FORMULATION AND EVALUATION OF FAST DISSOLVING FILM OF LORNOXICAM

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INTRODUCTION

Despite so much of advancements in various delivery systems developed for the administration of various drugs through different routes such as oral, parenteral, transdermal, and nasal, the oral route is considered as the most convenient and the preferred route of administration [1]. The oral route of administration still continues to be widely used accepted route, contributing to 50–60% of total drug formulations due to ease of administration, self-medication, and pain avoidance as compared to parenteral [2]. Fast-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute, without needing water or chewing [3]. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients [4]. Fast dissolving films are very similar to ultra-thin strip of a postage stamp in their shape, size, and thickness. Fast dissolving film is simply placed on the patient’s tongue or any oral mucosal tissue, instantly wet by saliva the film, and rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oramucosal absorption that is at the site of application. It can also be expected to have a quick-onset effect, and the dissolution time is usually about 5 min. Fast-dissolving films are very similar to ultra-thin strips of a postage stamp in their shape, size, and thickness. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film, and rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oramucosal absorption that is at the site of application. It can also be expected to have a quick-onset effect, and the dissolution time is usually about 5 min. The main objective of the study was to formulate and evaluate mouth-dissolving film containing lornoxicam using hydroxypropyl methylcellulose (HPMC E5) and polyvinyl alcohol (PVA) as film-forming polymers by solvent casting method.

MATERIALS AND METHODS

Materials
Lornoxicam and HPMC E5 were purchased from Wuhan Senwayer Century chemical Co., Ltd. PVA was obtained from Fine Indian chemicals. All other reagents and chemicals used were of analytical grade.

Methods
Determination of λmax The standard solution of 100 µg/ml was scanned between 400 nm and 200 nm in ultraviolet (UV) spectrophotometer against phosphate buffer solution pH 6.8 as blank after baseline correction.

Calculation of dose The dose of lornoxicam is 4 mg. Therefore, the amount of lornoxicam in a film of 4 cm² is 4 mg. Area of the Petri dish of 9 cm diameter is 63.64 cm² so that the amount of drug present to be added to the 63.64 cm² area of Petri dish is 64 mg.

ABSTRACT

Objective: The aim of the present work was to formulate and evaluate fast dissolving film containing lornoxicam.

Materials and Methods: To prepare the film, hydroxypropyl methylcellulose E5 and polyvinyl alcohol (PVA) were used as film-forming polymers by solvent casting method. Glycerine was used as plasticizer, aspartame, and mannitol as sweetener. All prepared films were evaluated for its weight variation, disintegration time, thickness, drug content, pH, dissolution study, and folding endurance. The drug-excipients compatibility study was done using differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR).

Results: Satisfactory results obtained when PVA was used as film-forming polymer, and the drug was dispersed in the polymer solution using poloxamer 407 as a solubilizing agent. Formulation F2 is considered as the optimized formulation as it showed good folding endurance (>300), faster disintegration rate (30 s), and maximum in vitro drug release (87%) within 5 min. DSC and FTIR studies showed no interaction between drug and the polymers.

Conclusion: It can be concluded from the study that the fast dissolving film can be prepared for poorly water-soluble drug lornoxicam using PVA as a suitable film-forming polymer.

Keywords: Lornoxicam, Fast dissolving film, Hydroxypropyl methylcellulose E5, Polyvinyl alcohol, Solvent casting method.

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Preparation of HPMC E5 mouth dissolving film

Five formulas were prepared using HPMC E5 by casting method as shown in Table 1. The specified amount HPMC polymer was weighed and dissolved in sufficient quantity of water. The solution was kept aside for overnight for swelling of polymer. Further required quantities of aspartame and mannitol (as sweetening agents since lornoxicam has bitter taste) were dissolved in 2 ml of hot water and added to the polymer solution under continuous stirring using magnetic stirrer. Isopropyl alcohol was used as a solvent for the drug; polyethylene glycol (PEG) 400 was added to the solution as plasticizer at a concentration 20% of dry polymer. The resulting bubble-free solution was poured onto Petri dish and kept in oven at 40 °C for 24 h for drying [8].

Preparation of PVA film

Films were prepared using polyvinyl alcohol by casting method as shown in Table 2. The specified amount PVA was dissolved in sufficient quantity of water at 80°C at hot plate. Glycerin was added to the polymer solution as a plasticizer at concentration 20% of dry polymer, and the solution was sonicated for 15 min. Poloxamer 407 (act as a surfactant) was added to the polymeric solution with sonication. Further required aspartame and mannitol were added to the hot polymeric solution as sweetening agents. 64 mg of lornoxicam was dispersed in the polymer solution and sonicated for 30 min. Finally, vanilla was added as flavoring agent to the solution with sonication for 5 min. The resulting bubble-free solution was poured onto Petri dish and kept in an oven at 40°C for 24 h for drying. The film was removed from the mold and preserved in a aluminum paper and in a desiccator.

