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**Formulation Development and Evaluation of  
Mouth Dissolving Tablets of Loratadine**

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**ABSTRACT**

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Mouth dissolving tablets constitute an innovative dosage forms that overcome the problems of swallowing and provides a quick onset of action. The purpose of this study was to formulate and evaluate mouth dissolving tablet of loratadine using a special preparation technology (pharmaburst Technology) with a super disintegrating agent (Croscarmellose sodium). Tablets were prepared by direct compression technique. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausners ratio. The tablets were evaluated for hardness, thickness, uniformity of weight, friability, wetting time, water absorption ratio, disintegration time and drug content. *In vitro* release studies were performed using USP-II (paddle method) in 900ml of pH 1.2 at 50rpm. The physical properties of the prepared tablets did not show any significant variations and were found to have good physical integrity. Tablets prepared with pharmaburst B2 and Croscarmellose sodium showed a lesser disintegration time and wetting time of 27±0.10 and 38±0.13 seconds respectively. The best formulations were subjected to stability studies at 40°C/75% RH for 60 days.

**Key words:** Loratadine, pharmaburst B2, croscarmellose sodium, mouth dissolving tablets, direct compression.

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**INTRODUCTION**

Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes (David *et al* 2008). Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity. It is used for the symptomatic relief of allergic conditions such as runny nose, itchy or watery eyes, sneezing, and nasal or throat itching and chronic urticaria (Haria M, *et al* 1994). It is also licensed to alleviate itching due to hives. It does not readily cross the blood brain barrier. Due to a bypass of first-pass metabolism, approximately 40% of the absorbed loratadine is absorbed via the oral mucosa (Lene Noehr-Jensen 2006). Hence, an attempt was made for preparation of mouth dissolving tablets of loratadine with an aim of reducing the lag time and providing faster onset of action to relieve the allergic conditions immediately. Mouth dissolving tablets (MDT) are formulated by utilizing several processes, which differ in their methodologies and the MDTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating MDTs include Freeze-Drying or Lyophilization, cotton candy process, molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, direct compression). This study has been performed by using direct compression process (the simplest and most cost effective tablet manufacturing technique for MDTs) with a patent technology (Pharmaburst Technology).

## MATERIALS AND METHODS

### Experimental material

Loratidine and pharmaburst B2 were a gift sample from Square Pharmaceuticals Ltd, Bangladesh. Croscarmellose sodium, Strawberry and Aspartame were obtained from Tuhin Chemicals, Dhaka. Avicel Ph 102, Aerosil-200, Purified talc, Magnesium Stearate were purchased from local market, Dhaka. *Solvents and reagents*: Hydrochloric acid (Merck, Germany); Methanol and acetonitrile (Merck, Germany); All other ingredients used were of analytical grade.

*Equipments*: Single punch tablet press (Shanghai-Tianhe Pharmaceutical Machinery Company); HM Semi Auto Blister Pack Machine( China), UV Spectrophotometer (Shimadzu, Japan); Digital pH meter (Hach Company, USA); Electronic Hardness tester (Ereweka,Germany); Tablet Dissolution Tester (Electrolab, India); Sartorius Electronic Balance.

*Preparation of dissolution medium*: For the preparation of simulated gastric medium (0.1 N HCl, pH 1.3) 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml.

### Preparation of tablets

The tablets were prepared by simple blending of active ingredient with polymer, filler, binder, lubricant and flow promoter followed by direct compression (Table-1). 50 tablets were prepared for each proposed formulation. Properly weighed Croscarmellose Sodium, Pharmaburst B2 Ph. Grade, Avicel Ph 102, Aspartame, Strawberry, Aerosil-200, Purified talc, Magnesium Stearate and the active ingredient were sieved through sieve no. 40 and then taken in a photo film container and blended in a laboratory designed small drum blender machine for 30 minutes to ensure thorough mixing and phase homogenization. This mixed blend was compressed into tablet weighing 195 mg using 10.00 × 7.00 mm oval shaped, flat bevel Single punch tablet press (Shanghai-Tianhe Pharmaceutical Machinery Company) to a hardness of 4-7 Kp. The compressed tablets were dedusted and evaluated for various tablet properties.

