Formulation and Evaluation of Cetrizine Fast Dissolving Tablets

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Abstract **- Orally disintegrating tablets (ODTs) are a rapidly growing category of dosage form in the pharmaceutical industry which has received ever-increasing demand during the last decade. They especially find application in target category like geriatrics and pediatrics. There are three main manufacturing methods used for the production of ODTs, namely, freeze drying, molding and compression method. Orally disintegrating tablets (ODTs) containing Cetrizine were prepared by direct compression method by using superdisintegrants such as crospovidone and croscarmellose. The prepared ODTs were characterized for their drug content, hardness, friability and wetting time. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The optimized formulation (F4) was showed satisfactory results with drug release and was physically stable during 3 months period.**

Index Terms **- API, Fast dissolving tablet, Oral route, Excipients, superdisintegrants.**

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (To accommodate various types of drug candidates) and most importantly, patient compliance (Sastry et al, 1997). Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture (Fasano et al, 2005). A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists. The concept of oral disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODDFs has enormously increased during the last decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy (Seager et al, 1998)

MATERIALS & METHODS

Cetrizine was obtained as gift sample from Dr. Reddy's, Hyderabad. MCC (Avicel PH 102) and Crospovidone was purchased from Orchid Chemicals & Pharmaceuticals Ltd, Chennai. All other excipients were purchased from S.D. Fine Chemicals, Mumbai.

Preformulation studies: Determination of maximum absorbance (λ_{max}) of a drug

An accurately weighed amount, 10 mg of Cetrizine was transferred into 10 ml volumetric flask containing 0.1N HCl and the volume was made upto the mark with 0.1N HCl. From these necessary dilutions were made and was scanned over the range of 200-400 nm using UV-Visible spectrophotometer and noted the λ_{max} values for Cetrizine.

Drug-excipient compatibility studies: Differential Scanning Calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients (Vaghani et al., 2010). Pure drug, 1:1 ratio of drug and polymer, and physical mixture of optimized formulations were subjected to the analysis. About 5-15 mg of sample to be analyzed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50-300°C. The heating rate was 10°C/min; nitrogen was served as purged gas and the system was cooled down by liquid

nitrogen. The differential scanning colorimeter (DSC 4000, Perkin Elmer) was used for this purpose.

Preparation of Cetrizine fast dissolving Tablets: Oral disintegrating tablet of Cetrizine were prepared by using direct compression method according to the formulae as shown in the table 1. This method involves a simple procedure of blending of API with other ingredients and the resulted mixture is subjected to direct compaction. The required ingredients were taken in a mortar and the powder blend was mixed for a time period of 15-20 min by using mortar and pestle. Then each mixture was passed through sieve no.60 and finally magnesium stearate was added as lubricant and thoroughly mixed. It was then compressed by using 10 station tablet compression machine (Rimek minipress-II MT,Karnavati Ltd.) to get at 8 mm size of tablets each weighing 150 mg.

Physical characterization of prepared tablets: The prepared tablets of Cetrizine were evaluated for following physical characteristics.

Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Hardness: The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

Friability test: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated using the formula

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test,
W2 = Weight of tablet after test

Disintegration test: The USP disintegration apparatus contains six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 ℃, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Mechanical strength: Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet is measured by using Pfizer hardness testers. Tensile strength for crushing (T) is calculated using equation

$T= 2F / \pi*d*t$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet respectively.

Uniformity of dispersion: Keep the Two tablets in 100ml water and stir gently for 2 minutes. The dispersion is passed through 22 meshes. The tablets will consider passing the test if no residue remained on the screen.

Wetting time: The wetting time of the tablets is measure by using a simple procedure. Place the five circular tissue papers of 10 cm diameter in a petridish containing 0.2% w/v solution (3ml). A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

Water absorption ratio: A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula .

Where, Wb is the weight of tablet before water absorption
Wa is the weight of tablet after water absorption

Taste/ Mouth sensation: Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch is tested for the sensation by placing the tablet on the tongue. The healthy human volunteers are used for evaluation of mouth feel. Taste evaluation is done by a panel of 5 members using time intensity method. Sample equivalent to 40 mg i.e. dose of drug is put in mouth for 10 seconds and record taste instantly and then after 10 secs, 1, 2, 4 and 6 minutes. Volunteer's opinion for the taste is rated by giving different score values i.e. 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

In -Vitro disintegration test: *In-vitro* disintegration time is measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation are randomly selected and *in vitro* dispersion time is carried out. (Shirai et al, 1993)

In-Vitro dissolution test: *In-vitro* dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which maintained at 37±0.5°C. Withdraw aliquot of dissolution medium (10 ml) at specific time intervals (2 min) and filter. The amount of drug dissolved is determined by suitable analytical technique. (Cirri et al, 2005)

