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Novel Approach in Designing Mouth Dissolving Tablets of Cetirizine Hydrochloride

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ABSTRACT

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The present work was to design and evaluation of mouth dissolving tablets of Cetirizine hydrochloride by using superdisintegrants. A novel approach has been made to develop Cetirizine hydrochloride mouth dissolving tablets by including clove oil as flavor and local anesthetic on taste buds. The drug and excipients were characterized using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) techniques. The drug excipient blend was evaluated for examined physicochemical properties. The prepared tablets were evaluated for thickness, hardness, friability, mouth feel, wetting time, content uniformity, *in vitro* disintegration time, *in vivo* disintegration time and in vitro dissolution studies. Formulation (F-4) showed quick disintegrating time of 228.26 s, which is very characteristic of mouth dissolving tablets. Further optimized formulations (F-4 and F-5) were subjected to accelerated stability studies for 3 months at temperature 40±5ºC/75±5%RH. The tested tablets did not show any changes with respect to taste, disintegration and dissolution profiles. In conclusion, the results of this work suggest the inclusion of Clove oil (which has both flavoring and local anesthetic actions), which reduces the processing charges and use of costlier taste masking agents.

Keywords: Mouth dissolving tablet, Cetirizine hydrochloride, Clove oil, superdisintegrants.

INTRODUCTION

Allergic disorders are most common worldwide. Cetirizine hydrochloride is an active non-sedative antihistamine. Mouth dissolving tablets undergo disaggregating in the mouth when in contact with the saliva in less than 60 s forming a suspension which is easy to swallow. Patients, particularly pediatric and geriatric patients, have difficulty in swallowing solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems has been developed. Mouth dissolving tablets dissolve rapidly in the saliva without the need for water, releasing the drug. The purpose of the present was to design Cetirizine hydrochloride mouth dissolving tablets using superdisintegrants, natural sweetener *Stevia (Stevia rebidiana)* leaf powders and local anesthetic flavor (Clove oil) in different proportions, to achieve patient compliance in allergic disorders[1-3].

MATERIALS AND METHODS

Materials

Cetirizine hydrochloride was a gift sample from Waksman Selman Pharmaceuticals, Anantapur, India. Stevia leaf powder was obtained from the medicinal garden of Sri Krishnadevaraya University, Anantapur, India and authenticated by the Botany department, Sri Krishnadevaraya University, Anantapur, India. Mannitol, Clove oil, talc, micro crystalline cellulose, Cross carmellose sodium, Cross Povidone, magnesium stearate and talc were purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmacopoeial or analytical grade.

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Evaluation of Pre-compression parameters

Compatibilities study

Fourier Transform Infrared Spectroscopic (FTIR) analysis

The FTIR spectrums of Cetirizine Hydrochloride and Formulation (F-5) blend were studied by using Fourier Transform Infrared (FTIR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.2510 mg sample in 300.2502 mg KBr). The scanning range was 500 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Flow properties of the blend[7,8]

Angle of repose

Funnel method was adopted to determine the Angle of repose. 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. The Angle of repose can be mathematically calculated by the following equation.

$$\tan(\theta) = h / r$$

Where,

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

Loose Bulk density

It was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. Mathematically loose bulk density can be calculated by the following equation.

$$LBD = M / V_b$$

Where,

M = Weight of powder and V_b = Bulk volume

Tapped Bulk density

Measuring cylinder method was adopted for this. A known quantity of formulation blend was taken in a graduated measuring cylinder and tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. Mathematically tapped bulk density can be calculated by the following equation.

$$TBD = M / V_t$$

Where,

M = Weight of powder and V_t = Volume after tapping

Compressibility index

It is an easiest way of measuring flow ability of powders. The loose and tapped bulk density values were considered in calculating compressibility index. Mathematically it can be calculated by the following equation.

$$I = [(V_b - V_t) / V_b] \times 100$$

Where,

V_b = Bulk volume and V_t = Tapped volume

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is the ratio of TBD to LBD. Mathematically loose bulk density can be expressed and calculated by the following equation.

$$\text{Hausner ratio} = TBD / LBD$$

Where,

TBD = Tapped bulk density and LBD = Loose bulk density

Preparation of Mouth Dispersible Tablets[9,10]

All the ingredients were passed through sieve # 60. Cetirizine hydrochloride, mannitol, Micro Crystalline Cellulose and Stevia leaf powder were triturated in a glass mortar. Micro crystalline cellulose, Cross carmellose sodium, Cross Povidone were incorporated in the powder mixture and finally magnesium stearate and talc were added. The mixed blend was then compressed with 10mm flat face surface punches using hydraulic press single tablet punching machine.

