DESIGN AND OPTIMISATION OF FAST DISSOLVING TABLETS CONTAINING METOPROLOL BY SUBLIMATION METHOD

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ABSTRACT
Metoprolol succinate is an anti-hypertensive and antianginal. It belongs to the class of beta blockers. Difficulty in swallowing primarily affects the geriatric populations whereas unpalatable taste of drugs leads to patient non-compliance. To eliminate these problems, fast-dissolving tablets of metoprolol have been developed like fast or orally disintegrating tablets. The present research work involves design and optimization of Metoprolol Succinate fast dissolving tablets by sublimation method.

Tablets were prepared by dry granulation using PVP in IPA as binder. Camphor and Ammonium Bicarbonate were used as subliming agents in two varying concentrations (10%, 20%), Croscarmellose Sodium (AcDiSol) and Sodium Starch Glycolate were used as superdisintegrants (2%, 4%, 8%) separately. Since metoprolol is bitter in taste Sodium Saccharine was used as sweetener. The resulting tablets were subjected to vaccum evaporation at 45°C, which led to evaporation of camphor creating porous tablets.

Camphor on sublimation aids in the formation of a porous matrix which aids in disintegration of tablets. Sodium Starch Glycolate and AcDiSol hastens the disintegration of tablets due its wicking action on contact with water. Both when used in combination have a synergistic effect on the disintegration time and dissolution of the tablets.

KEYWORDS: Metoprolol succinate, Camphor, Ammonium bicarbonate, Croscarmellose sodium, Sodium starch glycolate, sublimation, superdisintegrants.

INTRODUCTION
A fast dissolving or disintegrating system can be defined as a novel dosage form for oral administration, which when placed in the mouth, disintegrates rapidly or dissolves and can be swallowed in the form of a liquid.

Dysphagia, or difficulty in swallowing, is common among all age groups. According to a study, dysphagia is common in about 35% of the general population, as well as an additional 30–40% of elderly patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. These studies show an urgent need for a novel dosage form that can improve patient compliance.

Fast disintegrating tablets (FDTs) also are called orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and freeze-dried wafers. FDTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. They serve as an alternative dosage form for patients who experience dysphagia (difficulty in swallowing). Orally disintegrating dosage forms have to be placed in mouth and then get dispersed in saliva without the need of water.
United States Food and Drug Administration (FDA) define orally disintegrating tablets as “A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue.”

US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the ‘Orange Book’, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”

European Pharmacopoeia has described orally disintegrating tablets as ‘uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed’ and as tablets which should disintegrate within 3 min.

Orally disintegrating tablets have been found to be the choice for Psychiatric as well as patient suffering from stroke, thyroid disorder, Parkinson’s diseases and multiple sclerosis, patients with nausea, vomiting and motion sickness 3-8.

MATERIALS AND METHODS

Metoprolol Succinate was obtained as a gift sample from IPCA Laboratories Pvt. Ltd., Mumbai. Avicel PH 102 (microcrystalline cellulose; MCC), AcDiSol (Croskarmellose sodium ACD), Sodium starch Glycolate (SSG), were obtained from Signet Chemicals, Mumbai. Polyvinylpyrrolidone (PVP K 30) was obtained from Arihant Trading Co. Mumbai. Camphor, Ammnonium Bicarbonate, Sodium Saccharine, Talc and Magnesium Stearate used were of analytical grade.

Formulation Of Tablets

All the ingredients were sieved through 60# sieve. The subliming agents camphor 9 and ammonium bicarbonate 10 were used (separately) in two varying amounts (10%, 20%) respectively, the active ingredient and MCC were mixed together, PVP in IPA 11 was used as binder, the wet mass was then sieved through 20# sieve. The resulting granules were dried at room temperature. These were then passed through 20# sieve and those retained on 40# were used further, mixed with the sweetener (0.5% Na Saccharine) 12, superdisintegrants like ACD and SSG in three varying amounts (2%, 4%, 8%) 13-16, talc and magnesium stearate. The granules were then weighed to a weight of 200 mg 11 and punched into tablets using 8mm punch 17-23 (Table 1, 2 & 3 Figure 1).

