FORMULATION AND EVALUATION OF ORODISPERSIBLE FILM OF ANTIHISTAMINIC DRUG DIPHENHYDRAMINE HCl

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ABSTRACT
The aim of this study was to develop a fast releasing oral polymeric thin film, prepared by solvent casting method, with good mechanical properties, instant disintegration and dissolution. Diphenhydramine hydrochloride, an antihistamine drug belonging to BCS class I was used for oral thin film preparation. The formulations from the preliminary trial were analyzed which was applied to optimize the type of polymers (Gelatin and HPMC E15), concentration of polymers, plasticizer (Glycerol, Propylene Glycol, PEG 400), surfactant (TWEEN 80) and sweetener (Mannitol). The resultant films were evaluated for thickness, folding endurance, drug content, Surface pH, in vitro disintegration time, in vitro dissolution studies etc. Oral thin films which were prepared with surfactant showed better results i.e., good disintegrating and dissolution properties than without surfactant. The optimized film disintegrated in less than 30s, releasing more than 90% of drug within 90sec.

KEYWORDS: Diphenhydramine hydrochloride, Orodispersible film, pH, folding endurance etc.

INTRODUCTION
The oral route is most popular route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to high levels of patient compliance. In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. The main advantage of this technology is the administration to
pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated orally. Fast dissolving film is the type of drug delivery system which, when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. New taste-masking agents allow bitter ingredients to be successfully formulated. Oral thin fast dissolving films (OTFDFs) can be formulated by reduced dosages frequency with selected oral cavity absorption enhancers in a suitable oral cavity film carrier. This facilitates the rapid absorption in the oral cavity for drugs with low GIT-bioavailability and intensive first-pass effects. Thus, it offers shortening onset time, enhancing bioavailability and reducing the probability of first pass side effect (Patel et al 2010).

Saliva is a secretion of three salivary glands (parotid, submandibular and sublingual) present in the oral cavity. Saliva is relatively less viscous compared to GI fluids and it mainly contains water and 1% organic and inorganic material and is a weak buffer having pH ranges from 5.5-7. The total volume of saliva secreted from the salivary gland is 0.5-2 liters and it is enough to hydrate oral mucosal dosage form. Oral films rapidly disintegrate within seconds when it comes in contact with saliva without the need of water. (Dixit et, al 2009).

The name “fast dissolving” indicates that these dosage forms dissolves quickly and disintegrates into smaller particles by saliva and swallowed into the stomach. The time to reach from mouth to the stomach is estimated to be between 5 and 10 minutes. Hence, fast dissolving drug delivery system has the advantage of liquid dosage form i.e. convenient drug administration. The fast passage of dissolved dosage form to the stomach provides a better opportunity for the medication to be absorbed through the membrane of the buccal cavity, pharynx and esophagus for improved bioavailability and quick onset of drug action. (Fu et, al 2014). Recent advances in novel drug delivery system aim to enhance safety and efficacy of
drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Fast dissolving oral dosage that provides highest compliance among oral forms like ensuring dose delivery due to the immediate dissolution in the mouth.

MATERIALS AND METHODS

Materials
Diphenhydramine HCl was gift sample from IndSwift Laboratories Pvt. Ltd., Derra Basi Hydroxy propyl methyl cellulose, glycerol, propylene glycol, Propylene glycol Propyl ethylene glycol 400, Tween 80 were purchased from sigma eldirch, Agra. Sodium hydroxide and Potassium dihydrogen phosphate were purchased from CDH, New Delhi, India. Ethanol was purchased from Qualigens fine chemicals, Mumbai.

Preparation of Oral Thin Films

Solvent casting method
Oral thin films were prepared by dissolving the polymer (HPMC with or without surfactant Tween 80) in solvent mixture (Distilled water and Ethanol), with continuous stirring Drug, Saccharin sodium is added. To the resulting solution plasticizers (Glycerol, PEG 400, Propylene glycol) and surfactants (Tween 80) are added subsequently and stirred for 15 minutes. These solutions were casted slowly on to a glass plate of diameter 5cm without formation of air bubbles. (Each strip 2*2 cm² consists of 25mg of drug) film dried at 50°C then these plates were kept aside for 48 hrs. and dried films are carefully separated from the plate and evaluated. Various formulations were prepared as per table 1 & 2.

