FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL MELT-IN-MOUTH OF LORAZEPAM FOR SUBLINGUAL USE

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ABSTRACT
The present study is an attempt to formulate and develop fast dissolving oral melt-in-mouth of Lorazepam by solvent casting method using pectin as a polymer for sublingual use. Solvent casting method was used for formulation of films where the required percentage of polymer solution was prepared by dispersing the polymer powder in distilled water with other excipients like plasticizer, sweetener, solvent etc separately with continuous stirring and then this solution was poured in the mould. The films prepared using pectin were evaluated for thickness, swelling index, tensile strength, % elongation, folding endurance, disintegration time and % drug release. Out of these films, C5 batch showed optimum performance against all other prepared formulations and was subjected to weight variation, thickness, tensile strength, % elongation, swelling index, folding endurance, surface pH, drug content, disintegration time, in-vitro dissolution % drug release, ex-vivo diffusion for % drug permeated and stability studies. Thus, fast dissolving film using water soluble polymer like pectin can be prepared using solvent casting method for a poorly water soluble drug such as Lorazepam.

KEYWORDS: Fast dissolving oral melt-in-mouth, sublingual use, disintegration time.

INTRODUCTION
The Fast Dissolving Drug Delivery Systems was a headway that started to be in the early 1970's and combats over the utilization of the tablets, syrups, Capsules which are the other oral drug delivery system.[1] Fast Dissolving Drug Delivery Systems serves as a real benefit
over the conventional dosage forms since the drugs gets quickly disintegrated & dissolves in
the salivation without the utilization of water. These systems offer superior clinical profiles
with potential oro-mucosal absorption thus increasing the drug bioavailability with respect to
oral administration. Fast dissolving tablets are the solid dosage form which disintegrates
rapidly in the oral cavity without the need of water. Some problems are associated with the
OFDF like they are sometime difficult to carry, to store and handle (friability and fragility)
and these are prepared using the expensive lyophilisation method. To overcome these
problems oral films were developed, which are very popular now a days. Orally fast-
dissolving film is new drug delivery system for the oral delivery of the drugs. It was
developed on the basis of technology of the transdermal patch. The delivery system consists
of a very thin oral strip, which is simply placed on the patient’s tongue or any oral mucosal
tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of
application. The use of natural polymers as pharmaceutical excipients has received a
renewed research interest due to the advantages of natural polymers such as low cost,
biocompatibility, biodegradability, non-toxicity, local availability, environment-friendly
processing, better patient tolerance and acceptance. Natural polysaccharides of plant origin
are among the most widely used excipients in the formulation of different dosage forms.
There are many natural polymers such as gaur gum, pectin, xanthan gum, tragacanth etc. are
used for the fabrications of fast dissolving films. A number of plant based polysaccharides,
such as starch, agar, acacia, alginate, celluloses, mucilage are used in pharmaceutical
formulations as diluents, binders, adhesive, disintegrating agents, gelling agents and drug
release sustaining agents. Lorazepam which is a BCS Class II drug having low solubility
and high permeability is selected as the drug taking into consideration the above given
parameters as the drug is having metallic taste with a maximum dose up to 10 mg/day in case
of anxiety, with molecular weight of 321.1581g/mol, and good permeability for oral mucosal
tissue. Also lorazepam is not available in such dosage form in India. In general Epileptic
patients have to strictly adhere to the dosage schedule and any non-compliance of dosage
administration may lead to sub-therapeutic levels of drug in the systemic circulation, and
hence recurrence of seizures. Since a fast dissolving film of the drug rapidly disintegrates in
the mouth without need of water, such a dosage form will definitely enhance the patient
compliance, especially, during travelling or in situations where water is not easily available.
Hence, there is an obvious need for the development of fast dissolving film to overcome
patient non-compliance.
MATERIALS AND METHODS

Materials

Lorazepam was received as gift samples from Centaur pharmaceuticals Ltd., Mumbai, India. Pectin was obtained from Loba Chemicals, Mumbai. Sodium starch glycolate, Microcrystalline Cellulose and Cross Carmellose was obtained from Loba Chemicals, Mumbai. Mannitol, Citric acid, Amaranth red, Ethanol, Acetone, Propylene glycol and Glycerine were procured from Loba Chemicals, Mumbai.