Evaluation

Evaluation of Tablet Blends 24:

Angle Of Repose

Angle of repose is determined by the following formula,

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

Therefore,

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Where,

\[ \theta = \text{Angle of repose} \]
\[ h = \text{height of the cone} \]
\[ r = \text{Radius of the cone base} \]

Angle of Repose less than 30° shows that material is free flowing.

Bulk Density

Bulk density was measured using a Densitometer. The bulk density is given by

\[ P_b = \frac{M}{V_p} \]

Where,

\[ P_b = \text{Bulk Density} \]
\[ M = \text{Weight of sample in gm} \]
\[ V_p = \text{Final volume of blend in cm}^3 \]

Tap Density

The tap density is given by,

\[ P_u = \frac{M}{V_u} \]

Where,

\[ P_u = \text{Tap Density} \]
\[ M = \text{Weight of sample in gm} \]
\[ V_u = \text{Final volume of blend after tapping in cm}^3 \]
Percent Compressibility

It is an important measure obtained from bulk density and is defined as,

\[ C = \frac{P_b - P_u}{P_b} \times 100 \]

If the bed of particles is more compressible the blend will be less flowable and flowing materials.

Where,

- \( C \) = % Compressibility
- \( P_b \) = Bulk Density
- \( P_u \) = Tap Density

Evaluation of tablets

Appearance

The tablets were evaluated for shape, color, odor, taste.

Thickness & Diameter

The size of tablets were evaluated by measuring their thickness and diameter by Vernier callipers.

Hardness

Crushing strength of the tablets was evaluated using Pfizer type Hardness Tester\(^25\).

Friability

Tablets were evaluated for friability using Roche Friability tester. Twenty tablets were weighed and placed into the friability tester, carried out at 25 rpm for 4 min (100 rotations). The tablets were dedusted and weighed. The pharmacopoeial (IP) limit of friability test for a tablet is not more than 1% of the original weight of the tablets\(^26\).

Uniformity of weight

IP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of the tablets was determined\(^25, 26\).

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<thead>
<tr>
<th>Average weight of tablets (mg)</th>
<th>Maximum percentage difference allowed</th>
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<tbody>
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<td>10</td>
</tr>
<tr>
<td>130-324</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 324</td>
<td>5</td>
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</table>

Drug Content

Twenty tablets were weighed and powdered. Accurately a quantity of the powder equivalent to about 0.12 g of Metoprolol Succinate was weighed, dissolved in ethanol and appropriately diluted with ethanol, the resulting solution was filtered. Absorbance of the solution was measured at 273nm using UV-vis spectrophotometer\(^25\).

In Vitro Disintegration Time

Time taken by the tablets to disintegrate was performed on USP Disintegration Test Apparatus using 900ml of water as medium at 37°C with disks\(^25, 27, 28\).

Wetting Time

Five circular tissue papers were placed in a Petri dish, 10 ml of water containing eosin, was added, tablet was placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time\(^29, 30, 31\).

Modified Disintegration Test (I)

Disintegration time of tablets was measured using a modified disintegration test method. Water (10ml) was taken in a petridish and tablet was carefully placed in the centre and agitated mildly. Time required for complete disintegration of tablet into fine particles was noted as the disintegration time\(^31, 32\).

Modified Disintegration Test (II)

This disintegration test was carried by placing the FDT in the basket of the USP dissolution basket type apparatus, water was dropped on it from a burette at a rate of 4 ml/min. The time required by the tablet to completely break into particles and pass down through the bottom mesh of the basket was noted as disintegration time\(^27, 32\).

In Vitro Dissolution Studies

The dissolution test for fast disintegrating tablets of Metoprolol Succinate was performed as follows, Apparatus: USP Type II.
Dissolution Medium: Simulated gastric fluid pH 1.2
Volume: 900ml
Speed: 100rpm
Time Interval: 2, 5, 10, 15, 20, 30 mins.
5ml of the sample was withdrawn at specific time interval and replaced with fresh dissolution medium. The sample solution was diluted with the dissolution medium and analyzed by UV-vis spectrophotometer at 273nm

RESULTS

Tablet Blend parameters
The angle of repose of all batches was found to be in the range of 20.15 -26.54, which indicated a good flow characteristic.
The percent compressibility was found in the range of 1.2-13.20, which indicated excellent flow characteristic.
Hausner’s ratio for all batches was found to be 1.02 -1.15, which is less than 1.25, hence indicating good flow properties of the tablet blends

