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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF FAST DISSOLVING TABLETS OF CEFIXIME TRIHYDRATE

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ABSTRACT

Cefixime is an oral third generation cephalosporin antibiotic. It is used to treat gonorrhea, tonsillitis, and pharyngitis.

Objective: The main objective of the present investigation is masking the bitter taste of drug,

Enhance drug solubility and it's bioavailability by enhancing the dissolution and disintegration profiles using super disintegrating agents etc.,

Method: The methodology technique depends on using various excipients like Croscarmellose sodium, sodium starch glycolate, Crosspovidone, Doshion p-544DS (ion exchange resin) as superdisintegrants. Tween 40, Tween 80, S.L.S used as a wetting agents. Camphor, Thymol, Menthol used as subliming agents. The method preferred is direct compression technique. The prepared formulas were evaluated for hardness, friability, disintegration time, content uniformity etc.,

Results and conclusion: Depending on the *in-vitro* and *in-vivo* disintegration time, the promising formulations were studied further for drug release pattern. From the results obtained it can be concluded that the tablets of batch CF8 had shown better drug release profile even comparing with the marketed product.

Keywords: Cefixime trihydrate, Wetting agents, Subliming agents, Fast dissolving tablets.

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric, geriatric, bedridden, psychiatry and traveling patients have difficulty for swallowing or chewing solid dosage forms [1-3]. These patients develop unwilling tendency to take these solid preparations due to fear of choking and unavailability of water during traveling.

In order to assist these patients, several fast-dissolving drug delivery systems have been developed. Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. There are multiple fast-dissolving OTC and Rx products on the market worldwide, most of which have been launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need for water or chewing [4]. Perhaps the simplest definition of an ODT is: a single unit dose that disintegrates in the oral cavity. The Center for Drug Evaluation and Research states an ODT to be: "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients [5]

The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wetted by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for Oromucosal absorption or with formula modifications will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed Traditional tablets and capsules administered with a glass of water may be inconvenient or impractical for some patients. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eight-year-old with allergies could use a more convenient dosage form than antihistamine syrup. Fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for these patients. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate[6,7].

MATERIALS AND METHODS

Cefixime trihydrate was obtained as a gift sample from Parabolic drugs ltd. Doshion P-544C and Doshion P-544D was obtained from Doshion ltd. S.S.G, S.L.S, Tween 40, Tween 80, Camphor, Thymol, Menthol from S.d Fine chem limited, Mumbai. Cross carmellose sodium and Polyplasdone XL were obtained from FMC Pharma agencies

Formulation of cefixime trihydrate tablets

Specified amount of cefixime trihydrate + Doshion P-544C complex was mixed with the required quantity of four different superdisintegrants namely Croscarmellose sodium, Sodium starch glycolate, Crosspovidone and DoshionP-544D separately. Then the required amount of excipients are added and mixed. In the present study bitter taste of the drug is masked by using ion exchange resin, Doshion P- 544C. Resinate was prepared by using different ratios of drug and resin and it was tested for in vitro taste evaluation in SSF of pH 6.2 and the drug polymer ratio was explained in table 2.

Table 1: Selection criteria of different ratios of drug and resin complex

S. No.	Formulation code	Drug: polymer	%drug release in SSF
1	TM1	1:1	12.31
2	TM2	1:2	4.34
3	TM3	1:3	Not detectable
4	TM4	1:4	Not detectable

By fixing this ratio the formulation chart was developed and it was reported in table 3.

Table 2: Composition of Cefixime trihydrate fast dissolving tablets

S. No.	Ingredients	mg per tablet									
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10
1	cefiximetrihydrate+Doshion P-544C complex eqv to 50mg of										
2	cefixime trihydrate	200	200	200	200	200	200	200	200	200	200
3	Dummy granules	49	49	49	49	47.5	47.5	47.5	-	-	-
4	Sodium starch glycolate	12	-	-	-	-	-	-	-	-	-
5	Polyplasdone XL	-	12	-	-	-	-	-	-	-	-
6	Cross carmellose sodium	-	-	12	-	-	-	-	-	-	-
7	Doshion P-544D	-	-	-	12	12	12	12	12	12	12
8	Sodium lauryl sulphate	-	-	-	-	1.5	-	-	-	-	-
9	TWEEN-80	-	-	-	-	-	1.5	-	-	-	-
10	TWEEN-40	-	-	-	-	-	-	1.5	-	-	-
11	Camphor	-	-	-	-	-	-	-	30	-	-
12	Thymol	-	-	-	-	-	-	-	-	30	-
13	Menthol	-	-	-	-	-	-	-	-	-	30
14	Avicel PH-112	15	15	15	15	15	15	15	34	34	34
15	Aerosil	6	6	6	6	6	6	6	6	6	6
16	Magnesium stearate	6	6	6	6	6	6	6	6	6	6
17	Talc	6	6	6	6	6	6	6	6	6	6
18	Aspartame	3	3	3	3	3	3	3	3	3	3
	Orange flavor	3	3	3	3	3	3	3	3	3	3
	TOTAL WEIGHT	300	300	300	300	300	300	300	300	300	300

