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FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF CETIRIZINE HYDROCHLORIDE

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Abstract:

Recent developments in fast dissolving tablets have brought convenience in dosing to pediatric and elderly patients who have trouble in swallowing tablets. Cetirizine HCl is a potent second-generation histamine H1 antagonist that is effective in the treatment of allergic rhinitis, chronic urticaria and pollen-induced asthma. In the present study an attempt has been made to prepare fast dissolving tablets of cetirizine HCl in the oral cavity with enhanced dissolution rate. The concept of formulating fast dissolving tablets containing cetirizine HCl offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Fast dissolving tablets of cetirizine HCl were prepared by direct compression methods and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using croscarmellose sodium and sodium starch glycolate as superdisintegrants in different concentration along with magnesium stearate microcrystalline cellulose and talc. Total six formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and invitro drug release. In-vitro dissolution studies are performed by using phosphate buffer pH 6.8 at 75 rpm by paddle method. Overall, the formulation F5 containing of croscarmellose sodium was found to be promising and has shown a disintegration time 45±2sec. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

Keywords: *Cetirizine HCl, Fast dissolving tablets, Direct compression, Superdisintegrants, Pre-compression*

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INTRODUCTION:

In spite of the increased focus and interest generated in the area of controlled release and targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate and release their medicaments rapidly in the gastrointestinal tract still remain the formulation of choice from both a manufacturing as well as a patient acceptability point of view. Thus, a drug given in the form of a tablet must undergo dissolution before being absorbed and eventually transported into systemic circulation [1]. Difficulties with and resistance to tablet taking are most common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphasia) can occur at any age but are particularly prevalent in geriatric, pediatric, and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability [2]. By considering the above points, patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems; one of such approaches is fast disintegrating drug delivery system [3]. Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and, at the same time, offer added advantages over both traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. FDDDS offer the luxury of much more accurate dosing than the primary alternative, oral liquids [4]. Recent advances in novel drug delivery systems (NDDS) aim at enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance [5]. US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the Orange Book a FDT as a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. European Pharmacopoeia described FDTs as uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 minutes [6]. Fast dissolving tablets (FDT) are also known as fast disintegrating, mouth dissolving, rapid-dissolving, quick disintegrating, orally disintegrating, rapimelt, fast melt, orodispersible, meltin-mouth, quick dissolving, porous tablets and EFVDAS (Effervescent Drug Absorption System) [7]. The bioavailability of drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to the first pass metabolism is reduced as compared to standard tablet [8]. Formulation of the drug chosen for the treatment of allergic cough and other respiratory disorders is available in market in conventional tablet and liquid dosage forms. Liquid dosage forms are having their own limitation from stability and dose measurement perspectives. Tablets to be swallowed are resisted by pediatric patients and patient compliance is an issue with such dosage forms. Hence they do not comply with the prescription, which results in high incidence of noncompliance and ineffective therapy. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make fast dissolving tablets popular as a dosage form of choice in the current market [9]. Cetirizine HCl is the active metabolite of the piperazine H1-receptor antagonist hydroxyzine. It is a nonsedative second generation antihistamine drug used in the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, chronic urticaria and atopic dermatitis and also used as adjuvant in seasonal asthma and allergic cough. Cetirizine inhibits the release of histamine and of cytotoxic mediators from platelets, as well as eosinophil chemotaxis during the secondary phase of allergic response. Due to sore throat conditions, the patient experiences difficulty in swallowing a tablet type of dosage form. Thus, fast dissolving tablets would serve as an ideal dosage form pediatric patients who find it difficult to swallow the conventional tablets and capsules [10]. Hence an attempt was made for preparation of fast dissolving tablet of cetirizine HCl with an aim of improving/enhancing patient convenience and compliance, reducing the lag time and providing faster onset of action to relieve the allergic and respiratory disorders immediately.

MATERIALS AND METHODS:

Materials:

Cetirizine HCl was a gift sample from Hetero Drugs Ltd., (Hyderabad, India). Sodium starch glycolate and sodium croscarmellose was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Microcrystalline cellulose, talc and magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

METHODS:

Standardization of cetirizine HCl by UV-Visible spectrophotometry:

Accurately weighed 10mg of drug was dissolved in 10ml of phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with phosphate buffer pH 6.8 solution prepare suitable dilution to make it to a concentration range of 2-10µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Drug-excipients compatibility study:
FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of tablets of cetirizine HCl:
Fast dissolving tablets of cetirizine HCl were prepared by direct compression [11] according to the formulae given in Table 1. All the ingredients were passed through # 60 meshes separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 600 mg using 8 mm round flat punches on 10-station rotary tablet machine.

