Optimization of taste-masked dapoxetine oral thin films using factorial design: \textit{in vitro} and \textit{in vivo} evaluation

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To cite this article: Ibrahim A. El-said, Ahmed A. Aboelwafa & Omaima N. ElGazayerly (2021): Optimization of taste-masked dapoxetine oral thin films using factorial design: \textit{in vitro} and \textit{in vivo} evaluation, Pharmaceutical Development and Technology, DOI: 10.1080/10837450.2021.1894445

To link to this article: https://doi.org/10.1080/10837450.2021.1894445

Published online: 11 Mar 2021.
Optimization of taste-masked dapoxetine oral thin films using factorial design: in vitro and in vivo evaluation

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ABSTRACT
Dapoxetine HCl is used for the treatment of premature ejaculation. Dapoxetine is primarily metabolized in the liver and kidney and its metabolites are inactive; resulting in reduced bioavailability. Also, one of the commonly encountered issues in the oral dapoxetine formulae is its bitter taste. Thus, the objective of this study was to develop and to optimize novel dapoxetine taste-masked oral thin films (OTFs), to offer a faster dissolution rate, rapid release pattern, lower liver metabolism, and better patient compliance. To achieve our goal, the applicability of either pullulan or maltodextrin as strip forming polymers were investigated in the preparation of OTFs, while glycerol was used as a plasticizer. Also, the physicochemical characteristics of dapoxetine in a resinate complex with AmberLite™-IRP69 as taste masking was evaluated. Furthermore, a 2³ factorial design was used to study and to optimize the effect of the independent variables (strip forming polymer (X₁), glycerol (X₂) and AmberLite™ (X₃) amounts) on the disintegration time (Y₁), degree of elongation (Y₂), and degree of in vitro drug release in phosphate buffer pH 6.8 at 5 minutes (Q₅min, Y₃) as responses. P₂ batch (OTF) (pullulan 96 mg, glycerol 12 mg, AmberLite™ 32 mg, and dapoxetine 30 mg) was identified as an optimized formulation showing an in vitro disintegration time 9.33 s, 35.56% elongation, and 91.43% Q₅min; excellent in vivo disintegration time; good overall taste acceptability and stable resinate complex.

Introduction
Among the delivery routes, orally disintegrating films show unique benefits over the existing benefits of the liquid and solid oral dosage forms together, which are: good stability, simple manufacturing, simple handling, the small size of packing, no danger of obstruction of the gastrointestinal tract (GI), fast onset of action, and finally the pre-gastric drug absorption bypass the liver metabolism, resulting in decreasing the dose and maximizing the drug bioavailability (Brown 2003; Aguilar et al. 2013). Oral thin films (OTFs) become more popular for various potent medications; as they have the superiorities of large surface areas for rapid disintegration/dissolution (ElMeshad and El Hagrasy 2011). The OTFs are ultra-thin strips, ‘a size of a postage stamp’, with an active pharmaceutical component and other excipients, that rapidly melt on the tongue when used without water (Bhyan et al. 2011). Recently, research work on the use of OTFs as promising carriers for multiple active pharmaceutical ingredients has emerged (e.g. analgesics, antihistamines, cardiovascular drugs, neuroleptics, and drugs for erectile dysfunction) (Prajapati et al. 2013). The OTFs provide acceptable mechanical properties, rapid dissolution in saliva, and excellent mouth feeling. The addition of a plasticizer is necessary to obtain flexible and non-brittle OTFs. Glycerol, propylene glycol, sorbitol, macrogols, or phthalates are commonly used (Hoffmann et al. 2011).

Dapoxetine ((+)-(S)-N, N-dimethyl-(a)-(2-(1-naphthalenylox-yethyl)-benzenemethanamine)HCl is a ‘selective serotonin (5-HT) reuptake inhibitor (SSRI)’ (McCarty and Dinsmore 2012). Dapoxetine is originally generated as an antidepressant, but it’s now mainly used in the management of premature ejaculation (Pryor et al. 2006). Dapoxetine affects premature ejaculation by increasing serotonin’s action at pre and postsynaptic receptors (Gengo et al. 2005). The pharmacokinetic parameters of dapoxetine are characterized by 42% bioavailability, T max = 1.27-1.8 h, C max 349-398 ng/ml and elimination half-life 1.5–1.6 h (Andersson et al. 2006; McMahon 2012). Dapoxetine is metabolized widely in the kidney and liver by various enzymes such as CyP3A4, CyP2D6, and flavin monoxygenase 1 (FMO1). The main metabolite is a weak SSRI and has no clinical effect; resulting in reduced bioavailability. Furthermore, oral dapoxetine has a bitter taste, currently marketed only as oral coated tablets (Priligy™), and this is a big challenge that limits its formulation commercially as fast oral disintegration systems, therefore it’s important to exploit other dosage forms (Turkyilmaz and Yelken 2015).

AmberLite™ IRP69 is a strong cationic exchange resin resulting from a sulfonated copolymer of styrene and divinylbenzene (Rehman and Khan 2012). The exchanging counter ions are sodium or protons (salt form) (Robleg et al. 2010). It binds to free attached counter ions which can be easily substituted with...
ionized drugs forming the resinate complex. The resinate complexes are used widely as carriers for many pharmaceutical compounds as it has no local or systemic side effects and elicits high chemical/physical stability (Daihom et al. 2016). It has been extensively used in taste masking as a drug carrier (Han et al. 2019). The mechanism of taste masking of AmberLite(TM) is to bind the drug molecules into the insoluble framework of the AmberLite(TM) and consequently decrease its contact to the taste buds while keeping the concentration of the drug in saliva below the taste threshold value (Elder 2005).

This research aims to formulate and develop novel taste-masked dapoxetine OTFs using a 2³ full factorial design. Based on our preliminary investigations to get the best fitting components, the applicability of either pullulan or maltodextrin polymers were studied in the formulation of dapoxetine (OTFs), while Glycerol was used as a plasticizer. AmberLite(TM) was used to form resinate complex with dapoxetine to mask its bitterness followed by physicochemical characterization of the formed resinate complex. The factorial design aimed to carry out planned evaluations and optimization of process factors, to generate an optimized formulation by administering it to healthy volunteers.

Materials and methods

Materials

Dapoxetine HCl (Batch no. 515DA0F001) was gifted from Al-Andalus Company, Egypt. AmberLite(TM) IRP69 (10–150 μm) was procured from Dow Chemical Company, USA. Pullulan (Aureobasidium Pullulans) was procured from International Laboratory, USA. Maltodextrin (dextrose equivalent 13–17), glycerol (Ph. Eur.), and aspartame were procured from Sigma Aldrich Chemical Company, USA. Polysorbate 80, L-menthol 99%, and citric acid were procured from Alfa Aesar, Germany. Chlorophyll E141 "Green" was procured from RD Health Ingredients Co., China. Absolute ethanol was acquired from Prolabo, France. All materials were utilized as received and all solutions were formulated using double-distilled water.

Analytical method

The calibration curve of dapoxetine was constructed in distilled water and phosphate-buffered saline (PBS) at pH 6.8 (2.38 g Na₂HPO₄, 0.19 g KH₂PO₄, and 8.00 g NaCl/1L of distilled water). Stock solutions were made by dissolving 10 mg dapoxetine to 20 mL of the medium. Serial dilutions of the stock solutions were prepared, and their absorbance values were measured using an ultraviolet-visible (UV-Vis) spectrophotometer (Shimadzu, UV-1601 PC, Japan) at λmax 292 nm. No interference from the excipients used was noticed at that wavelength. Linearity was observed over a concentration range of 5–50 μg/mL, with an R² = 0.994.

