FORMULATION AND INVITRO CHARACTERIZATION OF AMITRIPTYLINE BUCCAL FILMS

Krishnaveni Manubolu*1, Abbineni Venkata Chandana2, Pasupuleti Prakash3, Byna Sujatha4, Somavarapu Usha Rani5, Karnati Venkata Radhika6

1,2 Department of Pharmaceutics, Narayana Pharmacy college, Chinthareddy Palem, Nellore-524002
3,4 Department of Pharmaceutical Analysis, Narayana pharmacy College, Chinthareddy Palem, Nellore-524002
3 Department of Pharmaceutics, Sri Padmavathi School of pharmacy, Tiruchanaru, Tirupathi.
5 Narayana Pharmacy College, Chinthareddy Palem, Nellore-524002.

ABSTRACT
Oral drug delivery is the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation. Buccal drug delivery system which is painless, without discomfort, precise dosage form, facilitates ease of removal without significant associated pain. Administration of lidocaine and non-steroidal anti-inflammatory drugs (NSAID’S) as a routine procedure for the relief of dental pain and restricted to some side effects. Amitriptyline is a tricyclic antidepressant that provides local anesthetic effects by blocking the sodium channels. It inhibits reuptake of nor epinephrine and serotonin almost equally. The aim of this work is to design Amitriptyline muco-adhesive buccal films, using muco-adhesive polymers, widely employed for the successful treatment of depression, psychotic conditions, facial pain and dental pain management. Amitriptyline buccal films were prepared using HPMC in different proportions in combination with glycerin as plasticizer, acetone as solvent. The thickness values of the films ranged between 0.1753 ± 0.0055mg and 0.2125 ± 0.0053mg. The weight of films ranged between 19.4 ±1.3115mg and 20.5±1.36mg. The invitro release of Amitriptyline from the F2 to F4 was in the range of 70 to 96 % in 80 min in phosphate buffer solution pH – 6.6. Films did not show any cracks even after folding for more than 300 times. The surface pH of all Amitriptyline patches was within ± 0.3 units of the neutral pH and hence no mucosal
irritation is expected. The films exhibited satisfactory characteristics regarding integrity, flexibility, dispersion of drug and other quality control parameters. Ultimately patient compliance is achieved.

**Key Words:** Amitriptyline Hcl, Oral Drug Delivery, Buccal Films, Bioadhesion, solvent casting method.

**INTRODUCTION**

Oral drug delivery is the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation etc. The oral cavity on the other hand is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. There is novel drug delivery system like buccal drug delivery system which is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

Amitriptyline is chemically (±) - (E)-5-[3- (Dimethylamino) propylidene]-10, 11-dihydro-5H-dibenzo [a, d] cyclohepten-10-ol, inhibits reuptake of nor epinephrine and serotonin almost equally. These actions help as an antidepressant and antipsychotic drug. Topical anesthetics are widely used in dentistry. One of their indications is to diminish the pain of the injection of anesthetics. Amitriptyline is a tricyclic antidepressant that provides local anesthetic effects by blocking the sodium channels. Administration of lidocaine and non-steroidal anti-inflammatory drugs (NSAID’S) as a routine procedure for the relief of dental pain and restricted to some side effects. The present aim of this work is to design Amitriptyline muco-adhesive buccal films, using muco-adhesive polymers. Amitriptyline is widely employed for the successful treatment of depression, psychotic conditions, facial pain and dental pain management. The bio availability of the drug should be low/ variable. For the amitriptyline it is about 60% therefore this drug is suitable for buccal absorption. So the combined properties of medicament and polymers are employed in the present work.
MATERIALS AND METHODS

Amitriptyline HCl was obtained as a gift sample from glochem industries. Hydroxypropyl Methyl Cellulose was procured from Oxford laboratory, Mumbai. Acetone was procured from Finar chemicals ltd, Ahmadabad. Glycerine was procured from Arihant chemicals, Hyderabad. Buccal mucosal membrane was obtained from a slaughter house.

Methods

Preparation of Buccal Mucoadhesive Films

The solvent casting method was followed in this study for preparation of films. About 6 patches of different composition of polymers were prepared. The films were observed for dispersion of drug, flexibility, and glossy structure. Based on the above observations, 5 formulations were selected and used for further analysis. The “film” represents the one, which was prepared from the mould and was bigger in size (5 x 3 cm²) and patch represents the one, which was obtained by cutting the film and was smaller in size (1 x 1 cm²).

