FORMULATION AND EVALUATION OF FAST DISSOLVING FILMS OF LORATADINE FOR SUBLINGUAL USE

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ABSTRACT
Loratadine is a second generation orally administered non-sedative antihistamine used in the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticarial (hives) and other skin allergies. In the work undertaken, an attempt was made to prepare quick release films of loratadine with the purpose of developing a dosage form for very quick onset of action, which will be beneficial in managing severe condition of allergies, aiding in enhancement of bioavailability and very convenient for administration, without the problem of swallowing & without using water. The drug has salty taste and hence an attempt was made to mask the taste by using artificial sweetener aspartame which also acts as a saliva stimulant. The films of loratadine were prepared by using polymers such as hydroxypropyl methylcellulose (HPMC) & polyvinyl pyrrolidone (PVP) and hydroxypropyl cellulose (HPC) by solvent casting method. The IR studies showed no interaction between drug and polymer. They were evaluated for physicochemical tests such as thickness, uniformity of weight, uniformity of drug content, folding endurance, surface pH, tensile strength and % elongation, disintegration test, all of which showed satisfactory results. The formulations were also subjected for in vitro drug release by using USP dissolution apparatus. Ex vivo drug release was also carried out using paracrine membrane as the model. All the formulation showed 70-92% release within 4 min by the in vitro method and 64-86% within 4 min during ex vivo drug release studies. The stability studies conducted showed that there was no appreciable change when stored at refrigeration temperature 2-8°C, room temperature 25-30°C and oven temperature 45-50°C.

KEY WORDS: Fast dissolving films, Loratadine, Sublingual films, Solvent casting

INTRODUCTION
Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of a drug molecule by formulating into a convenient dosage form for administration and to achieve better patient compliance. Some companies introduced more robust forms of fast dissolving drug delivery such as Lavipharm laboratories Inc. (Lavipharm) have invented an ideal fast dissolving drug delivery system, trademarked Quick-DisTM, is Lavipharm’s proprietary patented technology and is a thin, flexible, and quick dissolving film. The film is placed on the top or the floor of the tongue.1

When this film put on tongue, disintegrates instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets.2

Loratadine is a derivative of azatadine and is a second generation orally administered non-sedative antihistamine used in the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticarial (hives) and other skin allergies.3 Loratadine is well absorbed following oral administration, with the peak plasma concentration usually attained in 1 h. Antihistaminic effects occur within 1 h. The duration of antihistaminic effects persist for at least 24 h.4,5 Hence, for an antihistamine drug like loratadine, a quick disintegrating dosage form will be suitable, since the disintegration and dissolution of the dosage form occurs rapidly, thus providing rapid onset of action. Hence it was thought worth to formulate oro-dispersible formulations of the drug so that the patient can ingest the dosage form anywhere and at anytime without the aid of water which would be helpful especially in cases of unavailability of water, motion sickness, sudden episodes of allergic attacks, deglutition problems.

In view of the above facts, in the present investigation, an attempt was made to develop fast dissolving films of loratadine using suitable polymers like hydroxypropyl methyl cellulose (HPMC), polyvinylpyrrolidone (PVP) and hydroxypropyl cellulose (HPC) in different ratios and combination with sweetener like aspartame along with plasticizer such as propylene glycol, and evaluate them for physical characteristics. The formulation will also be evaluated for drug release both in vitro and ex vivo.

MATERIALS AND METHODS
Materials
Loratadine was obtained as a gift sample from Vasudha Pharma Chem Ltd, Hyderabad. Hydroxypropyl methylcellulose HPMC (15cps), polyvinyl pyrrolidone (PVP) and hydroxypropyl cellulose (HPC) were procured from CDH Laboratories, New Delhi. All other chemicals used were of analytical grade.

METHODS
Formulation of fast dissolving films
In the present study, fast dissolving films of loratadine were prepared by solvent casting technique. Flat, square-shaped, glass moulds having a surface area of 25 cm² were fabricated for casting the films.

Preparation of casting solutions
The casting solutions were prepared by dissolving weighed quantities of polymers (Table 1) in 10 ml of ethanol taken in a beaker. The drug and aspartame were dissolved in 5 ml of ethanol and added to the above polymer solution along with propylene glycol, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 20 ml with ethanol. The beaker was covered with aluminium foil
and the solution was allowed to stand overnight to remove air bubbles.

**Preparation of fast dissolving films**

The casting solution (20 ml) was poured into glass moulds and kept a side covered with funnel to allow for controlled evaporation. The films were removed by peeling and cut into square dimension of 2 x 2 cm (4 cm²), so that each film contained about 10 mg of drug. These films were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, and packed in self-sealing covers.

