersions were performed in phosphate buffer pH 7.2 buffer. 1:3 kneading system showed better results when compared to the dispersions prepared by other methods. Tablets were prepared by direct compression technique using super disintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium. Prepared tablets were evaluated for different properties like drug content, hardness, friability, disintegration time and in vitro dissolution study. The different formulations showed disintegration time between 30 to 56s. Among all the formulations, C6 showed 99 % drug release within 20 min. Thus, C6 was considered best among the other formulations.

Keywords: Cefixime, taste masking, cyclodextrin, binary systems

INTRODUCTION:

Formulation of orally disintegrating tablets (ODTs) has enormously increased as it is in continuous demand and it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. ODT s is not only specific with pediatric and geriatric population but also with institutionalized patients and patients with nausea, vomiting and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population[1].

Due to several reasons and undesirable taste, most of the pharmaceuticals are administered orally but bitter taste is one of the formulation problem encountered with such oral products [2, 3]. Taste of pharmaceutical product is important parameter in governing the patient compliance. Thus taste masking of oral pharmaceutical formulations has become important tool to improve patient compliance and especially the quality of treatment [4, 5].

Address for correspondence

B. Radha Madhavi*
A. N.U. College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar – 522 510, Guntur

β-cyclodextrin is most widely used complexing agent for inclusion type complexes. Cyclodextrins (CD) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. On account of their relatively hydrophobic interiors, CDs have the ability to form inclusion complexes with a wide range of substrates [6]. This complex-forming ability of CD has been widely exploited in the pharmaceutical field for various applications, including taste-masking of bitter drug [7].

The use of CD as a taste-masking agent has been widely reported [8, 9]. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma and beta cyclodextrin stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste [10,11].

Cefixime **Figure 1** is used to treat infections caused by bacteria such as pneumonia, bronchitis, gonorrhoea, and ear, lung, throat, and urinary tract infections. Cefixime has bitter taste so; an attempt has been made to mask the bitter taste of the drug by complexation with β-cyclodextrin [12].

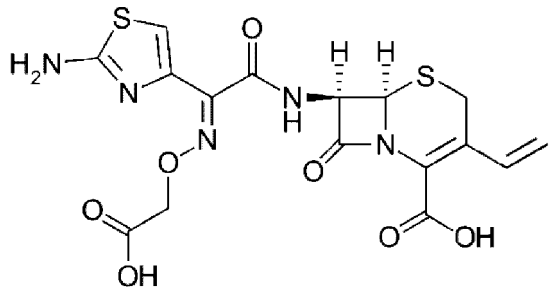

Figure 1: Chemical Structure of Cefixime

MATERIALS AND METHODS

MATERIALS:

Cefixime was kindly gifted by Dr. Reddy's laboratory, Hyd., All the other chemicals and solvents used were of Pharmaceutical and analytical grade obtained from commercial sources.

METHODS:

A) Preparation of solid dispersion of Cefixime

Cefixime solid dispersions were prepared by physical mixing and kneading methods using drug: beta cyclodextrin in ratios, viz. 1:1, 1:2, 1:3 (Drug:Carrier). Methanol is selected as common solvent for preparation of solid dispersions.

- ***Physical mixture:***

Accurately weighed amount of drug and beta cyclodextrin were taken into glass mortar and then mixed for 10 minutes to get good mixture of drug and polymer. Then the product was stored in the desiccator for further study.

- ***Kneading method:***

Accurately weighed amount of Cefixime and β-cyclodextrin were taken into glass mortar and then methanol was added in small quantity and the mixture was kneaded for 45min and then dried in oven at 40 ^{0}C. The product obtained was pulverized and passed through mesh (#) 80 and stored in desiccator for further study.

Evaluation of β-CD inclusion complexes:

- ***FTIR studies:***

IR spectrophotometer was used for infrared spectroscopy analysis of drug and complexes. The samples were prepared in KBr disk by means of a hydrostatic press. The scanning range was 400- 4000 cm^{-1}.