**Table 1. Formulation of Mouth dissolving tablets of Loratidine in mg.**

Formulation Ingredients	F-1	F-2	F-3	F-4
Loratidine	10	10	10	10
Croscarmellose Sodium	-	-	-	3
PharmaburstB2Ph.Grade	130	140	150	150
Avicel Ph 102	35	25	15	12
Aspartame	3	3	3	3
Strawberry essence	4	4	4	4
Aerosil-200	2	2	2	2
Purified talc	6	6	6	6
Magnesium Stearate	5	5	5	5
Total weight	195	195	195	195

### Evaluation of Granules

#### Angle of repose

Angle of repose ( $\theta$ ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface<sup>7</sup>. The diameter of the granular cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r), \text{ Where } h \text{ and } r \text{ are the height and radius of the cone.}$$

#### Bulk Density

Bulk density is a characteristic of a powder rather than individual particles and is given by the mass, M, of powder occupying a known volume, V, according to the relationship (Aulton 1998).

$$\text{Bulk density} = \frac{\text{Mass of powder (M)}}{\text{Volume of powder (V)}}$$

It is expressed by gm/cc.

### ***Tapped Density***

Tapped density is the ratio between mass of granules and volume of the granules after tapping (USP-30 NF 2007). It is expressed by gm/cc.

Tapped Density = Weight of granules/ Tapped volume

### ***Bulkiness***

Reciprocal of bulk density is known as bulkiness (Patrick 2006). It is expressed by cc/gm.

Bulkiness= 1/ Bulk density

### ***Compressibility index and hausner ratio***

The compressibility index and the closely related hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The compressibility index and hausner ratio were determined by measuring both the bulk density and tapped density of granules.

Compressibility Index =  $100 \times (1 - \text{Bulk density/Tapped density})$

Hausner ratio = Tapped density/ Bulk density

### ***Evaluation of tablets***

#### ***Hardness***

The strength of tablet is expressed as tensile strength (kp). The tablet crushing load, which is the force required to break a tablet by compression (Rudnic 1990). It was measured using a tablet hardness tester (Ereweka, Germany).

#### ***Thickness***

Checked the thickness of 05 tablets by a thickness tester (Ereweka, Germany) calculated and recorded the average of thickness of 10 tablets.

#### ***Weight variation***

Twenty tablets were randomly selected and individually weighed (Sartorius Electronic Balance). The average weight of the selected tablets was calculated (USP-30 NF 2007).

#### ***Friability***

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. Prewedged sample of ten tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Calculate the percentage loss in weight as follows.

Calculation:

$$\% \text{ of loss} = \frac{(A-B)}{A} \times 100 \%$$

Where, A = Initial weight of 20 tablets, B = Final weight of 20 tablets.

Compressed tablets should not loose more than 1% of their weigh (USP-30 NF 2007).

#### ***Disintegration Time***

The test was carried out on six tablets using distilled water at 37°C + 2°C was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds (Mukesh, 2009).

#### ***Wetting time***

Five circular tissue paper of 10cm diameter were placed in a petridish with a 10cm diameter. 10 ml of simulated saliva pH (phosphate buffer pH 6.8) was poured into the tissue paper placed in the petridish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time (Mukesh, 2009).

#### ***Water absorption ratio***

The weight of the tablet before keeping in the petridish was noted (Wb). Fully wetted tablet from the petridish was taken and reweighed (Wa). The water absorption ratio R can be determined according to the following formula.

$$R = (W_a - W_b) / W_a \times 100$$

### **Estimation of drug content**

Transfer 10 Tablets into a 250ml volumetric flask; add 100ml of 0.05N Hydrochloric acid and shake for 40 minutes or until the Tablets are completely disintegrated. Add 75ml of a mixture of methanol and acetonitrile (1:1), and mix. Add 20 ml of 0.6M Dibasic potassium phosphate, and mix for 5 minutes. Dilute with a mixture of methanol and acetonitrile (1:1) to volume, and mix. From this suitable dilution was prepared and the solution was analyzed at 280 nm using UV Spectrophotometer (Shimadzu, Japan) using 0.1N Hydrochloric acid solution as a blank.

### **In-Vitro Release Profile of Formulated Tablets**

The dissolution of mouth dissolving tablets of loratadine was carried out in USP-II (paddle type) dissolution apparatus. The dissolution medium was 900 ml of gastric simulated fluid (without enzyme) pH 1.2 maintained at 37°C. The paddle was rotated at 50 rpm for 20 min. The sample of 10 ml was withdrawn after every 2 min. and its absorbance was measured at 280 nm.