**EVALUATION OF FAST DISSOLVING FILMS**

**Film thickness**

The thickness of 3 films of each formulation was performed by screw gauge at different position of the film and the average thickness was calculated.

**Uniformity of weight**

The film (4 cm²) was cut at five different places in the cast film. The weight of each filmstrip was taken and the weight variation was calculated.

**Uniformity of drug content**

This parameter was determined by dissolving one film of dimension 2 x 2 cm containing 10 mg of loratadine by homogenization in a mixture of 5 ml of ethyl alcohol and 100 ml of simulated saliva of pH 6.75 for 30 min with continuous shaking. Then the solution was filtered and after suitable dilution with simulated salivary fluid, the absorbance was measured at 247.2 nm using a UV spectrophotometer and the drug content was calculated.

**Folding endurance**

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2 x 2 cm (4 cm²) was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the values were reported.

**Surface pH**

The film to be tested was placed in a petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. the average of three determinations for each formulation was done.

**Tensile strength and %Elongation**

This mechanical property was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely tensile strength and percentage elongation were computed for the evaluation of the film. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and the cross sectional area of the fractured film as described in the equation:

\[
\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample}}
\]

Percentage elongation can be obtained by following equation:

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

**Disintegration test**

Disintegration test was performed to ensure the disintegration of the film in water. One film from each formulation was introduced into one tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing simulated saliva and the apparatus was operated until the film disintegrated. Test was performed in triplicate.

**In vitro dissolution studies**

The simulated salivary fluid containing 2% ethanol after considering solubility factors of the drug was taken as the dissolution medium to determine the drug release.

The dissolution profile of quick release films of loratadine was carried out using USP type II (paddle apparatus) with 300 ml of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at every 30 sec time interval and replacing the same amount with the fresh medium. Amount of drug in the withdrawn samples was determined by UV spectrophotometer at 247.2 nm. Three trials were carried out for all the samples and the average value was taken. The percentage of drug dissolved at various time intervals was calculated and plotted against time.

**Ex vivo studies**

This was performed by application of the film on freshly cut porcine buccal mucosa. The porcine tissues were fixed on the internal side of a beaker with cyanoacrylate glue. The beaker was filled with 200 ml of simulated salivary fluid and kept at 37 °C. After 2 minutes a 50 rpm stirring was applied to simulate the buccal cavity environment and 5 ml sample were withdrawn at every 30 sec time interval, replacing the same amount with fresh medium. After filtration the amount of drug in the withdrawn samples was determined by UV spectrophotometer at 247.2 nm.

**Stability studies**

The stability study of the formulated fast dissolving films was carried out under different environmental conditions. The film was packed in the aluminium foil and stored in a stability chamber for stability studies at 2-8 °C (45%RH), 25-30 °C (60%RH) and 45-50 °C (75%RH) for a period of 45 days. The films were characterized for the drug content and other parameters during the stability study period.

**RESULTS AND DISCUSSION**

**Formulation of fast dissolving films**

Six formulations of fast dissolving films of loratadine were prepared by solvent casting method on glass moulds, using HPMC 15cps, PVP and HPC as polymers. Propylene glycol was used as plasticizer and aspartame as sweetener. Effect of concentration ratio of polymers and nature of polymers was studied by preparing various formulations of fast dissolving films. In all these formulations a constant amount of drug (65 mg) was maintained. The casting solution (20 ml) was poured into 25 cm² moulds, so that each cm² contains approximately
10 mg of drug. Polymers were used in different concentrations and the concentration of other ingredients such as plasticizer and sweetener were kept constant (Table 1).

**Evaluation of fast dissolving films**

Fast dissolving films of loratadine were evaluated for various parameters. In the present study six formulations were prepared by varying polymer concentration, and by using different polymers. The physical appearance of the films was evaluated. All the films prepared with different polymer concentration were found to be flexible, smooth, transparent, nonsticky and homogeneous. The thickness of the films in each set was measured. The marginal difference in the thickness was observed among each group indicated that more the amount of polymer, higher the thickness values. The individual weight of samples of each type formulation was determined and the average weight was calculated. It was observed that weight of the entire film sample in each formulation was uniform. No significant difference in the drug content among the films, indicated good content uniformity. All the films showed good folding endurance greater than 300, indicated that the films have good flexibility. The surface pH was found to be in the range of 6.2 to 7.06, which is close to neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, thereby they are comfortable. The disintegration time of the film was done by using disintegration test apparatus. The formulation FA1 shows 51 sec disintegration time. Disintegration time of the films was found to be decreased with increase in the concentration of the HPMC 15cps polymer (Table 2). When placed over the tongue, the film dissolved instantly. Dissolution was also found to be improved due to saliva stimulation in the presence of the sweetener (aspartame).