- **Drug content:**

An accurately weighed amount of complex (equivalent to 50 mg of cefixime) was dissolved in small volume of methanol in 50 ml volumetric flask and made upto the volume .From this solution 1 ml was diluted with methanol in 10 ml volumetric flask, again 1 ml of this solution was taken and diluted to 10 ml. The absorbance of this solution was measured at 282 nm using appropriate blank.

- **Evaluation of taste masking character of drug/ β-CD complex**

Taste masking ability of prepared formulations was evaluated using taste panel of six healthy human volunteers. In this test, volunteers were given a little sample of pure drug (2 mg) and equivalent sample from β-CD complex formulations to taste and evaluate the bitterness and give their response after ten seconds. The response was evaluated on a scale from 0-4, where 0 = good, 1= tasteless, 2= slightly bitter, 3= bitter and 4 = very bitter. Each volunteer was asked to detect the taste of both drug and the complex to act as his or her own control. The results of this test indicated a score of 1which indicated that the complexes formed between drug and β-CD are tasteless.

- ***In-vitro* dissolution studies of pure drug and complex:**

Dissolution study of samples (equivalent to 50 mg cefixime) was performed using USP XXIV type II apparatus with 900 ml of phosphate buffer pH 7.2. The stirring speed employed was 50 rpm, and the temperature was maintained at 37 ± 0.5 ^{0}C. Five millilitre aliquots of dissolution medium was withdrawn at predetermined time intervals and replaced by 5 ml of fresh dissolution medium. The filtrates of the samples were analyzed for the content of drug by UV spectrophotometer at 282 nm.

B) Formulation of Oral Disintegrating Tablets by Direct Compression Method

Fast dissolving tablets of cefixime were prepared by direct compression method according to the formulae given in **Table 4**. All the ingredients were passed through sieve # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 350 mg using 12mm, flat punches on 10-station rotary tablet machine (Riddhi, Ambalacant).

- **FTIR studies**

IR spectra of cefixime and the finalised formulation were obtained by potassium bromide pellet method using Bruker – Alpha FTIR spectrophotometer in order to rule out drug-carrier interactions.

Evaluation of blends:

The powder blend was evaluated for its flow properties such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio.

- ***Angle of Repose:***

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

$$ɵ = \text{Tan}^{-1} [h/r]$$

- ***Bulk density:***

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\text{Apparent bulk density} = M/ V_b$$

- ***Tapped density:***

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M)

of the blend was measured. The tapped density was calculated using the formula:

Tapped density = M/ V_t

➢ ***Compressibility index:***

Compressibility index I is calculated as follows:

$I = V_b - V_t / V_b \times 100$

Where - V_b is the bulk volume; V_t is the tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.

➢ **Hausner's ratio:**

Hausner's ratio10 is an indirect index of ease of powder flow. It is calculated by the following formula Hausner's ratio =T apped density/Bulk density Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25)

Evaluation of tablets

➢ **Weight variation**

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation.

➢ **Drug content**

The cefixime content in the filtrate was determined by measuring the absorbance at 282 nm after appropriate dilution with distilled water. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

➢ **Disintegration test**

Tablets were taken and introduced one tablet in each tube of disintegration apparatus and the tablet rack of the disintegration apparatus was positioned into a 1 – litre beaker and the time of disintegration was recorded.

➢ **Wetting time**

A piece of tissue paper folded twice was placed in a small petridish (Internal diameter = 6.5 m) containing 5 ml of distilled water. A tablet was placed on the paper, and the time of complete wetting of the tablet was measured in seconds.

➢ **Dissolution study**

In vitro dissolution of cefixime fast disintegrating tablets was studied in USP XXIII type-II dissolution apparatus (Lab India – Disso 8000) employing a paddle stirrer at 50 rpm using 900 ml of pH 7.2 phosphate buffer at 37 ± 0.5 ^{0}C as a dissolution medium.

RESULTS AND DISCUSSION

Drug content of solid dispersions

The Cefixime solid dispersions were tested for drug content and it was found that the drug was within the compendial limits 95-101% w/w. All the solid dispersions were uniform in drug content. The results were shown in **Table 1**.

