FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF CINNARIZINE USING SUBLIMATION TECHNIQUE

Dr. C.S.R. Lakshmi, Nitesh J. Patel*, Hitesh P. Patel, Sagar Akul
Department of Pharmaceutics, Nargund college of Pharmacy, Bangalore-85, Karnataka, India.
*Corresponding author’s E-mail: nitspatel86@gmail.com

ABSTRACT
The purpose of the present research was to compare the effect of subliming agents on the oral dispersible property of cinnarizine tablets. The fundamental principle used in the development of the oral dispersible tablets by sublimation technique is to maximize pore structure of the tablets. Compressed tablets prepared using a water soluble material like mannitol, does not rapidly disperse in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, subliming agents such as camphor, menthol, ammonium bicarbonate or thymol are to be used. A high porosity was achieved due to the formation of many pores where camphor, menthol, ammonium bicarbonate and thymol particles previously existed in the compressed mannitol tablets prior to sublimation of these subliming materials. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 25 s in the mouth. We developed a direct compression method for the formulation of cinnarizine (an anti emetic drug) tablets with high porosity which dissolves rapidly using mannitol as diluent and camphor, menthol, ammonium bicarbonate or thymol as subliming agents.

Keywords: Oral dispersible tablet; subliming material; High porosity; direct compression.

INTRODUCTION
Over the last few years, a great deal of interest has been directed towards formulating solid oral dosage forms that disintegrate/dissolve rapidly in the mouth without the need for water. These dosage forms are known as rapid disintegrating or oral dispersible tablets¹. The term 'Oral dispersable Tablet' as appears in European Pharmacopoeia is defined as "uncovered tablet for buccal cavity, where it disperses before ingestion"².

Many patients find difficulty in swallowing tablets and hard gelatin capsules; consequently they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy. For this reason the development of orally disintegrating or rapidly disintegrating tablets (RDT) have recently interested not only the pharmaceutical industry, but also academia³,⁴. ODT will avoid missing out of dose even during travelling, busy or other situations where there is no access to water⁵.

They undergo disaggregation 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 been generally paediatric, geriatric, bedridden or mentally disabled patients⁶.

The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market⁷.

A major claim of some oral dispersible tablets is increased bioavailability compared to traditional tablets. Because some of the drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly increased over those observed in the conventional tablet dosage form⁸.

Kei-ichi Koizumi et al., confirmed that a compressed tablet prepared with crystalline cellulose and low-substituted hydroxypropylcellulose (L-HPC) rapidly disintegrated (within 15 s) in saliva (or a small amount of water) in the mouth of humans. However, patients sometimes feel a rough texture in their mouth due to the incomplete solubilisation of this type of tablet in saliva. To eliminate the rough texture in the mouth, we attempted to use a water-soluble material (mannitol) as an excipient instead of crystalline cellulose and L-HPC, in the preparation of this type of tablet. However, the compressed tablet prepared using mannitol did not rapidly dissolve in saliva since it is difficult for water to penetrate into the tablet due to its low porosity. We therefore investigated a new convenient method of preparing compressed tablets with high porosity, which dissolve rapidly in the mouth, using mannitol and a subliming material. We chose camphor, menthol, ammonium bicarbonate and thymol as subliming materials⁹.

The basic approach used in the development of the fast-dissolving tablet is the use of superdisintegrants like croscarmellose sodium, sodium starch glycolate, and crospovidone. Another approach used in developing ODT...
tablets are maximizing pore structure of the tablets. Freeze-drying and vacuum-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields fragile and hygroscopic product. Therefore, it was decided to adopt the oven-drying technique in the present investigation. Oven drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Cinnarizine is a H1-receptor antagonist. It is widely used in the treatment of motion sickness, vomiting and vertigo. It is water insoluble and tasteless drug. Hence it was selected as a model drug for the preparation of oral dispersible tablets using Sublimation Technique.

**MATERIALS AND METHODS**

Cinnarizine purchased from Seva fine chem, Ahmedabad, Mannitol (pearlitol SD-200) gift sample from Amneal pharmaceutical pvt, Ahmedabad, ammonium bicarbonate purchased from Merck specialities private limited, Mumbai, camphor, menthol and thymol purchased from S d fine chemicals, Mumbai. A schematic representation of tablet preparation is shown in Fig1. For compression of materials, into tablets using tablet machine Rimek mini press-1, Karnavati Engineering Ltd, Mehsana, Gujarat (punches flat-faced, 8 mm diameter) was employed. To prepare 200 mg tablets, mixture of cinnarizine, mannitol and camphor, menthol, ammonium bicarbonate and thymol in various concentrations were compressed. For sublimation of camphor, menthol, ammonium bicarbonate and thymol from the tablets, the tablets are placed in an oven at 60°C until constant weight is obtained. The crushing strength (kg) of tablets was measured using a tablet hardness tester.

