DESIGN, FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING FILMS CONTAINING DEXTROMETHORPHAN

SAYED H. AUDA\textsuperscript{a,b}, MAHMOUD EL-BADRY\textsuperscript{a,c}, MOHAMED A. IBRAHIM\textsuperscript{a,b}
\textsuperscript{a}Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
\textsuperscript{b}Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt
\textsuperscript{c}Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

The aim of this study was to formulate and characterize fast dissolving films containing dextromethorphan hydrobromide (DM) for oral use. Hydroxylpropyl methylcellulose E15 (HPMC) was used as the film forming polymer and crosspovidone (CPV), microcrystalline cellulose (MCC) were used as superdisintegrants. In this study, medicated films were prepared by solvent casting method. The physicochemical characterizations were done by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) for DM-loaded fast dissolving films and their corresponding physical mixtures as well as the individual components to investigate the drug polymer interaction. The obtained DSC and FTIR results indicated that DM was molecularly dispersed in the matrix of HPMC. The prepared films were also characterized for their tensile strength, percentage of elongation, taste palatability, surface pH, weight and their content uniformity. In addition, DM-loaded oral films were elegant enough, transparent, flexible, smooth, homogeneous and palatable. It was found also that both of film disintegration and drug release increased as the concentration of disintegrant in the film increased.

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1. Introduction

The oral route of administration is the most acceptable for the patients due to ease of ingestion and avoidance of pain. Among the new developed oral dosage form is the oral dissolving films (ODFs), which are thin films that formulated from hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity.

Due to the high vascularity of the oral or buccal mucosa, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect [1].

Sometimes, the ODFs technology is viewed as an alternative for oral disintegrating tablets (ODTs) products. Although, the oral disintegrating tablets (ODTs) in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”, the ODFs derived products were readily popular in the market in the form of breath-freshening strips, no further efforts were needed to re-instruct the populace about the technique of administration of this dosage form [2].

As compared to ODTs, ODFs have a larger surface area that leads to rapid disintegration and dissolution in the oral cavity. In addition, the films are flexible and not as fragile as most of the ODTs. Hence, there is an ease of transportation and during consumer handling and storage.
On the other hand, patient can administer the film at any time and any place without need to water because the large surface area available in the strip dosage form allows rapid wetting in the moist buccal environment. Patients who are unable to swallow large quantity of water such those suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form. The disintegrating materials that contained in ODTs are insoluble and remain into the mouth cavity until swallowing. In such cases formulation of ODFs will be advantageous [3-4].

As compared to drops or syrup formulations, ODFs are more precise in the administered dose from each of the strips than that from drops or syrups. However, not all drugs can be incorporated into this dosage form. The disadvantage of ODFs is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active ingredient can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip [5].

Dextromethorphan hydrobromide (DM) is a non-opioid antitussive agent, used to temporarily relieve cough due to the common cold, hay fever, upper respiratory tract infections, sinus inflammation, sore throat, or bronchitis. It will not treat a cough that is caused by smoking, asthma, or emphysema. DM affects the signals in the brain that trigger cough reflex [6-7]. The United State Food and Drug Administration (FDA) approved dextromethorphan as a prescription antitussive drug on September 24, 1954, and subsequently as an over-the-counter cough suppressant in 1958 [8].

In view of all the above reasons, the aim of this study is to investigate the availability of formulation of DM in oral fast dissolving films.

2. Material and method

2.1 Materials

Dextromethorphan hydrobromide (DM) was kindly supplied by SPIMACO (Qassem, KSA), Hydroxypropyl methylcellulose E15 was purchased from Dow Chemical Co. (Midland, Michigan, USA). Microcrystalline cellulose (Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Crospovidone (CPV) was kindly supplied by Riyadh Pharma (Riyadh, KSA). Polyethylene Glycol 400 (PEG 400) was supplied from BDH Chemicals Ltd (poole, England). Saccharine and Menthol were purchased from Sigma-Aldrich (St Louis, MO, USA). Other chemicals and reagents were of analytical grade.

2.2 Preparation of fast dissolving films

Fast dissolving films of dextromethorphan were prepared by solvent casting technique. Composition of various formulations is mentioned in Table 1. Specified weights of polymer, drug and other excipients were gradually transferred to a100 ml beaker containing 20 ml of the casting solvent (distilled water); the final volume was adjusted to 25 ml with distilled water and the beaker was covered with aluminum foil paper to prevent solvent evaporation. The casting solution was subjected to gentle stirring for 2 h using magnetic stirrer (Bibby, L32, Staffordshire, UK). The casting solution (25 ml) was transferred into a previously cleaned and dried Teflon coated plate (area = 28 cm²), in a way that each 1cm² contains 1 mg of drug. The solvent was allowed to evaporate for 72 h; the film was then removed from the Teflon plate and was allowed to dry in a desiccator at least 48 h before evaluation. The patches were punched into size 10 cm² containing 10 mg of dextromethorphan, then wrapped in an aluminum foil (to maintain the integrity and elasticity of the films) and were finally stored in a dry place at ambient room temperature. The films were subjected to evaluation within one week of their preparation.