FTIR studies:

The IR spectrum of Cefixime, Cefixime: β-CD complex were shown in the **Figure 2(a) and 2(b)** respectively. The IR spectrum of Cefixime exhibited peak at 3370 cm^{-1} due to N-H stretching, while peak at 1338 cm^{-1} indicate SO2 stretching. The IR spectrum of β-cd showed peak at 3394 cm-1. The IR spectrum of Cefixime: β-CD (1:3) inclusion complex prepared by kneading method has shown peaks at 3374 cm^{-1}and 1340 cm^{-1}.

Taste evaluation of Cefixime -β-CD sloid dispersions

The efficiency of taste masking was evaluated by six human volunteers. It was observed that there was no bitter taste percepted for both binary systems viz. physical mixture and kneading mixture when compared with the pure drug. The results have been shown in **Table 2**. It is confirmed that the bitter taste of Cefixime was masked by complexing with β –cyclodextrin.

***In-vitro* dissolution studies**

Cefixime release from the solid dispersion and the drug alone was studied up to 60 minutes. The average percentage release of the pure drug was found to be 36.8% in 60 minutes. In the solid dispersions formulation, β-cyclodextrin was used as carrier and the dissolution rate increased with increased amount of cd. The best results among solid dispersions with β-cd were obtained for the complex C-6 **Figure 3**. Dissolution data of Cefixime and its cyclodextrin complexes prepared by three methods in different ratios were given in **Table 3**. The increased dissolution rate may be due to the higher solubility of β-cd in dissolution medium and better wettability of Cefixime in the complex.

EVALUATION OF TABLETS:

The FTIR spectra of cefixime with the excipients and the final formulation were shown in the **Figure 4**. The spectrum obtained has shown that there is no interaction of excipients with the drug. The final blend of tablets was evaluated for flow properties and was found that the flow property of prepared blends was good and the values of different physical tests are given in the **Table 5**. The tablets obtained had drug contents in the range of 98 to 100%.

This is within the acceptable limit. Hardness of tablet was found to be in the range of 2.5 to 3.30 kg/cm2. Friability was found to be below 1% which indicates good mechanical strength of the tablets. The results were shown in the **Table 6**. In-vitro dissolution studies for F-6 tablet which is based on Cefixime with 15% crospovidone showed good dissolution efficiency. The cumulative percent drug released data was shown in the **Table 7** and **Figure 5**. Wetting time the critical parameter for evaluation of performance of ODT's was found to be in the range of 26 to 50 second respectively. All the formulations found to have much faster wetting time. The disintegration time (DT) for the formulation prepared with Sodium Starch glycolate (F1 to F3) was found to be in the range of 40-48seconds and the formulations prepared with crospovidone (F4 to F6) showed the disintegration time within the range of 28-42.

In case of formulation prepared with Croscarmellose sodium (F7 to F9) the DT was found to be 50-58 seconds. Among all the formulations F6 was showing promising results as the DT was 26 seconds. Wetting time prepared for all the formulations was found to be in the range of 22-44. Among all the formulations F6 showed less wetting time of 22 seconds. The results are shown in the **Table 8 and Figures 6 and 7**.

Various dissolution parameters values viz., Dissolution efficiency at 30 min (DE30%), Percent drug dissolved in 10 min(D10),Percent drug dissolved in 30 min (D30),Time taken to dissolve the 50%.70% and 90%drug(t50, t70, t90 respectively) were given in the **Table 9**. Based on the data obtained on the dissolution rate, the disintegrants can be ranked as crospovidone > Sodium starch glycolate > croscarmellose sodium. The results were shown in **Fig 6**.

15% crospovidone showed better dissolution efficiency among the disintegrants studied at three levels (5%, 10% and 15%). Hence crospovidone was recommended as suitable disintegrant and the study shows that the dissolution rate of Cefixime can be enhanced to a great extent by Direct- compression technique with the addition of super disintegrants, which gives quick relief.

