FAST DISSOLVING FILMS: A NOVEL APPROACH FOR THE DELIVERY OF MONTELUKAST SODIUM

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INTRODUCTION
Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.

Although oral disintegrating tablets have an advantage of oral disintegration time and drug content of F2 was observed during storage at 40±2°C/75±5% RH for 3 months. The data demonstrated that 4% crospovidone and 4% croscarmellose sodium with 4% HPMC as a film base was suitable for developing fast dissolving films of Montelukast sodium.

Keywords: Fast dissolving films, Montelukast sodium, HPMC, Crospovidone, Croscarmellose sodium.

MATERIALS AND METHODS
Montelukast sodium was obtained as a gift sample from Matrix India (P) Ltd., Mumbai. Glycerin, Citric acid and Sucrose were obtained from S.D. Fine Chemicals (P) Ltd., Mumbai. Crospovidone and croscarmellose sodium were obtained from Signet Chemical Corporation, Mumbai. Trusil mixed flavor RSV obtained from International flavors of fragrance India Ltd. All other chemicals and solvents used were of analytical grade.

Preparation of fast dissolving films
HPMC is known for its good film forming properties and has an excellent acceptability. Glycerin as a plasticizer. Crospovidone and croscarmellose sodium were used as a superdisintegrants. Citric acid as saliva stimulating agent, sucrose as a sweetening agent and Trusil mixed fruit RSV as a flavoring agent. The fast dissolving films of montelukast sodium were prepared by solvent casting technique using HPMC as a film forming polymer. Glycerin is used as a plasticizer. The calculated amount of polymer was dispersed in 3/4th volume of water with continuous stirring using magnetic stirrer and the final volume was adjusted up to 10 ml with distilled water. The calculated amount of montelukast sodium was incorporated in the polymeric solutions after levigation with required volume of glycerin. The solution was casted on to Petri dish (Anumbra*, area of 66.31cm²) then kept in hot air oven at 40°C for 24 h. Films of various formulations are mentioned in Table-1. The films were punched in to size of 2 cm diameter (an area of 6.28 cm²) containing 5 mg of montelukast sodium.

Table 1: Formulation of Fast Dissolving Films of Montelukast sodium

<table>
<thead>
<tr>
<th>Ingredients*</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast Sodium (mg)</td>
<td>52.79</td>
<td>52.79</td>
<td>52.79</td>
<td>52.79</td>
<td>52.79</td>
<td>52.79</td>
</tr>
<tr>
<td>HPMC (% w/v)</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>--</td>
<td>2.0</td>
<td>4.0</td>
<td>--</td>
<td>6.0</td>
<td>--</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Sucrose</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Citric acid</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Trusil flavor</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Glycerin</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

*Quantities are expressed in %w/w of polymer

Evaluation of fast dissolving films
The fast dissolving films were evaluated for physical appearance, surface texture, thickness, weight uniformity, folding endurance, surface pH and drug content uniformity of films. The physical appearance was checked with visual inspection of films and texture by feel or touch, thickness was measured by micrometer screw gauge (Mitutoyo, Japan) at different points and the mean values were calculated. The film weights were determined by using electronic balance. Disintegration test was performed in the USP...

ABSTRACT
Montelukast sodium fast dissolving films were prepared by solvent casting method using HPMC as film base with different concentrations of superdisintegrants like crospovidone and croscarmellose sodium using glycerin as plasticizer. The physicochemical parameters of the fast dissolving films were evaluated. The compatibility of the drug in the formulation was confirmed by IR and DSC studies. Scanning electron microscopy revealed the morphology of the films. In vitro dissolution studies and mechanism of drug release was identified. The formulation F2 and F5 with 4% of crospovidone and 4% croscarmellose sodium respectively shows a maximum cumulative percentage drug release of 97.42% and 99.27% at the end of 30 min respectively. The release of drug from the films has followed first-order kinetics. No significant change in the physical parameters, in vitro disintegration time and drug content of F2 was observed during storage at 40±2°C/75±5% RH for 3 months. The data demonstrated that 4% crospovidone and 4% croscarmellose sodium with 4% HPMC as a film base was suitable for developing fast dissolving films of Montelukast sodium.