Evaluation of Post compression parameters[11-14]

Thickness

The thickness of the tablets was determined using a thickness screw gauge (ISC Technologies, Kochi, India). Five tablets from each batch were used and average values were calculated.

Hardness test

The hardness of the formulated tablets was determined using Monsanto hardness tester (Cadmach, Ahmedabad, India). It is expressed in kg/cm^2. Five tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

Friability test

The friability of tablets was determined using Roche Friabilator (Campbell Electronics, Mumbai, India). The friabilator was operated at 25 rpm for 4 min(totally 100 revolutions). The % friability was then calculated by the following equation.

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

Where,

F= friability (%), $W_{initial}$ = initial weight and W_{final} = Final weight

Weight variation test

Twenty tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was conducted as per the official procedure.

Drug content uniformity

Tablet containing 10 mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve and the solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted with 0.1N HCl and analyzed spectrophotometrically (Elico SL 210, India) at 233 nm. The concentration of Cetirizine hydrochloride mg/ml was obtained by using standard calibration curve of Cetirizine hydrochloride. Drug content studies were carried out in triplicate for each formulation batch.

Wetting time

The tablet was placed in a petridish of 6.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

Water absorption ratio

A small piece of tissue paper folded twice and placed in a petri dish containing 6ml of distilled water. A tablet was kept on the paper and time taken by the tablet for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using the following equation.

$$R = 10 X (Wa – Wb) / Wb$$

Where,

Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

Three tablets from each formulation were analysed performed and standard deviation was also determined.

***In-vitro* dispersion time**

Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5^{0}C. Time required for complete dispersion of a tablet was measured.

***In-vitro* disintegration time**

The *in vitro* disintegration time of tablets were performed by placing one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2^{0}C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per min in the pH 6.8 maintained at 37±2^{0}C. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the basket was measured and recorded.

***In-vivo* disintegration time**

Six healthy human volunteers (both sexes) were selected and their written statement was obtained. Each volunteer was allowed to one tablet and kept on the tongue. The time taken by the tablet (in seconds) for complete disintegration on the surface of the tongue was noted. After the test, mouth was washed with distilled water. Three trials were performed with 2 days interval, between trials.

***In-vitro* dissolution studies**

In vitro dissolution studies were carried out using dissolution test apparatus USP XXIII[15]. The following procedure was employed throughout the study to determine the *in vitro* dissolution rate for all the formulations. The parameters *in vitro* dissolution studies were tabulated in Table No. 5.

Accelerated Stability studies:

The promising formulations (F-4 and F-5) was tested stability for a period of 3 months at accelerated storage conditions of a temperature 40^{0}C and a relative humidity of 75% RH, for their drug content[16].

Table 1: Composition of Mouth Dissolving Tablets of Cetirizine hydrochloride

Ingredients (mg)	Formulation				
	F-1	F-2	F-3	F-4	F-5
Cetirizine hydrochloride	10	10	10	10	10
Mannitol	50	50	50	50	50
Cross carmellose sodium	10	20	30	40	50
Cross povidone	10	20	30	40	50
Stevia leaf Powder	5	5	5	5	5
Micro crystalline cellulose	204	184	164	144	124
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Clove oil (Flavoring and local anesthetic agent)	5	5	5	5	5
Total weight of the tablet 300mg					

RESULTS AND DISCUSSION

Results of Compatibility studies

The FTIR spectrum of Cetirizine hydrochloride showed characteristic peaks at 3444.97 and 3291.18 (3300-3500) (N-H), 2922.37 (2850 – 3000) (C-H), 2854.79 and 2796.22 (3300 - 2500 (O-H), 1442.66 and 1368.13 (1350 –1550) (N=O), 1123.61 (1220 -1020) (C-N), 1287.13, 1240.80 and 1006.79 (1000 –1300) (C-O) (Figure 1). Whereas the FTIR spectrum of Cetirizine hydrochloride mouth dissolving tablets showed characteristic peaks at 3402.09 (3300-3500) (N-H), 2910.50 (2850 – 3000) 2910.50 (C-H), (3300 - 2500 (O-H), 1427.36, 1283.08 (1350 –1550) (N=O), 1161.61 and 1081.98 (1220 - 1020) (C-N) and 1020.53 (1000 –1300) (C-O) (Figure 2). This indicates the characteristic peaks of Cetirizine hydrochloride were present even in formulated Cetirizine hydrochloride tablets, indicates that the drug was found to be compatible with the polymers used.