Dummy granules: Granules containing Lactose60% + Starch 40%

Evaluation of Precompression Properties

Angle of repose

Angle of repose was determined by using funnel method. A glass funnel with flat bottom was placed with a clamp a ring support over a glass plate. One graph paper placed on a horizontal glass plate. The powder sample was poured from a funnel, that can be raised vertically until a maximum cone height (h) was obtained and diameter of heap (D) was measured the angle of repose 'θ' was calculated by the formula.

$\tan \theta = 2h/D$

Percent compressibility

It was measured from bulk density determinations. Apparent bulk density was determined by pouring pre-sieved drug – excipient blend of each formulation into a 100ml graduated cylinder. Noted the volume and weight calculated the bulk density (untapped) (a).The cylinder was fixed on the density apparatus and the time knob was set for tapping and measured the final volume after tapping. The bulk density of the powder mass (b) was calculated by following equation.

Bulk density $_{(untapped)}$ a = weight / final volume

Bulk density $_{(tapped)}$ b = weight / final volume

The percent compressibility was calculated by using the equation

$C = 100 (b - a) / b$

Hausner's ratio

It was determined form the ratio of the bulk density $_{(tapped)}$ and bulk density $_{(untapped)}$ of powder blend. All the results of precompression parameters were reported in the table 4.

After the compression of tablets, they were evaluated for following characteristics.

Hardness test [8]

Pfizer hardness tester was used for the determination of hardness of tablets. Tablet was placed in contact between the plungers and handle was pressed the force of the fracture was recorded and mentioned in the table 5.

Friability [8]

Five tablets were accurately weighed and placed in friabilater (cambel electronics) and operated for 100 revolutions. The tablets were de-dusted and reweighed the tablets that lost less than 1% weight was considered to be complying as per I.P. The values were tabulated in table 5.

Weight variation [8]

The weight variation test was done by weighing 10 tablets individually calculating the average weight and comparing the individual tablet weight to the average weight and the obtained result were mentioned in the table 5.

Disintegration test [9, 10]

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 – liter beaker and the time of disintegration was recorded. To discriminate between the formulation disintegration was done at room temperature and disk was not used for the study. According to I.P. 1996 dispersible tablets should disintegrate within 3 minutes by using water at 19^0C to 21^0 C unless otherwise in the individual monograph. The time required for the formulations to disintegrate was reported in the table 5.

Wetting time [11]

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 and thus measured values were reported in the table 5.

Drug content [12]

Five tablets were weighed and powdered, powder equivalent to 100mg of drug was weighed and dissolved in 0.1N Hcl and filtered the solution through the whatman filter paper. The filtrate was collected and diluted to a sufficient amount with 0.1N Hcl till the concentration of the drug lies within the standard plot range. The diluted solution was analyzed for the content by UV – spectrophotometer

Dissolution studies [13, 14**]**

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (Electro lab TDT – 08 L Dissolution testers USP) type II (Paddle) 900ml of medium 0.1N Hcl was used at 37± 0.5^0C. The speed of the paddle was set at 100rpm. Sampling was done at every 5 min interval. For each sample 5 ml of the dissolution medium was withdrawn and same amount of dissolution media at 37^0C was replenished to the dissolution medium. The sample with drawn was filtered with whatman filter paper and diluted with water. The

sample absorbance was measured by using UV spectrophotometer. The cumulative % of drug release was calculated and explained in table 5.

RESULTS

Evaluation of physical blend

The physical blend was evaluated for angle of repose, compressibility index and Hausner's ratio. The results were tabulated in table no.3.

Evaluation of fast dissolving tablets

The fast dissolving cefixime trihydrate tablets were evaluated for post compression parameters like weight variation, friability, hardness, thickness, in vitro disintegration and wetting time. The results were tabulated in table no.4.