For Total amount of Drug Require

Calculation of Diameter of Petridish or glass plate

Diameter of glass plate

Radius of the Petridish = 7.3cm Diameter = Radius/2 = 7.3/2 = 3.65 cm.

\[
\pi r^2 = 3.14 \times 3.65 \times 3.65 = 41.83 \text{ cm}^2
\]

Now, Dose is 25 mg and Cut the pieces in 2cm X 2cm = 4cm²

4cm² contain 25mg Drug

So, 41.83 cm² contain (?) Drug = 261.43 Drug

10 ml contain 261.43 Drug.
Table 1: Preparation without surfactant

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>API (mg)</th>
<th>Polymer (mg)</th>
<th>Plasticizer Glycerol+PG+PEG400 (ml)</th>
<th>water</th>
<th>Ethanol (ml)</th>
<th>Sweetener (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>261</td>
<td>139</td>
<td>0.6 (0.2ml each)</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>F2</td>
<td>261</td>
<td>175</td>
<td>0.6</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>F3</td>
<td>261</td>
<td>261</td>
<td>0.6</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 2: Preparation with surfactant

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>API (gm)</th>
<th>Polymer (mg)</th>
<th>Plasticizer Glycerol+PG+PEG400 (ml)</th>
<th>Water</th>
<th>Ethanol (ml)</th>
<th>Sweetener (ml)</th>
<th>Surfactant (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>261</td>
<td>139</td>
<td>0.6 (0.2ml each)</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>F5</td>
<td>261</td>
<td>175</td>
<td>0.6</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>F6</td>
<td>261</td>
<td>261</td>
<td>0.6</td>
<td>q.s</td>
<td>1</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Evaluation of fast dissolving oral film (Bhyan et al 2010)

**Thickness:** A thickness of film should be measured with the help of micrometer screw gauge or calibrated digital vernier calipers. The thickness of the film sample should be measured at five locations (centre and four corners), and the mean thickness is calculated. Typical thickness for film is 130 ±3µm. It is necessary to determine the uniformity of thickness as it is directly related to accuracy of dose in the film.

**Weight variation:** Four centimeter square (2×2 cm) of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

**Folding endurance:** The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Typical folding endurance for film is between 100-150.

**Tensile strength:** Tensile testing was conducted using the modified method. The film was cut into 30 × 20 mm strips. Each test strip was stick on the surface of Glass slide with the help of Feviquick. Initial grip separation was 20 mm. The test was considered concluded when the film breaks. Tensile strength was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross sectional area of the specimen and it was expressed in force per unit area (MPa). Typical tensile strength for film is 1.80± 0.20MPa.
Tensile strength (N/mm²) = breaking force (N)/cross-sectional area of sample (mm²)

Swelling index: Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed. The degree of swelling was calculated using parameters.

\[ \text{wt-wo/wo}, \]
\[ \text{wt is weight of film at time t,} \]
\[ \text{wo is weight of film at time zero.} \]

Percentage elongation: For the determination of percentage elongation of the film formulations the distance between the tensile grips of the tensile strength testing film was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below

\[ \% \, E = \frac{D_f - D_0}{D_0} \times 100 \]
\[ \% \, E = \text{Percentage elongation} \]
\[ D_0 = \text{Distance between the tensile grips before the fracture of the film.} \]
\[ D_f = \text{Distance between the tensile grips after the fracture of the film} \]

Surface pH: The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.

Disintegration Time: Disintegrating time is defined as the time (seconds) at which a film breaks when brought in contact with water or saliva. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30s.

Slide frame method: One drop of distilled water was dropped by a Pipette onto the oral films. Therefore, the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.
Petri dish method

2ml of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.

% Drug Content: This parameter can be determined by dissolving known weight of film by homogenization in 100 ml of simulated saliva of pH 6.8 for 30 min with continuous shaking. Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85-115%.

In vitro dissolution Studies

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 artificial saliva maintained at 37 °C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 artificial saliva maintained at 37°C. Diphenhydramine HCl in the samples was then determined spectrophotometrically at λmax of 258nm. The results were expressed as mean of three determinations.