Stability Studies: The optimized formulation of ODTs is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

RESULTS & DISCUSSION

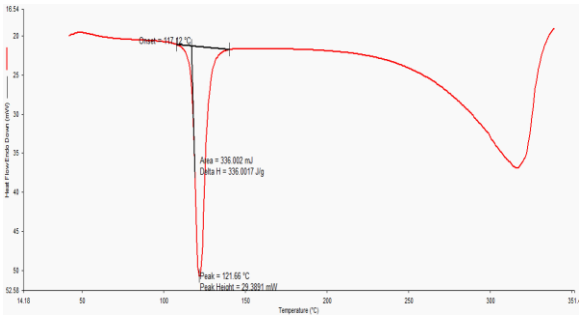

Figure 1: DSC thermogram for pure drug

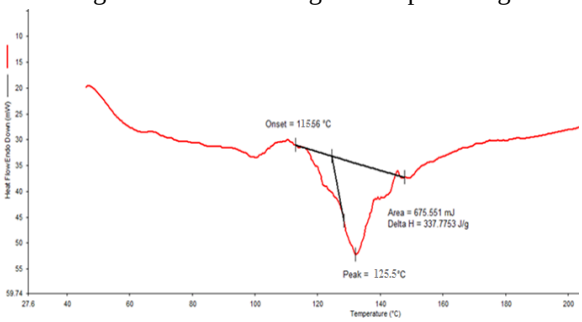

Figure 2: DSC thermogram for drug + physical mixture

Table 1: Composition of the Cetrizine fast dissolving tablets

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Cetrizine	5	5	5	5	5	5	5	5	5	5
MCC	98	96	93	91	88	85	81	78	75	73
Crospovidone	10	12	15	18	20	-	-	-	-	-
croscarmellose	-	-	-	-	-	10	12	15	18	20
Mannitol	15	15	15	15	15	15	15	15	15	15
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aspartame	7	7	7	7	7	7	7	7	7	7
Raspberry	10	10	10	10	10	10	10	10	10	10
Total	150	150	150	150	150	150	150	150	150	150

Table 2: Physico-chemical parameters of Cetrizine fast dissolving tablets

Formulation	Weight variation (mg),(n=20)	Hardness (kg/cm^2), (n=6)	Thickness (mm), (n=6)	Friability (%),(n=10)	Disintegration time (sec)	Drug content (%), (n=3)
F1	150±1.02	3.5±0.13	1.86±0.16	0.85±0.03	34	95±0.13
F2	150±1.58	3.4±0.21	1.83±0.19	0.83±0.13	40	96±0.10
F3	149±0.32	3.5±0.23	1.82±0.09	0.84±0.10	37	96±0.19
F4	150±1.32	3.3±0.20	1.85±0.10	0.86±0.12	38	97±0.51
F5	151±0.61	3.4±0.27	1.86±0.19	0.85±0.43	35	95±0.20
F5	150±1.40	3.5±0.43	1.86±0.12	0.82±0.13	22	96±0.21
F6	151±1.12	3.5±0.53	1.86±0.51	0.84±0.23	18	98±0.12
F7	149±0.32	3.3±0.13	1.86±0.19	0.83±0.18	16	97±0.16

F8	150±1.70	3.4±0.23	1.86±0.16	0.85±0.25	16	98±0.31
F9	150±0.32	3.2±0.31	1.86±0.19	0.84±0.43	15	97±0.25
F10	151±1.32	3.5±0.23	1.86±0.15	0.85±0.13	15	98±0.13

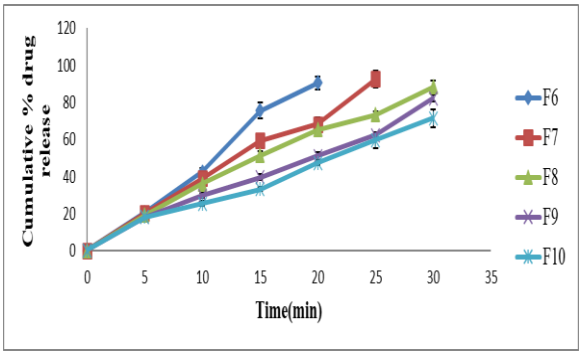

Figure 3: Drug release profiles of Cetrizine fast dissolving tablets prepared with Crospovidone (F1-F5) (Mean ± SD)

