REPORT

FORMULATION AND EVALUATION OF CETIRIZINE DIHYDROCHLORIDE ORODISPERSIBLE TABLET

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ABSTRACT

Cetirizine orodispersible tablets were prepared to achieve quick onset of action and for maximum bioavailability. Tablets were prepared using cetirizine along with camphor and mannitol in the proportion of 1:1:1, 1:1:3, and 1:1:6. The flow property of granules was found to be good for the formulation CZ2 (1:1:3). The hardness and friability of all the formulations were found to be within the standard limit for orodispersible tablets. Disintegration time was found to be rapid in formulation CZ2 (1:1:3).The *in vitro* dissolution time was found to be 100% in 11 minutes for the formulation CZ2 (1:1:3).

Keywords: Cetirizine orodispersible tablets, HPLC method, hausner ratio, wetting time.

INTRODUCTION

Allergic disorders are of significant public health concern in many countries. Cetirizine dihydrochloride is an active non-sedative antihistamine. Orodispersible tablets are of fast disintegrating type. They undergo disaggregating in the mouth when in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow. The target population for these new fast-dissolving / disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or mentally disabled patients. A major claim of some orodispersibles is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulation, in cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are areas of absorption of the formulation. (Jha *et al.,* 2008). However, other formulations show nearly identical plasma-concentration profiles. Any pre-gastric absorption avoids first pass metabolism and can be of great advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is a potential for inconsistent bioavailability. While the claimed increase in bioavailability is disputable, it is clear that the major advantage of these formulations is convenience (Bandari *et al.,* 2008). The aim of the present study is to formulate Cetirizine dihydrochloride orodispersible tablets using camphor and mannitol as super disintegrates in different proportions, to achieve patient compliance in allergic disorders.

MATERIALS AND METHODS

Cetirizine dihydrochloride was provided as gift sample by Micro Labs Ltd, Bangalore. Camphor and mannitol were purchased from Loba Chemie Pvt Ltd, Mumbai. Acetonitrile, Triethanolamine, HPLC Water and Phosphoric acid were of analytical grade and purchased from Merck (India) Ltd, Mumbai.

Preformulation studies

Infra Red Spectroscopy

The drug cetirizine dihydrochloride, fast disintegrant was subjected to FTIR studies to confirm the compatibility of disintegrants with drug (Chaudhri *et al*., 2007).

Preparation of granules

The granules were prepared by sublimation method using different proportions of mannitol and camphor as super disintegrants (table.no:1). Tablets were compressed by direct compression technique.

Evaluation of granules

Angle of repose

Angle of repose was determined by 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 was calculated. It is the angle produced between the heap of the pile and base (Khan *et al*., 2007).

$$\text{Angle of repose, } \tan(\theta) = h / r$$

where θ = Angle of repose,
h = Height of heap,
r = Radius of pile.

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Bulk density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined (Khan *et al*., 2007).

$$\rho b = M / Vb$$

where M = Weight of powder

Vb = Bulk volume

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured (Khan *et al*., 2007).

$$\rho t = M / Vt$$

where M = Weight of powder

V t = Volume after tapping

Compressibility index

The simplest way of measurement of free flow of powder is compressibility.The indication of the ease with which a material can be induced to flow is given by compressibility index (Khan *et al*., 2007).

$$I = [(Vb - Vt) / Vb] \times 100$$

where Vb = Bulk volume

Vt = Tapped volume

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow (Khan *et al*., 2007).

$$\text{Hausner ratio} = \rho t / \rho d$$

where ρt = Tapped density

ρd = Bulk density

Evaluation of tablets

Hardness

Hardness or tablet crushing strength (Fc), the force required to break a tablet in a diametric compression, was measured using Premier Tablet Hardness Tester (Kuchekar *et al.,* 1998).

Friability test

Friability of tablets was determined using Roche Friabilater. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches at each revolution. Preweighed sample of tablets was placed in a friabilater and the tablets were subjected to 100 revolutions. Tablets were then dusted using a soft muslin cloth and reweighed (Kuchekar *et al*., 1998).

$$\text{Friability (F)} = (1- Wo / W) \times 100$$

where Wo = weight of the tablets before the test.

W = weight of the tablet after the test.

