PREPARATION AND EVALUATION OF ATORVASTATIN CALCIUM POROUS TABLETS BY SUBLIMATION TECHNIQUE

ABSTRACT

In the present study, porous tablets of atorvastatin calcium (Antihyperlipidemic Agent) were prepared by sublimation method with a view to enhance patient compliance. In this technique, croscarmellose sodium (2-8% w/w) was used as superdisintegrate and camphor (15%) was used as subliming agent to increase the porosity which helps water to penetrate into the tablets. The tablets were evaluated for hardness, friability, thickness, drug content uniformity and in-vitro disintegration time. Based on in-vitro disintegration time (approximately 42 sec) the formulation containing 7.5% croscarmellose sodium and 15% camphor was found to be promising and tested for in-vitro drug release pattern (in pH 6.8 phosphate buffer). The optimized formulation F6 containing 15% of camphor showed in-vitro drug release of 98.06% of atorvastatin calcium in 14 min and the disintegration time was found to be 42 sec. The tablets tested for stability at 40°C and 75% RH for 1 month and 3 months and did not show much effect on the dissolution and drug content and are within the limits as per ICH guidelines therefore ensuring that the formulation F6 is a stable formulation. It was concluded that the porous tablets of atorvastatin calcium containing suitable subliming agent could be prepared by sublimation was a good approach for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Key Words: Atorvastatin calcium, Camphor, Porosity, Sublimation.

INTRODUCTION

Solid dosage forms like tablet and capsule are most popular and preferred drug delivery system because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing, and good physical and chemical stability. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms [1]. In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, recent developments in technologies have come out with mouth dissolving tablets (MDT) that can be ingested simply by placing them on the tongue. MDT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste [2].

The Compressed tablets prepared using mannitol did not rapidly dissolve 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, developing a novel method whereby camphor, a subliming material, is removed by sublimation from compressed tablets prepared using a mixture of mannitol and camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva in the mouth. Atorvastatin Calcium is an Anti hyperlipidemic drug which selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase. As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, these results in a subsequent decrease in hepatic cholesterol levels [3]. The Bioavailability of Atorvastatin is 14% due to its poor aqueous solubility. In the present study porous tablets of Atorvastatin calcium using camphor and menthol as a subliming agents were prepared to improve its dissolution profile and bioavailability.

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MATERIALS AND METHODS

Materials:
Atorvastatin, camphor, menthol, PVP Microcrystalline cellulose (MCC), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG), Crospovidone (CP), Sodium Lauryl Sulphate, Magnesium stearate were supplied from Standard reagents Hyderabad. All other chemicals and reagents used were of analytical grade.

Methods:

PRE FORMULATION STUDIES

Drug-Excipient Compatibility Studies
FTIR was used for the detection of any possible chemical reaction between the drug and the excipients. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks [4].

Formulation of Atorvastatin porous tablets by direct compression method:
Porous tablets of Atorvastatin were prepared by direct compression method employing camphor and menthol as sublimating agents. PVP is used as rate controlling polymers. The drug was mixed with the release rate enhancing disintegrants and other excipients, except magnesium stearate, in ascending order of their properties than higher ones (>1.25)

Post Compression parameters:
Physical appearance:
The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Uniformity of weight (Weight Variation)
Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness
The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto Hardness Tester (Sheetal Scientific Industries, Mumbai, India) [8].

Friability
Friability of tablets was measured by Friabilator USP (Electrolab, Mumbai, India). Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabitator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable. The percentage friability was then calculated by,

\%
Friability = [(W1 − W2) / W1] × 100

Disintegration time
Disintegration time is considered to be one of the important criteria in selecting the best formulation, One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2°C and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated [9].