***Invitro* Dissolution studies**

All the formulations were subjected to in-vitro dissolution studies by using 900ml of medium 0.1N Hcl as dissolution medium.

Comparison of best formulation with marketed formulation

The optimized formulation CF8 was compared with marketed tablet for different tests like hardness, friability, thickness, uniformity of drug content, in-vitro disintegration time, wetting time and in-vitro dissolution study. The results are tabulated in table no.4 and 5.

Drug release kinetics

The drug release kinetics based on dissolution profile were calculated and mentioned in table 6. The kinetic parameters like t_{50}% (min), t_{75}% (min), t_{90} % (min), DE_{30} (%) and regression values of first order and zero order were calculated.

Table 3: pre-compression parameters of Cefixime trihydrate fast dissolving tablets

Formulation Code	Angle of repose (θ)	Compressibility (%)	Hausner's Ratio
CF1	26.56"±25"	13.84±0.39	1.16±0.002
CF2	24.17"±32"	12.12±0.24	1.13±0.001
CF3	27.05"±21"	13.63±0.19	1.15±0.005
CF4	25.74"±42"	12.94±0.51	1.34±0.004
CF5	24.64"±24"	13.63±0.34	1.14±0.006
CF6	28.95"±32"	12.30±0.19	1.08±0.002
CF7	24.62"±14"	11.59±0.26	1.17±0.003
CF8	25.08"±25"	13.63±0.43	1.18±0.004
CF9	24.62"±19"	12.12±0.27	1.13±0.005
CF10	28.46"±28"	13.25±0.37	1.23±0.008

Table 4: Evaluation of Cefixime trihydrate fast dissolving tablets

Formulation Code	Wt.variation (%deviation)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (Sec)	Wetting Time (Sec)	Assay (%)
CF1	1.07	4.5	0.61	120	90	99.80
CF2	0.26	4.1	0.56	90	95	100.51
CF3	0.74	3.9	0.68	70	83	99.08
CF4	0.58	4.4	0.49	60	69	99.71
CF5	1.07	4.0	0.51	40	36	99.80
CF6	0.26	4.2	0.58	53	48	100.51
CF7	0.74	4.0	0.49	65	54	99.08
CF8	0.26	3.5	0.85	12	18	97.81
CF9	0.40	3.3	0.93	19	22	100.32
CF10	0.40	3.3	1.12	38	41	96.86
M.P	1.21	3.7	0.62	23	27	99.71

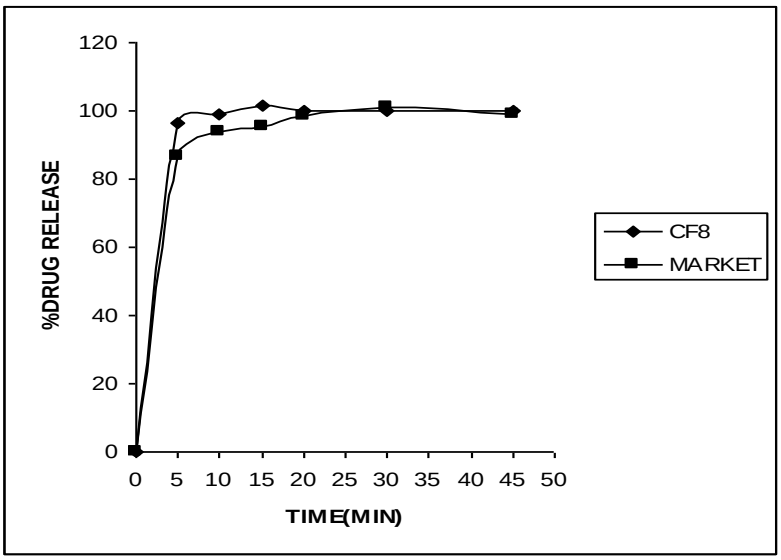

Fig. 1: Comparative dissolution profile of tablets CF8 and marketed product

Table 5: Dissolution profile of formulated batches of Cefixime trihydrate fast dissolving tablets