Preparation of taste-masked dapoxetine oral thin films

Preliminary trials of dapoxetine oral thin films

Preliminary trials of dapoxetine (OTFs) were prepared by the solvent casting method as described below to identify the best compatible concentrations of film-forming polymers, plasticizers, taste-masking agents, and sweeteners while keeping the amount of dapoxetine HCl constant at 30 mg, to determine the optimum amounts needed.

Preparation of dapoxetine–resin complex

Dapoxetine–resin complex (resinate) was prepared by a simple aqueous binding process (Shang et al. 2018). The amount of resin needed to obtain the best taste-masking effect for dapoxetine HCl without affecting the synthesis of the films was determined. Different amounts of AmberLite(TM) were weighed (20, 25, 30, 32, 34, 36, 38, 40, 42, 45, 50 mg) while keeping the amount of dapoxetine HCl constant at 30 mg. The amounts of weighed AmberLite(TM) were placed in scintillation vials, then 30 mg of dapoxetine hydrochloride were weighed and dissolved in 5 mL distilled water. The vials were stirred at 1000 rpm and 70°C for 3 h using a magnetic stirrer. Thereafter, the content of the vials was filtered using Millipore filters (0.22 μm). Dapoxetine resinate on the filters were washed several times with distilled water and were kept in a desiccator under vacuum until reaching a constant weight (becoming completely dry). Then, the dried resin powders were stored in tight glass containers until further use. The filtrates were then determined at 292 nm using a UV spectrometer to determine the amounts of free dapoxetine. The amounts of bound dapoxetine were calculated by subtracting free dapoxetine from the total amounts added.

To determine the time required to reach binding equilibrium, 32 mg of resin, and 30 mg of dapoxetine HCl were used to prepare the resinate complex using the before mentioned procedure (Tan et al. 2018). Different samples of 100 μL were withdrawn at several periods (5, 10, 15, 30, 45, 60, 75, 90, 120, 180, and 240 min) and were filtered using 0.22 μm filters. The filtrates were then determined at 292 nm using a UV spectrometer to determine the amounts of free dapoxetine. The amounts of bound dapoxetine were calculated by subtracting free dapoxetine from the total amounts added.

To assess the binding of dapoxetine to AmberLite(TM), binding efficiency evaluation was performed. Binding efficiency is simply the ability to bind successfully. The percent binding efficiency of dapoxetine to AmberLite(TM) (while keeping the amount of AmberLite(TM) constant) was calculated from the following equation (Daihom et al. 2016):

\[
\text{Binding efficiency} \% = \frac{\text{Amount of dapoxetine added} - \text{the amount of free dapoxetine}}{\text{amount of dapoxetine added}} \times 100
\]

Films preparation using factorial design

Our film formulations were prepared by the solvent casting technique (Abruzzo et al. 2012). In this method, we began to mix the polymers, glycerol, and citric acid into 5 mL water and 1.5 mL ethanol at 1000 rpm. Then, the polymeric mixture was heated on a magnetic stirrer. Thereafter, the content of the vials was filtered using Millipore filters (0.22 μm). Dapoxetine resinate on the filters were washed several times with distilled water and were kept in a desiccator under vacuum until reaching a constant weight (becoming completely dry). Then, the dried resin powders were stored in tight glass containers until further use. The filtrates were then determined at 292 nm using a UV spectrometer to determine the amounts of free dapoxetine. The amounts of bound dapoxetine were calculated by subtracting free dapoxetine from the total amounts added.

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To assess the binding of dapoxetine to AmberLite(TM), binding efficiency evaluation was performed. Binding efficiency is simply the ability to bind successfully. The percent binding efficiency of dapoxetine to AmberLite(TM) (while keeping the amount of AmberLite(TM) constant) was calculated from the following equation (Daihom et al. 2016):

\[
\text{Binding efficiency} \% = \frac{\text{Amount of dapoxetine added} - \text{the amount of free dapoxetine}}{\text{amount of dapoxetine added}} \times 100
\]
A 2^3 randomized full factorial design was exercised to investigate the common impact of three formulation variables using Design Expert® software (version 10.0.6.0, Stat-Ease Inc., USA) using a polynomial equation. In this design, three factors were tested, each at two levels. Experimental trials were performed at all eight possible combinations. Our preliminary studies provided a set of levels for each formulation variable. The polynomial equation is:

\[
Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}(X_1X_2) + b_{13}(X_1X_3) + b_{23}(X_2X_3)
\]

where \(Y\) is the dependent variable; \(b_0\) is the intercept and \(b_{1}, b_{2}, b_{3}, b_{12}, b_{13}, b_{23}\) are the polynomial coefficients for the factors \(X_1\), \(X_2\), and \(X_3\) and their interaction terms (Singh et al. 2008). The standardized effect of the independent variables and their interaction on the dependent variable was investigated by preparing three-dimensional (3D) surface plots. Surface plots not only show the individual data points, but also show a functional correlation between a designated dependent variable (\(Y\)), and two independent variables.

The amount of strip forming polymer “pullulan or maltodextrin” (\(X_1\)), glycerol (\(X_2\)), and AmberLite™ (\(X_3\)) were selected as independent variables (Table 1). Disintegration time (\(Y_1\)), degree of elongation (\(Y_2\)), degree of in vitro drug release in phosphate buffer pH 6.8 at 5 min (\(Q5\), \(Y_3\)) were used as responses. Table 2 depicts the composition of the prepared dapoxetine (OTFs) per strip.

### Table 1. The full-factorial design used to optimize preparation.

<table>
<thead>
<tr>
<th>Factor (mg)</th>
<th>Level used</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_1) Strip forming polymer amount</td>
<td>80 96</td>
</tr>
<tr>
<td>(X_2) Plasticizer amount</td>
<td>16 24</td>
</tr>
<tr>
<td>(X_3) Taste masking agent amount</td>
<td>32 40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Y_1) Disintegration time</td>
<td>(Y_1 \leq 30) Seconds</td>
</tr>
<tr>
<td>(Y_2) % elongation</td>
<td>Maximize</td>
</tr>
<tr>
<td>(Y_3) Drug release after 5 min (Q5)</td>
<td>(Y_3 \geq 80)%</td>
</tr>
</tbody>
</table>

[Strip forming polymer " indicates either pullulan or maltodextrin]