Dissolution study
Dissolution media was taken as 0.1N HCL, 500ml was placed in the vessel and the USP apparatus –I (Basket Method) was assembled. The medium was allowed to equilibrate to temp of 37 ± 0.5°C. Tablet was
Drug-excipient compatibility studies:

The IR spectra of pure Atorvastatin calcium hydrate exhibits peaks at 3458.32 cm⁻¹, 1592.84, 1512.45, 1326.45, 1163.56, 772.53 and 673.24 cm⁻¹. In the IR spectra of the optimized formulation (F6) were 3492.56 cm⁻¹, 1598.26, 1535.63, 1334.69, 1165.66, 774.21 and 674.59 cm⁻¹ wave numbers were observed (Figure 1). However, some additional peaks were observed with optimized formulation, which could be due to the presence of excipients. These results suggest that there was no interaction between the drug and excipients used in the present study.

Pre compression Studies:

The present investigation was undertaken to formulate and evaluation of porous tablet of atorvastatin calcium by sublimation technique. All the formulations were evaluated for bulk density, tapped density, % compressibility, Hausner’s ratio and angle of repose. The results of Pre compression parameters were shown in Table 2. These results show that the formulations have fair to very good flow properties.

Blend Uniformity:

Uniformity of the blend during dry mixing and lubrication stages for atorvastatin Calcium porous tablets were analyzed and the results were presented in the table 3. It was observed that the assay results during dry mixing and lubrication stages were found to be within limits.

Evaluation Parameters of Tablets:

The prepared tablets were evaluated for thickness, hardness, friability, weight variation and content uniformity of the porous tablets before drying were in the passable range. From the Table 4 it is observed that the thickness, hardness, weight variation and drug content of the tablets were in the passable range. The F1 to F5 formulations containing camphor as the subliming agent didn’t show much effect on the Disintegration time where as the optimized formulation F6 15% camphor and CCS 7.5% showed better results. 5% of camphor containing formulations F7, F8, F9 and 15% menthol of F10 showed Disintegration time of 75sec, 83sec, 84sec, and 92sec respectively. The Disintegration time of F6 formulation after drying was found to be of 42 sec which is satisfactory.

In-Vitro Drug Release Studies:

The in-vitro drug release profiles of Atorvastatin Calcium from all the formulations F1 to F10 are shown in the Table 5. From the results, it is observed that the dissolution profiles of the formulated products with 15% of camphor (F1, F2, F3, F4& F5) didn’t meet the proper dissolution profile of atorvastatin Calcium i.e. 85% of drug release in 12mins shown in Figure 2. The formulations F6 showed 98% of drug release within 14mins. The formulations F7, F8, F9 also showed 92% in 14min and F10 containing 15% of menthol exhibited 96% drug release at 14mins compared to other subliming agents shown in Figure 3.

Discussion of Results:

Immediate release tablets of Atorvastatin Calcium were formulated by direct compression method using Camphor and Menthol as subliming agents. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied as shown in figures and the peaks obtained in the spectra’s of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The blends were analyzed for parameters such as Bulk density, Tapped density, Compressibility index and Hausner’s ratio and the results were found to be within limits. Bulk density and tapped density values were found to be within limits. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area and cohesiveness of material. The powdered blend has good flow property. After compression, all the tablets were dried at 60°C for 12hrs and were evaluated for various parameters like weight variation, hardness, thickness, friability, disintegration and in-vitro drug release. All formulations were found to have good hardness so they were taken for further studies. The measured hardness of tablets of each batch is in the range of 3.7 to 4.1 gm/cm².

Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.52 to 2.6 mm. Friability values are found to be less than 1% in all the cases and considered to be satisfactory. The total weight of each formulation was maintained constant and the weight variation of the tablets was within limits of 5%. All the tablets passed the pharmacopoeial specifications for disintegration of Atorvastatin Calcium porous tablets within 3 minutes. The first trial (F1) was performed by wet granulation using 15% of camphor as subliming agent and it was observed that the disintegration time of the product was on higher side. The reason behind this is due to closure of pores of the granules at the time of compression. In order to overcome these problem next trials (F2, F3) were planned using higher concentrations of super disintegrants. In formulations (F2, F3) containing 15% camphor, and 5%, 7.5% of CP as superdisintegrants the disintegration time was found to be around 3mins and the in-vitro drug release was not satisfactory as they showed only 90 % drug release in 14mins. In order to overcome this problem, the next trials (F4, F5) were planned by incorporating higher concentrations of super disintegrants (3% CCS, 5% CCS) and the results showed disintegration time around 3mins. Both the formulations F4 and F5