**Evaluation of Powder Blends:** The powder blend was evaluated for flow properties as follows and reported in table 2:

**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.

\[
\tan(\theta) = \frac{h}{r}
\]

Where,

\[
\theta = \text{Angle of repose,}
\]

\[
h = \text{Height of heap,}
\]

\[
r = \text{Radius of pile.}
\]

**Carr’s index:**

\[
\text{Carr’s } \text{index} = \left( \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \right) \times 100.
\]

**Hausner ratio:** Hausner ratio is an indirect index of ease of powder flow.

\[
\text{Hausner ratio} = \frac{\rho_{\text{tap}}}{\rho_{\text{bul}}}
\]

Where,

\[
\rho_{\text{tap}} = \text{Tapped density} = \text{weight of powder / tapped volume of powder}
\]

\[
\rho_{\text{bul}} = \text{Bulk density} = \text{weight of powder / bulk volume of powder}
\]

**Friability:** The friability of a sample of six tablets was measured using a Roche Friabilator (Electrolab EF-2, USP). Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal
of fine’s using 60 mesh screens and the percentage of weight loss was calculated.

\[
\% \text{ Friability} = \left( \frac{\text{Loss in weight}}{\text{Initial weight}} \right) \times 100
\]

**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.

**Drug content uniformity**: 10 tablets from each formulation were powdered and the blend equivalent to 25 mg of cinnarizine was weighted and dissolved in 100ml of 0.1 N HCl solutions. The solution was filtered, and 1ml of first stock solution was diluted up to 100ml with 0.1N HCl. Drug content was analyzed spectrophotometrically at 253.2 nm. Each sample was analyzed in triplicate.

**In vitro disintegration time**: In vitro disintegration time was measured by using 200ml distilled water in 250ml beaker at 37± 0.5°C temperature. Time required for disintegration of the tablets was noted.

**In vitro dissolution studies**: ODTs were evaluated for dissolution behaviour. Dissolution tests used the USP apparatus 2, paddle types (Elect lab, Mumbai, India.). Dissolution was carried out with the rotation speed of 50 rpm using 500 ml of 0.1 N HCl as the dissolution medium maintained at a temperature of 37 ± 0.5°C. Samples were withdrawn at predetermined time interval and diluted suitably and analyzed at 253.2 nm for cumulative drug release using Schimadzu UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate, shown in Fig.2.

### Table 1: Formulation of cinnarizine oral dispersible tablets

<table>
<thead>
<tr>
<th>NAME OF EXCIPIENT</th>
<th>FS1</th>
<th>FS2</th>
<th>FS3</th>
<th>FS4</th>
<th>FS5</th>
<th>FS6</th>
<th>FS7</th>
<th>FS8</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMPHOR</td>
<td>20</td>
<td>40</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>AMMONIUM BICARBONATE</td>
<td>----</td>
<td>----</td>
<td>20</td>
<td>40</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>MENTHOL</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>20</td>
<td>40</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>THYMOL</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>MANITOL</td>
<td>155</td>
<td>135</td>
<td>155</td>
<td>135</td>
<td>155</td>
<td>135</td>
<td>155</td>
<td>135</td>
</tr>
</tbody>
</table>

### Table 2: Physical Characteristics of Powder Blends

<table>
<thead>
<tr>
<th>FORMULA NO</th>
<th>BULK DENSITY</th>
<th>TAPPED DENSITY</th>
<th>CARR’S INDEX</th>
<th>HAUSNER RATIO</th>
<th>ANGLE OF REPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS1</td>
<td>0.532</td>
<td>0.632</td>
<td>15.95</td>
<td>1.18</td>
<td>32.62</td>
</tr>
<tr>
<td>FS2</td>
<td>0.505</td>
<td>0.588</td>
<td>14.14</td>
<td>1.16</td>
<td>35.86</td>
</tr>
<tr>
<td>FS3</td>
<td>0.526</td>
<td>0.617</td>
<td>14.73</td>
<td>1.17</td>
<td>29.28</td>
</tr>
<tr>
<td>FS4</td>
<td>0.549</td>
<td>0.641</td>
<td>14.28</td>
<td>1.16</td>
<td>33.69</td>
</tr>
<tr>
<td>FS5</td>
<td>0.510</td>
<td>0.602</td>
<td>15.30</td>
<td>1.18</td>
<td>32.27</td>
</tr>
<tr>
<td>FS6</td>
<td>0.537</td>
<td>0.617</td>
<td>12.90</td>
<td>1.14</td>
<td>32.27</td>
</tr>
<tr>
<td>FS7</td>
<td>0.520</td>
<td>0.595</td>
<td>12.5</td>
<td>1.14</td>
<td>34.59</td>
</tr>
<tr>
<td>FS8</td>
<td>0.515</td>
<td>0.609</td>
<td>15.46</td>
<td>1.18</td>
<td>32.59</td>
</tr>
</tbody>
</table>