Table 1: Drug content of prepared solid dispersions

Cefixime: β-CD	Ratio	Product name	Percent drug content present
Physical Mixture	1:1	C1	98.3±1.02
	1:2	C2	99.6±0.08
	1:3	C3	98.9±0.06
Kneading method	1:1	C4	97.4±0.01
	1:2	C5	98.4±0.04
	1:3	C6	99.1±0.02

Table 2: Bitterness evaluation by taste panel

Solid dispersions	1	2	3	4	5	6
C1	4	4	4	4	4	4
C2	1	2	2	2	2	1
C3	1	1	2	1	2	1
C4	1	1	1	1	2	2
C5	0	0	1	1	1	1
C6	0	0	0	0	0	0

Table 3: Cumulative Percent Drug Released data of Cefixime from Inclusion complexes in pH 7.2 phosphate buffer

Time (min)	Pure drug	Physical mixtures			Kneading method		
		C1	C2	C3	C4	C5	C6
5	10.6±1.40	29.1±1.56	32.6±0.74	48.1±0.50	52.4±0.50	57.8±0.91	64.6±1.05
10	18.8±1.04	41.8±1.19	49.7±1.04	56.8±0.70	59.1±0.70	63.0±0.82	69.7±1.01
15	24.6±1.02	55.2±0.98	58.8±1.02	60.8±0.90	62.6±0.90	65.2±0.12	75.2±0.45
30	42.2±1.68	75.7±1.04	79.8±0.81	82.1±0.90	85.4±0.90	90.1±0.75	94.2±0.67
45	50.0±1.11	82.0±0.98	86.0±0.64	89.4±1.51	90.1±1.51	95.8±0.91	96.6±0.35
60	54.1±0.91	92.4±0.90	94.7±0.89	95.9±.0.24	96.5±0.24	98.6±1.06	99.8±0.65

Table 4: Formulation of Oral disintegrating tablets of cefixime

Formulation ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime and β-CD (1:3) complex equivalent to 50mg Cefixime	200	200	200	200	200	200	200	200	200
Sodium starch glycolate	17.5	35	52.5	-	-	-	-	-	-
Crospovidone	-	-	-	17.5	35	52.5	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	17.5	35	52.5
Pearlitol SD 200	126	108.5	91	126	108.5	91	126	108.5	91
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colloidal Silicon Dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Strawberry flavor	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Total weight(mg)	350	350	350	350	350	350	350	350	350

Table 5: Evaluation of flow properties of powder blend

Formulation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (gm/cm^3) (mean±SD)	0.404±0.02	0.421±0.04	0.418±0.06	0.429±0.04	0.401±0.02	0.417±1.05	0.424±0.06	0.412±1.01	0.431±0.06
Tapped density (gm/cm^3) (mean±SD)	0.442±0.01	0.463±0.03	0.470±0.02	0.474±0.03	0.440±0.02	0.469±0.02	0.463±0.01	0.468±0.44	0.472±0.04
Hausner's ratio (mean±SD)	1.094±0.02	1.099±0.02	1.124±0.04	1.104±0.01	1.097±0.03	1.124±0.01	1.091±0.02	1.135±0.02	1.095±0.04
Compressibility index (%) (mean±SD)	8.59±0.94	9.97±1.13	11.06±.0.92	8.64±0.83	8.86±1.14	11.08±0.87	8.42±0.92	11.96±0.99	8.68±0.87
Angle of repose (^{0}) (mean±SD)	25.44±1.20	26.21±1.52	25.43±1.31	26.18±1.22	24.22±1.12	26.32±0.98	24.90±1.45	26.19±1.24	23.48±1.46

Table 6: Evaluation of prepared tablets

Formulation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight (mg) (±SD) n=6	349.2±1.81	350.8±1.23	350.2±1.22	351.4±1.91	349.6±1.07	350.0±1.72	351.1±1.22	350.8±1.41	351.9±1.22
Thickness (mm) (±SD) n=6	3.81±0.014	3.87±0.016	3.89±0.012	3.87±0.013	3.89±0.015	3.90±0.012	3.89±0.008	3.88±0.009	3.91±0.012
Hardness (Kg/cm^2) (±SD) n=6	4.09±0.29	4.14±0.32	4.67±0.34	4.78±0.12	5.14±0.23	4.56±0.11	4.08±0.28	4.16±0.41	4.14±0.36
Friability (%)	0.45	0.32	0.37	0.40	0.38	0.43	0.36	0.42	0.39