### **Stability studies**

Tablets of formulation (F-4) were blistered in HM Semi Auto Blister Pack Machine (China) for accelerated stability study. Blisters were kept in stability chamber at 40°C/75% RH for 60 days. At 30 and 60 days, the tablets were examined for physical changes, properties, drug content and in vitro release studies (Swamy 2008). (Tables 5, 6)

## **RESULTS AND DISCUSSION**

In the present study, mouth dissolving tablets of loratadine were prepared by using pharmaburst B2 and croscarmellose sodium as superdisintegrants. These four formulations were prepared by direct compression technique. The formulated granules were evaluated and the results are shown in the table 2. The angle of repose was in the range of 16.25±0.057 to 17.88±0.072 which was less than 25 indicating good flow property. The bulk density and tapped density was in the range of 0.3250± 0.0135 to 0.3398±0.0198 gm/cc and 0.3802± 0.0151 to 0.3902±0.0219 gm/cc. The bulkiness was in the range of 2.9429±0.1713 to 3.0769±0.1275 cc/gm. The compressibility index and Hausner ratio were in the range of 12.9241± 0.8370 to 15.0136±1.6498 % and 1.1485±0.0110 to 1.1771±0.0227 indicating good flow property.

**Table 2. Evaluation of prepared granules of Loratadine**

<b>Formulation Code</b>	<b>Angle of repose (θ)</b>	<b>Bulk density (gm/cc)</b>	<b>Tapped density (gm/cc)</b>	<b>Bulkiness (cc/gm)</b>	<b>Compressibility index (%)</b>	<b>Hausner ratio</b>
F-1	17.88±0.072	0.325±0.013	0.380±0.015	3.076±0.127	14.521±0.775	1.170±0.010
F-2	17.59±0.051	0.328±0.018	0.385±0.019	3.048±0.167	15.013±1.649	1.177±0.022
F-3	17.03±0.049	0.330±0.012	0.387±0.017	3.028±0.117	14.422±1.609	1.168±0.022
F-4	16.25±0.057	0.339±0.019	0.390±0.021	2.942±0.171	12.924±0.837	1.1485±0.011

The compressed tablets were evaluated for physical properties and the results are tabulated in table 3. The hardness was in the range of 4.49±0.17 to 5.48±0.32 Kp. Uniformity of weight was found to be in the range of 196.72±0.69 mg to 199.48±0.58 mg. The friability of all the formulation was within 1% which was in the range of nil to 0.06%. The wetting time for all the formulated tables was in the range of 38±0.13 to 105±0.43 sec. The water absorption ratio was found to be in the range of 44.80±0.84 to 47.87±0.52 %. The disintegration time of all the formulated tablets between 27±0.10 to 48±0.19 sec. The drug content was in the range of 99.8±0.29 to 102.60±0.42 %. F-2, F-3 and F-4 formulations were selected for the *In vitro* release studies.

**Table3. Evaluation of Loratadine mouth dissolving tablets**

<b>C</b>	<b>Hard</b>	<b>Thickn</b>	<b>Uniformity</b>	<b>Friabili</b>	<b>Wetting</b>	<b>Water</b>	<b>DT</b>	<b>Drug</b>
<b>o</b>	<b>ness</b>	<b>ess</b>	<b>of weight</b>	<b>ty</b>	<b>time</b>	<b>absorption</b>	<b>(sec)</b>	<b>content</b>
<b>d</b>	<b>(Kp)</b>	<b>(mm)</b>	<b>(mg)</b>	<b>(%)</b>	<b>(sec)</b>	<b>ratio (%)</b>		<b>(%)</b>
<b>e</b>								
F-1	5.17± 0.21	2.94± 0.01	198.21±0.81	0.03	105±0.43	44.80±0.84	48±0.19	102.60±0.42
F-2	4.76± 0.26	2.91± 0.00	197.56±0.57	0.06	57±0.17	45.27±0.74	41±0.12	100.30±0.29
F-3	4.49± 0.17	2.93± 0.00	199.48±0.58	0.01	49±0.14	45.43±0.49	36±0.10	99.8±0.29
F-4	5.48± 0.32	2.97± 0.01	196.72±0.69	Nil	38±0.13	47.87±0.52	27±0.10	101.4±0.36