Preparation of Amitriptyline Films

Buccal mucoadhesive films were prepared by solvent casting method using polymer or polymer blends along with the drug and a suitable solvent. HPMC was weighed accurately and added in acetone. The contents in the beaker were stirred on mechanical stirrer for 30 min for swelling of polymer. Further acetone was added to the above polymer solution and stirred the dispersion. Then glycerin was added as plasticizer to the polymer solution. Amitriptyline was weighed and dissolved in acetone and in another beaker. The drug solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a mechanical stirrer. The glass mould of size 2 cm diameter was placed over a flat surface, which was ensured using spirit level. The drug-polymer mixture was poured into the glass mould. An inverted funnel was placed over the mould overnight for controlled evaporation of the solvent. The film was removed from the mould and packed in wax paper and stored in desiccators.

TABLE NO: 1: Formulation of Amitriptyline Buccal Films

<table>
<thead>
<tr>
<th>S.NO</th>
<th>MATERIALS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amitriptyline</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
</tr>
<tr>
<td>2</td>
<td>HPMC</td>
<td>3%</td>
<td>3.5%</td>
<td>4%</td>
<td>4.5%</td>
<td>5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
<td>3.2%</td>
<td>3.2%</td>
<td>3.2%</td>
<td>3.2%</td>
<td>3.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>q.s to100</td>
<td>q.s to100</td>
<td>q.s to100</td>
<td>q.s to100</td>
<td>q.s to100</td>
<td>q.s to100</td>
</tr>
</tbody>
</table>
Evaluation Studies

1. **Physical Appearance**: includes visual inspection of patches\(^6\).

2. **Surface Texture**: It can be evaluated by touching the patches\(^6\).

3. **Surface pH Study**: Surface pH evaluation is performed inorder to evaluate the possible irritation on the buccal mucosa\(^5\). A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1ml of phosphate buffer (pH 6.6) for 10 minutes at room temperature and pH was noted by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The mean of three readings was recorded.

4. **Swelling Percentage Study**

Swelling study of prepared buccal patch was calculated by function of weight due to swelling, which was measured for each formulation as follows Weight increase due to swelling. A patch of 10mm size (1x1 cm\(^2\)) diameter from every batch was weighed on a preweighed cover slip. It was kept in a petridish and 10ml of phosphate buffer, ph 6.6 was added. After one hour the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch area: Similarly patch of 10mm diameter from each batch was placed on cover slip and it was placed in a petridish. Ten ml of phosphate buffer, pH6.6, was poured into the petridish\(^3,12\). The percentage weight swelling ratios was calculated from the average of three measurements using the following equation

\[
\%S = \left( \frac{X_t - X_0}{X_0} \right) \times 100
\]

Where \( X_t \) – weight or area of the swollen patch after time \( t \) and \( X_0 \) – is the original patch weight or area at zero time.

5. **Invitro Bioadhesion Measurement**

Bovine cheek pouch was used as a model mucosal membrane. In this study a double beam Physical balance was taken, the left pan was removed. To the left arm of the balance a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean glass mortar was placed below the hanging stopper. In this mortar was placed, clean 500 ml glass beaker within which was placed another glass beaker of 50 ml capacity in inverted position and weighed with 500g to prevent floating. The temperature control system involves placing thermometer in 500ml beaker and continuously adding hot water in outer mortar filled with water. The balance of right hand side adjusted
and the bioadhesion was measured using fixed number of weights.

6. Folding Endurance Test

The folding endurance of patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

7. Content Uniformity

Drug content uniformity was determined by dissolving the buccal patch (10 mm in diameter) from each batch by homogenization in 100ml of an isotonic phosphate buffer (pH 6.6) for 6hrs under occasional shaking. The 5ml solution was taken and diluted with isotonic phosphate buffer PH 6.6 upto 20 ml, and the resulting solution was filtered through a 0.45 mm what man filter paper. The drug content was then determined after proper dilution at 240 nm using a UV spectrophotometer.