### Table 2. Composition of the prepared dapoxetine oral thin films.

<table>
<thead>
<tr>
<th>Preparation code</th>
<th>(X_1)</th>
<th>(X_2)</th>
<th>(X_3)</th>
<th>(Y_1)</th>
<th>(Y_2)</th>
<th>(Y_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pullulan OTFs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>80</td>
<td>16</td>
<td>32</td>
<td>14.23 ± 0.61</td>
<td>39.62 ± 1.87</td>
<td>81.53 ± 3.92</td>
</tr>
<tr>
<td>P2</td>
<td>96</td>
<td>16</td>
<td>32</td>
<td>9.22 ± 0.44</td>
<td>35.56 ± 1.71</td>
<td>92.99 ± 4.49</td>
</tr>
<tr>
<td>P3</td>
<td>96</td>
<td>24</td>
<td>32</td>
<td>24.19 ± 1.08</td>
<td>52.66 ± 2.45</td>
<td>47.44 ± 2.11</td>
</tr>
<tr>
<td>P4</td>
<td>96</td>
<td>24</td>
<td>40</td>
<td>19.70 ± 0.92</td>
<td>44.88 ± 2.19</td>
<td>61.01 ± 3.06</td>
</tr>
<tr>
<td>P5</td>
<td>96</td>
<td>24</td>
<td>32</td>
<td>24.84 ± 1.35</td>
<td>50.74 ± 2.60</td>
<td>46.62 ± 1.53</td>
</tr>
<tr>
<td>P6</td>
<td>96</td>
<td>16</td>
<td>40</td>
<td>18.68 ± 0.86</td>
<td>28.82 ± 0.33</td>
<td>58.72 ± 2.64</td>
</tr>
<tr>
<td>P7</td>
<td>96</td>
<td>32</td>
<td>32</td>
<td>29.84 ± 1.35</td>
<td>35.04 ± 1.60</td>
<td>46.62 ± 1.53</td>
</tr>
<tr>
<td>P8</td>
<td>96</td>
<td>40</td>
<td>40</td>
<td>25.35 ± 1.24</td>
<td>31.88 ± 1.24</td>
<td>56.67 ± 2.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maltodextrin OTFs</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>80</td>
<td>16</td>
<td>32</td>
<td>45.91 ± 2.13</td>
<td>14.78 ± 0.66</td>
<td>60.41 ± 2.30</td>
</tr>
<tr>
<td>M2</td>
<td>96</td>
<td>16</td>
<td>32</td>
<td>33.26 ± 1.30</td>
<td>13.32 ± 0.48</td>
<td>70.82 ± 3.05</td>
</tr>
<tr>
<td>M3</td>
<td>96</td>
<td>24</td>
<td>32</td>
<td>81.51 ± 3.84</td>
<td>20.44 ± 0.97</td>
<td>30.23 ± 1.47</td>
</tr>
<tr>
<td>M4</td>
<td>96</td>
<td>24</td>
<td>32</td>
<td>66.43 ± 2.58</td>
<td>6.96 ± 0.72</td>
<td>53.71 ± 2.64</td>
</tr>
<tr>
<td>M5</td>
<td>96</td>
<td>16</td>
<td>40</td>
<td>75.82 ± 3.65</td>
<td>12.50 ± 0.13</td>
<td>46.97 ± 2.23</td>
</tr>
<tr>
<td>M6</td>
<td>96</td>
<td>24</td>
<td>32</td>
<td>61.75 ± 2.28</td>
<td>9.78 ± 0.13</td>
<td>46.97 ± 2.23</td>
</tr>
<tr>
<td>M7</td>
<td>96</td>
<td>24</td>
<td>40</td>
<td>99.10 ± 4.71</td>
<td>13.24 ± 0.61</td>
<td>31.18 ± 1.56</td>
</tr>
<tr>
<td>M8</td>
<td>96</td>
<td>40</td>
<td>40</td>
<td>86.43 ± 3.92</td>
<td>11.98 ± 0.35</td>
<td>34.87 ± 1.18</td>
</tr>
</tbody>
</table>

\{\(X_1\), Strip forming polymer amount, \(X_2\), Plasticizer amount, \(X_3\), Taste masking agent amount, \(Y_1\), Disintegration time, \(Y_2\), Elongation, \(Y_3\), Drug release after 5 min\}

### Evaluation of the novel taste-masked dapoxetine oral thin films

#### Uniformity of film weight and thickness

Fils were weighed using an analytical balance (Sartorius, Germany). The film’s thickness was measured using a digital Vernier caliper (China). The thickness of the prepared film was measured at five different locations (four corners and center) (Kumar et al. 2014). Data on film weight or thickness were presented as a mean ± standard deviation (SD) of three replicate determinations.

#### Surface pH

The film of each batch was placed in a closed Petri plate containing 5 ml of distilled water at room temperature and the surface pH was measured using a digital pH meter, Jenway (UK) to check whether the film irritates the tongue or mouth. Firstly, the oral film was moistened, then the pH probe was placed near to the wetted film and the surface pH was recorded. The entire process was performed three times to get the mean surface pH (Dinge and Nagarsenker 2008).

#### Drug content and uniformity

Drug content was examined by dissolving the prepared film in 50 ml of phosphate buffer (pH 6.8) then filter it using a 0.45 μm filter in a beaker (ElMeshad and El Hagrasy 2011). The mean content of dapoxetine was determined at 292 nm using (UV–VIS) spectrophotometer. A blank film containing equivalent amounts of excipients was treated similarly as that of the samples and absorbance was recorded at 292 nm. The interference was corrected by subtracting blank absorbance from the sample absorbance. In USP 42, the acceptance value (AV) should be within a range between 85% and 115%, and the relative standard deviation should be less than or equal to 6%. The entire process was performed in triplicate to get mean drug content.

#### In vitro disintegration of films

Disintegration assay was carried out using a visual technique (ElMeshad and El Hagrasy 2011). Each film was put in a glass Petri dish containing 30 ml of phosphate buffer (pH 6.8) at 37 °C to stimulate saliva pH. The disintegration time was reported as the time when the film begins to split or dissolve. The whole process was performed three times and then the mean disintegration time was calculated.

#### Ultimate tensile strength (UTS) and elongation at break (EL%)

The mechanical strength of prepared (OTFs) was tested using a texture analyzer (Universal testing machine, INSTRON 3366- 0 kN) equipped with a 10 kN load cell (Mashru et al. 2005; Shiledar et al. 2014). The film strip (2 x 3 cm) was held in between the two clamps. Both clamps were positioned at 1 cm apart. The film was pulled by the upper clamp at the rate of 5 mm min⁻¹ until it tears, to determine the tensile strength. The software was used to collect data and performance of calculations. The exercise was repeated 3 times and then the mean was calculated. Tensile strength is the maximum stress applied to a point at which the film specimen starts to break. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below (Jutaporn et al. 2011):

\[
\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness} \times \text{Strip width}}
\]

Elongation at break (EL%) is a signal for the film’s ductility and flexibility. When stress is applied to the film, it stretches, and this...
is termed as a strain. The strain is the increase in the length of the film divided by the initial length of the film. It was calculated using a formula (Dixit and Puthli 2009):

\[
\text{Elongation at break (EL\%)} = \frac{\text{Increase in length of strip}}{\text{Initial length of the strip}} \times 100
\]

**In vitro release**

The in vitro dissolution test was carried out in the USP 42 basket apparatus (type I) (Nagaraju et al. 2013). Sink conditions were kept during the dissolution. The medium used was 200 ml of phosphate buffer (6.8 pH) (Nagaraju et al. 2013). The rotation rate was 50 rpm at a temperature of 37 ± 0.5 °C. At predetermined intervals, samples of 5 ml were collected and refilled with an equal volume of the same fresh media. Then, the collected samples were filtered by a 0.45 μm filter. The mean content of dapoxetine was determined at 292 nm using UV spectroscopy. A blank film containing equivalent amounts of excipients was treated similarly to that of the samples and absorbance was recorded at 292 nm. The interference was corrected by subtracting blank absorbance from the sample absorbance. This study was performed in triplicate. The cumulative amount of drug release against time was calculated using a standard calibration curve of dapoxetine in phosphate buffer (pH 6.8). The release mechanism of dapoxetine was determined by fitting the release data to different kinetic models (zero-order, Higuchi, and Korsemeyer–Peppas (Higuchi 1963; Wagner 1969; Korsmeyer et al. 1983; Peppas 1985)) to evaluate the kinetics of drug release from the prepared formulations. The large value of the coefficient of determination (R²) indicated a superiority of the dissolution profile fitting to mathematical equations.

**Physicochemical characterization for the dapoxetine-resinate complex of the optimized formula**

*Flow properties*

It is well known that no distinct examination method designed for powder flow will sufficiently and efficiently describe the large range of powder flowability (Sinha et al. 2005). For that reason, it is advised to examine multiple standardized tests to verify the flowability profile of any powder. In this study, we used three methods to measure the flowability index (FI) of the dapoxetine HCl and the resinate complex of the optimized (OTFs). The angle of repose, Carr’s index, and Hausner ratio tests were exercised in this study (Sinha et al. 2005).

**The angle of repose measurement**

The angle of repose for each powder (dapoxetine and resinate complex) was measured by the fixed height cone technique. A cut-stem glass funnel was placed at 2.5 cm (h) from the horizontal surface. The powder sample was poured smoothly through the funnel until a cone was created and touched the funnel surface orifice. Then, powder flow was stopped and the diameter of the produced cone (d) was determined. The tan of the angle of the cone was calculated by the below equation:

\[
\tan(\theta) = \frac{h}{d}
\]

Where h and d are the height and the diameter of the cone, respectively.