Organoleptic Properties, Hardness & Friability
The appearance of all the batches was found to be white, round and flat faced as all the excipients used were white in color, the punches used during compression were round and flat- faced. All the batches were found to be uniform in appearance.
Test for tablet thickness and diameter was performed to ensure the batch-to-batch uniformity in thickness and diameter among all the formulations. The thickness of all the batches was found to be in the range of 3.9-4.3 mm and the diameter of all batches was found to be between 8.0-8.3 mm, which was in compliance with the punch size (8mm) used during compression.
The hardness of all batches was found to be in range of 3.8-4.3, as it was to be kept constant in this range during compression. Three tablets from each batch were tested with Pfizer hardness tester and the average of three was found.
The friability of all the batches was found to less than 1% ranging from 0.087-0.243 %, thereby all the batches were found to pass the test for friability of tablets as per IP. Ten tablets were taken from each batch to test friability, the test was performed in triplicate.
The bitter taste of Metoprolol Succinate was masked in all batches, with Na Saccharine, the tablets were found to be sweet in taste. The tablets were found to be free of any odour.

Uniformity of Weight
Weight variation test was performed as per IP, the test ensured that the fill in the die cavity was uniform for all the batches. Ten tablets were weighed individually and the average weight was found. The percent deviation calculated was less than 7.5% of the average weight (200 mg) of the tablet that is the tablet weight should lie between 185-215 mg for all batches. Hence, all batches comply with the test for weight variation as per IP.

Drug Content Evaluation
Assay/determination of drug content was done spectrophotometrically on three tablets per batch and the average value was calculated. The drug content was found to be from 97.93% to 101.34% for all the batches. This suggested that the drug was dispersed uniformly between the tablet blend for all the batches.

Disintegration Tests (Table 4, Figure 2, 3, 4 & 5)
The disintegration test was performed as per IP on six tablets with discs, the average of six was taken as the disintegration time (seconds).
The disintegration time range for batches containing 10% camphor (MS 1-MS 6) was found to be 12.42-50.44 and those containing 20% camphor (MS 7- MS 12) showed a disintegration time from 3.50-28.40. Batches containing 10% ammonium bicarbonate (MS 13- MS 18) showed a range between 31.39-49.56, while those containing 20% ammonium bicarbonate (MS 19- MS 24) showed disintegration time between 32.10-55.93.
Among the batches made with a combination of 20% camphor & ACD (2%, 4%, 8%), the least disintegration time was found to be 3.50 which is for MS 8 (20% camphor, 4% ACD). Batches with combination of 20% camphor & SSG (2%, 4%, 8%), 7.26 was found to be the least disintegration time, which was for MS 11.

Wetting time test was performed on three tablets of each batch, the average was taken as wetting time. The wetting time was found to be less than 1 min for all the batches, this is similar to the disintegration time of all the batches.

The modified disintegration test I (MDT I), was also performed on three individual tablets from each batch. This test was performed to mimic the conditions of the tongue where the agitation is much less as compared to the stomach. Due to lack of agitation, the disintegration time by this method was found to be more as compared to that obtained from the USP disintegration test. All the tablets were found to disintegrate within 60 secs.

Modified disintegration test II was performed to mimic the less amount of volume of the disintegration medium present in the mouth. Modified disintegration test II was performed on three tablets of each batch, the disintegration time was found to be less than 1 min for all batches.

The fig. above states the correlation between the various disintegration test performed. As seen in the fig. disintegration time for MDT I and MDT II is similar for the respective batches as the conditions involve less volume of water and no agitation, the disintegration time obtained by the USP disintegration test differs significantly from these tests. The batches taken for comparison are those with least disintegration time among all batches.

Dissolution Studies (Figure 6)
The dissolution test was performed on six tablets as per IP. The two batches MS 8, MS 11 which were found to show the least disintegration time were found to show complete drug release in 10 mins as compared to the marketed product which showed complete drug release at the end of 30mins. Batches MS 8 and MS 11 were studied for stability under different conditions of temperature and relative humidity as per ICH for a period of 3 months and were found to be stable.