The tensile strength gives an indication of the strength and elasticity of the film reflected by the parameters, tensile strength (TS) and elongation at break (E/B). The results showed that, among the formulations FA and FB, the tensile strength and % elongation increased with the increase in the percentage of mucosalhesive polymer, HPMC 15cps. Proportions of PVP higher than that used in these films makes them weaker. In the case of HPMC-PVP films TS and E/B is the greatest for FA1 and least for FA3, indicating that the inclusion of PVP decreased the tensile strength. Tensile strength and % elongation of the films was recorded in the Table 3.

FT-IR spectroscopy was employed to ascertain compatibility of loratadine with polymers. The individual drug and drug with polymers were separately scanned. Both the spectra were compared for confirmation of common peak. The spectra are showed in the figure 1 2 and 3. Loratadine with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. Hence it can be concluded that the drug is in free state.

**In vitro drug release studies**

*In vitro* drug release study was carried out using USP dissolution apparatus, type II. Among all HPMC-PVP films (FA1, FA2 and FA3) extent of drug release was greater in FA3 films. It was observed that with the increased content of PVP, the rate and extent of drug release was faster. This was because of water soluble polymer PVP that results in increase wettability and penetration of water into the film matrices and hence increased diffusion of the drug. Among all HPMC-HPMC films (FB1, FB2 and FB3), those formulations with more amounts of HPC i.e., FB3 showed slower release, this may be due to extensive swelling of HPC, which created a high viscosity gel barrier for drug diffusion. The drug release profile of marketed product of loratadine (Lormeg-10 mg) was also determined and compared with the best formulation among all batches. It was observed that the drug release from fast dissolving film was much faster than that of the tablet (Table 4).

Among the six formulations (FA1, FA2, FA3, FB1, FB2, and FB3), formulation FA3 and FB1 were found to be best formulations in terms of drug release. The order of drug release in each set of formulation can be given as

FA1 < FA2 < FA3
FB1 > FB2 > FB3

**Ex vivo studies**

From *ex vivo* drug release, it was observed that formulations containing HPMC-PVP (FA1, FA2 and FA3) showed that, extent of drug release was greater in FA3 films, as the increased content of PVP, the rate and extent of drug release was faster. This was because of water soluble polymer PVP that results in increase wettability and penetration of water into the film matrices and hence increased diffusion of the drug. These findings coincided exactly with *in vitro* drug release profile. Thus *ex vivo* results justified the *in vitro* release profiles further.

**Stability studies**

A stability study was carried out for 45 days at 2-8 °C (45%RH), 25-30 °C (60%RH) and 45-50 °C (75%RH). The films were observed for physical change, drug content, and % drug release. Fast dissolving films of loratadine were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics and drug content at a lower temperature and room temperature. However, when stored at 45-50 °C for 45 days, films became brittle.

**CONCLUSION**

The main objective of the study was to formulate and evaluate fast dissolving film containing Loratadine. The fast dissolving films can be easily formulated by solvent casting method by using polymers such as HPMC, PVP and HPC in different ratios with suitable plasticizer like propylene glycol and sweetener like aspartame. Compatibility of Loratadine with polymers was confirmed by FT-IR studies. It was observed that the physicochemical characteristics such as uniformity of weight, thickness, folding endurance, surface pH, and uniformity of drug content of all the film samples showed satisfactory results with respect to variation of these parameters between films of same formulation. Tensile strength and percentage elongation of the films were increased with increase in the concentration of HPMC polymer. Disintegration time of the films was found to be decreased with increase in the concentration of the HPMC 15cps polymer. Based on the physicochemical parameters and *in vitro* drug release studies, formulation FA3 and FB1 were considered as the best formulations which exhibited the drug release of 92.79% and 90.09% respectively at the end of 240 sec. *Ex vivo* drug release studies through porcine buccal mucosa also showed similar results. Present study reveals that all the six formulated films showed satisfactory film parameters. From the present investigation it can be conclude that fast dissolving film formulation can be a potential novel drug dosage form for paediatric, geriatric and also for general population.
ACKNOWLEDGEMENT
The authors are thankful to VASUDHA PHARMA CHEM LIMITED, HYDERABAD, INDIA for the gift sample of loratadine and NITTE University, Mangalore for providing the necessary facilities to carry out this study.