![Figure 2: In vitro drug release profile of various cinnarizine formulations.](image-url)
RESULTS AND DISCUSSION

All the formulations were prepared by direct compression followed by sublimation Techniques. The data obtained from pre-compression parameters such as bulk density, tapped density, Hausner’s ratio, Carr’s index and angle of repose is given in Table 2 and is found to be within acceptable pharmacopoeia limits. Post-compression parameters like hardness, friability, weight variation, drug content, wetting time, in vitro disintegration time are mentioned in Table 3. The tablets measured hardness was found to be in the range of 2.7±0.273 to 3.1 ± 0.547 kg/cm². The percentage friability was less than 1% for all formulations ensuring mechanical stability of the formulated tablets. All formulations are then evaluated for variation in weight and results indicated that for all formulations the dispersible tablet must disintegrate within 3 min. But all formulated batches have shown very low disintegration time 5.67±0.294 to 33.28±2.018 seconds indicating suitability of formulation for fast dissolving tablet. Wetting time is found to be less for the formulation FS6 containing sublimating agent menthol as compared to other formulations. The in vitro dissolution profile (Fig. 2) indicated that among the all formulations, faster and maximum drug release was obtained from formulation FS6 due shorter wetting time and formation of porous structure by sublimation of menthol.

CONCLUSION

Oral dispersible tablets (ODT) of Cinnarizine are successfully prepared by using sublimation method. Undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, and rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. Oven-drying technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of mouth dissolving tablets.

Table 3: Evaluation of Oral dispersible Tablets

<table>
<thead>
<tr>
<th>FORMULATION NO</th>
<th>WEIGHT VARIATION (mg) ± S.D</th>
<th>HARDNESS* (kg/cm²)±0.5 S.D</th>
<th>FRIABILITY (%)</th>
<th>% ASSAY</th>
<th>WETTING TIME* (sce)±S.D</th>
<th>IN-VITRO DISINTEGRATION TIME* (sce)±S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS1</td>
<td>200.8±5.411</td>
<td>2.8±0.273</td>
<td>0.494</td>
<td>98.98</td>
<td>6.56±0.292</td>
<td>6.97±0.347</td>
</tr>
<tr>
<td>FS2</td>
<td>197.7±4.738</td>
<td>2.9±0.418</td>
<td>0.558</td>
<td>98.30</td>
<td>6.26±0.058</td>
<td>6.71±0.170</td>
</tr>
<tr>
<td>FS3</td>
<td>201.8±8.154</td>
<td>2.9±0.418</td>
<td>0.531</td>
<td>97.62</td>
<td>5.73±0.291</td>
<td>6.1±0.111</td>
</tr>
<tr>
<td>FS4</td>
<td>203.2±7.451</td>
<td>2.7±0.273</td>
<td>0.713</td>
<td>99.20</td>
<td>5.37±0.072</td>
<td>5.86±0.105</td>
</tr>
<tr>
<td>FS5</td>
<td>197.8±6.084</td>
<td>3.0±0.50</td>
<td>0.474</td>
<td>96.72</td>
<td>5.34±0.120</td>
<td>5.96±0.234</td>
</tr>
<tr>
<td>FS6</td>
<td>197.8±7.324</td>
<td>3.1±0.547</td>
<td>0.536</td>
<td>97.62</td>
<td>5.01±0.109</td>
<td>5.67±0.294</td>
</tr>
<tr>
<td>FS7</td>
<td>198.2±4.389</td>
<td>2.7±0.447</td>
<td>0.498</td>
<td>98.98</td>
<td>20.26±1.05</td>
<td>33.28±2.01</td>
</tr>
<tr>
<td>FS8</td>
<td>195.7±6.149</td>
<td>2.9±0.418</td>
<td>0.661</td>
<td>98.75</td>
<td>19.16±1.18</td>
<td>30.36±0.615</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD, n=3

REFERENCES

8. Furtado S, Deveswaran R, Bharath S, Basavaraj BV, Abraham S, Madhavan V, Development and


---

**About Corresponding Author: Mr. Nitesh Patel**

Mr. Nitesh Patel graduated at Saurashtra University, Gujarat, India and post graduated from Rajiv Gandhi University of Health Science, Bangalore, India. At post graduation level taken specialization in Pharmaceutics.