Table 7: Cumulative Percent Drug Release data of Cefixime from Prepared Formulations in pH 7.2 phosphate buffer

Time (min)	Sodium starch glycolate			Crospovidone			Croscarmellose Sodium		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	51.7±1.19	56.2±0.74	57.3±0.8	64.1±0.75	67.2±0.84	74.2±0.25	41.6±0.91	46.1±1.14	48.3±1.09
10	62±1.06	76.0±1.06	76.5±0.7	78±0.69	82.6±0.81	88.8±0.65	55.5±0.82	56.2±1.32	58.9±1.01
15	72.8±1.56	77.6±1.82	79.8±0.5	80.5±0.81	88.5±1.02	94.5±1.05	63.0±0.67	65.0±1.19	69±0.75
20	75±1.04	81.8±0.81	88.9±0.9	90.7±0.64	94.1±1.08	100.2±1.01	66.4±0.75	70.1±0.64	74±0.67
30	79.8±0.85	84.6±0.64	90.8±1.5	94.6±0.92	100±0.90	-	69.8±0.82	74.8±0.91	77.2±0.35
45	84.1±0.90	88.7±0.89	92.1±1.8	96.8±0.91	-	-	74.5±1.06	79.6±0.19	81.8±0.65

Table 8: Disintegration time and wetting time of the prepared formulations

Formulation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Disintegration time (sec) (±SD) n=6	48±1	46±2	40±1	42±2	39±1	28±1	58±2	53±2	50±1
Wetting time (sec) (±SD) n=6	40±2	38±1	32±2	36±1	34±1	22±2	50±1	44±3	41±3

Table 9: *In vitro*-Dissolution parameters of different formulations

Formulation	DE_5 (%)	DE_{20} (%)	D_{10} (%)	D_{20} (%)	t_{50} (min)	t_{70} (min)	t_{90} (min)	K_{min}^{-1}	r^2
F1	25.8	37.3	62	75	4	15	>45	0.024	0.904
F2	28.1	41.7	76	81.8	4	14	>45	0.042	0.859
F3	28.6	43	76.5	88.9	3	18	14	0.061	0.818
F4	32	44.6	78	90.7	3	9	20	0.090	0.935
F5	33.6	47.5	82.6	94.1	3	5	17	0.103	0.992
F6	37.1	51.25	88.8	100	1	3	10	0.154	0.996
F7	20.8	32.2	55.5	66.4	8	30	>45	0.025	0.863
F8	23	24.6	56.2	70.1	6	20	>45	0.030	0.931
F9	24.1	35.5	58.9	74	5	16	>45	0.033	0.893

DE_5=Dissolution efficiency in 5 min
DE_{20}= Dissolution efficiency in 20 min
D_{10}= Percent drug dissolved in 10 min
D_{20}= Percent drug dissolved in 20 min
t_{50} =Time taken to dissolve 50% of the drug
t_{70} =Time taken to dissolve 70% of the drug
t_{90} =Time taken to dissolve 90% of the drug
K_{min}^{-1}=first order rate constant
r^2 = correlation coefficient values of first order plots