**Hausner ratio (HR) and Carr index (CI)**

The powder (dapoxetine and resinate complex) were flowed smoothly through a glass funnel into a graduated glass cylinder exactly to 10 ml mark. Any excess powder was rubbed by a spatula. Then, the weight of the powder needed for filling the cylinder volume was determined. Afterward, the cylinder was tapped from 2 cm (h) until the moment when there was no further decline in the volume. Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below (Sinha et al. 2005):

\[
HR = \frac{\text{tapped density}}{\text{bulk density}} - 1 \times 100
\]

\[
C_I = \left( \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \right) \times 100
\]

Here, tapped density (\(\rho_t\)) = Mass of powder/Volume of powder after tapping (V), while Bulk density (\(\rho_b\)) = Mass of powder/Volume of powder before tapping (\(V_0\)).

V and \(V_0\) are the volumes of the samples after and before the standard tapping, respectively. The entire process was performed in triplicate.

*Differential scanning calorimetry*

To evaluate the crystalline state of dapoxetine in the optimized (OTFs), differential scanning calorimetry (DSC) thermograms were performed for each of the following samples (dapoxetine HCl, AmberLite™ IRP69, resinate complex and physical mixture of AmberLite™/dapoxetine at a ratio of 1:1) using in a Shimadzu thermal analyzer (Shimadzu DSC 60, TA-60 WS, Japan) (Han et al. 2019). The DSC was calibrated with indium (99.99% purity, melting point 156.6 °C). A sample of 2–3 mg was crimped, and the thermal analysis occurred in a standard aluminum pan at a nitrogen atmosphere with a 10 °C/min heating rate over a temperature range of 0–250 °C. An empty pan sealed in the same conditions was employed as a reference. The distinctive peaks were determined.

*X-ray powder diffraction (XRPD)*

Diffraction X-ray spectra for each of the following samples (dapoxetine HCl, AmberLite™ IRP69, physical mixture of AmberLite™/dapoxetine (ratio of 1:1), and resinate complex) were collected on a Bruker D8 Advance using Cu-Kα radiation at 40 kV and 40 mA power (Han et al. 2019). The diffraction profiles were reported in the 2θ scan range of 5–400 at a rate of 0.2 s per step with a step size of 0.05°.

*Structural analysis by Fourier transform infrared (FTIR)*

The optimized dapoxetine formula (P2) was assessed via FTIR spectroscopy. FTIR spectra of dapoxetine HCl, AmberLite™ IRP69, physical mixture of AmberLite™/dapoxetine (ratio of 1:1), and resinate complex were collected on a Bruker IFS-66; Bruker (USA).

*Scanning electron microscopy*

The morphology of the following samples (optimized dapoxetine (OTFs), blank film, dapoxetine powder, and the prepared complex powder) was examined using a scanning electron microscope (JEOL-JSM 5610LV, Japan). Such specimens were mounted on a metal stub with double-sided adhesive tapes and images were taken at 15 kV at magnification 1000X.

*Stability studies*

The optimized dapoxetine film was packaged in a tightly closed rectangular aluminum sachet (3 x 3 cm). The storage conditions at which formulations were kept should be 40 °C/75% RH.
programmable environmental test chambers for 6 months (Ostwald Scientific Equipment Pvt. Ltd., Mumbai, India) (Prajapati et al. 2018). A stability-indicating HPLC-UV method was then applied to determine the dapoxetine content in the prepared optimized film (Liew and Peh 2014). The mobile phase was composed of acetonitrile and 0.2M ammonium acetate buffer at 50: 50 ratio (pH 6), Column: a Synchronize (Waters Corporation, USA) C-18 column (150 × 4.6 mm ID, 5 μm), run time 10 min and waters 996 PDA Detector. Ten films were weighed and dissolved in a 100 ml volumetric flask with mobile phase then filtered it using a 0.45-μm filter. The sample of 0.1 ml was drawn and diluted with mobile phase to 10 ml in a volumetric flask to give a drug concentration of 30 μg/mL. The sample of 10 μL was injected into the HPLC system. This study was performed in triplicate. The dapoxetine content in the prepared optimized film was calculated using a standard calibration curve. The optimized film was also examined for surface pH, in vitro disintegration time, and physical appearance examination.

**Palatability assessment**

The study was designed to determine either the disintegration time of the optimized dapoxetine taste-masked (OTFs) in the buccal cavity or to evaluate the palatability compliance of the optimized dapoxetine taste-masked (OTFs) in comparison with a placebo film. The assessment was enrolled following the ethical values and responded to the local regulatory requests. The study was approved by the Cairo University Protection of Human Subjects Committee and the protocol complies with the Declaration of Helsinki and Tokyo for humans and followed the ICH GCP guidelines (Directive 75/318/EEC-1996).

The subjects were well known regarding the pertinent details and the objective of this study. The volunteers were informed by consent procedure, dapoxetine properties, side effects, and precautions. A written consent form was completed, understood, and signed by each subject before providing the test materials. Films were randomly administered to six adult healthy male volunteers (age range 29 to 56) with no previous suffering from any buccal cavity or to evaluate the palatability compliance of the optimized film. The objective of this study. The volunteers were informed by the Cairo University Protection of Human Subjects Committee and the protocol complies with the Declaration of Helsinki and Tokyo for humans and followed the ICH GCP guidelines (Directive 75/318/EEC-1996).

The subjects were well known regarding the pertinent details and the objective of this study. The volunteers were informed by consent procedure, dapoxetine properties, side effects, and precautions. A written consent form was completed, understood, and signed by each subject before providing the test materials. Films were randomly administered to six adult healthy male volunteers (age range 29 to 56) with no previous suffering from any buccal disease and they were not taking any other medication. A sample of 0.45-μm filter. The sample of 0.1 ml was drawn and diluted with mobile phase to 10 ml in a volumetric flask to give a drug concentration of 30 μg/mL. The sample of 10 μL was injected into the HPLC system. This study was performed in triplicate. The dapoxetine content in the prepared optimized film was calculated using a standard calibration curve. The optimized film was also examined for surface pH, in vitro disintegration time, and physical appearance examination.

**Results and discussion**

**Preparation of taste-masked dapoxetine oral thin films**

The solvent-casting method has been the core approach in the industry of the synthesis of marketed oral thin films due to the simplicity of the manufacture and the low cost of the system setup (Dixit and Puthli 2009; Hoffmann et al. 2011). Initial screening investigations were focused on the development of novel dapoxetine films with good peel-ability, maintenance of film integrity during peeling, uniform appearance, thin, non-tacky, and adequate flexibility. Therefore, our objective was to find the optimum compatible amounts and concentrations of film-forming polymers, plasticizers, taste-masking agents, and sweeteners while keeping the amount of dapoxetine constant at 30 mg.