Results of flow properties

The formulated blend was evaluated for various parameters such as angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The values were within the official limits with less standard deviation. The results of angle of repose was ranged from 26.300.15 to 29.320.81^0 indicate good flow properties. Loose bulk density of the blends was ranged from 0.550.052 to 0.590.066 g/cm^3 and tapped bulk density was ranged from 0.650.083 to 0.710.051 g/cm^3. The LBD and TBD values were considered in calculating compressibility index, which was ranged from 12.12±0.10 to 22.50±0.02% and Hausner ratio ranged from 1.141±0.03 to 1.291±0.04. These values indicate that the formulated powder blend shows satisfactory flow property. All these values were represented in Table No. 2.

Results of physicochemical properties of tablets

The mean thickness of formulated tablets was found to be uniform (2.980.15 to 3.050.02 mm), the hardness of formulated tablets was more than 5 kg/cm^3 (5.940.26 to 7.95±0.19 kg/cm^3) and the loss in friability was less than 1% (0.26±0.08 to 0.56±0.09 %) indicated the formulated tablets have good mechanical strength. All the tablets passed weight variation test as per the pharmacopoeial limits. The Wetting Time (928.95 to 1005.66 s) indicates that all the formulated tablets has quick wetting, this may be due to ability of swelling and also capacity of absorption of water. The water absorption ratio (12.51±0.02 to 16.59±0.15g) favors the wetting of the tablet in saliva. The disintegration time (228.26 to 392.32 s) was within the pharmacopoeial limits aided with the presence of cross cormilose sodium and cross Povidone, in direct compression method results in hydrophilicity and swelling which in turn causes rapid disintegration. The volunteers felt good taste in all the formulations. As the formulation was not bitter due to the presence of stevia leaf powder, which is 400 times sweeter than sucrose and the Euginol in clove oil which acts as both flavoring and local anesthetic agent to block the sensation of taste buds. In oral disintegration all the formulations showed rapid disintegration in oral cavity. All these values were represented in Table No 3.

In all the formulations the drug release was nearer to 100% within 6 min. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants. The parameters

Fig.1: FTIR spectrum of Cetirizine hydrochloride

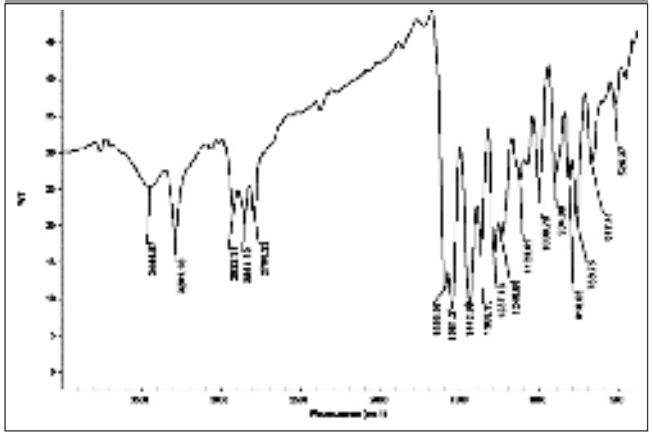

Fig.2: FTIR spectrum of Cetirizine hydrochloride formulation (F-5)

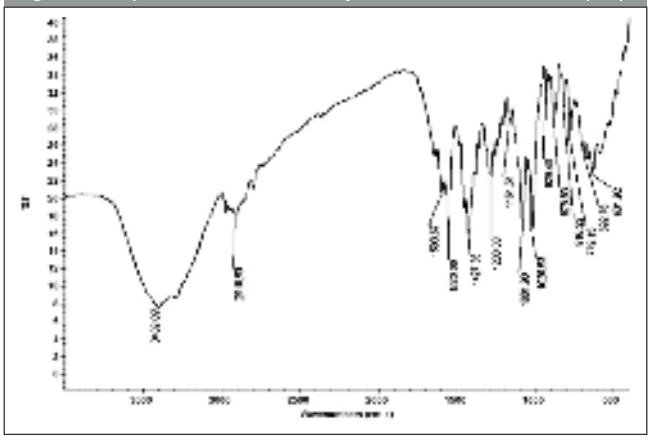

Table 2: The physicochemical properties of powdered blend

Formulation	Angle of Rpose (ø)	Loose Bulk Density (g/cm^3)	Tapped Bulk Density (g/cm^3)	Carr's Index (%)	Hauser's Ratio
F-1	29.32±0.81	0.57±0.077	0.68±0.023	16.18±0.05	1.192±0.01
F-2	28.98±0.48	0.55±0.052	0.71±0.051	22.50±0.02	1.291±0.04
F-3	28.73±0.86	0.59±0.066	0.69±0.065	14.56±0.02	1.169±0.01
F-4	27.20±1.57	0.57±0.032	0.65±0.083	12.35±0.06	1.141±0.03
F-5	26.30±0.15	0.58±0.075	0.66±0.094	12.12±0.10	1.143±0.02