Table 1 Composition of cetirizine HCl fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Cetirizine hydrochloride	10	10	10	10	10	10
Sodium Starch glycolate	20	25	30	-	-	-
Croscarmellose sodium		_	_	20	25	30
Microcrystalline cellulose	109	104	99	109	104	99
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	150	150	150	150	150	150

Evaluation of fast dissolving tablets of cetirizine HCl:
Precompression parameters:
Angle of repose (θ):
The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.
Tan θ = h/r
θ = tan-1 (h/r)
Where, θ is the angle of repose, h is the height, r is the radius.
The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density:
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.
LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing
TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

Compressibility index:
The compressibility index of the granules was determined by Carr's compressibility index**.**
Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio:
Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [12].
Hausner's ratio = Tapped density/Bulk density.

Post compression parameter:
Shape and colour of tablets:
Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light [13].

Thickness test:
Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test:
Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Hardness test:
The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Friability test:
For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%Friability = (Loss\ in\ weight/Initial\ weight) \times 100$$

Uniformity of drug content:
The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10mg of drug dissolved in 10 ml phosphate buffer pH 6.8 sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 232nm.

***In vitro* dissolution rate studies:**
The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 50rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml 0.1 N HCl. The samples withdrawn were assayed spectrophotometrically at 232nm using UV visible spectrophotometer.

RESULTS AND DISCUSSION:

The λ_{max} of cetirizine HCl was found to be 232 nm by using U.V. spectrophotometer (Systronics 1700 UV-Vis) in linearity range 2-10µg/ml. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility index and hauser's ratio of all the formulations was found to be within the range and showing that the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 3.5±0.1to 3.8±0.5kg/cm^2 and the friability values were less than 0.98% indicating that the tablets were compact and hard. All the formulations satisfied the content of the drug as they contained 98.78±0.14to 99.74±0.25% of cetirizine HCl and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The result in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets Table 4. The tablets were evaluated for in vitro dissolution studies in0.1N HCl for 10 min. The results of the optimized formulation F5 showed maximum drug release i.e. 99.12% at the end of 10min. The results of release studies of all formulations were shown in Table 5. The *in vitro* drug release data of the optimized formulation F5 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Higuchi's was maximum i.e. 0.993 hence indicating drug release from formulations was found to follow Higuchi's models kinetics Table 6.

Table 2 Results of pre-compression parameters of cetirizine hydrochloride

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.395	0.512	22.852	1.296
F2	0.412	0.528	21.970	1.282
F3	0.385	0.565	31.858	1.468
F4	0.392	0.547	28.336	1.395
F5	0.405	0.512	20.898	1.264
F6	0.383	0.498	23.092	1.300

Table 3 Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.6±0.2	0.785±0.045	152±5	1.25±0.23	98.85±0.32
F2	3.5±0.1	0.652±0.035	155±4	1.23±0.21	98.78±0.14
F3	3.7±0.3	0.741±0.026	148±6	1.25±0.25	98.99±0.25
F4	3.5±0.4	0.851±0.034	145±5	1.24±0.14	98.85±0.23
F5	3.8±0.5	0.658±0.047	150±4	1.26±0.16	99.74±0.25
F6	3.7±0.6	0.741±0.025	152±3	1.21±0.19	98.84±0.41

Table 4 Results of disintegration time parameters of all formulations

Formulation code	Disintegration Time (Sec.) Mean ± SD
F1	85±5
F2	78±4
F3	69±6
F4	73±4
F5	45±2
F6	62±1

***Average of three determinations (n=3)**

Table 5 *In-vitro* drug release data for optimized formulation F5

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	38.85	1.589	61.15	1.786
3	1.732	0.477	55.56	1.745	44.44	1.648
5	2.236	0.699	74.45	1.872	25.55	1.407
10	3.162	1.000	99.12	1.996	0.88	-0.056

Table 6 Regression analysis data

Batch	Zero Order	First Order	Higuchi
	r^2		
F5	0.974	0.936	0.993

CONCLUSION:

Thus from the whole research work it can be concluded that, the oral fast dissolving tablet of cetirizine HCl were formulated and evaluated for various parameters. From the compatibility studies by IR of drug it was found to be compatible with other formulation excipients. All evaluation parameter were within specification. The croscarmellose sodium shown faster drug release than sodium starch glycolate. Formulation F5 release maximum drug within the 10mins.ie. 99.12% and shown minimum

disintegration time i.e. 45±2sec than other formulation and hence considered best formulation.

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