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Research Article

FORMULATION OF RAPID MOUTH DISSOLVING TABLETS OF CETIRIZINE di HCL USING SUBLIMATION METHOD

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ABSTRACT

Patient compliance is a prerequisite for the success of any drug delivery system which culminated into the design of mouth dissolving drug delivery system beside older NDDS. Cetirizine dihydrochloride is a non-sedative antihistamine with potent antiallergic action. The purpose of this study was to formulate mouth-dissolving tablet that have quick onset of action, not require water for swallowing of tablet, less disintegration and dissolution time, hence providing faster relief to the patient. In order to eliminate the rough texture in mouth, we attempted to prepare high porosity rapidly mouth-dissolving tablets by using water soluble material (Mannitol) along with a subliming material (Camphor) and to select the best formulation based on *in vitro* and *in vivo* study. In this study, Cetirizine diHCl E.P, D-Mannitol, DL-Camphor was used in various ratios. The drug (5%) with excipients was mixed in modified rotary flask shaker at 30 rpm (inclined at an angle of 50^0) for 30 minutes and compressed into tablet followed by sublimation using vacuum oven at 600mm Hg at 80^0C for 1 hour. Tablets prepared with drug, mannitol and camphor in ratio 1:16:3 showed least disintegration time (less than 1min. without shaking), maximum *in vitro* dissolution rate ($T_{50\%}$=4.75 min., $T_{90\%}$ = 13.75min.) and least *in vivo* mouth disintegration time (17.58 sec).

Keywords: Mouth dissolving tablets (MDTs), Sublimation, Cetirizine diHCl, Simulated Saliva

INTRODUCTION

Mouth dissolving Drug Delivery System gain their attention in order to improve efficacy and patient compliance in one of the most convenient dosage form i.e. Tablet due to difficulty in swallowing them[1] and this lack of convenience results in high incidence of non-compliance and ineffective therapy. It was envisaged to prepare tablet that should have quick onset of action and should not require water for swallowing of tablet[2], which is a usual inconvenience with conventional tablets especially during traveling. It should have less disintegration and dissolution time, hence faster relief to the patient can be provided. Since it was confirmed that a compressed tablet prepared by using superdisintegrant (Crystalline cellulose or low substituted hydroxypropyl cellulose L-HPC) rapidly disintegrates in saliva[3], however patient feel rough texture in their mouth due to incomplete solubilization of this type of tablets in saliva[4]. In order to eliminate the rough texture in mouth, we attempted to prepare high porosity rapidly mouth dissolving tablets[5] of Cetirizine dihydrochloride[6], a non sedative antihistamine bitter drug with potent antiallergic action, by using water soluble material (Mannitol) as excipients along with a subliming material (camphor[7]). Best formulation was selected on the basis of *in vitro* and *in vivo* studies.

MATERIALS AND METHODS

Materials

Cetirizine dihydrochloride European Grade was obtained as a gift sample from Himalayan Laboratories (H.P, India). D-Mannitol, DL-Camphor was purchased from S.D Fine Chem. Limited (Mumbai). All the other excipients of analytical grade were used.

Methodology

Cetirizine dihydrochloride complex was added with water soluble polymer (D-Mannitol) along with subliming agent (DL-Camphor). DL Camphor was powdered and passed through standard sieves to obtain the particles size in range of 250 to 425 µm. The tablet weight was adjusted to 200mg so as to contain 10mg of Cetirizine (normal dose) in each tablet. Tablets were prepared using Mannitol/camphor in various ratios as 18:1, 17:2, 16:3 and 15:4. The drug with excipients including 0.1% magnesium stearate was mixed and tablets were compressed using 8mm punch die in R&D tablet punching machine. For elimination of Camphor from the tablets, the compressed tablets were subjected for sublimation using vacuum oven[5] at 600mm Hg at 80^0C for 1 hour.

Evaluation

For weight variation study, twenty tablets were weighed individually before and after sublimation and from the average weight, standard deviation was determined. The crushing strength (Kg/cm^2) of prepared tablets was measured by using Monsanto tablet hardness tester. For *In vitro* disintegration time study, no method is available for mouth dissolving tablets, as these tablets have to disintegrate and dissolve within minutes. Therefore a modified method was used, which involves dropping the dosage form in a petridish containing 25ml of water and visualized through camera[8] (for better visualization methylene blue (1%w/v) was added for producing contrast colored background)

For determination of disintegration time in saliva, *In vivo* mouth disintegration study was carried out by sensory test in human subjects[9]. Four healthy volunteers (protocol IEC/21 approved by the Institutional Ethical Committee, M.M. University, Mullana and informed consent was obtained from the volunteers) took one tablet at random times and each volunteer licked (without biting) the tablet without drinking water and the time (in seconds) required for complete disintegration of the tablet was noted.