Number of trials (n)=5

Table 3: Evaluation parameters of Tablets

Formulation	Thickness (mm)	Hardness (kg/cm^3)	Friability (5)	Wetting Time(s)	Water absorption Ratio	Disintegration Time(s)	Mouth Feel
F-1	3.0±20.08	6.38±0.13	0.35±0.01	100±5.66	12.51±0.02	35±4.25	Good
F-2	3.0±30.05	6.10±0.17	0.56±0.09	92±8.95	13.56±0.10	39±2.32	Good
F-3	2.9±80.15	7.95±0.19	0.29±0.09	95 ±6.66	14.25±0.14	32±6.59	Good
F-4	3.0±30.01	6.95±0.51	0.26±0.08	99±4.59	15.16±0.09	22±8.26	Good
F-5	3.0±50.02	5.94±0.26	0.54±0.05	98±3.87	16.59±0.15	31±4.61	Good

Number of trials (n) = 5

in *In-vitro* dissolution studies were shown in Table No. 4. The *In-vitro* dissolution profile of formulated tablets was shown in Figure 3. The optimized formulations F-4 and F-5 were subjected to accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation. The comparative parameters of optimized formulations (F-4 and F-5) before and after the accelerated stability studies were shown in Table 5.

Fig.3: In-vitro dissolution profile of formulated tablets

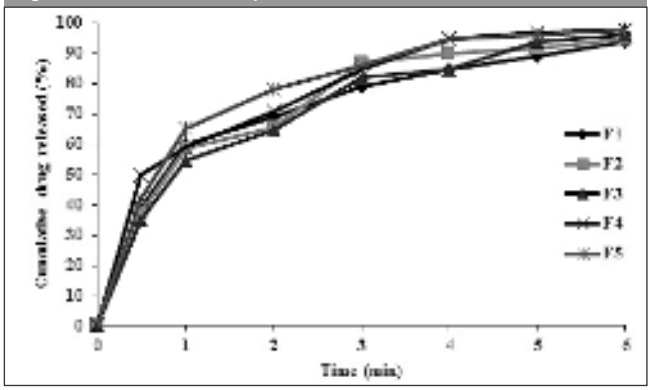

Table 4: Tablet dissolution apparatus parameters

Parameter	Value
Dissolution medium	900 ml of 0.1N Hcl
Temperature	37^0C1^0C
RPM	50
Tablet taken	One tablet (Known drug content)
Volume withdrawn	5 ml every 2 min
Volume made up to	5 ml
λ_{max}	233 nm
Beer's range	1-10 g/ml
Dilution factor	10

CONCLUSIONS

This study concludes that Clove oil can be incorporated in mouth dissolving tablets as it has both flavoring and local anesthetic actions, which reduces the processing charges and use of costlier taste masking agents. Additionally inclusion of Stevia (*Stevia rebidiana*) leaves powder still makes the formulation elegant as it is 400 times sweeter than Sucrose and diabetic friendly.

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Table 5: Physical properties of F-4 & F-5 till 90 days when stored at 40^0C/75% RH

Formulation	Tested After Time (days)	Hardness (kg/cm^2)	Disintegration time (s)	Wetting time (s)	Friability (%)
F-4	0	6.95±0.51	22±8.26	99±4.59	0.26±0.08
	30	6.95±0.68	21±5.62	98±6.51	0.28±0.05
	60	6.94±0.48	20±4.54	97±2.51	0.27±0.07
	90	6.94±0.26	21±5.89	98±2.64	0.28±0.03
F-5	0	5.94±0.26	31±4.61	98±3.87	0.54±0.05
	30	5.95±0.27	30±2.87	99±4.85	0.55±0.01
	60	5.91±0.24	30±3.57	97±5.98	0.58±0.04
	90	5.90±0.15	29±5.21	96±5.62	0.57±0.06

Number of trials (n)=3

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