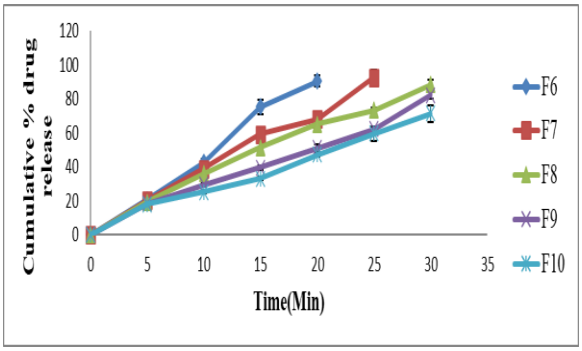

Figure 4: Drug release profiles of Cetrizine fast dissolving tablets prepared with croscarmellose (F6-F10) (Mean ± SD)

Table 3: Results of correlation coefficients (R^2) and diffusion exponent (n) of release data of Cetrizine fast dissolving tablets by curve fitting method.

Formulations	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2	n
F1	0.9412	0.5238	0.9732	0.9803	0.5138
F2	0.9437	0.5276	0.9754	0.9854	0.5343
F3	0.9576	0.5132	0.9862	0.9767	0.5471
F4	0.9885	0.6087	0.9953	0.9928	0.6012
F5	0.9531	0.5043	0.9845	0.9833	0.5735
F6	0.9541	0.4918	0.9814	0.9875	0.5538
F7	0.9567	0.5124	0.9895	0.9749	0.5631
F8	0.9589	0.5037	0.9787	0.9816	0.5754
F9	0.9673	0.4493	0.9868	0.9905	0.5982
F10	0.9642	0.4929	0.9736	0.9854	0.5813

Drug-Excipient compatibility study: Differential scanning calorimetry studies indicated a sharp endothermic peak at 210-°C corresponding to its melting point, for pure Cetrizine (Figure 1). No significant change in the position of this peak or broadening of peak in the thermogram of drug and excipient mixture was observed with respect to the thermogram of pure drug (Figure 2). So, it can be concluded that the drug and excipients do not interact with each other.

In-vitro characterization of oral disintegrating tablets: The tablets of Cetrizine were prepared by direct compression method using super disintegrants like crospovidone and croscarmellose sodium. The data of physical parameters was presented in Table 1 &2. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The physical evaluation of the tablets revealed uniform thickness and weight for all the tablets (evident from low SD values). The hardness values between 3.2-3.5 kg/cm^2 and low friability values (below 0.85%) across all formulations indicated that the tablets had sufficient mechanical strength. The drug content uniformity studies revealed that drug content between 96.33± 2.3% and 98.91 ±2.8% is acceptable.

In-vitro dissolution studies: *In-vitro* dissolution studies of all the formulations of Cetrizine tablets were carried out in 0.1 N HCl (pH 1.2). The study was performed for 30 min and cumulative drug release was calculated. Formulations F1-F5, were prepared with

varying concentrations of crospovidone and formulations F6-F10 were prepared with varying concentrations of croscarmellose sodium. The drug release profiles of the formulations, F1-F5 prepared with crospovidone shown in Figure 3. The effect of crospovidone concentration on drug release was evaluated. As the concentration of crospovidone increased, the drug release from the tablets was also increased upto optimum concentration. After that further enhancement of concentration of super disintegrant leads to decreased drug release. F4 was considered as the best formulation among all the five formulations of this series.

Drug release profiles of formulations F6-F10, composed of croscarmellose sodium, are shown in Figure 4. F9 was considered as the best formulation among all the five formulations of this series. This unexpected behavior of CCS on the *in vitro* disintegration time may be attributed to the formation of a viscous gel layer by CCS which may impede further penetration of the disintegration medium and hinder the disintegration of tablet content (Swamyet al., 2007; Setty et al., 2008). The overall enhanced dissolution rate of the poorly soluble drug in its ODTs containing a composite formed of mannitol and CCS might be attributed to the hydrophilic nature of mannitol and its ability to aid the dissolution rate of poorly soluble drugs (McLaughlin et al., 2009). Also, mannitol is readily soluble; it also has the function of improving texture, taste, and mouth feel

Analysis of drug release kinetics for Cetrizine formulations :Data of the *in-vitro* release of all formulations was fit in to different kinetic models to explain the release kinetics of Cetrizine from the floating tablets. The kinetic models used were a zero-order equation, first-order equation, Higuchi and Korsmeyer and Peppas models (Table 3). Optimized formulation follows Higuchi model compared to all other models.

CONCLUSION

The fast-dissolving tablets of Cetrizine were successfully formulated and evaluated. Drug-excipients compatibility study was done by using DSC and found that the drug was compatible with all the excipients used in the study. The optimized formulation (F4) was showed satisfactory results with drug release and was physically stable during 3 months period.

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