FORMULATION & EVALUATION OF TRANSDERMAL PATCHES OF BUCLIZINE DIHYDROCHLORIDE


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1.1. ABSTRACT
Transdermal drug delivery has made an immense contributions in pharmaceutical field. It's a patch that delivers a specific amount of medication through the skin into the bloodstream. The main advantage of the transdermal patch is that drug delivery takes place directly into the systemic circulation, bypassing the gastrointestinal system and thus avoiding a first-pass effect in the liver. One advantage of the transdermal route of drug delivery over other types of drug delivery is that the patch allows a controlled release of the drug into the patient, usually through a porous membrane that covers a drug reservoir or melts it. Thin layers of medicine are embedded in a binder using body heat. The present investigation aimed to construct buclizine dihydrochloride transdermal films, using the mercury substrate method, and to evaluate physicochemical parameters such as thickness, weight change, moisture absorption, moisture content, folding strength and drug content value. Three transdermal patches were prepared using different concentrations of ethyl cellulose. It was concluded that as the polymer concentration increased, the thickness of the patch, weight uniformity and folding strength also increased. The percentage of moisture and the percentage of moisture absorption decreased with increasing polymer concentration.

KEYWORDS: Transdermal Patch, Skin, Buclizine Dihydrochloride, Ethyl cellulose.

1.2. INTRODUCTION
Although many medications are now taken orally, it no longer effectively monitors when necessary, hence TDDS was developed as a character enhancement. Through skin contact, a medicine's systemic impact is achieved through administered drug administration. As a
method of transdermal medication administration.[1] These are art dosage forms with medication administration at affordable rates that occasionally have a therapeutic impact on the dermal tissue of the skin.[2] Drug divisions are conveyed in the blood throughout the body traffic congestion despite being of utmost importance. The transdermal skin patch is identified as a medicated adhesive plaster that should be put to the skin and release a predetermined amount of medicine via the skin before entering the circulatory system.[3]

1.2.1. Transdermal medication delivery methods provide the following benefits[4,5]
1. Possibility of self-medication.
2. Fewer adverse effects.
3. The medication concentration in plasma is maintained.
4. A decrease in administration frequency.
5. More widespread applicability and simple to memorise than nasal and oral cavity.

1.2.2. Transdermal drug delivery method drawbacks[6,7]
1. The potential for allergic responses.
2. Drugs with a high molecular weight have no therapeutic benefit.
3. Delivered to Ion Pharmaceuticals
4. There must be a significant gap in time.

1.2.3. Skin anatomy and physiology
The human skin is made up of three separate but related tissues[8-11]
"Epidermis" cells that are stratified and vascular, "lower dermis connective tissue," and the subcutaneous layer

• Cuticle
Depending on the size and quantity of the cells in the cuticles, the thickness of the epidermis varies, ranging from 0.8 mm at the base of the palm to 0.06 mm above the eyelid. It possesses a viable epidermis and an exterior stratum corneum.

i) Stratum Corneum
The stratum corneum, the skin's outermost layer, is another name for it. It is around 10 mm thick while dry, but when fully hydrated, it expands to a thickness several times greater. It has between 10 and 25 layers. Keratinocytes are dead cells that have been keratinized. Although flexible, it is largely waterproof. The stratum corneum acts as a significant
impediment to drug entry. A wall-like structure can be used to simulate the stratum corneum's architecture. According to this paradigm, keratinized cells serve as "bricks" made of proteins and lipids as "mortar." Numerous bilayers are used to organise lipids. The polar free fatty acids and cholesterol found in lipid fractions are enough amphoteric substance to keep the bilayer structure.

ii) Viable Epidermis
The epidermis ranges in thickness from 0.06 mm on eyelids to 0.8 mm on the palm and is found underneath the stratum corneum. It has several layers within, including a light layer, layer seeds, spines, and bottoms. The epidermis is continually renewed by cells going through mitosis at the basal layer, and this proliferation makes up for the loss of horny, dead skin cells from the skin's surface. The outermost layer of the stratum corneum is formed when cells produced by the base layer travel outward, change shape, and chemically go through keratinization.

• Dermis
The dermis is a layer that is 3 to 5 mm thick and is made up of a matrix of connective tissue that houses nerves, lymphatic vessels, and blood vessels. The skin's ability to circulate blood is crucial for controlling body temperature. While eliminating pollutants and waste, it also gives the skin nutrition and oxygen. The capillaries penetrate 0.2 mm of the skin's surface, creating favourable circumstances for most molecules to get through the skin barrier. Blood keeps the concentration of skin with very low permeability and the resultant concentration at a constant level. The necessary gradient of concentration is provided by differentiation via the epidermis for transdermal penetration.

• Hypodermis
Subcutaneous tissue or the subcutaneous layer helps the dermis and epidermis to function. It functions as a place to store fat. This layer offers mechanical and nutritional support as well as temperature regulation. Large blood arteries, nerves, and even pressure-sensing organs are carried there to the skin. When taking only topical medications, penetration through the stratum corneum is necessary and it is preferable to keep the drug within the layers of the skin because drug transport through the skin requires the drug to pass through these three layers in order to achieve systemic circulation.
1.3. AIM AND OBJECTIVE
Main objective of study is to develop transdermal patch

- To achieve more patient compliance.
- To reduce the dosing frequency.
- To enhance the release rate of drug for quick onset of action.
- To avoid the oral administration of drug to omit the GIT related bioavailability problems.
- To avoid the First Pass Effect.