The common therapeutic dose of dapoxetine is 30 mg and so is a very good candidate for this type of dosage form; as the maximum limit of drug incorporated in a film is 30% (w/w) to the total weight (Dixit and Puthli 2009). Either the selection of the film-forming polymer or its amount is equally important as it is typically the main constituent in the formulation (50 to 60% of the dry weight) (Leung et al. 2006; ElMeshad and El Hagrasy 2011). Polymers have an important role, not only in presenting the required mechanical characteristic to the oral strip, but also affecting the release of the active ingredient through disintegration into the oral cavity. Pullulan is a water-soluble polysaccharide polymer and they are synthesized from starch by the fungus Aureobasidium pullulans (Garsuch and Breitkreutz 2010). Maltodextrin is a mix of water-soluble poly and oligosaccharides which are formed by partial hydrolysis of starch (McCleary 1986). Pullulan and maltodextrin are widely used in the synthesis of commercial (OTFs) like Snooreze®, Gas-X®, Triaminic®, and Theraflu®. Also, Cilurzo et al. demonstrated that maltodextrins are suitable for manufacturing (OTFs) by both solvent casting and hotmelt extrusion (Cilurzo et al. 2008). Kulkarni et al. studied the properties of pullulan regarding its film-forming capacity, appearance, and disintegration time (Kulkarni et al. 2010). In this study, they were examined as a film-forming polymer. Glycerol was selected as plasticizers as it produced moderately viscous, clear homogeneous solution type preparation compatible with all incorporated ingredients. The oral thin films having 10-15% w/w (16 to 24 mg) of glycerol was found flexible, simplicity in handle with good mechanical strength. Among all sweeteners, (OTFs) made of glycerol and aspartame mixture were found good in taste and palatable as it is non-toxic, having high relative sweetness (Leung et al. 2006).

The binding of ion exchange resins to a drug is a well-known technique that is generally used to mask the bitter taste of many acidic and basic active ingredients (Walsh et al. 2014; Brady et al. 2017). This approach has many features over other known taste-masking techniques. For instance, the binding process of the drug with ion exchange resins is easy and simple. Besides, it doesn’t need any particular apparatus or high temperatures. It can occur at room temperature which is suitable for thermolabile materials. Ion exchange resins don’t cause any local or systemic side effects (Daihom et al. 2016). Ion exchange resins can stabilize many drugs against chemical and physical degradation. They offer also

**Table 3. Palatability measurement attributes.**

<table>
<thead>
<tr>
<th>Comfort</th>
<th>Initial taste</th>
<th>Mouthfeel</th>
<th>Flavor</th>
<th>Aftertaste flavor</th>
<th>Overall acceptability</th>
<th>Rating scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomfortable</td>
<td>Bitter</td>
<td>Very gritty</td>
<td>Unpleasant</td>
<td>Bitter</td>
<td>Not acceptable</td>
<td>1</td>
</tr>
<tr>
<td>Slightly uncomfortable</td>
<td>Slightly bitter</td>
<td>Gritty</td>
<td>Slightly unpleasant</td>
<td>Slightly bitter</td>
<td>Not acceptable</td>
<td>2</td>
</tr>
<tr>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Acceptable</td>
<td>3</td>
</tr>
<tr>
<td>Slightly comfortable</td>
<td>Slightly creamy</td>
<td>Moderate sweet</td>
<td>Slightly pleasant</td>
<td>Good</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Comfortable</td>
<td>Sweet</td>
<td>Creamy</td>
<td>Pleasant Sweet</td>
<td>Pleasant</td>
<td>Best</td>
<td>5</td>
</tr>
</tbody>
</table>
high loading ability for pharmaceutical active materials in comparison with microencapsulation techniques (Daihom et al. 2016). AmberLite™ IRP69 is a carrier for cationic drugs, and it showed the highest binding efficiency among numerous cation exchange resins in previous studies (Daihom et al. 2016). Therefore, in this study, AmberLite™ was selected as a taste masking agent.

To determine the optimum quantity of resin that binds 30 mg of dapoxetine, several binding tests were examined with different amounts of AmberLite™. Figure 1 shows that by increasing the amount of resin, the percent of dapoxetine bound to the resin increases. It was noticed that by using 32 mg of AmberLite™, almost 90% of the dapoxetine amount was bounded without interrupting the synthesis of the oral film. However, increasing the amount of resin beyond 40 mg exhibited struggle and difficulty in the synthesis of OTFs. Accordingly, the range of 32 to 40 mg of AmberLite™ was selected in this study.

To find the time required to reach binding equilibrium, an additional binding exercise was performed. Different samples were taken at different time intervals then the percentages of dapoxetine bound were calculated and plotted against time (Figure 1). The maximum binding was marked by the beginning of a plateau at 180 min which indicated that it takes about 180 min to reach binding equilibrium under the mentioned conditions. Binding efficiency for the dapoxetine–Amberlite complex was 93.7625%. The high binding efficiency value is a good indicator of the high capability of the dapoxetine–Amberlite complex to bind successfully.

Lastly, visual inspection of the appearance of the novel taste-masked dapoxetine (OTFs) preparations exhibited uniform appearance, thin, non-sticky, and virtuous flexibility. This reflects that optimum compatible amounts and concentrations of film components were accomplished.
Table 4. Film weight, thickness, surface pH and drug content of dapoxetine oral thin films ‘values are Mean ± S.D of 3 replicates’.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Surface pH</th>
<th>Drug content (%)</th>
<th>Tensile strength (N/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pullulan OTFs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>151.16 ± 6.23</td>
<td>0.55 ± 0.02</td>
<td>6.51 ± 0.45</td>
<td>96.71 ± 3.30</td>
<td>9.55 ± 0.28</td>
</tr>
<tr>
<td>P2</td>
<td>157.08 ± 5.61</td>
<td>0.42 ± 0.01</td>
<td>6.75 ± 0.72</td>
<td>97.16 ± 2.71</td>
<td>10.42 ± 0.46</td>
</tr>
<tr>
<td>P3</td>
<td>160.76 ± 5.42</td>
<td>0.63 ± 0.03</td>
<td>6.66 ± 0.61</td>
<td>98.24 ± 2.25</td>
<td>8.21 ± 0.31</td>
</tr>
<tr>
<td>P4</td>
<td>164.34 ± 6.63</td>
<td>0.49 ± 0.01</td>
<td>6.83 ± 0.58</td>
<td>99.36 ± 1.16</td>
<td>9.29 ± 0.39</td>
</tr>
<tr>
<td>P5</td>
<td>165.81 ± 4.18</td>
<td>0.57 ± 0.02</td>
<td>6.42 ± 0.19</td>
<td>100.11 ± 3.48</td>
<td>11.57 ± 0.52</td>
</tr>
<tr>
<td>P6</td>
<td>171.05 ± 7.53</td>
<td>0.45 ± 0.01</td>
<td>6.64 ± 0.39</td>
<td>100.35 ± 4.53</td>
<td>12.45 ± 0.47</td>
</tr>
<tr>
<td>P7</td>
<td>175.63 ± 2.81</td>
<td>0.64 ± 0.03</td>
<td>6.71 ± 0.82</td>
<td>102.18 ± 2.81</td>
<td>10.64 ± 0.34</td>
</tr>
<tr>
<td>P8</td>
<td>179.14 ± 4.29</td>
<td>0.51 ± 0.02</td>
<td>6.79 ± 0.67</td>
<td>102.92 ± 4.16</td>
<td>11.51 ± 0.20</td>
</tr>
<tr>
<td><strong>Maltodextrin OTF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>153.09 ± 6.74</td>
<td>0.62 ± 0.02</td>
<td>6.83 ± 0.63</td>
<td>97.49 ± 1.74</td>
<td>21.26 ± 1.03</td>
</tr>
<tr>
<td>M2</td>
<td>157.66 ± 7.85</td>
<td>0.48 ± 0.01</td>
<td>6.96 ± 0.52</td>
<td>101.06 ± 3.55</td>
<td>23.84 ± 0.75</td>
</tr>
<tr>
<td>M3</td>
<td>162.22 ± 8.32</td>
<td>0.72 ± 0.03</td>
<td>6.54 ± 0.29</td>
<td>98.23 ± 4.32</td>
<td>20.27 ± 0.91</td>
</tr>
<tr>
<td>M4</td>
<td>164.84 ± 3.19</td>
<td>0.56 ± 0.01</td>
<td>7.01 ± 0.46</td>
<td>100.91 ± 3.27</td>
<td>21.65 ± 0.78</td>
</tr>
<tr>
<td>M5</td>
<td>166.58 ± 4.96</td>
<td>0.66 ± 0.03</td>
<td>6.66 ± 0.42</td>
<td>96.96 ± 4.94</td>
<td>26.60 ± 1.26</td>
</tr>
<tr>
<td>M6</td>
<td>171.95 ± 8.51</td>
<td>0.33 ± 0.02</td>
<td>6.75 ± 0.38</td>
<td>98.95 ± 3.41</td>
<td>28.53 ± 1.05</td>
</tr>
<tr>
<td>M7</td>
<td>176.27 ± 2.77</td>
<td>0.74 ± 0.03</td>
<td>6.83 ± 0.29</td>
<td>102.77 ± 2.17</td>
<td>24.47 ± 1.19</td>
</tr>
<tr>
<td>M8</td>
<td>179.93 ± 5.3</td>
<td>0.58 ± 0.02</td>
<td>6.91 ± 0.50</td>
<td>103.13 ± 5.23</td>
<td>26.82 ± 1.12</td>
</tr>
</tbody>
</table>