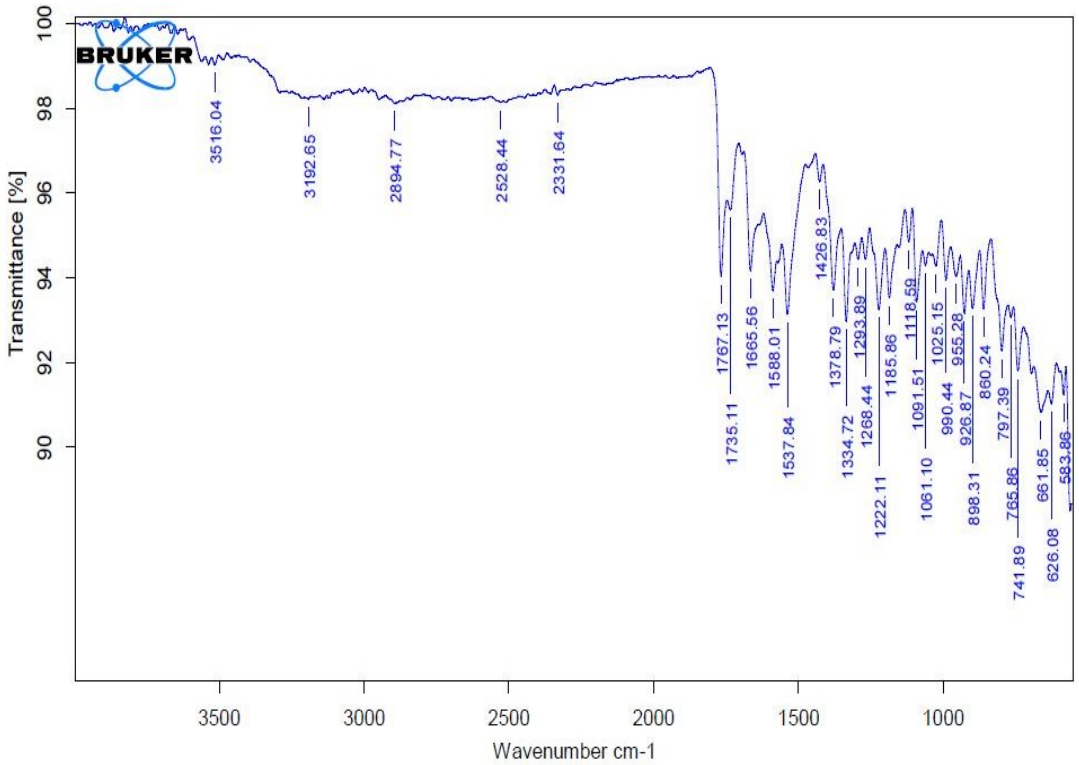

Figure 2(a): FTIR Spectra of Cefixime

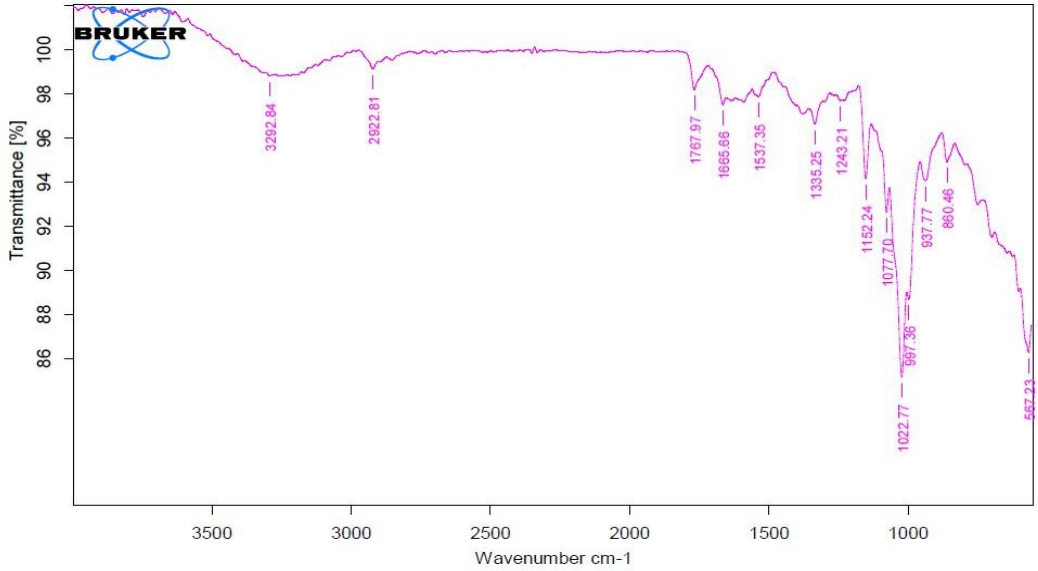

Figure 2(b): Cefixime + β-CD

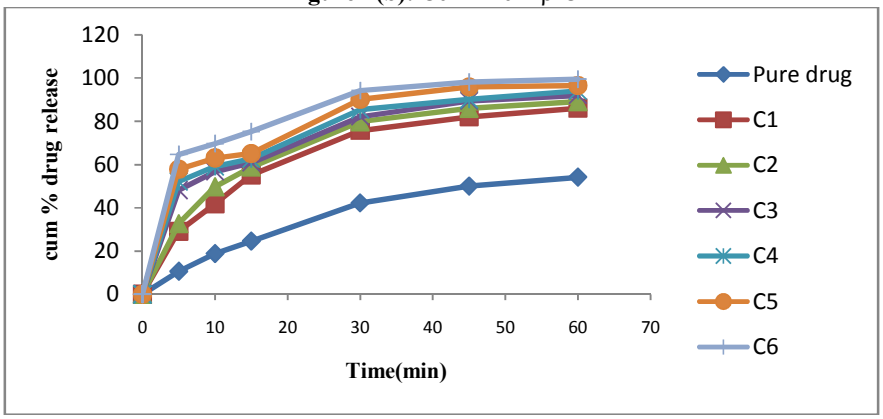

Figure 3: *In-vitro* drug dissolution of solid dispersions

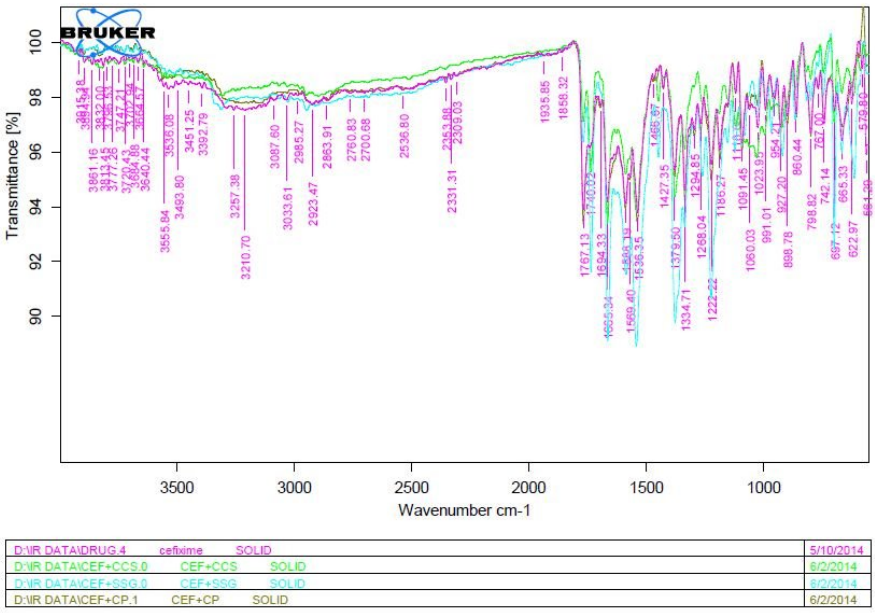

Figure 4: Comparative FTIR Spectra of pure drug cefixime and with excipients

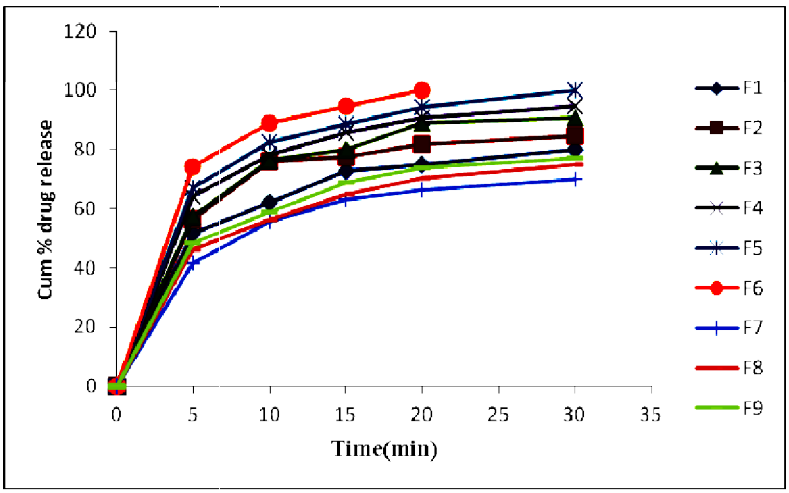

Figure 5: In-vitro drug dissolution of prepared formulations