RESULT AND DISCUSSION

Table 3 Evaluation parameters of all formulations

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formulation Code</th>
<th>Weight (mg)/4cm²</th>
<th>Folding Endurance</th>
<th>Swelling index (% wt-w0/w0, *100)</th>
<th>Tensile Strength (M Pa)</th>
<th>Percentage elongation (mm)</th>
<th>Disintegration time(sec)</th>
<th>% Drug Content</th>
<th>% Cumulative Drug Release</th>
<th>Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>55.2</td>
<td>128</td>
<td>99</td>
<td>0.87</td>
<td>6</td>
<td>55</td>
<td>88.40</td>
<td>83.59</td>
<td>0.08-0.09</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>57.1</td>
<td>85</td>
<td>110</td>
<td>1.22</td>
<td>8</td>
<td>50</td>
<td>88.20</td>
<td>83.59</td>
<td>0.07-0.08</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>60.7</td>
<td>123</td>
<td>113</td>
<td>1.90</td>
<td>9</td>
<td>26</td>
<td>92.60</td>
<td>83.59</td>
<td>0.12-0.12</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>57.7</td>
<td>147</td>
<td>106</td>
<td>0.96</td>
<td>12</td>
<td>37</td>
<td>89.20</td>
<td>83.59</td>
<td>0.07-0.09</td>
</tr>
<tr>
<td>5.</td>
<td>F5</td>
<td>60.7</td>
<td>122</td>
<td>116</td>
<td>1.30</td>
<td>14</td>
<td>26</td>
<td>94.20</td>
<td>83.59</td>
<td>0.08-0.09</td>
</tr>
<tr>
<td>6.</td>
<td>F6</td>
<td>62.2</td>
<td>99</td>
<td>136</td>
<td>2.10</td>
<td>16</td>
<td>23</td>
<td>98.40</td>
<td>83.59</td>
<td>0.07-0.08</td>
</tr>
</tbody>
</table>
The thickness of formulated films were found to be in range of 0.07 to 0.09 ± 0.01 mm. The values were almost uniform in all F1 to F6 formulations (Table 3) It was observed that all the batches were uniform in weight with no significant difference in the weight of the individual formulation from the average value. Weight variation was found to be in the range of 0.082 ± 0.002 to 0.189 ±0.006 mg for films prepared. Folding endurance of the oral thin films was found to be in the range 35-180. The films shows better plasticity. All the drug andpolymer ratio were able to give the acceptable folding endurance values. Tensile strength was found to be increase with increase in concentration of HPMC whereas the increase in the concentration of PEG 400 leads in the decrease in the tensile strength. The tensile strength of formulation F6 was found maximum 2.10. The percentage elongation of all the batches ranges from 5-20. It was increased with increasing in the amount of plasticizer and polymer. Formulation F6 showed highest percentage elongation. Swelling index of the oral thin films was found to be in the range 93-157. Polymer HPMCo of weight 261 mg showed better swelling property. The drug content of the oral strip of 4cm2 was determined and it varies with the range of 88.20±0.0 to 98.40%. The drug content was found to be high in F6. As per USP, the drug content was found to be in range of 85-115%. Surface pH of the drug was found to be 4.28. Disintegration of films were found in of 22 to 55 sec. It was found that as the amount of HPMC increases there was increase in disintegration time as shown in table. But in case of adding surfactant Tween 80 in formulation then disintegration of film was decrease. In-vitro drug release study was performed up to 300 seconds. In-vitro drug release studies showed that drug get rapidly released from all formulations. Maximum in-vitro release was found to be 98.40% over a period of 5 min in batch F6 while minimum in-vitro release was found to be 83.59 % in batch F1. The results for release studies are shown in Table 3. The graph was plotted between cumulative percentage drug release and time and shown in (Fig. 2&3). The result of in-vitro release show that increase in HPMC concentration increase % drug release and formulation with surfactant (F4,F5,F6) shows better % in vitro release compare to without surfactant Formulations (F1,F2, F3). in all formulation F6 formulation in vitro release result found to be better. The thicknesses of formulated films were found to be in range of 0.07 to 0.09 ± 0.01 mm. The values were almost uniform in all F1 to F6 formulations. Variation in the weights of the formulations was determined by weighing 2 cm² section of each film on a digital balance and then calculating the average weight. From the results shown in table; it was observed that all the batches were uniform in weight with no significant difference in the weight of the individual formulation from the average value. The films prepared using HPMC and Glycerol, PG and PEG400 with surfactant tween 80
showed the best result among all other films. Formulation F6 (HPMC E6: Drug, 261:261 with plasticizer glycerol, PG, PEG400 with surfactant tween 80) disintegrated in 23 seconds and released 98.40 % of drug within 5 minutes and was considered as the best formulation. As the concentration of film forming polymers gets increased it also increases the film forming capacity of the films.

CONCLUSION

Diphenhydramine Hydrochloride oral thin films were successfully prepared by solvent casting method using the following polymers: Gelatin, HPMC E15. 1:1 ratio of drug and polymer ratio was optimized. The films prepared by using Tween 80 which was used as solubilizing agent has more percentage drug release. Among all formulations, Films prepared
using HPMC E15 with Tween 80 showed best results. OTF prepared by using HPME15, Plasticizers (Glycerol, Propylene Glycol, PEG 400) and solubilizing agent Tween 80 would be promising oral delivery systems for Diphenhydramine Hydrochloride.

REFERENCES