PEG 400 was used as a plasticizer and saccharine as a sweetener. CPV and MCC were used as disintegrants. Menthol was added to give mouth refreshment feeling. Concentrations of plasticizer and sweetener were kept constant. Disintegrants were used in different concentrations. In all these formulations, a constant amount of drug (28 mg) was maintained. The casting solution (25 ml) was poured into 28 cm² molds, that is mean each 1cm² contains approximately 1 mg of
drug. The patches were punched into size 10 cm² containing 10 mg of dextromethorphan for evaluations.

Table 1: Composition of different dextromethorphan fast dissolving films.

<table>
<thead>
<tr>
<th>% of ingredients</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>5.18</td>
<td>5.18</td>
<td>5.18</td>
<td>5.18</td>
<td>5.18</td>
<td>5.18</td>
<td>5.18</td>
</tr>
<tr>
<td>CP</td>
<td>-</td>
<td>1.5</td>
<td>2.22</td>
<td>2.96</td>
<td>3.70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.70</td>
<td>7.40</td>
</tr>
<tr>
<td>PEG</td>
<td>18.51</td>
<td>18.51</td>
<td>18.51</td>
<td>18.51</td>
<td>18.51</td>
<td>18.51</td>
<td>18.51</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>Saccharine</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
<td>7.40</td>
</tr>
<tr>
<td>HPMC E15</td>
<td>To 100 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

2.3 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of medicated film compared to its corresponding physical mixture and the individual solid components were recorded using FTIR Perkin Elmer spectrophotometer (Spectrum BX). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm⁻¹. The data was analyzed using Perkin Elmer software (Spectrum V5.3.1).

2.4 Differential scanning calorimetry (DSC)

DSC scans were recorded for medicated film, its corresponding physical mixture and the individual solid components. The samples (3-5 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25 °C to 200 °C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N₂ was used as purging gas at rate of 40 ml/min.

2.5 Weight uniformity

Weight variation was studied using Analytical balance (Mettler, AJ150, Greifensee, Switzerland). It was done by taking individual weights of ten randomly selected patches 10 cm² for each formulation prepared in different batches. The results were analyzed for mean and standard deviation.

2.6 Surface pH

For determination of surface pH, three films of each formulation were allowed in contact with 1mL of distilled water for 1 h at room temperature and measured by pH meter (Mettler Toledo, Greifensee, Switzerland). The surface pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 min. A mean of three reading and standard deviation was recorded.

2.7 Drug content uniformity

The patches were tested for drug content uniformity by UV Spectrophotometric method. Patches of 10 cm² were cut from 2 different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in phosphate buffer (pH 6.8), then 0.2 ml is taken and diluted with phosphate buffer (pH 6.8) to 10 ml. The absorbance of the solution was measured at 278 nm. The percentage of the drug content was determined using the standard graph. The same procedure was repeated for three patches of each formulation. The results were analyzed for mean and standard deviation.
2.8 Measurement of tensile strength and percentage elongation

Tensile strength and percentage elongation of the produced films were measured using Instron universal tensile strength testing instrument, model F. 4026,(Instron Ltd., Japan, NITK, Surathkal) with a 5-kg load cell. Intact film strips of special dimension (5x12 cm) and free from air bubbles were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties namely; tensile strength (TS) and percentage elongation were computed for the evaluation of the film. TS is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film from the following equation [9].

\[
\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of the sample (mm}^2\text{)}}
\]

Percentage elongation can be obtained by the following equation

\[
\%\text{Elongation at break} = \frac{\text{Increase in length}}{\text{Original length}} \times 100
\]

2.9 Disintegration Time

Disintegration of DM-loaded oral films was performed using disintegration tester (Electrolab, ED-21, Mumbai, India). A minimum of 3 films of each product were tested. One film of each product was placed in each of the six tubes of the basket. Then the apparatus was operated using phosphate buffer pH 6.8 maintained at 37±2°C as a disintegration medium.

2.10 In-vitro dissolution experiments

The previously prepared film was removed from the plate, cut in area of 10 cm², weighed on an analytical balance and then it was tested for its dissolution property. The dissolution experiments were performed using USP dissolution apparatus 2, paddle method, (Caleva Ltd., Model 85T), at 50 rpm using a continuous automated monitoring system. This system consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump. The dissolution medium used was 300 mL phosphate buffer (pH= 6.8) and the temperature was maintained at 37 ± 0.5 °C. It was taken into consideration that the used buffer volume affords sink conditions. Samples (5 ml each) were obtained while the film remained completely immersed throughout the release study. At predetermined time intervals, the removed sample (5 ml) from the release medium was replaced by an equal volume of buffer. All samples were analyzed spectrophotometrically at 278 nm. Blank samples were obtained from the release experiments films containing the same components except the drug.

2.11 Palatability studies

A taste panel consisting of 15 healthy male volunteers (25-45 years old) has tried a selected formula (F₄). The tested film was kept in mouth until disintegration. The taste, its extent, after taste and other effects such as mouth refreshment-if any were evaluated.
3. Results and discussion

3.1 Film appearance and weight
Prepared films were elegant enough, transparent, flexible, smooth and homogeneous. The data of physicochemical evaluation of the different films are presented in Table 2. The weight of films (10 cm² each) varies from 191.81 to 196.21 mg.

3.2 Tensile strength
Tensile strength of the prepared films and their % elongation are recorded in Table 2. The results showed that the tensile strength of prepared films varies from 0.598 ± 0.033 to 0.782 ± 0.031 kg/cm² and % elongation varies from 26.22 ± 0.65 to 30.21 ± 0.231, revealing that the films had a good mechanical strength and flexibility. It can be noted that the inclusion of CPV and MCC as disintegrants decreased both the tensile strength and % elongation of the films. Decreasing the elasticity of oral films by high concentration of some additives has been reported by Khanusiy et al[10].

3.3 Surface pH
Mean values of pH for the tested films and standard deviation were recorded in Table 2. No significant difference was found in surface pH of different films. The surface pH of films was found to be around neutral pH and hence, they are comfortable and there will not be any mucosal lining irritation to the oral cavity is expected.

3.4 Drug contents
Regarding the drug contents in films, it was found that the content of dextromethorphan in films varies from 94.23 ± 3.5 to 100.08 ± 2.4 (Table 2). All the formulations contain almost uniform quantity of drug indicating reproducibility of the technique.

Table 2: Physicochemical and mechanical properties of dextromethorphan fast dissolving films.

<table>
<thead>
<tr>
<th>Films</th>
<th>Weight</th>
<th>Surface PH</th>
<th>Tensile strength (Kg/cm²)</th>
<th>% Elongation</th>
<th>Drug content (%)</th>
<th>Disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>195.07</td>
<td>6.9 ± 0.25</td>
<td>0.782 ± 0.031</td>
<td>30.21 ± 0.231</td>
<td>96.98 ± 3.2</td>
<td>142 ± 3</td>
</tr>
<tr>
<td>F1</td>
<td>192.03</td>
<td>7.07 ± 0.032</td>
<td>0.712 ± 0.011</td>
<td>28.88 ± 0.892</td>
<td>97.21 ± 2.5</td>
<td>63 ± 1</td>
</tr>
<tr>
<td>F2</td>
<td>191.81</td>
<td>6.81 ± 0.21</td>
<td>0.631 ± 0.021</td>
<td>27.33 ± 0.253</td>
<td>98.06 ± 1.9</td>
<td>59 ± 0.3</td>
</tr>
<tr>
<td>F3</td>
<td>194.09</td>
<td>6.62 ± 0.036</td>
<td>0.611 ± 0.036</td>
<td>26.64 ± 0.056</td>
<td>96.71 ± 2.8</td>
<td>44 ± 0.6</td>
</tr>
<tr>
<td>F4</td>
<td>194.32</td>
<td>6.85 ± 0.22</td>
<td>0.584 ± 0.025</td>
<td>26.22 ± 0.65</td>
<td>94.23 ± 3.5</td>
<td>39 ± 0.8</td>
</tr>
<tr>
<td>F5</td>
<td>193.05</td>
<td>7.02 ± 0.025</td>
<td>0.621 ± 0.042</td>
<td>29.36 ± 1.1</td>
<td>100.08 ± 2.4</td>
<td>117 ± 2</td>
</tr>
<tr>
<td>F6</td>
<td>196.21</td>
<td>6.98 ± 0.033</td>
<td>0.598 ± 0.033</td>
<td>27.14 ± 0.985</td>
<td>98.05 ± 1.7</td>
<td>122 ± 1</td>
</tr>
</tbody>
</table>

Evaluated film is 10 cm² in size, (2.5 x 4 cm) and containing 10 mg of the drug.

3.5 Fourier transforms infrared spectroscopy (FTIR)
Figure 1 displays the FR-IR spectra of DM, HPMC, their casted film (DM is 5.18% of polymer weight) as well as the corresponding physical mixture. DM spectrum (Figure 1A) shows that prominent absorption bands at 2165 and 2590 cm⁻¹, corresponding to the NH⁺ stretching vibration in the tertiary amine group of the drug. These finding was agreement by the data of Fayed et al [11]. HPMC showed a characteristic band at 3477 cm⁻¹ due to O–H stretching vibration (Figure 1B). The FT-IR spectra of the drug in case of both casted film and physical mixture showed a characteristic band at 3468 cm⁻¹ due to O–H stretching vibration of HPMC. In addition, the characteristic stretching vibration band of the drug is hidden due to the existence of the polymer (HPMC) broad O-H stretching band at the same position (Figure 1C and 1D).
Fig. 1. Infrared spectra of A) untreated DM; B) untreated HPMC; C) DM- HPMC (DM = 5.18% w/w of polymer) physical mixture; D) DM- HPMC (DM = 5.18% w/w of polymer) casted film.

3.6 Differential scanning calorimetry (DSC)

DSC scans were performed on medicated film, its corresponding physical mixture and the individual solid components. The DSC scan of untreated dextromethorphan showed an endothermic peak (Figure 2A), at 132°C which is corresponding to DM melting point. Concerning the corresponding physical mixture (Figure 2C), characteristic endothermic peak of dextromethorphan was seen at 123 °C but with low intensities. Upon scanning the DSC thermogram of dextromethorphan-HPMC film, a complete disappearance of the drug fusion peaks (Fig. 2D), suggesting a homogeneous dissolution of the drug in the polymer matrix [12, 13, 14, 15].

Fig. 2. DSC thermograms of A) untreated DM; B) untreated HPMC; C) DM- HPMC (DM = 5.18% w/w of polymer) physical mixture; D) DM- HPMC (DM = 5.18% w/w of polymer) casted film.
3.7 Disintegration time

As shown in Table 2, disintegration time of the seven films varies from $39 \pm 0.8$ to $142 \pm 3$ seconds. It was noted that as the concentration of disintegrant increased, disintegration time decreased. The increased disintegration time with higher concentration of MCC, as the case of F6, may be attributed to blockade of capillary pores which prevent the entry of fluid in to the film [14].

3.8 In-vitro drug release

Figure 3 illustrates the dissolution profiles of DM fast dissolving films. The data revealed that the drug dissolution rate from the prepared films was greatly influenced by the film composition. The dissolution rate of DM from the plain film; F0 (not containing CPV or MCC) was found slow, in which only 37% of the loaded drug were dissolved within 5 min., and 82% were dissolved after 30 min. In contrast, the drug showed faster dissolution rate from the film formulation containing CPV higher than 8% (F2, F3 and F4), in which complete drug dissolution was achieved within the first 5 min. also, increasing CPV level in the film caused enhanced drug dissolution. For example, DM exhibited dissolution of 75% of the loaded drug from the film containing 20% CPV, while only 66 and 68% of the loaded drug were released from film formulae containing 12 and 16% CPV, respectively. Moreover, incorporation of MCC in the film instead of CPV (F5 and F6) enhanced the drug release rate, but to an extent smaller than that has been observed of incorporating CPV. The enhancement of DM dissolution from the film formulae containing high percentages of CPV is due to its high capillary action. crospovidone rapidly absorbs water into the formulation leading to swelling resulting in a rapid disintegration [16-17].

![Fig. 3. In vitro drug release of fast dissolving films containing DM in phosphate buffer pH 6.8.](image)

3.9 Palatability Evaluation

Table 4 shows the results of palatability test carried out on film formula F4. The addition of saccharine was to stimulate salivation causing enhanced dissolution and to mask the drug undesirable taste as well. On the other hand, menthol gives a refreshment feeling to the mouth cavity. Taste evaluation results show that 13.3% of response of the volunteers was acceptable, 66.7% showed good response and 20% showed excellent response. Only two volunteers out of fifteen complained a mild bitter after taste. Mouth feel results show that the response of 26.7% of the volunteers was acceptable while 46.6% showed good response and 26.7% had an excellent response. 86.67% of the volunteers exhibited feeling of mouth refreshment. These results indicate that the prepared ODFs have acceptable palatability.
Table 3: Palatability evaluation code.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Scale</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>After Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste</td>
<td>Bad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth feel</td>
<td>Gritty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After taste</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Palatability evaluation of Formula F4

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>Taste</th>
<th>Mouth feel</th>
<th>After taste</th>
<th>Mouth refreshment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>+</td>
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<td>-</td>
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<tr>
<td>15</td>
<td>2</td>
<td>4</td>
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</table>

4. Conclusion

Formulation of dextromethorphan in ODF produces elegant, transparent, flexible, smooth, homogeneous and palatable films. The formulation excipients showed a pronounced impact on the film physicochemical properties as well as the drug dissolution rate. In addition, the presence of saccharin and menthol may increase patient's palatability toward the formulated DM-loaded oral films. This could enhance drug absorption and bioavailability with a rapid relief of cough, resulting in improved patient compliance and convenience.

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Disclosure

The author report no conflicts of interest in this work.

References