S. No.	Time (min)	Percentage of drug release (X ± sd) CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10	M.P
1	5	51.6± 1.03	55.3± 0.55	59.8± 0.87	71.2± 0.35	76.51± 0.45	72.5± 0.23	71.5± 1.04	96.54± 1.03	78.21±1.01	74.41±0.55	86.92±0.89
2	10	56.7± 0.85	58.6± 1.02	63.3± 0.43	79.3± 0.42	78.65± 0.33	76.2± 0.36	74.7± 1.19	98.75± 0.85	80.41±0.86	75.81±0.59	93.81±0.78
3	15	64.8± 0.77	67.8± 0.71	71.5± 1.21	85.2± 0.67	80.69± 1.02	78.5± 0.68	76.2± 0.22	100.5± 0.79	87.85±0.89	82.75±1.34	95.21±0.61
4	20	69.8± 0.55	71.2± 0.42	77.2± 1.35	85.7± 0.42	84.35± 1.09	81.5± 0.89	79.5± 0.87	99.81± 0.66	91.36±0.65	87.65±1.52	98.31±0.35
5	30	77.3± 1.22	80.4± 0.56	84.5± 0.75	94.6± 0.79	89.95± 0.87	86.8± 0.75	84.3± 0.76	99.91± 0.21	98.61±0.52	91.37±.86	101.2±1.04
6	45	89.7± 0.86	91.2± 0.88	93.5± 0.92	99.8± 0.43	97.89± 0.11	95.6± 0.88	93.8± 0.33	100.2± 0.47	100.6±0.88	99.81±0.23	-

Table 6: Dissolution kinetics of all batches of cefixime trihydrate tablets

Formulation code	Ingredients	Correlation coefficients		K value (min-1)	t_{50}% (min)	t_{75}% (min)	t_{90}% (min)	DE_{30} (%)
		First order	Zero order					
CF1	SSG	0.9407	0.8485	0.0735	4.5	27	>45	55.07
CF2	Polyplasdone-XL	0.9411	0.8732	0.0872	4	25	42.5	56.69
CF3	AC-DI-SOL	0.9414	0.7595	0.0921	3.7	18.5	40.5	60.88
CF4	Doshion P544(DS)	0.9466	0.8521	0.872	2.6	7	26	70.71
CF5	SLS	0.9746	0.7321	0.1227	2.3	4.4	31.5	69.32
CF6	Tween 80	0.9793	0.7598	0.1021	2.5	8	34.5	66.98
CF7	Tween 40	0.9741	0.8042	0.1043	2.5	12	39	65.46
CF8	Camphor	0.980	0.7764	0.1131	.5	3.8	4.5	82.83
CF9	Thymol	0.9532	07708	0.1280	3	4.6	17.5	73.69
CF10	Menthol	0.9765	0.7588	0.1193	3.5	4.8	24	69.71

DISCUSSION

The formulations TM1, TM2, TM3 and TM4 were prepared for taste masking of drug and evaluated for drug release in Simulated salivary fluid of pH 6.2, and among them formulations TM3 and TM4 didn't show the drug release from resinate in SSF.So, the formulation TM3 was selected as taste masked and further used for preparing tablets. The formulations (CF1, CF2, CF3, CF4, CF5, CF6, CF7, CF8, CF9 and CF10) have been seen with good flowability and compressibility properties in prepared powder material. The formulation of (CF1, CF2, CF3 and CF4) cefixime trihydrate dispersible tablets prepared with four super disintegrating agents such as S.S.G, crospovidone croscarmellose sodium and Doshion P-544[DS] respectively. Among these four formulations CF4 formulation has shown best release when compared with other formulations CF1, CF2, CF3.The rank order release is as follows

CF4>CF3>CF2>CF1

The tablet formulations (CF5, CF6and CF7) were prepared with three different surfactants such as 0.5%w/w SLS , 0.5%w/v Tween 80, 0.5%w/vTween 40 with Doshion P-544C as common super disintegrating agent respectively. The CF5 formulation has shown better released compared to other CF6and CF7 formulations. The rank order release is as follows

CF5 >C F6 > CF7

The tablet formulations (CF8, CF9, CF10 and CF11) were prepared with three different subliming agents such as Camphor (10%w/w), Thymol (10%w/w), Menthol (10%w/w) with Doshion P-544C as common super disintegrating agent respectively. The CF9 formulation has shown better release compared to other CF10and CF11 formulations. The rank order release is as follows

CF8 >CF9 > CF10

CONCLUSION

The fast dissolving tablets of cefixime trihydrate proved to show better release profile in all aspects as compared to marketed formulation. The use of superdisintegrants sodium starch glycolate and croscarmellose showed faster disintegration and dissolution profile. Among all the above formulations, CF8 shows better released compared to other formulations (CF1, CF2, CF3, CF4, CF5, CF6, CF7, CF9 and CF10).The formulation (CF8) shows better release compared with innovator sample or marketed product (MP). This may be due to the addition of subliming agents with the combination of super disintegrants Doshion P-544[DS].

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