**Table 4. *In vitro* dissolution profile of formulation F-1 to F-4 and the conventional tablet**

<b>Time</b>	<b>Formulation Code</b>				
	<b>F-1</b>	<b>F-2</b>	<b>F-3</b>	<b>F-4</b>	<b>Conventional</b>
<b>(min)</b>					<b>Tablet</b>
2	71.43	77.65	85.05	94.49	16.56
4	79.78	86.95	88.21	98.35	28.85
6	87.05	90.83	91.96	98.62	46.94
8	88.90	91.06	92.56	98.97	52.48
10	89.01	91.45	93.98	99.13	59.36

**Table 5. Result of evaluation for hardness, friability and disintegration time in stability studies of mouth dissolving tablet of loratadine(F-4)**

<b>Time(days)</b>	<b>Hardness(kp)</b>	<b>Friability (%)</b>	<b>Disintegration time(sec)</b>
30	5.49±0.3196	0.02±0.0012	31.0±0.11
60	5.46±.3178	.04±0.0023	30±0.10

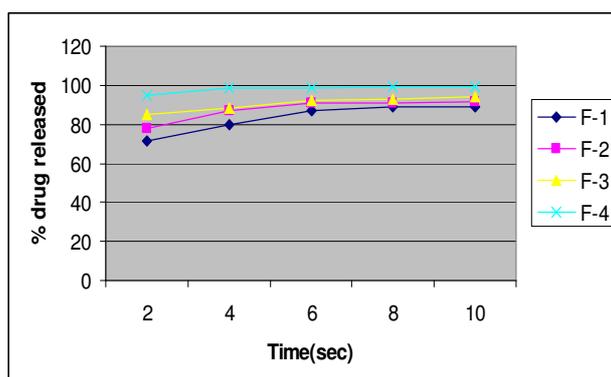
**Table 6. Result of evaluation for hardness, friability and disintegration time in stability studies of mouth dissolving tablet of Loratadine(F-4)**

<b>Time</b>	<b>02min</b>	<b>04 min</b>	<b>06 min</b>	<b>08min</b>	<b>10 min</b>
<b>(days)</b>					
30	94.85±0.334	98.30±0.398	98.55±0.347	98.99±0.287	99.03±0.349
60	95.17±0.276	98.32±0.285	98.63±0.399	98.96±0.348	98.99±0.287

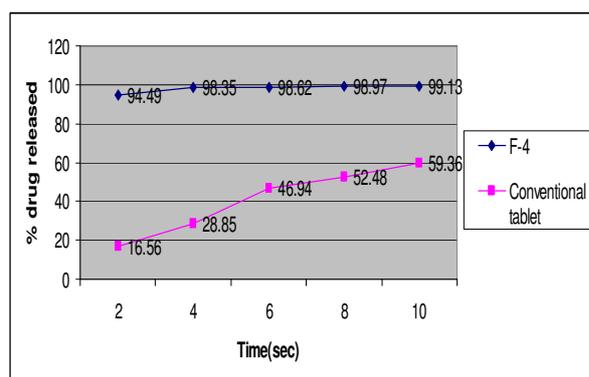
The *In vitro* release study for the formulations F-2, F-3 and F-4 were shown in the figure 2. Over all the MDT formulations of loratadine showed an average of 89.01 to 99.13 % drug release range at the end of 10 min and it was also observed that F-4 took shortest time to release the maximum amount of drug whereas the other formulation took more than 10 min to release the drug. In comparison with other formulations, F-4 shows a better drug release of 99.13% at the end of 10 min.



**Figure 1: Wetting of mouth dissolving tablet of Loratadine (F-4) at 05, 25 and 38 second respectively**



**Figure 2: *In vitro* dissolution profile of mouth dissolving tablet of loratadine (F-4)**



**Figure 3: Comparison of dissolution profile of F-4 and the conventional tablet**

Further the F-4 was compared with marketed conventional formulation (Loratin tablet, Square Pharmaceuticals Ltd) and found to be superior in terms of dissolution profile. F-4 formulation was selected for accelerated stability study. F-4 formulation was placed at 40°C/75% RH for 60 days. At 30 and 60 days, the tablets were examined for physical parameters and *In vitro* release studies as per ICH guidelines Q1C<sup>11</sup>. There were no significant changes found when the values are compared with 0 day of formulation.

## CONCLUSION

The release of drug from the F-4 formulation was quick when compared to F-2 and F-3 formulation. It shows that the combined effect of crosscarmellose sodium and pharmaburst B2 gives synergistic effect. Undoubtedly the availability of various technologies and the manifold advantages of MDT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in near future.

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