Discussion

The fast dissolving films were evaluated for various parameters, such as surface texture, thickness, weight uniformity, folding endurance, surface pH and drug content uniformity of films. The physical appearance was checked with visual inspection of films and texture by feel or touch, thickness was measured by micrometer screw gauge (Mitutoyo, Japan) at different points and the mean values were calculated. The film weights were determined by using electronic balance. Disintegration test was performed in the USP...
disintegration time testing apparatus (Electro lab Mumbai) \textsuperscript{15}. To check the uniformity of the drug in the cast film, films were cut at different places in cast film and each film was placed in 100 ml of 0.5% SLS to extract drug, the resulting solution was filtered and further dilution was made with 0.5% SLS and the absorbance at 342 nm was measured spectrophotometrically. The concentration of the drug was determined from the standard curve. Same procedure was adopted for other formulations of cast films in the triplicates and mean drug content and standard deviation were calculated \textsuperscript{9}.

**In vitro Dissolution Study**

*In vitro dissolution of montelukast sodium fast dissolving film was studied in USP XXIV dissolution test apparatus (Electro lab, Mumbai) using 900 ml of 0.5% SLS solution at 50 rpm\textsuperscript{11-13}. The temperature was maintained at 37 ± 0.5°C throughout the experiment. 5 ml Sample was withdrawn by means of syringe fitted with pre-filter at 5 min intervals and the same quantity was replaced with 0.5% SLS solution. The cumulative percentage of drug released was determined using Shimadzu spectrophotometer at 342 nm. The experiment was carried out in triplicate and average values were reported.*

**Compatibility studies by FTIR:**

The compatibility of drug in the formulation was confirmed by IR spectra of pure drug and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by KBr Disc method.

**Differential scanning calorimetry (DSC)** \textsuperscript{14}:

The DSC measurements were performed using a mettler equipped with an intracooler 2P cooling accessory. Samples of 4 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 10°C/min were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35°C to 380°C. An empty aluminum pan was used as reference.

**Scanning Electron Microscopy (SEM)** \textsuperscript{15}:

The surface morphology of the fast dissolving film was observed with scanning electron microscope, Model QUANTA-200 FEI Netherlands. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 2000X magnification.

**Accelerated Stability studies**

The optimized formulation in its final pack was stored at 40±2°C/75±5% RH for 3 months in Stability chamber (Thermo lab). The sample was withdrawn at every 10 day time intervals and analyzed for physical parameters, in vitro disintegration time and drug content.

**RESULTS AND DISCUSSION**

Physical appearance and surface texture of films were found to have smooth surface and they are elegant enough to see. The physicochemical evaluation data presented in Table 2 indicating thickness of the films varies from 0.130 to 0.155 mm. The weight of films varies from 64.01 to 67.89 mg. The folding endurance of the films varies from 275 to 283, as the plasticizer concentration increases the flexibility of the film increases thus folding endurance. Since the surface pH of films was found to be around neutral pH, there will not be any kind irritation to the mucosal lining of the oral cavity.