Evaluation of lornoxicam film using PVA as a film-forming agent

Appearance of films

Appearance of strip was evaluated by visual observation such as transparent and semitransparent nature of strip [9].

Fig. 1: Chemical structure of lornoxicam

Table 1: Formulation of lornoxicam films using HPMC E5

<table>
<thead>
<tr>
<th>Formula</th>
<th>Lornoxicam (mg)</th>
<th>HPMC (mg)</th>
<th>PEG 400 (ml)</th>
<th>Aspartame (mg)</th>
<th>Mannitol (mg)</th>
<th>Water (ml)</th>
<th>Isopropyl alcohol (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>64</td>
<td>750</td>
<td>0.15</td>
<td>100</td>
<td>100</td>
<td>q.s</td>
<td>20</td>
</tr>
<tr>
<td>F2</td>
<td>64</td>
<td>1000</td>
<td>0.2</td>
<td>100</td>
<td>100</td>
<td>q.s</td>
<td>20</td>
</tr>
<tr>
<td>F3</td>
<td>64</td>
<td>1250</td>
<td>0.25</td>
<td>100</td>
<td>100</td>
<td>q.s</td>
<td>20</td>
</tr>
<tr>
<td>F4</td>
<td>64</td>
<td>1500</td>
<td>0.3</td>
<td>100</td>
<td>100</td>
<td>q.s</td>
<td>20</td>
</tr>
<tr>
<td>F5</td>
<td>64</td>
<td>2000</td>
<td>0.4</td>
<td>100</td>
<td>100</td>
<td>q.s</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2: Formulation of lornoxicam films using PVA

<table>
<thead>
<tr>
<th>Formula</th>
<th>Lornoxicam (mg)</th>
<th>PVA (mg)</th>
<th>Glycerin (mg)</th>
<th>Poloxamer 407 (mg)</th>
<th>Aspartame (mg)</th>
<th>Mannitol (mg)</th>
<th>Vanilla (ml)</th>
<th>Water (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>64</td>
<td>400</td>
<td>80</td>
<td>120</td>
<td>45</td>
<td>45</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>F2</td>
<td>64</td>
<td>500</td>
<td>100</td>
<td>120</td>
<td>45</td>
<td>45</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>F3</td>
<td>64</td>
<td>600</td>
<td>120</td>
<td>120</td>
<td>45</td>
<td>45</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>F4</td>
<td>64</td>
<td>700</td>
<td>140</td>
<td>120</td>
<td>45</td>
<td>45</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

PVA: Polyvinyl alcohol

HPMC: Hydroxypropyl methylcellulose, PEG: Polyethylene glycol
released was determined using UV visible spectrophotometer at 376 nm [16,17].

**Fourier-transformed infrared (FTIR) spectroscopic analysis**

FTIR spectra of pure lornoxicam, PVA, and the physical mixture of lornoxicam and PVA at ratio (1:1) were analyzed using FTIR lambda 7600-Australia spectroscopy. FTIR spectrum was recorded between 400 and 4000 cm\(^{-1}\) by KBr disc method.

**Differential scanning calorimetry (DSC)**

DSC thermograms were recorded using a differential scanning calorimeter (DSC-60 plus, Shimadzu). An accurately weighed sample (2–4 mg) of pure drug, PVA, and the physical mixture of lornoxicam and PVA at ratio (1:1) was heated in hermetically sealed aluminum pans under nitrogen purge (100 ml/min) over a temperature range of 25°C–300°C at a constant rate of 10°C/min [18].

**Statistical analysis**

ANOVA test (one-way analysis of the variance) and student t-test were employed for statistical analysis. When \(p<0.05\), then there would be a significant statistical differences [19].

**RESULTS AND DISCUSSION**

\(\lambda_{\text{max}}\) for pure lornoxicam in phosphate buffer solution pH 6.8

100 μg/ml sample was prepared and scanned between 200 and 400 nm. The drug showed maximum absorption at 376 nm. Hence, the \(\lambda_{\text{max}}\) of lornoxicam was found to be 376 nm as shown in Fig. 2.