**Evaluation of the novel taste-masked dapoxetine oral thin films**

**Uniformity of film weight and thickness**

The mean weight of (OTFs) batches was found in the range of 0.151–0.179 g, while the mean thickness values of all batches were found in the range of 0.42–0.74 mm (Table 4). Within the respective batch of the prepared (OTFs), the casting and the weight variation were uniform.

**Surface pH**

The surface pH of prepared oral thin films was found in the range of 6.42–7.01 as shown in Table 4, almost neutral pH. This indicates that the prepared novel films will not irritate the tongue or the mucosal of the oral cavity.

**Drug content and uniformity**

Table 4 shows also the results of dapoxetine loading content in the prepared novel (OTFs) formulations. The content values of (OTFs) were within the accepted ranges that we mentioned earlier, and these results ensured the uniformity of dapoxetine loading content.

**Analysis of the statistical design**

Design of experiment is a helpful tool used to reduce the number of exercises needed to improve the formulations and help researchers to prospect the relations between studied factors and responses of interest. The fitted models are presented below as regression equations generated by the software. Only statistically significant (p < 0.05) coefficients are included in the equations. A negative sign of the coefficient means it has an antagonistic effect while a positive sign of the coefficient means it has an agonistic effect. The coefficients’ value of independent variables X₁–X₃ is related to the effect of these variables on the responses. The higher coefficient value means the independent variable has a more effective influence on the response. Coefficients representing more than one-factor term show the interaction terms. The constructed three-dimensional ‘3d’ surface plots are shown in Figure 2(a–i). Graphically, in the experimental design, lack of interactions was obtained, and this indicated that the experimental design had maximum efficiency in estimating the main effects.

**In vitro disintegration of films**

The volume of saliva is less than 6 ml in the human buccal cavity and so the traditional disintegration evaluations that use 900 ml of the media will not reflect the actual in vivo disintegration rate (Shukla et al. 2009). So, in this study, a Petri dish with a 6.5 cm diameter was utilized to assess the in vivo disintegration rate. It’s comparable to that of the sublingual area with a diameter of approximately 3–4 cm (Shukla et al. 2009). Moreover, the volume of the medium and the comparatively low stirring applied during the study look-alike the saliva volume and the motionless environment in the buccal cavity, respectively.

This study represents an indication of the onset of action of dapoxetine desired for (OTFs) formulations. Figure 3(a–d) illustrates the in vitro disintegration study of dapoxetine (OTFs) in phosphate buffer (pH 6.8) at a specific time interval. The meantime for completing the disintegration was obtained ranges from 9 to 99 s (Table 2). According to previous investigation (Lee et al. 2019), films showed dissolution of 45% only in 5 min. This means that the novel dapoxetine (OTFs) established acceptable unique disintegration time ranges (Hoffmann et al. 2011).

It’s been seen that pullulan (OTFs) had lower disintegration time than maltodextrin films. Also, as the amount of glycerol or Amberlite™ increased, the disintegration time of the film was increased, while as the amount of pullulan/maltodextrin increased, the disintegration time of the film was decreased (Table 2). This could be attributed to the higher portion of pullulan/maltodextrin in the latter that facilitates water penetration into the film structure due to its high water solubility (ElMeshad and El Hagrasy 2019). So, in this study, a Petri dish with a 6.5 cm diameter was utilized to assess the in vitro disintegration rate of dapoxetine (OTFs).
Figure 2. Images of three-dimensional ‘3D’ surface plots of $Y_1$, $Y_2$ and $Y_3$ responses of the prepared dapoxetine oral thin films. (TMA) taste masking agent.

Figure 3. In vitro disintegration study of the prepared dapoxetine oral thin films in phosphate buffer (pH 6.8).
It indicates that $X_2$ (amount of plasticizer) and $X_3$ (amount of taste-masking agent) have a positive influence on disintegration time; while $X_1$ (polymer amount) has a negative effect. This means an increase in the amount of $X_1$ can lead to a decrease in the disintegration time of (OTFs) while the increase of $X_2$ and $X_3$ amounts makes the disintegration time of (OTFs) longer. The combined influence of $X_1$, $X_2$, and $X_3$ can be further interpreted using 3D plots (Figure 2(a–c)). The influence of $X_2$ on response was found to be more significant than that of $X_1$ and $X_3$.

Ultimate tensile strength (UTS) and elongation at break (EL%)

Not only rapid disintegration is important in developing dapoxetine (OTFs), but also their mechanical properties. Our target was to formulate (OTFs) that maintain good flexibility and ductility. Therefore, the prepared films should have the optimal polymeric mixture to give acceptable tensile strength and elongation to tolerate the handling. Nevertheless, it must possess a certain flexibility to guarantee patient compliance. The results of EL and UTS testing were displayed in Tables 2 and 4, respectively. The obtained EL and UTS values for the investigated films ranged from 9.78 to 52.66% and from 9.29 to 28.53 N/mm² respectively. This means that the novel dapoxetine (OTFs) demonstrated adequate flexibility and ductility, especially when it compared with previous investigations (Aldawsari and Badr-Eldin 2020).

It is clear to see that pullulan (OTFs) showed higher flexibility than maltodextrin films. Moreover, as the amount of pullulan/maltodextrin or AmberLite™ increased, the ductility of films was decreased, while as the amount of glycerol increased, the ductility of (OTFs) was increased. Generally, the flexibility of OTFs depends on the type of polymer and plasticizer used. Pullulan has a unique structure that is responsible for pullulan’s high flexibility and solubility in water (Trinetta and Cutter 2016). Pullulan is used extensively in the formulation of marketed oral films; as a reason for its high flexibility results (Prajapati et al. 2018) and this was clearly seen in our study when it was compared with maltodextrin. Also, it’s well-known that plasticizers (like glycerol) work by introducing themselves between the polymer strands, thereby disconnecting the polymer-polymer interactions and increasing the molecular movement of the polymer strands (Entwistle and Rowe 1979). Thus, it is to be expected that as the concentration of the plasticizer increases, the degree of film stiffness decreases, whereas the film flexibility increases. Consequently, either the amount of film-forming polymer/AmberLite™ decreases or the amount of plasticizer increases, the overall concentration of the plasticizer in the formulation matrix increases, and hence the ductility and flexibility of the prepared (OTFs) will be increased.

A linear model was suggested by software for response $Y_2$ (degree of elongation) and found significant ($p < 0.05$). ANOVA analysis showed that the independent variables have a significant effect on the response ($p < 0.05$). The model of response $Y_2$ is obtained as:

$$Y_2 = 25.86 - 1.71 X_1 + 2.53 X_2 - 3.92 X_3 - 0.25 (X_1X_2) + 0.38 (X_1X_3) - 1.43 (X_2X_3) + 0.47 (X_1X_2X_3)$$

$$[F\text{– value} = 31.11, \ p = 0.001 \text{ and } R^2 = 0.972]$$

Statistical analysis revealed that $X_1$ (polymer amount) and $X_3$ (amount of taste-masking agent) showed a negative effect on the elongation, while $X_2$ (amount of plasticizer) has a positive impact. It means that an increase in the amount of $X_1$ or $X_3$ can lead to a decrease in the elongation values of (OTFs) while the increase of $X_2$ amounts elevates the elongation values. The combined influence of $X_1$, $X_2$, and $X_3$ can be further interpreted using 3D plots (Figure 2(d–f)). The influence of $X_3$ on response was found to be more significant than that of $X_1$ and $X_2$.