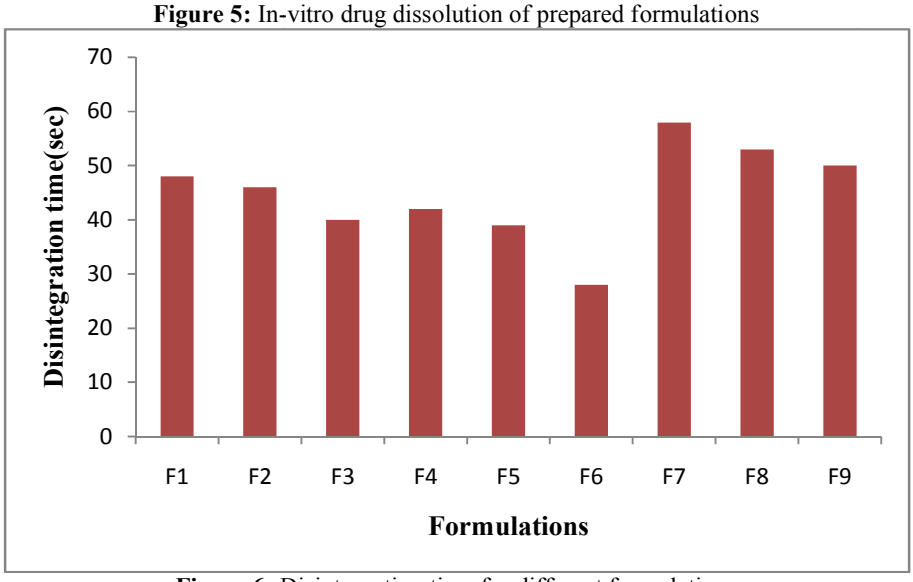

Figure 6: Disintegration time for different formulations

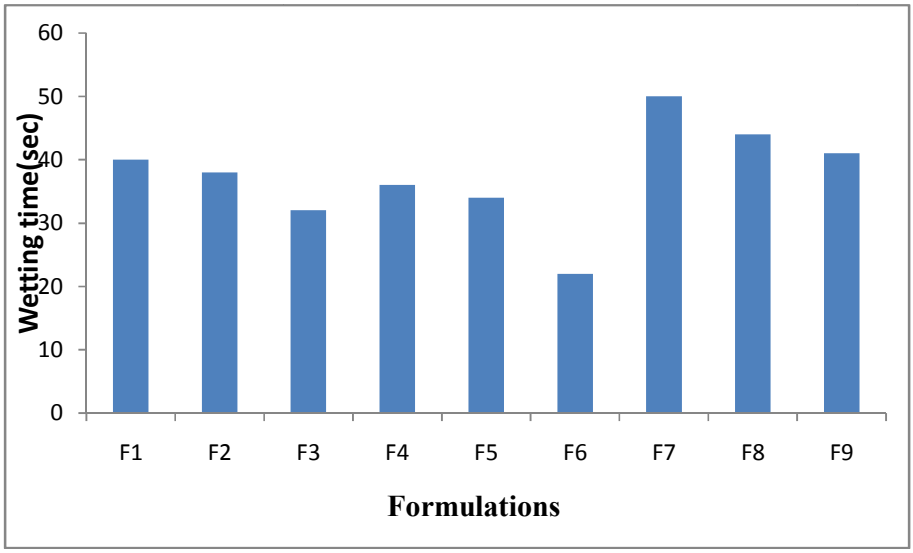

Figure 7: Wetting time for different formulations

CONCLUSION:

Cefixime, a bitter drug, could be successfully taste-masked using β-CD by complexation method. The taste-masked complex was incorporated to prepare fast disintegrating tablets. Tablets were formulated using three super disintegrants in three ratios (5%, 10% and 15%). Among all F6 showed faster disintegration and drug release. The prepared formulation offered significant results in terms of improving taste and bioavailability. The results conclusively demonstrated effective taste masking by β-Cyclodextrin in both binary systems, which can be utilized as a novel alternative approach for effective taste masking.

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