Water absorption capacity

Water absorption ratio was determined by the following ratio (Singh *et al*., 2008).

$$R = 100 \times Wb / Wa$$

here Wb = Weight of tablet before water absorption

W =Weight of tablet after water absorption

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured (Jashanjit Singh *et al*., 2008).

Drug content uniformity

The prepared five tablets were powdered and the blend equivalent to10 mg of cetirizine was weighted and dissolved in suitable quantity of methanol. The solution was filtered, suitably diluted and drug content was analyzed spectrophotometrically at 239 nm (El Walily *et al*., 1998). Each sample was analyzed in triplicate (Kuchekar *et al*., 1998).

In vitro disintegration time

Tablets were added to 10 ml of Sorenson's buffer solution of pH 6.28 at 37 ± 0.5^{o}C. Time required for disintegration of the tablets were noted (Khan *et al*., 2007).

In vitro dissolution studies

Dissolution studies were carried out by USP-II dissolution apparatus. The tablet was taken from each formulation to carry out the dissolution study in the pH 6.2 buffer solution as dissolution medium (pH of saliva). Five milliliter samples were collected every minute and after proper dilution they were analyzed (Khan *et al*., 2007) at 239 nm against the blank pH 6.2 buffer solution by Elico UV Double Beam Spectrophotometer (El Walily *et al*., 1998).

HPLC Analysis

The results of U.V.method also confirmed by RP-HPLC method for the formulation CZ2 (1:1:2) using C18 column with mobile phase of acetonitrile : water : triethanolamine (40 : 60 : 0.1) and the pH was adjusted to 3.5 with phosphoric acid and triethanolamine. Flow rate was 1.5 ml / minute with retention time 5.50 minutes. The sample injected was 25 µl and analyzed by UV detector at 215 nm using La Chrom Merck HPLC instrument. Concentration of Cetirizine in the sample was determined using a standard graph (0.5 µg / ml to 3.0 µg / ml).

Table 1: Formulation of cetirizine dihydrochloride orodispersible tablets

Ingredients	CZ1	CZ2	CZ3
Cetirzine(mg)	10	10	10
Camphor(mg)	10	10	10
Mannitol(mg)	10	30	60

RESULTS AND DISCUSSION

Preformulation studies

The IR study revealed that camphor, mannitol is compatible with cetirizine dihydrochloride.

Evaluation of granules

The prepared granules were evaluated for various parameters such as angle of repose, bulk density, tapped density, compressibility index, hausner ratio; the values were within the standard limit fixed for orodispersible tablets (D P Venkatesh, C G Geetha Rao 2008). The results of angle of repose (26°-29°) indicate good flow properties. Bulk density (0.385-0.388 g/cc), tapped density (00.30-0.64 g/cc) and hausner ratio (1.5-1.6) values indicate that the formulated powder blend shows satisfactory flow property, compressibility index values(35%-40%) were found to be higher (table 2).

Table 2: Evaluation of granules

Tests	CZ1	CZ2	CZ3
Angle of repose (˚)	29.82° ± 0.36	26.18° ± 0.29	27.43° ± 0.31
Bulk density (g / cc)	0.3866 ± 0.021	0.3854 ± 0.023	0.3884 ± 0.21
Compressibility index	40% ± 0.48	38.38% ± 0.39	35.29% ± 0.38
Hausner ratio (g / cc)	1.666 ± 0.12	1.623 ± 0.10	1.545 ± 0.13
Tapped density (g /cc)	0.6443 ± 0.02	0.6255 ± 0.03	0.6003 ± 0.07

All values are mean ± SD (n =3)

Table 3: Evaluation of tablets

Tests	CZ1	CZ2	CZ3
Hardness(kg)	3.6 ± 0.21	3.1± 0.18	3.5 ± 0.15
Friability (%)	0.3% ± 0.09	0.7% ± 0.07	0.8% ± 0.06
Water absorption capacity(gm)	13.1± 0.29	14.48 ± 0.31	14.99 ± 0.37
Wetting time(sec)	10	5	8
Drug content uniformity(mg)	9.8 ± 0.33	9.92 ± 0.17	9.93 ± 0.17
Disintegration Time(sec)	22	16	19

All values are mean ± SD (n =3)