METHODS

1. Drug and Polymer Compatibility Studies

Drug polymer compatibility studies were carried out using Differential Scanning Calorimetry (DSC).

2. Formulation of Sublingual Fast Dissolving Oral Strips

Solvent casting method was used for formulation of films. The required percentage of polymer solution was prepared by dispersing the polymer powder in distilled water with continuous stirring using magnetic stirrer (2 MLH, Remi Equipments, Mumbai). After continuous stirring the solution was left undisturbed for three to four hours to remove all the air bubbles. Accurately weighed quantity of drug, plasticizer and all other excipients was separately dissolved in distilled water in another beaker. After complete hydration of the polymer with water, drug-plasticizer and all other excipient solutions were added and mixed thoroughly, and the volume was made up ten millilitres with distilled water. The polymeric solutions were then poured on the mold, allowed to dry and stored in aluminium foil.

Table 1: Formulation of Fast Dissolving Oral Strips containing Pectin

<table>
<thead>
<tr>
<th>Code</th>
<th>LZM (mg)</th>
<th>Pectin (mg)</th>
<th>CC (mg) *</th>
<th>Mannitol (mg)</th>
<th>Citric Acid (mg)</th>
<th>PG (ml) **</th>
<th>Color</th>
<th>Flavour (mg)</th>
<th>Methyl Paraben (mg)</th>
<th>Water (ml)</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>2</td>
<td>200</td>
<td>-</td>
<td>80</td>
<td>25</td>
<td>0.5</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>C2</td>
<td>2</td>
<td>300</td>
<td>-</td>
<td>80</td>
<td>25</td>
<td>0.75</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>C3</td>
<td>2</td>
<td>400</td>
<td>-</td>
<td>80</td>
<td>25</td>
<td>1</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>C4</td>
<td>2</td>
<td>200</td>
<td>8</td>
<td>80</td>
<td>25</td>
<td>0.5</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>C5</td>
<td>2</td>
<td>300</td>
<td>12</td>
<td>80</td>
<td>25</td>
<td>0.75</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>C6</td>
<td>2</td>
<td>400</td>
<td>16</td>
<td>80</td>
<td>25</td>
<td>1</td>
<td>q.s</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

* - Quantities are mentioned as %w/w of polymer, **- Quantities are mentioned as %w/v of solvent, LZM- Lorazepam, CC- cross Carmellose, PG- Propylene Glycol
3. Evaluation of Sublingual Fast Dissolving Oral Strips

a. Weight variation\(^{[7]}\)
For weight variation three films of every formulation were taken weighed individually on a digital balance (Wensar, PGB200 Mumbai).

b. Film thickness\(^{[7]}\)
The thickness of each film was measured using a digital vernier calliper (Mitutoyo, Japan) at different positions of the film.

c. Surface pH \(^{[7]}\)
Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and means ± S.D calculated.

d. Swelling Index \(^{[8, 9]}\)
For studying swelling properties, a drug loaded film of 4cm\(^2\) was weighed on previously weighed cover slip. It was kept in a petridish and 50 ml of pH 6.8 salivary fluid was added. After every 30 sec, the coverslip was removed and film was weighed for 5 min. The difference in weight is because of absorption of water and swelling of film. The % film was calculated using following equation.

\[
\text{Swelling index} = \frac{X_0 - Xt}{X_0} \times 100
\]

Where, \(X_0\) = initial weight of film, \(Xt\) = final weight of film
e. Percent Elongation\textsuperscript{[8, 9]}

The prepared film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The elongation was determined by noting the distance travelled by pointer before break of film on the graph paper. The percent elongation was calculated by using formula (mm\(^2\)) as given below;

\[
\text{Percent elongation} = \frac{L_1 \times 100}{L_0}
\]

Where, \(L_1\) = increase in the length, \(L_0\) = Initial length

f. Tensile Strength\textsuperscript{[8, 9]}

Film strip of dimension 2 X 2 cm\(^2\) and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke.