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exhibited in-vitro drug release of 90 % in 14mins. The trials (F6, F7) were planned using 15% camphor as sublimating agent and 7.5% CCS, 3% SSG as super disintegrants so as to improve the dissolution rate and the results showed disintegration time around 42sec for F6 and 75 sec. The next trials (F8, F9, and F10) were carried out containing 15% camphor 5% and 7.5% SSG in F8, F9 and 15% of menthol, 7.5% CCS in F10 as subliming agents, in the formulations.

The tablets were evaluated for various parameters. The optimized formulation F6 containing 15% of menthol showed in-vitro drug release of almost 98.06% of Atorvastatin Calcium in 14 minutes and the disintegration time was found to be 42sec. The tablets loaded for stability at 40°C and 75% RH for 1 month and 3 months respectively did not show much effect on the dissolution and drug content and are within the limits as per ICH guidelines therefore ensuring that the formulation F6 is a stable formulation.

### Table: 1 Formulation of Atorvastatin Calcium Porous tablets

<table>
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<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
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<tr>
<td>Atorvastatin calcium</td>
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<td>10</td>
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<td>10</td>
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<td>10</td>
<td>10</td>
<td>10</td>
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</tr>
<tr>
<td>Camphor</td>
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<td>30</td>
<td>30</td>
<td>30</td>
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<td>12</td>
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<td>12</td>
<td>12</td>
<td>12</td>
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<td>CP</td>
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<td>-</td>
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<td>10</td>
<td>15</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>SSG</td>
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<td>6</td>
<td>10</td>
<td>15</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Mg.stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total weight(mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<td>200</td>
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</tbody>
</table>

### Table: 2 Pre Compression Parameters for Powder blend

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Compressibility index (%)</th>
<th>Hausner's ratio</th>
<th>Angle of repose</th>
<th>Flow property</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.721±0.045</td>
<td>0.87±0.01</td>
<td>17.126±0.6</td>
<td>1.206±0.06</td>
<td>36.62±0.21</td>
<td>Fair</td>
</tr>
<tr>
<td>F2</td>
<td>0.710±0.043</td>
<td>0.873±0.04</td>
<td>19.714±0.7</td>
<td>1.251±0.04</td>
<td>37.46±0.11</td>
<td>Fair</td>
</tr>
<tr>
<td>F3</td>
<td>0.41±0.045</td>
<td>0.483±0.5</td>
<td>15.113±0.8</td>
<td>1.178±0.08</td>
<td>38.32±0.31</td>
<td>Fair</td>
</tr>
<tr>
<td>F4</td>
<td>0.45±0.045</td>
<td>0.52±0.9</td>
<td>15.60±0.2</td>
<td>1.15±0.02</td>
<td>28.06±0.31</td>
<td>Very good</td>
</tr>
<tr>
<td>F5</td>
<td>0.45±0.045</td>
<td>0.50±0.7</td>
<td>12.23±0.6</td>
<td>1.11±0.04</td>
<td>27.58±0.15</td>
<td>Very good</td>
</tr>
<tr>
<td>F6</td>
<td>0.44±0.044</td>
<td>0.50±0.9</td>
<td>12.58±0.8</td>
<td>1.13±0.08</td>
<td>28.44±0.11</td>
<td>Very good</td>
</tr>
<tr>
<td>F7</td>
<td>0.45±0.045</td>
<td>0.52±0.4</td>
<td>15.19±0.1</td>
<td>1.15±0.06</td>
<td>28.36±0.13</td>
<td>Very good</td>
</tr>
<tr>
<td>F8</td>
<td>0.44±0.044</td>
<td>0.52±0.1</td>
<td>15.48±0.6</td>
<td>1.18±0.08</td>
<td>28.52±0.19</td>
<td>Very good</td>
</tr>
<tr>
<td>F9</td>
<td>0.45±0.045</td>
<td>0.51±0.4</td>
<td>13.48±0.8</td>
<td>1.13±0.09</td>
<td>29.32±0.19</td>
<td>Very good</td>
</tr>
<tr>
<td>F10</td>
<td>0.51±0.045</td>
<td>0.59±0.4</td>
<td>14.48±0.8</td>
<td>1.15±0.09</td>
<td>29.69±0.19</td>
<td>Very good</td>
</tr>
</tbody>
</table>