8. Invitro Drug Release Studies

The test was carried out using buccal mucosa because of non-keratinized buccal mucosa similar to that of human. The modified Franz diffusion cell was used to study permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment of 25 ml capacity. The receptor compartment maintained at a temperature 37°C. The separated buccal epithelium was mounted between the compartments and receptor chamber phosphate buffer solution having PH 6.6 was filled and buccal patch was kept on epithelium and periodically (for 5 min) samples were withdrawn and maintain sink condition. The aliquot were analyzed spectrophotometrically at 240 nm. The release data of Amitriptyline are given in the graph for the patches F2 to F6.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Average thickness (mm) AM±SD</th>
<th>Average weight (mg) AM±SD</th>
<th>Swelling index AM±SD(%)</th>
<th>Folding Endurance AM ±S.D.</th>
<th>Drug content %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>F2</td>
<td>0.01951 ± 0.0040</td>
<td>16.2330 ±0.3076</td>
<td>118.000 ± 1.3527</td>
<td>355±0.03</td>
<td>80.26±0.3918</td>
</tr>
<tr>
<td>F3</td>
<td>0.2125 ± 0.0053</td>
<td>20.5±1.36</td>
<td>145.6000 ± 7.5545</td>
<td>379±0.38</td>
<td>87.72±4.3960</td>
</tr>
<tr>
<td>F4</td>
<td>0.1753 ± 0.0055</td>
<td>19.4 ±1.3115</td>
<td>179.2666 ± 4.1621</td>
<td>519±0.54</td>
<td>88.72±4.3960</td>
</tr>
<tr>
<td>F5</td>
<td>0.2272 ± 0.0074</td>
<td>22.85±1.4167</td>
<td>180.1000 ± 8.4640</td>
<td>498±0.04</td>
<td>86.46±1.8892</td>
</tr>
<tr>
<td>F6</td>
<td>0.1858±0.0089</td>
<td>22.85±1.1725</td>
<td>188.3333 ±12.4597</td>
<td>220±0.22</td>
<td>81.93±2.2332</td>
</tr>
</tbody>
</table>

AM- arithmetic mean
SD- standard deviation

TABLE NO 2: Evaluation of Amitriptyline Buccal Films
RESULTS AND DISCUSSION

Amitriptyline buccal films were prepared by solvent casting method. In the present study HPMC is used as polymer and glycerol as plasticizer in 3.2% concentration. Glycerol gave the films flexibility due to which folding endurance was good.

The patches were translucent, having good strength, and visually smooth surfaced. The drug and polymer distribution was uniform. All the drug-loaded films have uniform thickness throughout. The thickness values are tabulated in table 2. The thickness values were ranged between 0.1753 ± 0.0055mm and 0.2272 ± 0.0074mm. Standard deviation of all the films ranged between 0.0040 and 0.0089. Drug loaded patches (1 x 1 cm²) were tested for uniformity of weight and the results are given in the Table 2. All the patches were found uniform. The average weight values ranged between 19.4 ±1.3115mg and 20.5±1.36mg. Standard deviation of all the patches ranged between 0.1725 and 0.4167. Films did not show any cracks even after folding for more than 300 times. The mucoadhesion properties of all formulations were satisfactory. The surface pH of all Amitriptyline patches was within ± 0.3 units of the neutral pH and hence no mucosal irritation was expected.

Swelling behavior of selected patches as a function of time is illustrated in fig 2. The swelling indices(%) were found to be varied between 118 to 188.33. Swelling behavior increased with increase in the proportion of HPMC and increased water uptake of the polymer. It is in the order of F2<F34<F4<F5<F6. The patches did not show variation any appreciable change in shape, integrity of buccal films during study period. Ultimately patient compliance is achieved.

The invitro release of Amitriptyline from different patches is shown in fig 1. All the formulations released the drug >70% within 80 minutes. Formulation F6 showed the maximum release of 96.41% at the end of 80 min with increase in the proportion of HPMC in the buccal films, the amount of drug released also increased. This represents the polymer concentration influenced the drug release. The formulation F5 showed sudden increase in the drug release from 60 min to 70 min range. Formulations F4 and F5 gave drug release in the range of 88.2-89.52% at the end of 80 min. Formulation F2 and F3 showed the drug release 70.06% and 72.03%. From these two observations, a small increase in the proportion of the HPMC contributed a little variation in the drug release pattern. The formulations F2 to F6 showed the drug release in the range of 70 to 96 % in the time period of 80 min in phosphate buffer solution pH – 6.6.
CONCLUSION

The conclusions drawn from the present investigations are Mucoadhesive buccal films of Amitriptyline containing 10 mg of drug were prepared successfully using HPMC polymer in different proportions and totally six films were prepared based on the observations, five formulations were selected and used for further analysis. The films exhibited satisfactory characteristics regarding integrity, flexibility, dispersion of drug and other quality control parameters. The F1 formulation patch was not formed. The invitro release of Amitriptyline from the F2 to F6 was in the range of 70 to 96 % in 80 min in phosphate buffer solution pH – 6.6. Thus the objectives of the present work were achieved, the F6 formulation giving the good results. Good results were obtained from invitro conditions for Amitriptyline films.
Hence the development of bioadhesive buccal formulations for Amitriptyline may be a promising dosage form and hence side effects may be reduced.

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REFERENCES