In vitro release

Rapid release of dapoxetine is necessary to match its effect for the treatment of premature ejaculation. Thus, dapoxetine release (%) in 5 min at pH 6.8 of saliva is the main parameter and it was employed as the criterion for comparing the release results of different films, hence it was selected as a response of design (ElMeshad and El Hagrasy 2011; Prajapati et al. 2018). The results of the release profile of dapoxetine from the different prepared taste-masked oral thin films are shown in Figure 4 and depicted in Table 2. These results indicate that the prepared novel dapoxetine taste-masked oral thin films significantly provided a high rate of dapoxetine release. The results for the prepared dapoxetine oral thin films showed that the drug release was not less than 80% within 4-25 min meeting the standard dissolution criteria of

![Figure 4. Release profiles of the prepared dapoxetine oral thin films in phosphate buffer, pH 6.8.](image-url)
fast disintegrating preparations (Anand et al. 2011; Mushtaq et al. 2020).

It is worth mentioning that many factors contributed to the rate and release characteristics from resinate complexes (Daihom et al. 2016). The degree of cross-linking of the resin is one of the factors which affect the drug release which accordingly impacts the porosity of the resin and its swelling properties. This may aid or prevent the diffusion of both the drug and the ions in and out of the resin. The lower the crosslinking degree of resin-like AmberLiteTM, the wider the pore size in the resin structure and the more swelling behavior of the resin upon hydration. Also, the small particle size of AmberLiteTM can be considered as one of the causes. The particle size of the resin beads affects the rate of the ion exchange within the resin. The smaller the diameter of the beads, the shorter the diffusion path, and hence the faster the rate of ion exchange. Also, the properties of the drug such as its selectivity to the resin and its hydrophobicity have a great effect on its rate and extent of the release. Hydrophobic drugs usually desire to form hydrophobic connections with the aromatic rings of the resin leading to a slow rate of release (Daihom et al. 2016). In our study, the low cross-linking and small particle size of AmberLiteTM, in addition to the high hydrophilicity of the drug (dapoxetine HCl), might be the reasons for the rapid release of dapoxetine from the prepared taste-masked (OTFs).

It is clear to find that pullulan films showed a higher release rate than maltodextrin films. Furthermore, a higher amount of Pullulan/maltodextrin exhibited a faster dapoxetine release rate. On the other hand, the high amounts of plasticizer or taste-masking agents decreased the dapoxetine release rate among all (OTFs) formulae. It might due to the high-water solubility manner of pullulan/maltodextrin. In contrast, the higher amount of plasticizer or taste-masking agent impeded the penetration of dissolution

Figure 5. DSC patterns of dapoxetine, AmberLITE™ and resinate complex.
medium penetration which could be attributed to the higher binding capacity at higher amounts of taste-masking agent or plasticizer. The release kinetics study showed that formulations followed the Korsmeyer-Peppas model indicating drug release from modified release dosage form (fast disintegrating dosage forms) (Mushtaq et al. 2020). The ($R^2$) coefficient values obtained from the Korsmeyer-Peppas model were higher as compared to other models for all formulations.

A linear model was suggested by software for response $Y_3$ (degree of in vitro dapoxetine release after 5 min QS of dapoxetine (OTFs)) and found significant ($p < 0.05$). ANOVA analysis showed that the independent variables have a significant effect.

Figure 6. The X-ray powder diffraction profiles of dapoxetine, Amberlite$^\text{TM}$ and resinate complex.
The response was found to be more significant than that of $X_1$ and $X_3$.

Figure 7. FTIR spectra of dapoxetine, AmberLite™ and resinate complex.

The model of response $Y_3$ is obtained as:

$$Y_3 = 54.14 + 5.43X_1 - 8.92X_2 - 8.13X_3 + 1.01(X_1X_2) - 2.03(X_1X_3) + 5.25(X_2X_3) - 0.89(X_1X_2X_3)$$

$[F-value = 12.82, p = 0.0015 and R^2 = 0.978]$

It indicates that $X_2$ (amount of plasticizer) and $X_3$ (amount of taste-masking agent) have a negative influence on degree of in vitro dapoxetine release, while $X_1$ (polymer amount) has a positive effect. Means an increase in the amount of $X_1$ can lead to an increase in the degree of in vitro dapoxetine release of (OTFs) while the increase of $X_2$ and $X_3$ amounts makes the release slower. The combined influence of $X_1$, $X_2$, and $X_3$ can be further interpreted using 3D plots (Figure 2(g-i)). The influence of $X_2$ on response was found to be more significant than that of $X_1$ and $X_3$.

**Optimization of factorial design**

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the novel (OTFs) that were prepared in this study. Dapoxetine oral thin film formulation was optimized for the responses $Y_1$, $Y_2$, and $Y_3$. The optimum values of these responses were to minimize disintegration time $\leq 30$ s, maximize elongation, besides, to maximize the percentage drug released after 5 min. The optimum values of the variables were obtained by graphical and numerical analysis using the Design-Expert™ software and based on the criterion of desirability. Based on the statistical analysis, it can be concluded that the optimum formulation was this prepared using 96 mg of pullulan as a strip forming polymer, 16 mg of glycerol as a plasticizer, and 32 mg of AmberLite™ as a taste masking agent, with composite desirability of 0.6915. Several evaluations for the optimized film formula (P2) were executed and they will be exhibited in the below sections including physicochemical evaluation for its complex resinate, differential scanning calorimetry, scanning electron microscopy, stability studies, and in vivo assessment.

**Physicochemical characterization of complex resinate for the optimized formula (P2)**

*Flow properties*

To enhance manufacturability, most of the drug powders must have a good flow property. This will guarantee the fast and full transfer of powders from their containers into the manufacturing tools and vice versa. To determine if the dapoxetine–Amberlite resinate powder has good flow property, it was needed to assess the flow property. The angle of repose, Carr index, and Hausner ratio were determined to predict flowability. The angle of repose is a parameter commonly used for the evaluation of interparticle force. Once the angle of repose is lower than 25 degrees, the flow is considered to be excellent; while, if the angle of repose is higher than 40 degrees, the flow is said to be poor (Lachman et al. 1986). A Hausner ratio refers to greater cohesion between particles while a high Carr index is a reference of the tendency to form bridges. A Hausner ratio higher than 1.25 reflects a poor flowability. A Carr index greater than 25 reflects a poor flowability, and below 15, of good flowability (Lachman et al. 1986).

Dapoxetine HCl powder has an average angle of repose of 34 degrees, Hausner ratio of 1.24, and Carr index of 23.93. On the other hand, dapoxetine-resin complex showed improvement in the flow properties; as the angle of repose, Hausner ratio, and the Carr index were reduced to 27, 1.18, and 19.62, respectively. Statistically significant differences (ANOVA, $p < 0.05$) were found between the angle of repose and CI values of dapoxetine powder and dapoxetine-resin complex. Thus, one of the most important micrometric properties of dapoxetine was improved by binding to AmberLite™. This will have a considerable influence on the ease of handling and operating during different large-scale manufacturing stages.