Table 4: *In vitro* dissolution of cetirizine orodispersible tablets

Time (min)	Cumulative percentage of drug release (%) for CZ 1	Cumulative percentage of drug release (%) for CZ 2	Cumulative percentage of drug release (%) for CZ 3
1	54.0 ± 0.59	50.4 ± 0.98	57.6 ± 0.38
2	58.5 ± 0.37	68.4 ± 0.21	61.2 ± 0.64
3	64.8 ± 0.78	72.0 ± 0.73	64.8 ± 0.61
4	72.0 ± 0.99	75.6 ± 0.59	68.4 ± 0.88
5	75.6 ± 0.34	79.2 ± 0.46	72.0 ± 0.75
6	76.5 ± 0.55	82.8 ± 0.94	75.6 ± 0.84
7	79.2 ± 0.64	86.4 ± 0.96	79.2 ± 0.61
8	82.8 ± 0.48	90.0 ± 0.77	79.2 ± 0.56
9	86.4 ± 0.58	93.6 ± 0.62	82.8 ± 0.42
10	86.0 ± 0.48	97.2 ± 0.81	86.4 ± 0.49
11	87.1 ± 0.93	100	90.0 ± 0.58
12	88.2 ± 0.95	-	93.6 ± 0.39
13	90.0 ± 0.78	-	-
14	93.6 ± 0.82	-	-

All values are mean ± SD (n =3)

Evaluation of tablets

The formulated mouth dissolving tablets were evaluated for various parameters such as hardness, friability, water absorption capacity, wetting time and drug content uniformity. Thus it was revealed that hardness was found to be high for formulation CZ1 (1:1:1) and low for formulation CZ1 (1:1:3). This acceptable hardness favors orodispersible tablets. Friability, water absorption capacity, drug content uniformity of all the formulations was with in the standard limits. Disintegration time of tablets was found to be good and in favour of orodispersible tablets (table 3). *In vitro* dissolution results revealed that 93.6% of drug was released at the end of 14 minutes of formulation CZ1(1:1:1), 100% of drug was released at the end of 11minutes for formulation CZ2 (1:1:3) and 93.6% of drug was released at the end of 12 minutes of formulation CZ3(1:1:6), (table 4, fig. 1). The rapid release from formulation CZ2 may be due to less hardness, wetting time and disintegration time. From the above results CZ2 was selected as the best formulation and *in vitro* dissolution study reproducibility was evaluated by RP-HPLC method (table 5), which also confirms the release of 100% at the end of 11 minutes for formulation CZ2 (1:1:3) with peak area of 19,845.

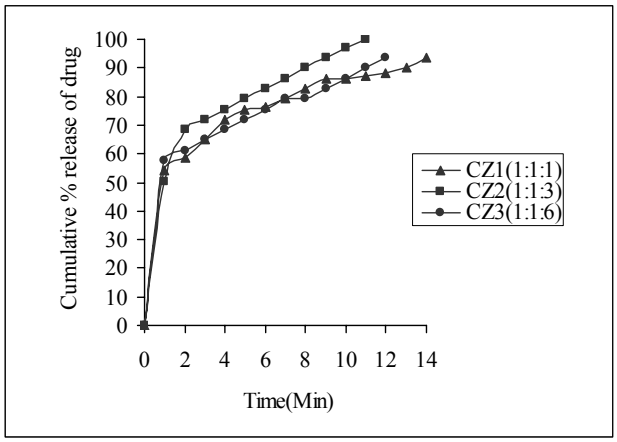

Fig. 1: Comparative *in vitro* dissolution of cetirizine dihydrochloride orodispersible tablets.

Table 5: Standard curve Cetirizine dihydrochloride by HPLC.

S. No.	Concentration (mcg/ml)	Peak area (Thousands)
1.	0.5	9941
2.	1.0	19845
3.	2.0	39694
4.	3.0	59605

CONCLUSION

Although there are several super disintegrates available, mannitol and camphor were found to be compatible with Cetirizine dihydrochloride. The granules prepared by sublimation process were found to be free flowing in nature. The tablets prepared by direct compression technique were found to have adequate hardness and friability. The formulated tablet CZ2 (1:1:3) showed fast disintegration and *in vitro* dissolution. Therefore these tablets which possess rapid disintegration may be useful for pediatric and geriatric population. However further work is needed to establish the stability and *in vivo* efficacy of these orodispersible tablets.

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