\[
\text{Tensile strength (kg/mm}^2\text{)} = \frac{\text{force at break}}{\text{Initial cross sectional area of the film (mm}^2\text{)}}
\]

g. Folding Endurance\textsuperscript{[8, 9]}

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

h. Disintegration Test\textsuperscript{[9]}

The disintegration time is the time when a film breaks or disintegrates. The film (2*2 cm) was placed in glass petridish containing 10ml simulated salivary fluid. Give slight agitation at every 10 second. The time required for breaking of film was note as in vitro disintegration time.

i. Drug Content\textsuperscript{[10, 11]}

The percent drug content of Lorazepam in fast dissolving films was estimated by dissolving film of 2x2cm and put in a volumetric flask containing 100 ml of simulated salivary fluid at pH 6.8. The samples were sonicated using ultrasonicator (Remi Equipments, Mumbai) for 15
min and the sample were filtered through Whatman filter paper (No. 41) analyzed using UV spectrophotometer (1601, Shimadzu Corporation, Japan) and absorbances were taken.

j. **In-vitro Dissolution Test**[^12]

The in vitro dissolution test was performed using the USP II paddle type apparatus. The dissolution studies carried out at 37±0.50°C; with stirring speed 50 rpm in 250ml simulated salivary fluid. The film size required for dose delivery was (2 x 2 cm). 5 ml aliquots of dissolution media collected at specific time interval of 30, 60, 90, 120, 150, 180, 210, 240, upto 4 min and equal volume of fresh dissolution medium was added. After each withdrawal sample was filtered through Whatman filter paper (No. 41) and analyzed for drug content using a UV spectrophotometer for cumulative percent drug release determined at 230nm wavelength using U.V- visible spectrophotometer was also studied.

k. **Ex-vivo Diffusion Study**[^13]

The Ex-vivo skin permeation studies were carried out using a Franz diffusion cell. The receptor compartment was filled with 15 ml of simulated salivary fluid pH 6.8. Goat oral mucosa (3 cm in length) was mounted between the donor and receptor compartment over which film of size 2 x 2cm was placed. The donor compartment was then placed and fixed over it with the help of rubber bandages. The whole assembly was placed on a magnetic stirrer and the solution in the receptor compartment was continuously stirred using magnetic bead. The temperature was maintained at 37 ± 2°C. Samples of 5 ml were withdrawn at time intervals of 30, 60, 120, 180, 210, 240 seconds and were analyzed at 230 nm spectrophotometrically for drug content against blank. The receptor phase was replenished with an equal volume of salivary fluid each time the sample was withdrawn. The percentage of the released drug was calculated and plotted against time.

l. **Comparative studies between optimised formulation and marketed formulation**

Comparative study of % drug release and ex-vivo % drug permeation in optimized batch C5 and marketed sublingual tablet of Lorazepam i.e ATIVAN 2mg SL was performed at salivary pH 6.8.

m. **Accelerated stability study of optimized batch**[^14]

The optimized formulation was subjected to stability studies as per ICH guideline. The sample was packed in aluminium foil. Then stored in stability chamber at 40°C/75% RH for 1 month and evaluated for their Disintegration time, Drug content, Drug release, and
mechanical properties at 15 days intervals of time and results were reported at the end of study.

RESULTS AND DISCUSSION

1. Drug Excipient Compatibility Study using Differential Scanning Calorimetry (DSC)

Fig no: 2 showing DSC of Lorazepam

Fig no: 3 showing DSC of Pectin

Fig no: 4 showing DSC of Lorazepam and Pectin
2. Evaluation of Formulation

**Figure 6: Thickness of formulation C batch**

**Figure 7: weight variation of formulation C batch**

**Figure 8: Disintegration time of formulation C batch**
Figure 9: Drug Content (%) of formulation C batch

Figure 10: Folding Endurance of Formulation C Batch

Figure 11: *In-Vitro* Drug Release of Formulation C Batch
Figure 12: *Ex-vivo* Drug permeation Study of Formulation C Batch

Figure 13: Comparative Dissolution Study of Optimized C5 batch and Marketed Tablet