In vitro dissolution study was carried out using USP-1 apparatus with slight modifications[10] in which 100ml beaker containing 85ml of simulated saliva solution was used and prepared tablets were placed in the baskets that rotate at 25rpm in the dissolution fluid. The composition of simulated saliva[11] used is shown in table 1

Table 1: Composition of Simulated Saliva solution

Ingredients	Composition
KH_2PO_4	12mM
NaCl	40mM
$CaCl_2$	1.5mM
NaOH	to pH 6.2

The withdrawn samples were analyzed at 230nm using UV Visible spectrophotometer (Systronic model-108).

RESULTS AND DISCUSSION

For 20 tablets prepared using different Mannitol/camphor compounding ratio, the mean weight before camphor sublimation and after sublimation is given in table 2 which shows that almost all the camphor was sublimed from the tablets.

Table 2: Tablet weight before and after sublimation

Camphor (mg)	Tablet Weight (mg)	
	Before sublimation	After sublimation
10	203 ± 1.6	193 ± 2.4
20	201 ± 2.2	182 ± 1.4
30	204 ± 1.8	175 ± 1.6
40	200 ± 1.6	161 ± 1.8

Each value represents the mean ± S.D for twenty tablets

The crushing strength (Kg/cm^2) of prepared tablets was observed to be 1.5 to 2.25Kg/cm^2. As the tablets were prepared by sublimation and high degree of porosity was induced within the tablets, hardness of these tablets was low as compared to the normal compressed tablets. However, the tablets prepared using mannitol/camphor ratio upto 17:2 have sufficient strength for practical use

In vitro disintegration study by dosage dropping method, without shaking revealed that least disintegration time was 1 minute for tablet containing Mannitol and camphor ratio 16:3. From the video clips and photographs, it was evidenced that tablets start disintegration after 38 seconds without any agitation and completely disintegrates after 55 seconds, which upon shaking completely disperse and dissolve in the medium (Fig. 1)

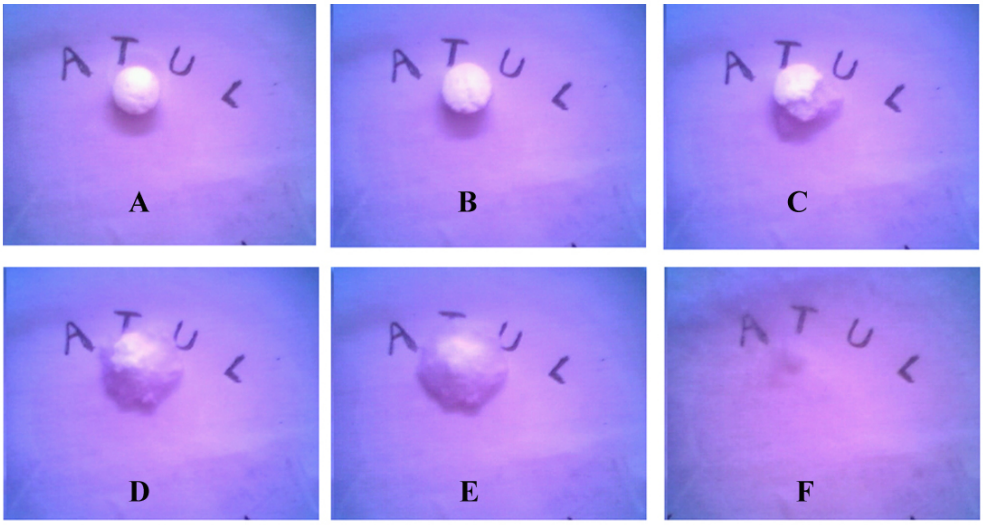

Fig. 1: *In Vitro* disintegration visualization: A. after dipping, B. after 38 seconds, C. after 45 seconds, D. after 50 seconds, E. after 55 seconds, F. after shaking

In vivo mouth disintegration test by mouth licking method also showed least mouth dissolution time (17.58 sec) in the same tablet shown in fig 2. With increases in camphor ratio, tablet disintegrates rapidly in the saliva, which may be related to an improvement of the water penetration into the tablets due to high porosity. However, further increases in the camphor to 15:4 ratio decreases the disintegration of tablets as shown in bar diagram (Fig 2). From the *in vitro* dissolution study of the different batches of Cetirizine diHCl tablets, increase in the percentage drug dissolution was observed with increase of subliming agent upto Mannitol/camphor ratio 16:3 and further increase causes the decline in the dissolution profile (Table 3, Fig 3)