### Table 2: Evaluation of Fast Dissolving Films of Montelukast sodium

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Folding endurance</th>
<th>Drug content uniformity (%)</th>
<th>In Vitro disintegration Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_h$</td>
<td>64.01±0.08</td>
<td>0.130 ± 0.010</td>
<td>279 ± 1.466</td>
<td>98.34 ± 1.657</td>
<td>75.57 ± 0.102</td>
</tr>
<tr>
<td>$F_1$</td>
<td>65.21±0.54</td>
<td>0.140 ± 0.010</td>
<td>274 ± 2.545</td>
<td>97.44 ± 0.540</td>
<td>15.11 ± 0.045</td>
</tr>
<tr>
<td>$F_2$</td>
<td>66.09±0.22</td>
<td>0.145 ± 0.015</td>
<td>288 ± 1.665</td>
<td>96.34 ± 1.002</td>
<td>9.74 ± 0.085</td>
</tr>
<tr>
<td>$F_3$</td>
<td>66.97±0.10</td>
<td>0.150 ± 0.005</td>
<td>275 ± 3.343</td>
<td>96.98 ± 1.963</td>
<td>11.09 ± 0.099</td>
</tr>
<tr>
<td>$F_4$</td>
<td>65.05±0.24</td>
<td>0.145 ± 0.020</td>
<td>287 ± 2.994</td>
<td>95.23 ± 0.355</td>
<td>13.21 ± 0.034</td>
</tr>
<tr>
<td>$F_5$</td>
<td>66.90±0.33</td>
<td>0.150 ± 0.025</td>
<td>283 ± 2.633</td>
<td>96.67 ± 0.889</td>
<td>7.25 ± 0.111</td>
</tr>
<tr>
<td>$F_6$</td>
<td>67.89±0.26</td>
<td>0.155 ± 0.015</td>
<td>282 ± 3.121</td>
<td>97.98 ± 2.403</td>
<td>9.98 ± 0.087</td>
</tr>
</tbody>
</table>

*All values are Mean ± SD, (n=3)*

All the formulations found to contain almost uniform quantity of drug as per content uniformity studies indicating reproducibility of the technique. IR spectra analytical reports shown in fig. 1 and 2 indicating that there was no interaction between drug and excipients used. DSC thermo grams of montelukast sodium with excipient does not show profound shift in peaks which indicates compatibility as shown in fig 3 and 4 and SEM of the film at 2000X magnification showed smooth surface with some little pores and without any scratches or transverse striations as shown in fig 5.

**Fig. 1: FTIR spectra of Montelukast sodium**
Fig. 2: FTIR spectra of Montelukast sodium + HPMC

Fig. 3: DSC of Montelukast sodium

Fig. 4: DSC of Montelukast sodium + HPMC
All the formulations of fast dissolving films were found to disintegrate in less than 30 sec. *In vitro* disintegration time was found to decrease with increase in concentration of superdisintegrants used in formulations. It is observed that disintegration time of the film decreased from 15.11 to 9.74 sec and 13.21 to 7.25 sec with increase in the concentration of crospovidone and croscarmellose sodium from 2 to 4% respectively, further increase in the concentration of crospovidone and croscarmellose sodium, increased the disintegration time due to blockade of capillary pores which prevents the entry of fluid in to the film.

The cumulative percentage drug release of all the formulations is shown in fig 6 and 7. Based on the trial basis it has been found that 10 ml of 4% w/v of HPMC solution in water shown as optimized film forming base. The fast dissolving film prepared with HPMC as a film base with crospovidone as a superdisintegrant in the concentration of 2, 4 and 6% shown 89.07, 97.42 and 93.71% respectively of drug release in 30 min and with croscarmellose sodium as a superdisintegrant in the concentration of 2, 4 and 6% shown 92.78, 99.27 and 96.49% of drug release in 30 min.

![Fig. 5: SEM of Montelukast sodium Fast Dissolving Films](image)

![Fig. 6: *In Vitro* drug release of Fast Dissolving Films containing Crospovidone](image)
It is observed that drug release from the film increased from 89.07 to 97.42% and 92.74 to 99.27% with increase in the concentration of crospovidone and croscarmellose sodium from 2 to 4% respectively, further increase in the concentration of crospovidone and croscarmellose sodium, decreased the drug release due to increase in the disintegration time. The release of the drug from the films follows first-order.

Among all the formulations, the best formulation was found to be F2 containing 4% crospovidone and F4 containing 4% croscarmellose sodium, because it has shown lesser disintegration time and faster release of drug. These formulations were subjected to stability studies; from the results of accelerated studies it was found that the formulations were stable.

CONCLUSION

Finally, it can be concluded that, fast dissolving films of montelukast sodium can be prepared by solvent casting technique using HPMC as film base, and with different concentrations of Crospovidone and Croscarmellose sodium as superdisintegrants.

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REFERENCES

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