**Calibration curve of lornoxicam**

Lornoxicam showed maximum absorption at wavelength 376 nm in phosphate buffer (pH 6.8) as shown in Fig. 2. Standard curve was plotted by taking absorbance of diluted stock solutions at wavelength 376 nm. A linear relationship was obtained in Beer–Lambert's plot of lornoxicam which is shown in Fig. 3.

**Effect of the type of polymer as film-forming agent**

HPMC is a film-forming polymer, having excellent film-forming ability, but it had not given satisfactory results to give a good film since the drug is water insoluble and isopropyl alcohol was not efficient to solubilize the drug and the dispersion of the drug was not achieved throughout the film, while the use of PVA gave a good film that can peel from the Petri dish and the drug was dispersed homogeneously throughout the film, so PVA was used as selected film-forming polymer.

**Effect of plasticizer type**

Plasticizers were used to maintain the flexibility of the films, and PEG 400 was used as plasticizer in the preparation of fast dissolving film, but it noticed that it had bitter taste affecting on the palatability of the film. Glycerin was found to be better when compared to PEG 400 since it acts as plasticizer and sweetening agent.

To improve the palatability of the mouth dissolving films, the natural sweeteners and artificial sweeteners are used in combination. Lornoxicam is being bitter in taste, and taste masking was achieved by the use of sweeteners (mannitol and aspartame) and flavors such as vanilla. Mannitol was used as natural sweetener; it was expected to give good mouthfeel and cooling sensation when incorporated with other sweeteners.

**Appearance of lornoxicam film using PVA as a film-forming agent**

The prepared films were found to be good without any major film manufacturing defects; the film was semitransparent with yellow color since the drug has yellow to dark-yellow color as shown in Fig. 4. The surface of the film was found to be smooth; there is no sign of picking, and cracking except F1 containing 30% of PVA was sticky and excluded from the evaluation. The other prepared films F2, F3, and F4 were evaluated for post-evaluation parameters.
Table 3: Evaluation of physicochemical parameters of fast dissolving film of lornoxicam

<table>
<thead>
<tr>
<th>Formula</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Folding endurance</th>
<th>pH</th>
<th>Disintegration time (s)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>82.9±1</td>
<td>0.081±0.02</td>
<td>&gt;300</td>
<td>6.76±0.12</td>
<td>30.3±3</td>
<td>95±1</td>
</tr>
<tr>
<td>F3</td>
<td>80.4±2</td>
<td>0.071±0.013</td>
<td>&gt;300</td>
<td>6.7±0.1</td>
<td>41±3</td>
<td>112±0.43</td>
</tr>
<tr>
<td>F4</td>
<td>85.1±3</td>
<td>0.114±0.016</td>
<td>&gt;300</td>
<td>6.57±0.21</td>
<td>52±3.6</td>
<td>96±0.1</td>
</tr>
</tbody>
</table>

The values represent mean ± standard deviation, n=3

Table 4: In vitro dissolution studies of lornoxicam from F2 to F4

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>7.16±0.08</td>
<td>11.0±0.7</td>
<td>9±0.03</td>
</tr>
<tr>
<td>2</td>
<td>25.0±0.9</td>
<td>13.5±0.3</td>
<td>9±0.06</td>
</tr>
<tr>
<td>3</td>
<td>51.5±0.02</td>
<td>20.3±0.06</td>
<td>22±0.4</td>
</tr>
<tr>
<td>4</td>
<td>77±0.04</td>
<td>29±0.07</td>
<td>36±1</td>
</tr>
<tr>
<td>5</td>
<td>87±0.1</td>
<td>40±0.5</td>
<td>50±0.03</td>
</tr>
<tr>
<td>10</td>
<td>95±0.045</td>
<td>66±0.021</td>
<td>76±0.05</td>
</tr>
<tr>
<td>15</td>
<td>98±0.2</td>
<td>77.5±0.05</td>
<td>82±0.06</td>
</tr>
<tr>
<td>20</td>
<td>99±0.3</td>
<td>80±0.04</td>
<td>87±0.63</td>
</tr>
<tr>
<td>30</td>
<td>100±0.4</td>
<td>87±0.2</td>
<td>93±0.09</td>
</tr>
</tbody>
</table>

All values expressed as mean ± SD (n=3); F: Formula, SD: Standard deviation

Fig. 5: Disintegration time of lornoxicam film

Fig. 6: Dissolution profile of lornoxicam film F2, F3, and F4. All values expressed as mean ± standard deviation (n=3). F = formula

film has a folding endurance value: a value more than 300 indicates acceptable results [19]. Glycerin acts as a plasticizer because it is capable to decrease the glass transition temperature. Lowering the glass transition temperature increases chain mobility and this, in turns, increases in folding endurance [1]. The folding endurance of all the formulations was >300, and the results are given in Table 3.

pH surface evaluation

Test the pH of the surface of oral film needs to be done to investigate the risk of side effects. Acidic or basic pH may cause disturbance in the oral mucosa and impact the rate of hydration of the polymers, so it is important to maintain the pH remains close to neutral pH. From Table 3, it can be seen that the film has a near neutral pH which is in the range of 6.57–6.76. Hence, the dosage has a very small probability to irritate the oral mucosa [20].