### Table: 3 Blend uniformity of Atorvastatin Calcium during dry mixing and lubrication stage

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulations</th>
<th>Assay%(w/w) of Atorvastatin Calcium Dry mixing</th>
<th>Assay%(w/w) of Atorvastatin Calcium Lubrication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>102.5</td>
<td>102.3</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>100.2</td>
<td>100.4</td>
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<td>3.</td>
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<td>101.3</td>
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<td>F4</td>
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<td>7.</td>
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<td>101.4</td>
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<td>8.</td>
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<td>100.1</td>
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<td>9.</td>
<td>F9</td>
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<td>101.5</td>
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<td>10.</td>
<td>F10</td>
<td>100.2</td>
<td>102.7</td>
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Table 4: Evaluation parameters for formulations of Atorvastatin Calcium Porous tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness ± S.D. (mm)</th>
<th>Hardness ± S.D. (gm/cm³)</th>
<th>Average weight variation (mg)</th>
<th>Drug content (%)</th>
<th>Friability (%)</th>
<th>Disintegration Time ± S.D. (Sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.6±0.05</td>
<td>3.7±1.0</td>
<td>165±1.19</td>
<td>99.26±0.45</td>
<td>0.54</td>
<td>62</td>
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<tr>
<td>F2</td>
<td>2.59±0.07</td>
<td>3.8±1.2</td>
<td>163±1.93</td>
<td>96.38±0.56</td>
<td>0.45</td>
<td>72</td>
</tr>
<tr>
<td>F3</td>
<td>2.57±0.06</td>
<td>4.1±1.7</td>
<td>166±1.82</td>
<td>97.03±0.61</td>
<td>0.35</td>
<td>68</td>
</tr>
<tr>
<td>F4</td>
<td>2.57±0.10</td>
<td>4.1±2.0</td>
<td>166±1.27</td>
<td>98.26±0.55</td>
<td>0.41</td>
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<tr>
<td>F5</td>
<td>2.58±0.09</td>
<td>4.2±1.5</td>
<td>163±1.67</td>
<td>98.29±0.42</td>
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<tr>
<td>F6</td>
<td>2.57±0.04</td>
<td>3.9±1.0</td>
<td>162±1.92</td>
<td>98.60±0.68</td>
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<tr>
<td>F7</td>
<td>2.54±0.07</td>
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<td>166±1.60</td>
<td>98.71±0.78</td>
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<tr>
<td>F8</td>
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<td>164±1.89</td>
<td>97.40±0.84</td>
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<td>F9</td>
<td>2.52±0.08</td>
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<td>164±1.24</td>
<td>98.25±0.79</td>
<td>0.31</td>
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<tr>
<td>F10</td>
<td>2.58±0.05</td>
<td>4.0±1.4</td>
<td>164±1.84</td>
<td>99.02±0.62</td>
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Table 5: In-Vitro Drug Release Profile of Atorvastatin Calcium porous tablets (F1-F10)

<table>
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<tr>
<th>Time (min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
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Figure 1: FTIR Studies of A) Atorvastatin Pure drug B) Atorvastatin Porous tablet (F6)

Figure 2: In-vitro drug release data for formulations (F1-F5)
CONCLUSION

Porous tablets of Atorvastatin calcium were successfully formulated using Menthol and Camphor as subliming agents by Sublimation technique. From in-vitro dissolution studies the formulation F6 was found to be better formulation and the dissolution efficiency was increased. FTIR study showed that there is no interaction between the drug and excipients. In conclusion, development of fast disintegrating porous tablets by Sublimation technique was an effective alternative approach compared with the use of more expensive adjuvant in the formulation of Mouth Dissolving tablets.

REFERENCES


How to cite this article: