FORMULATION AND EVALUATION OF DEXTROMETHORPHAN HYDROBROMIDE FAST DISSOLVING FILM

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ABSTRACT

The present investigation was undertaken with the objective of formulating fast dissolving films of the antitussive drug Dextromethorphan hydrobromide, to enhance the convenience and compliance by the elderly and pediatric patients. The films were prepared using hydroxypropyl methylcellulose E5 polymer by solvent casting method. Glycerine as plasticizer, sucralose as sweetner and crosspovidone and sodium starch glycolate as superdisintegrants were also included. The FTIR spectral studies showed no interaction between drug and polymer. Satisfactory results were obtained when subjected to physico-chemical tests such as film weight, thickness, folding endurance, tensile strength, surface pH, drug content, in vitro disintegration time and in vitro drug release studies. In-vitro disintegration time was found to be less than 30 seconds and in-vitro drug release studies indicated 97% release within 5 minutes. No significant change in the physical parameters, in vitro disintegration time and drug content was observed during storage for 30 days.

Keywords: Fast dissolving film, Dextromethorphan hydrobromide, HPMC E5, Solvent casting method.
INTRODUCTION

Despite of so much of advancements in various delivery system developed for administration of various drugs through different routes such as oral, parental, transdermal and nasal etc., the oral route is considered as the preferred route of administration which includes painless, more patient compliance, ease of administration, patient friendly and so on [1, 2].

Several new technologies had been developed for oral delivery is being available to address to improve the patient compliance. Fast dissolving film is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self-administration [3, 4].

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Fast dissolving films (FDFs) are the most advanced form of oral solid dosage form as they improve the efficacy of APIs by dissolving within a minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin [5,6].

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 [7, 8]. 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 [9,10]. The absolute bioavailability of dextromethorphan hydrochloride is around 11% due to a first pass effect in the gut and liver. 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.

EXPERIMENTAL WORK

Material

DextromethorphanHBr was purchased from Wockhardt, Hydroxypropyl methyl cellulose E5 (Colorcon Asia Pvt. Ltd., Goa), Sucralose (Gangwal chemicals Pvt. Ltd., Mumbai). All chemicals and buffers used were of analytical grade.
Drug Excipient Compatibility Study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm\(^{-1}\) by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymer and physical mixture of drug with polymer. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers [11].

Method of Preparation of Film

Hydroxypropyl methyl cellulose E5 (HPMC E5) is known for its good film forming properties and has an excellent acceptability. Glycerine as a plasticizer, Crospovidone and Sodium Starch Glycolate were used as a superdisintegrants. Citric acid as saliva stimulating agent, Sucralose as a sweetening agent [12].

Fast dissolving films of dextromethorphan were prepared by solvent casting method of various formulations is mentioned in Table 1. The calculated amount of polymer and plasticizer were dispersed in three forth volume of water with continuous stirring. API and other excipients are dissolved in water to form a clear viscous solution. Both the solutions are mixed. Solution was kept in sonicator for the removal of air bubbles. The resulting bubble free viscous solution was casted as a film into the glass moulds and kept at room temperature for a period of 24 hours to dry the films. After drying, films were removed and cut into desired size i.e. 2×2cm\(^2\), packs in aluminum foils until further use.

<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>Dextromethorphan HBr (gm)</td>
<td>0.0388</td>
<td>0.0388</td>
<td>0.0388</td>
<td>0.0388</td>
<td>0.0388</td>
<td>0.0388</td>
</tr>
<tr>
<td>HPMC E5 (%)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sodium Starch Glycolate (%)</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Crosspovidone (%)</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Glycerine (%)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Sucralose (mg)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Citric acid (mg)</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Raspberry flavor</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</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>
Evaluation of Fast Dissolving Films:

Fast dissolving films (FDFs) are evaluated for the following parameters:

Morphological Properties:
The fast dissolving films were evaluated by visual observation such as transparent or semitransparent nature of film, homogeneity, color, flexibility, brittleness, presence of air bubble and smoothness [13].

Weight of Film:
For evaluation of film weight, three films of every formulation are taken and weighed individually on a digital balance. The average weights were calculated [13].

Thickness:
The thickness of film can be measured by micrometer screw gauge at 3 different points of the film and then mean thickness is calculated. [15]

Tensile strength:
It was measured using peel adhesion tester (lemi coat equipment) equipped with 2 kg load cell. It consists of two load cell grips. The lower one was fixed and upper one was movable. The film of size 2 × 2 cm² and free from air bubbles or physical imperfections was placed between these cell grips. The film was pulled at a rate of 10 cm min⁻¹ and force required to break the film was measured when the film broke. The whole experiment was carried out in triplicate. [16]

Folding Endurance:
This property was determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value [17].

Surface pH of Film:
The film to be tested was placed in a petri dish and was moistened with 2 ml of distilled water and kept for a short period at room temperature and then the pH of the obtained solution was measured by pH paper [18].

Drug content:
The oral film of size 4 cm² was dissolved in 100 mL of phosphate buffer pH 6.8. Resulting solution was sonicated for 15 minute and filtered. The filtrate was appropriately diluted and analyzed at specified wavelength in UV spectrophotometer. The concentration of the drug was calculated using standard calibration curve. The average of drug contents of three films has to be taken as final reading [19].
**In-vitro disintegration time:**

The disintegration time can be visually determined by dipping the film of desired size in a Petri dish (internal diameter 5 cm) containing 10mL of phosphate buffer pH 6.8 at 37°C. Petri dish was swirled at every 10 seconds and the time was noted when the film starts to breaks or disintegrates. All the measurements were carried out in triplicate [13].

**In vitro drug release:**

To mimic the natural conditions in oral cavity the in vitro dissolution test was performed in a fabricated dissolution apparatus (shown in Figure 3). For in vitro dissolution studies, each film was placed with the help of U-clip in a beaker containing 100ml of phosphate buffer pH 6.8 as a dissolution medium, maintained at 37±0.5°C and magnetic stirrer was rotated at 100 rpm. Aliquot of 2mL was withdrawn at different time intervals and the same amount was replaced with the fresh medium. The samples were analyzed for the drug release using UV-VIS spectrophotometer [20].

**Stability Studies:**

The optimized formulation was subjected to stability studies as per International Conference on Harmonization (ICH guidelines). The sample was packed in an aluminium Foil then stored in stability chamber controlled at accelerated testing condition at 40 ± 2 °C temperature and 75 ± 5 % RH for 1 month to check the stability.

**RESULT AND DISCUSSION**

**Drug and excipient compatibility study using FTIR**

Figure1 and Figure 2 represents IR spectra of Dextromethorphan HBr and physical mixture of drug and polymer respectively.

Dextromethorphan HBr spectrum showed the prominent absorption bands at 2165 and 2590 cm\(^{-1}\), corresponding to the NH\(^+\) stretching vibration in the tertiary amine group of the drug.

HPMC showed a characteristic band at 3477 cm\(^{-1}\) due to O–H stretching vibration (Figure 2). The FT-IR spectra of the drug in case of physical mixture showed a characteristic band at 3472 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 [9,20].
Morphological properties:
Prepared films were found to be flexible, smooth, transparent, non-sticky and homogeneous.

Weight of films:
The results of weight of films are given in Table 2. The weight of prepared films (F1 to F6) was in the range of 29.33 ± 1.70 to 44.67 ± 3.00 mg. In all the cases the calculated standard deviation values were very low which suggest that the prepared films were uniform in weight.

Thickness:
The thickness of formulated films was found to be in range of 0.09 ± 0.008 to 0.12 ± 0.009 mm. The mean values are tabulated in Table 2. The values indicating that as the concentration of polymer increases thickness was gradually increased. In all the cases the calculated standard deviation values were very low suggesting the prepared films were uniform in thickness and ensuring suitability of solvent casting method for the preparation of fast dissolving films.

Tensile Strength:
The results of tensile strength from various formulations (F1 to F6) are given in Table 2. Tensile strength of all the films was in the range of 2.774 to 5.099 N/mm². The Formulation containing
Crosspovidone as superdisintegstant exhibited higher tensile strength compared to the other films containing Sodium Starch glycolate. The results suggest that all films were having good mechanical strengths to withstand mechanical damage during, production and application.

**Folding Endurance:**
Folding endurance measures the ability of film to withstand rupture, higher the folding endurance lower will be chances of films to rupture easily. The results of folding endurance of various formulations (F1 to F6) are given in Table 2. All the films were showing folding endurance in the range of 156 to 179. Results revealed that as the concentration of polymer increases folding endurance increases. F3 formulation showed high folding endurance of 179.

**Surface pH:**
The surface pH of fast dissolving oral films was determined in order to investigate the possibility of any side effects in-vivo. As an acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. Surface pH of the prepared films was in the range of 6 to 7. It assured that there will not be any kind of irritation to the mucosal lining of the oral cavity and hence, more acceptable by the patients.

**Drug Content:**
According to Table 3, the drug content was found to be in the range of 97.07 to 99.90%. The drug content of formulation batch F3 was found out to be higher than the remaining formulation batches.

**In-vitro Disintegration Time:**
The results of disintegration time of various formulations (F1 to F6) are given in Table 3. All the films were showing disintegration time in the range of 14 to 37. Results revealed that the in-vitro disintegration time was found to decrease with the addition of superdisintegants. It is observed that disintegration time of film decreased from 29 to 14 sec and 37 to 20 sec with the addition of Crospovidone and Sodium Starch glycolate respectively.

**In-Vitro Drug Release Study:**
From in vitro drug release studies, it was found that formulation containing Crospovidone showed high-percentage release compared to others. The formulation F3 showed a maximum percentage drug release of 97% in 5min followed by the formulation F2 and F6 with 94% and 93% respectively. The order of drug release in each set of formulation can be given as

F3 > F2 > F1
F6 > F5 > F4
The percentage amount of drug released is plotted against time to obtain the release profiles as shown in the Figure 4. The results suggest that superdisintegrants play an important role in the release of drug from the films.

**Stability Studies:**

The results of physical appearance, drug content, disintegration time and other parameters after 1 month storage of prepared fast dissolving films are shown in Table 5. Stability studies of optimized formulation F3 indicated that there are no significant changes in the film characteristics and the formulation was stable enough for the period of at least 1 month at mentioned condition.

**Table 2: Evaluation of Fast Dissolving Film of Dextromethorphan Hydrobromide**

<table>
<thead>
<tr>
<th>Batch Codes</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Tensile Strength (N/mm²)</th>
<th>Folding Endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.33 ± 1.70</td>
<td>0.09 ± 0.008</td>
<td>4.388</td>
<td>156</td>
</tr>
<tr>
<td>F2</td>
<td>35.67 ± 1.25</td>
<td>0.10 ± 0.005</td>
<td>2.774</td>
<td>160</td>
</tr>
<tr>
<td>F3</td>
<td>35.69 ± 2.87</td>
<td>0.11 ± 0.005</td>
<td>3.136</td>
<td>179</td>
</tr>
<tr>
<td>F4</td>
<td>39 ± 2.45</td>
<td>0.11 ± 0.005</td>
<td>5.099</td>
<td>167</td>
</tr>
<tr>
<td>F5</td>
<td>44 ± 2.94</td>
<td>0.12 ± 0.009</td>
<td>3.215</td>
<td>170</td>
</tr>
<tr>
<td>F6</td>
<td>44.67 ± 3.00</td>
<td>0.12 ± 0.005</td>
<td>4.887</td>
<td>174</td>
</tr>
</tbody>
</table>

**Table 3: Results of Surface pH, Drug Content and In-vitro Disintegration Time**

<table>
<thead>
<tr>
<th>Batch Codes</th>
<th>Surface pH</th>
<th>Drug Content (%)</th>
<th>In-vitro Disintegration Time (Sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6-7</td>
<td>97.91</td>
<td>29</td>
</tr>
<tr>
<td>F2</td>
<td>6-7</td>
<td>97.07</td>
<td>18</td>
</tr>
<tr>
<td>F3</td>
<td>6-7</td>
<td>99.90</td>
<td>14</td>
</tr>
<tr>
<td>F4</td>
<td>6-7</td>
<td>98.65</td>
<td>37</td>
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<tr>
<td>F5</td>
<td>6-7</td>
<td>97.92</td>
<td>25</td>
</tr>
<tr>
<td>F6</td>
<td>6-7</td>
<td>98.90</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 4: In-vitro Dissolution (% Release) Profile of Fast Dissolving Films**

<table>
<thead>
<tr>
<th>Batch Codes</th>
<th>1 mins</th>
<th>2 mins</th>
<th>3 mins</th>
<th>4 mins</th>
<th>5 mins</th>
<th>10 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>14</td>
<td>33</td>
<td>49</td>
<td>66</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>F2</td>
<td>37</td>
<td>52</td>
<td>67</td>
<td>81</td>
<td>94</td>
<td>92</td>
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<td>F3</td>
<td>40</td>
<td>58</td>
<td>71</td>
<td>85</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>F4</td>
<td>12</td>
<td>27</td>
<td>44</td>
<td>60</td>
<td>73</td>
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<td>F5</td>
<td>24</td>
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<td>62</td>
<td>79</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>F6</td>
<td>32</td>
<td>47</td>
<td>64</td>
<td>80</td>
<td>93</td>
<td>94</td>
</tr>
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</table>

**Table 5: Stability study of promising batch F3**

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>After 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Transparent</td>
</tr>
<tr>
<td>Disintegration Time (sec)</td>
<td>15</td>
</tr>
<tr>
<td>Tensile Strength (N/mm²)</td>
<td>3.102</td>
</tr>
<tr>
<td>Drug Content</td>
<td>99.43</td>
</tr>
<tr>
<td>Cumulative Drug Release (%)</td>
<td>96% in 5 mins</td>
</tr>
</tbody>
</table>
Fig. 3: Apparatus fabricated for carrying out dissolution of fast dissolving oral film

Fig. 4: In-vitro dissolution profile of dextromethorphan hydrobromide from all films.

CONCLUSION

Finally, it can be concluded that, fast dissolving films of Dextromethorphan Hydrobromide can be prepared by solvent casting technique using HPMC E5 as film base, Crospovidone as superdisintegrant and Sucralose as sweetner. The formulation F3 satisfied all pharmaceutical parameters of fast dissolving films and appears to be promising would be able to offer benefits such as rapid drug release, good disintegration time, tensile strength and thereby may help to improve the bioavailability of drug. It can also be a potential novel drug dosage form for geriatric and also for general population.

REFERENCES


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