*Differential scanning calorimetry*

We studied the thermal stability for dapoxetine, AmberLite™ IRP69, and resinate complex in DSC (Figure 5). The DSC thermogram for dapoxetine shows a sharp endothermic peak at nearly 183°C. This peak accounts for the dapoxetine transition from a solid into a liquid (melting). The thermogram for AmberLite™ showed a small endothermic peak at nearly 93°C which most likely is the glass transition temperature of the AmberLite™. The DSC thermogram of the mixture exhibited the existence of a characteristic peak of pure dapoxetine, although with a lower intensity (due to dilution) indicating that the drug kept its crystallinity. On the other hand, the thermogram for the resinate complex showed an endothermic degradation peak at nearly 104°C and the absence of the endothermic melting peak of dapoxetine. This suggests the absence of the crystallinity of dapoxetine inside the
resinate complex, i.e., the complexation process with the resin prevented the crystallization of the drug and turns into an amorphous state. This suggests that the binding between dapoxetine and AmberLite™ in the resinate complex is stable.

**X-ray powder diffraction (XRPD)**

To further examine the physical form of the drug for the optimized (P2) formula, powder X-ray diffraction was performed on dapoxetine HCl, AmberLite™ IRP69, and resinate complex. The profiles of X-ray diffraction are shown in Figure 6. Dapoxetine showed large intense peaks at 14.972, 25.177, 22.613, 18.764, 20.548, 17.681, 26.556, 29.402, 23.689, 28.917, 14.278, and 27.669 (2θ). This data suggested a crystalline state for dapoxetine and explained the sharp melting endothermic peak in the DSC at 183°C. The XRPD pattern of the mixture exhibited the existence of a characteristic peak of pure dapoxetine indicating that the drug kept its crystallinity. On the other hand, the XRPD pattern for the AmberLite™ had no intense peaks which ensured the amorphous nature of the resin. The lack of any intense peaks in the dapoxetine–Amberlite resinate complex spectrum suggested the absence of any crystalline structure of the dapoxetine inside the dapoxetine–resin complex. This suggests that the dapoxetine–AmberLite interaction prevented the drug from crystallization during the complexation process. These results are in good agreement with the DSC results and explain again the faster dissolution of the optimized (P2) formula, where the loss in drug crystallinity resulted in a significant increase in drug solubility and dissolution rate.

**Structural analysis by Fourier transform infrared (FTIR)**

FTIR studies were performed to detect the possible molecular interaction between dapoxetine and AmberLite™. The FTIR spectrum of dapoxetine HCl, AmberLite™ IRP69, resinate complex and physical mixture of AmberLite™/dapoxetine (ratio of 1:1) are shown in Figure 7. FTIR shows the characteristic dapoxetine peaks representing stretching of the C-H aromatic peak (3049 cm⁻¹), C-N (1268 cm⁻¹), C-H (2931 cm⁻¹), and C-O (1098 cm⁻¹) functional groups, respectively. In the resin’s spectrum, broad peaks at 2920 and 1705 cm⁻¹ represent carboxylic acid functional groups: O-H stretching and C=O (H-bonded) stretching, respectively. These peaks were present in the physical mixture but was absent or weak in the complex. Such absence of peaks in the complex corroborates the interpretation of the DSC results in which the complexes are different from the physical mixtures of the pure components (Figure 5). Furthermore, it provides evidence that interaction took place between the drug and the resin.

**Scanning electron microscopy**

The scanning electron micrographs of optimized dapoxetine (P2) formula, blank film, dapoxetine powder, and the prepared complex powder are shown in Figure 8, the dapoxetine powders were rod-shaped smooth-surfaced crystals, while the shape of the prepared complex demonstrated irregular block particles. Moreover, it was difficult to find the drug crystals in the optimized film, while crystals of the prepared complex were presented. Also, it is clear to see that the films are porous, and this explains more the faster dissolution of the optimized dapoxetine film. This means that our goal to form a novel resinate complex between dapoxetine and AmberLite™ and to be incorporated in an oral thin film was successfully achieved.

**Stability studies**

The objective of this analysis was to assess the stability of the optimized (P2) formula including its resinate complex. The Chromatogram of 30 µg/mL dapoxetine HCl solution versus the chromatogram of dapoxetine of the optimized P2 oral thin film
over a time of 6 months in a tightly closed aluminum sachet at 40°C/75% RH programmable environmental test chambers is shown in Figure 9. The drug content is quite constant in all the storage condition tested, moreover HPLC analysis confirms the absence of new peaks of possible degradation products. The result of assay content of dapoxetine from the stored optimized (P2) film showed 97.52% (Table 5). The stability studies showed also that there is no significant difference ($p < 0.05$) in required parameters such as in vitro disintegration time, surface pH, and physical appearance. We can conclude from this data that the optimized (P2) formula including its resinate complex was physically and chemically stable over 6 months.

**Table 5.** Evaluation of stability parameters over a period of six months ‘values are Mean ± S.D of 3 replicates’.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>After storage (40°C/75%RH)</th>
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<tbody>
<tr>
<td>Drug content (%)</td>
<td>97.52 ± 1.765</td>
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<tr>
<td>Disintegration time (s)</td>
<td>9.87 ± 0.82</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.68 ± 0.29</td>
</tr>
</tbody>
</table>

**Palatability assessment**

In vivo disintegration study of the optimized dapoxetine (P2) formula was very fast. It took 11.83 s for the complete disintegration of the films in the oral cavity as reported by the volunteers. This

![Figure 9](image_url). The Chromatogram of 30 μg/mL dapoxetine solution (a) and the chromatogram of dapoxetine of the optimized P2 oral thin film over a time of 6 months in a tightly closed aluminum sachet at 40°C/75% RH programmable environmental test chambers (b).
study correlates well with the in vitro disintegration study of optimized (P2) formula. Figure 10 shows the photographic images of the in vivo disintegration study of optimized dapoxetine (P2) formula on a tongue of the human volunteer with time ‘seconds’. The palatability of the optimized formulation (P2) was evaluated by measuring the initial taste, comfort, mouthfeel, flavor, after-taste, and overall acceptability with six healthy adult male volunteers. There was a ranking scale of 1–5, 1 was stood for the bitter taste and 5 referred to the pleasant palatable taste, and the higher PI referred to the better patients’ compliance.

In our study, the taste of dapoxetine was successfully masked, and the optimized film was found overall good acceptance. PI of optimized dapoxetine (P2) formula was 4.17 while the placebo film was 4.66. The optimized dapoxetine (P2) formula showed easy to handle, slightly comfortable initial taste, slightly creamy mouthfeel, following moderate sweet mouthfeel, and slight pleasant after taste. Also, the volunteers expressed a high degree of satisfaction concerning the ease of administration and sensation thereafter, where optimized P2 film disintegrated without water and there is no film residue existed in the mouth after film dissolution. These palatability results considered a great model when compared to previous papers intended for masking active ingredients (ElMeshad and El Hagrasy 2011; Prajapati et al. 2018; Han et al. 2019). This is most probably accredited to the rapid hydration of the film due to its thin and porous nature. Additionally, during the preparation of optimized dapoxetine-resin based (OTFs), the taste-masking property was improved due to the addition of glycerol, aspartame, and flavor in the formulation.

Conclusions

This study confirmed that a pre-formed resinate complex of dapoxetine and Amberlite™ can successfully mask the bitter taste of dapoxetine and improve the patient’s compliance. Dapoxetine resinate complex has shown good flow properties, good thermal properties, and chemical stability compliance and has the potential for further development as a taste-masked oral thin film. Accordingly, a novel optimized oral thin dapoxetine film was successfully prepared with a desirable disintegration profile, elongation, disintegration time, and stability. The novel optimized dapoxetine (OTFs) presented multiple competitive advantages over its marketed oral dosage forms such as ease of swallowing without water, accepted palatability, and easy to formulate. Hence, it can be concluded that optimized dapoxetine oral thin film was successfully formulated at the lab-scale and it can be commercially processed easily.

Disclosure statement

The authors report no declarations of interest.

References