REFERENCES
3. The Rx List. The Internet Drug Index. www.rxlist.com

Table 1. Composition of fast dissolving films

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Polymers</th>
<th>HPMC (mg)</th>
<th>PVP (mg)</th>
<th>HPC (mg)</th>
<th>Drug (mg)</th>
<th>Propylene glycol (ml)</th>
<th>Aspartame (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA1</td>
<td>HPMC 15cps + PVP (4:1)</td>
<td>400</td>
<td>100</td>
<td>-</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>FA2</td>
<td>HPMC 15cps + PVP (3.5:1:5)</td>
<td>350</td>
<td>150</td>
<td>-</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>FA3</td>
<td>HPMC 15cps + PVP (3:2)</td>
<td>300</td>
<td>200</td>
<td>-</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>FB1</td>
<td>HPMC 15cps + HPC (4:1)</td>
<td>400</td>
<td>-</td>
<td>100</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>FB2</td>
<td>HPMC 15cps + HPC (3:5:1:5)</td>
<td>350</td>
<td>-</td>
<td>150</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>FB3</td>
<td>HPMC 15cps + HPC (3:2)</td>
<td>300</td>
<td>-</td>
<td>200</td>
<td>65</td>
<td>0.25</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2. Physical characterization of film formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness* (mm)</th>
<th>Weight variation* (mg)</th>
<th>Drug content (%)</th>
<th>Folding endurance</th>
<th>Surface pH*</th>
<th>Disintegration time* (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA1</td>
<td>0.763 ±0.041</td>
<td>77.36 ±0.971</td>
<td>93.86</td>
<td>&gt;300</td>
<td>6.49 ±0.028</td>
<td>51.33 ±3.51</td>
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<tr>
<td>FA2</td>
<td>0.802 ±0.066</td>
<td>75.63 ±0.750</td>
<td>96.03</td>
<td>&gt;300</td>
<td>6.81 ±0.021</td>
<td>62.3 ±6.6</td>
</tr>
<tr>
<td>FA3</td>
<td>0.773 ±0.025</td>
<td>80.56 ±0.907</td>
<td>95.03</td>
<td>&gt;300</td>
<td>6.71 ±0.014</td>
<td>69.66 ±7.23</td>
</tr>
<tr>
<td>FB1</td>
<td>0.653 ±0.040</td>
<td>75.83 ±0.680</td>
<td>94.93</td>
<td>&gt;300</td>
<td>6.81 ±0.021</td>
<td>62.64 ±5.50</td>
</tr>
<tr>
<td>FB2</td>
<td>0.633 ±0.020</td>
<td>83.26 ±0.907</td>
<td>95.93</td>
<td>&gt;300</td>
<td>7.06 ±0.001</td>
<td>77.53 ±7.02</td>
</tr>
<tr>
<td>FB3</td>
<td>0.626 ±0.015</td>
<td>78.83 ±0.305</td>
<td>95.20</td>
<td>&gt;300</td>
<td>6.20 ±0.014</td>
<td>89.66 ±5.50</td>
</tr>
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</table>

*Each value is the mean ± SD; n = 3 determinations

Table 3. Results of tensile strength and percentage elongation of all formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Tensile strength* (kg/cm²)</th>
<th>% Elongation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA1</td>
<td>0.623 ±0.020</td>
<td>28.93 ±0.450</td>
</tr>
<tr>
<td>FA2</td>
<td>0.503 ±0.025</td>
<td>25.73 ±0.416</td>
</tr>
<tr>
<td>FA3</td>
<td>0.366 ±0.015</td>
<td>20.93 ±0.585</td>
</tr>
<tr>
<td>FB1</td>
<td>1.223 ±0.015</td>
<td>64.16 ±0.602</td>
</tr>
<tr>
<td>FB2</td>
<td>1.143 ±0.020</td>
<td>57.76 ±0.351</td>
</tr>
<tr>
<td>FB3</td>
<td>1.053 ±0.025</td>
<td>51.83 ±0.450</td>
</tr>
</tbody>
</table>

*Mean of 3 determinations ± SD

Table 4. Results of in vitro drug release studies of all formulations

<table>
<thead>
<tr>
<th>Time (Sec)</th>
<th>Percentage drug released*</th>
</tr>
</thead>
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<tr>
<td></td>
<td>FA1</td>
</tr>
<tr>
<td>00</td>
<td>0.000</td>
</tr>
<tr>
<td>30</td>
<td>29.20</td>
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<tr>
<td>60</td>
<td>41.58</td>
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<td>90</td>
<td>46.50</td>
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<td>120</td>
<td>51.99</td>
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<td>150</td>
<td>57.30</td>
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<td>180</td>
<td>64.50</td>
</tr>
<tr>
<td>210</td>
<td>72.60</td>
</tr>
<tr>
<td>240</td>
<td>78.30</td>
</tr>
</tbody>
</table>

*Average of 3 determinations
Figure 1. FT-IR spectrum of Loratadine

Figure 2. FT-IR spectrum of formulation FA

Figure 3. FT-IR spectrum of formulation FB

Figure 4. Comparison of dissolution profile of all formulations and marketed tablet

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