Figure: 14: Comparative drug permeation Study of Optimized C5 batch and Marketed of Tablet
The films were found to be uniform in thickness. All the films showed the increased thickness with increase in concentration in polymer. Amongst these strips, C4 has minimum thickness of 0.09 ±0.015mm. The films were found to be uniform in weight. Amongst these strips, batch C5 shows minimum disintegration time of 32.01±0.59 seconds. The drug content for batches C1, C2, C3, C4, C5 and C6 was found to be 94.93±1.45%, 95.72±0.81%, 96.06±0.37%, 97.75±1.35%, 98.01±0.06% and 96.01±0.08%. Amongst these strips, batch C5 shows maximum drug content of 98.01±0.06%. Surface pH of all the films was uniform and within the range. The folding endurance for C1, C2, C3, C4, C5 and C6 was found to be 368±17, 325±75, 382±9.2, 328±20.3, 402±15.5 and 361.3±9.25. Amongst these strips, C5 batch has shown maximum folding endurance of 402±15.5. The tensile strength and % elongation of batch C5 was found to be 5.6±0.28kg/mm² and 24.12±0.12 % mm⁻² respectively. The drug loaded films were tested for swelling index. The swelling index of the strip was found to be 42.52±0.17. The in-vitro dissolution test was performed using the USP II paddle type apparatus to study release of drug from the strips and this study depicted that amongst six batches, C5 batch was found to have the maximum drug release of 97.93±0.28% after 4 minutes. The ex-vivo drug permeation (ex-vivo diffusion) was performed using goat oral mucosa. Amongst the six batches, C5 batch was found to have maximum drug permeation with 76.35±1.52 %. Thus from the above results, C5 batch was selected as the optimized formulation. Comparative study of % drug release and ex-vivo % drug permeation in optimized batch C5 and marketed sublingual tablet of Lorazepam i.e. ATIVAN 2mg SL is been performed at salivary pH 6.8. From the comparative study of in-vitro % drug dissolution and ex-vivo % drug permeation, it can be concluded that the release of drug in optimized film was faster than the marketed ATIVAN 2mg SL tablet. Also, drug permeation shown better results than marketed tablet. The optimized formulation was subjected to stability studies. The prepared melt-in-mouth was packed in aluminium foil. After the stability study it was observed that the optimized formulation C5 film did not show any significant change in

<table>
<thead>
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<th>Parameters</th>
<th>0days</th>
<th>15days</th>
<th>30 days</th>
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<tbody>
<tr>
<td>Weight variation(g)</td>
<td>0.082±0.03</td>
<td>0.081±0.85</td>
<td>0.081±0.01</td>
</tr>
<tr>
<td>Thickness(mm)</td>
<td>0.11±0.010mm</td>
<td>0.12±0.54</td>
<td>0.12±0.05</td>
</tr>
<tr>
<td>Disintegration time(sec)</td>
<td>32.58±0.52</td>
<td>32.01±0.59</td>
<td>31.45±0.75</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>98.01±0.06</td>
<td>98.01±0.01</td>
<td>97±0.075</td>
</tr>
<tr>
<td>% drug release (%)</td>
<td>98.53±0.28</td>
<td>98.06±0.015</td>
<td>97.93±0.06</td>
</tr>
<tr>
<td>Folding endurance(number)</td>
<td>402±15.5</td>
<td>400±0.02</td>
<td>406±0.15</td>
</tr>
<tr>
<td>pH</td>
<td>6.67±0.06</td>
<td>6.67±0.02</td>
<td>6.65±63</td>
</tr>
</tbody>
</table>

Table 7: Accelerated Stability Testing Of Optimized Formulation C5 (40° C/75%RH)
appearance, weight variation, thickness, disintegration time, drug content, % drug release folding endurance and pH after 1 month. From these results it was concluded that, formulations C5 containing Lorazepam is stable and retained their original properties.

CONCLUSION
The fast-dissolving oral films for sublingual use of Lorazepam was prepared using different concentrations of pectin as a film former by the solvent-casting method which is simple and cost effective. Films showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst all formulae, the formulation C5 showed the faster dissolution rate with satisfactory physico chemical parameters. Films were found to be stable at accelerated stability conditions. Satisfactory results have been obtained in comparative study of formulated films of batch C5 have been done with marketed fast dissolving tablet of Lorazepam tablet for sublingual use. In the present work, it can be concluded that the fast dissolving films formulation can be an innovative and promising approach for the delivery of Lorazepam sublingually for the treatment of anxiety.

REFERENCES