In vitro disintegration time

It was observed that in vitro disintegration time varies from 30.3±3 to 52±3.6 s for the three formulations as demonstrated in Table 3 and Fig. 5. In vitro disintegration time of lornoxicam film containing PVA as polymer was affected by the thickness of the film, and as the amount of polymer increases [21], the disintegration time was increased significantly (p<0.05) by increasing the concentration of the polymer as in F3 and F4 that contain 50% w/w and 55% w/w of PVA, respectively, while the disintegration time for F2 (40% of PVA) was the lowest. This can be explained as the higher concentration of the polymer, the thicker gel will produce on contact with the media, which require a longer time to disintegrate [19].

Content uniformity evaluation

Content uniformity test performed to ensure that all films contain a uniform weight of drug as desired. Content uniformity is determined by estimating the active ingredient contained in each film. Limit of content uniformity is 85–115% with a SD which must be ≤6% [22]. From Table 3, it can be seen that the levels of drug in the film range between 95% and 112%. It showed that levels of drug in oral film fulfill the limit of content uniformity.

In vitro dissolution study

The in vitro drug release from film of the three formulations was performed in triplicate using USP apparatus II (paddle method). Dissolution study was performed in pH 6.8 phosphate buffer; the release profile was demonstrated in Fig. 6 and Table 4 shows the percentage of drug being dissolved in 30 min. In case of F2 that contains 40% of PVA formulation, about 87% of drug was released in 5 min and was considered as the best formulation. While in case of F3 and F4, containing 50% and 55% w/w of PVA, respectively, formulations about 40% and 50% of drug released, respectively, in 5 min. This drug release pattern indicates that the increased concentration of polymer decreases the drug release.

FTIR study

The FTIR spectrum of lornoxicam (Fig. 7) has a characteristic peak at 3066 cm⁻¹ corresponding to –CH starching of heteroaromatic ring, and sharp peak obtained at 1646 cm⁻¹ represents the stretching vibration of C=O in structure of primary amide. Other peaks were observed at 1595 and 1549 cm⁻¹ and were assigned to bending vibrations of the N–H group in the secondary amide. The stretching vibrations of the 0=5=S=0 and C=S groups appeared at 1326 cm⁻¹ and 1425±4 cm⁻¹, respectively. Other prominent peaks was appeared at 869.74 cm⁻¹ corresponding to –CH ammatic ring bending and heteroaromatics and at 790.67 cm⁻¹ due to the C–Cl bending vibration. C=N stretching was observed at 1084.51 cm⁻¹, 1425.46 cm⁻¹. The presence of all these groups shows similarity with actual drug structure which indicates the purity of drug substance [23].

The most characteristic band of PVA (Fig. 8) and its respective assignments is observed at 3423 cm⁻¹ and is ascribed to the –OH stretching from the intermolecular and intramolecular hydrogen bonds. The characteristic peaks of lornoxicam were still present in the physical mixture of drug and PVA (Fig. 9) at a ratio of 1:1, indicating no chemical interaction between the drug and polymer.
CONCLUSION
In the present research work, an attempt has been made to prepare mouth dissolving films of lornoxicam which is NSAID, water-insoluble with bitter taste. The fast dissolving films of lornoxicam were prepared by solvent casting method using film-forming polymer PVA and glycerol as plasticizer. Based on the in vitro disintegration time and dissolution profile, formulation F2 was found to be promising and showed a disintegration time of 30 s and 87% of drug released in 5 min.

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AUTHORS’ CONTRIBUTION
The three authors contributed equally to this work.

CONFLICTS OF INTEREST
The authors report no conflict of interests and are responsible for the content and writing of this article.
Fig. 10: Differential scanning calorimetry of lornoxicam

Fig. 11: Differential scanning calorimetry of polyvinyl alcohol

Fig. 12: Differential scanning calorimetry of physical mixture lornoxicam and polyvinyl alcohol
REFERENCES