DISCUSSION
The disintegration time results as in Table no. 4 suggest that camphor is a better subliming agent than ammonium bicarbonate to aid faster disintegration of the tablets and the optimum amount to be used for faster disintegration is 20%. Further the disintegration time of batches containing superdisintegrants show that the optimum amount of ACD and SSG was found to be 4% in combination with 20% camphor.

The batches with fastest disintegration time, MS 8 and MS 11 disintegrated in less than 30 secs, which is in compliance with the USFDA limit for disintegration time for ODT. The wetting time results of tablets containing ACD as super disintegrant showed a faster wetting time as compared to those containing SSG, as ACD readily breaks up the tablet into smaller particles as compared to the swelling nature of SSG, tablets containing SSG swell due to absorbance of water before breaking to smaller particles.

In the dissolution studies of the batches containing subliming agent (10% and 20% camphor and 10% and 20% of ammonium bicarbonate) and superdisintegrant, 80% drug release was seen within 5 mins for all the batches. Batches prepared by the addition of only superdisintegrant, showed 80% dissolution within 15 mins. This suggested that addition of subliming agent in combination with superdisintegrant aided the dissolution of tablets significantly.

Complete drug release was obtained in 10 mins for MS 8 (20% camphor, 4% ACD) and MS 11 (20% camphor, 4% SSG) batches whereas for other batches it was more than 15 mins. This indicated that the subliming agent camphor at the strength of 20% alongwith 4% superdisintegrant showed better dissolution profile.

The dissolution results supported the findings of disintegration test and thereby confirmed that the batches MS8 and MS11 were found to be optimized for the required parameters hence stable fast disintegrating tablets of Metoprolol succinate were successfully prepared.
ACKNOWLEDGEMENT
We would like to thank IPCA laboratories Pvt. Ltd. for providing the gift sample of drug, Signet and Arihant Trading Co. for providing gift samples of excipients.

REFERENCES
Table 1: Role and amount of ingredients used for preparation of fast disintegrating tablets by Sublimation method

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<thead>
<tr>
<th>Ingredients</th>
<th>Amount</th>
<th>Role</th>
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<td>Active</td>
</tr>
<tr>
<td>Camphor/NH$_4$ bicarbonate</td>
<td>10-20%</td>
<td>Subliming agent</td>
</tr>
<tr>
<td>PVP in IPA</td>
<td>qs</td>
<td>Binder</td>
</tr>
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<td>Na Saccharine</td>
<td>0.5%</td>
<td>Sweetner</td>
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<td>ACD/SSG</td>
<td>2-8%</td>
<td>Superdisintegrant</td>
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<td>Talc</td>
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<td>Microcrystalline cellulose</td>
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Table 2: Batch formula of batches MS 1- MS 12 prepared by Sublimation method using Camphor (subliming agent)

<table>
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<th>Ingredients (mg)</th>
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<th>MS 2</th>
<th>MS 3</th>
<th>MS 4</th>
<th>MS 5</th>
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<th>MS 10</th>
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<tr>
<td>ACD</td>
<td>4 (2%)</td>
<td>8 (4%)</td>
<td>16 (8%)</td>
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<td>-----</td>
<td>4 (2%)</td>
<td>8 (4%)</td>
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<tr>
<td>SSG</td>
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<td>-----</td>
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<td>4 (2%)</td>
<td>8 (4%)</td>
<td>16 (8%)</td>
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<td>-----</td>
<td>4 (2%)</td>
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Table 3: Batch formula of batches MS 13- MS 24 prepared by Sublimation method using Ammonium bicarbonate (subliming agent)

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<th>Ingredients (mg)</th>
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<th>MS 18</th>
<th>MS 19</th>
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<td>Ammonium bicarbonate</td>
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<td>BATCH</td>
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<td>Wetting Time (secs)</td>
<td>Modified Disintegration Time (I) (secs)</td>
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**TABLE 4: Various disintegration tests**

**Fig 1:** Process flow of Metoprolol Succinate tablets by sublimation method
Fig 2: Wetting Time of batch MS 8

Fig 3: Modified Disintegration Time (I) for batch MS 11
Fig 4: Modified Disintegration Time (II) for batch MS 8

Fig 5: Comparison of various disintegration tests for batches MS 8 and MS 11
Fig 6: Dissolution Profile of batches found to be optimized along with marketed product

Source of support: Nil, Conflict of interest: None Declared