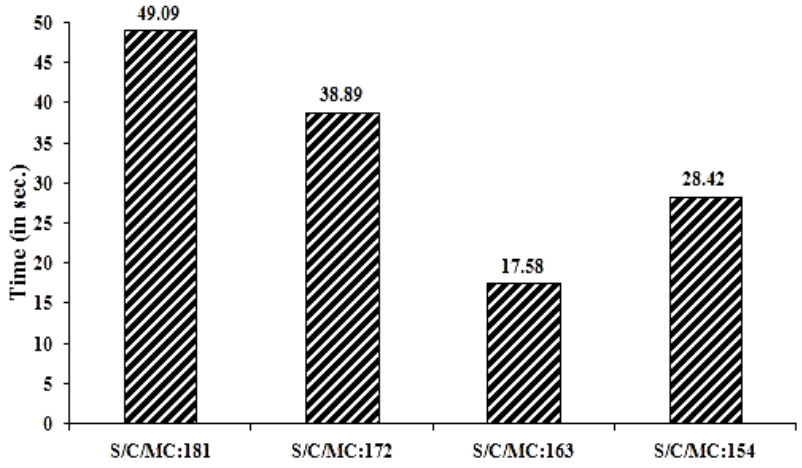

Fig. 2: *In Vivo* mouth dissolution test on healthy volunteers

Table 3: *In vitro* dissolution study of Cetirizine diHCl tablets

Time (min.)	Cumulative % Drug Dissolved			
	S/C/MC:181	S/C/MC:172	S/C/MC:163	S/C/MC:154
0	2.05 ± 0.12	4.06 ± 0.1	4.21 ± 0.09	1.75 ± 0.1
1	5.23 ± 0.15	6.94 ± 0.51	10.41 ± 0.04	5.87 ± 0.21
2	11.89 ± 0.25	9.73 ± 0.06	19.57 ± 0.26	15.79 ± 0.51
4	29.13 ± 0.31	17.22 ± 0.23	44.67 ± 0.31	38.58 ± 0.26
8	54.51 ± 0.14	52.05 ± 0.04	72.47 ± 0.25	60.03 ± 0.72
12	66.68 ± 0.28	74.96 ± 0.13	84.63 ± 0.05	69.46 ± 0.13
16	76.07 ± 0.37	87.53 ± 0.43	96.08 ± 0.21	75.13 ± 0.03
20	80.94 ± 0.16	95.54 ± 0.36	98.66 ± 0.13	84.09 ± 0.07

Each value represents the mean ± S.D data for six tablets

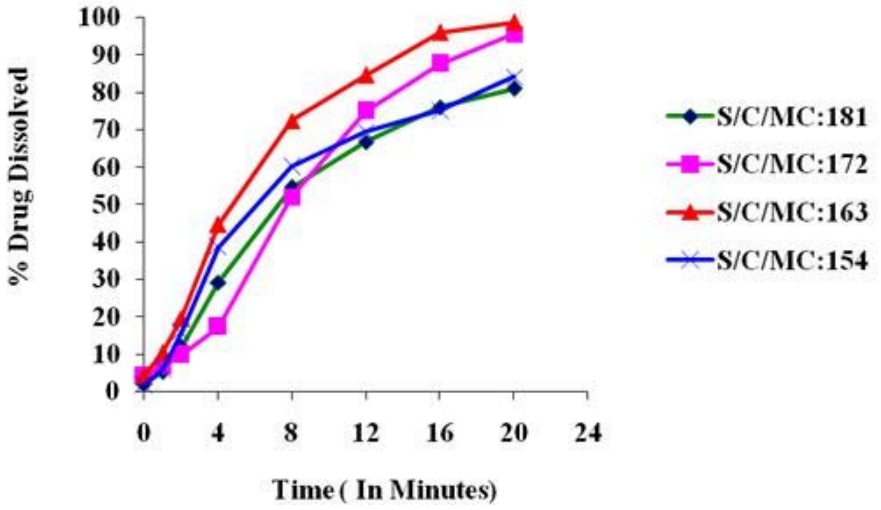

Fig. 3: In vitro dissolution study of cetirizine mouth dissolving tablets prepared by sublimation

For optimized formulation of the Cetirizine diHCl mouth dissolving tablet (batch no S/C/MC:163), $T_{50\%}$ and $T_{90\%}$ was 4.75min and 13.75min respectively which is well evident from the graph.

CONCLUSION

Minimum disintegration time and fastest dissolution rate was achieved with the formulation with drug, Mannitol, and camphor ratio 1:16:3 which was also confirmed by *in vitro* as well as *in vivo* disintegration study. The reason of faster rate of dissolution is due to high porosity created by sublimation technique, though with further increase in camphor induced porosity but causes newer problems like friability and inadequate hardness.

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