1.4. MATERIALS AND METHODS
Materials
All the chemicals used in this research were of standard pharmaceutical grade.

- Buclizine Dihydrochloride (Drug was bought from the Yarrow Chem Products, L.B.S. Marg, Ghatkopar West, Mumbai.)
- Ethyl Cellulose (Titan biotech Ltd., Bhiwadi, Rajasthan),
- Glycerine (Loba Chemicals, Mumbai.)
- HPMC (Loba Chemicals, Mumbai)
- Methanol (Nice Chemicals, Cochin) and
- Chloroform (SD Fine chemicals, Mumbai) were of analytical reagent grade.
Methods

- Buclizine Dihydrochloride was used for the treatment of allergies.
- Ethyl Cellulose was used for the formulation of Transdermal Patch.
- Glycerol was used as a plasticizer.
- DMSO is used as penetration enhancer.
- The polymer was dissolved in chloroform: methanol (1:1) solvent.
- The drug was dispersed uniformly in the viscous solution with continuous stirring.
- The resulting mass was poured into leveled mercury surface in a Petri dish covered with inverted funnel.
- The Petri dish was left undisturbed at room temperature for one day.
- The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of 2cm².

1.5. EXPERIMENTAL STUDY

PREFORMULATION STUDIES OF SELECTED DRUG.[12,13,14]

1. Detailed Description
Powder that is white or almost white, as stated.

2. Determination of Solubility
Buclizine hydrochloride solubility was determined by mixing 1 g of the medication with 10 ml each of distilled water, chloroform, ethanol, and methanol. It was decided what was soluble at room temperature.

3. Melting point
Using a melting point equipment, the pure drug's melting point was identified. The thermometer in question has been calibrated before. The procedure entails heating the powdered substance in a Thiele setup using a calibrated tube. The temperature at which a sample begins to melt is thought of as the lower limit, and the temperature at which it entirely melts as the upper limit of the melting range. The outcome was evaluated against the reference values.

4. Partition Coefficient
Buclizine Dihydrochloride in Water at a known concentration was shaken for 1 hour with an equivalent amount of n-octanol in a separating funnel. 4 hours of standing permission. The organic phase and aqueous phase were then separated and collected. After the proper dilution,
a U.V. spectrophotometer was used to measure the concentration of BUZ at 230 against a blank. The partition coefficient was obtained by dividing the drug concentration in n-octanol by the drug concentration in the aqueous phase. Three readings on average were collected.

**STUDIES ON FORMULATION**
- **Method of Solvent Evaporation**
  1) Suitably sized amounts of polymers were combined with various compositions of solvent. (For 1 to 2 hours, sonication)
  2) Next, 40 mg of the medication were gradually introduced. (One hour of sonication)
  3) Next, the necessary amount of glycerol & DMSO were added as plasticizer and penetration enhancer, respectively.
  4) Then it was put onto a Petri plate made of glass. Then it was put in a hot air oven to evaporate.
  5) An inverted funnel was positioned above the Petri plate to regulate the solvent's rate of evaporation.

**1.6. FORMULATION DESIGN**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buclizine Dihydrochloride(mg)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Methyl Cellulose (mg)</td>
<td>70</td>
<td>70</td>
<td>80</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Chloroform(ml)</td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Methanol(ml)</td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>DMSO(ml)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Glycerol in % w/w</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>HPMC In Parts(mg)</td>
<td>40</td>
<td>50</td>
<td>80</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

**1.7. EVALUATION & CHARACTERISTICS**

**Physical appearance**
Transperancy, Stickiness, flexibility, and smoothness were all checked visually on each transdermal film.

**Thickness**
The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.\(^{[15]}\)
Uniformity of weight
Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.\cite{16,17}

Folding Endurance
A strip of a particular area must be cut uniformly and folded repeatedly at the same spot until it breaks. The amount of simultaneous folds that a film could undergo location without breaking provided the folding endurance value.\cite{18}

Drug Content
A given patch area needs to be dissolved in a predetermined volume of a suitable solvent. Following the solution's filtering via a filter media, the drug content must be determined using the appropriate technology (UV or HPLC). Every number is the average over three samples.\cite{19-21}

Percentage Moisture Uptake
To maintain 84% RH, the weighted films must be stored in desiccators at room temperature for 24 hours with saturated potassium chloride solution. The films must be reweighed after 24 hours to calculate the % moisture absorption using the procedure below.\cite{22-23}

\[
\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} / 100
\]

Moisture Loss
Each of the manufactured films has to be weighed before being stored at 40°C in a desiccator with calcium chloride. The films must be reweighed after 24 hours in order to calculate the percentage of moisture loss using the formula below.\cite{24}

\[
\% \text{ Moisture loss} = \frac{\text{Initial wt} - \text{Final wt}}{\text{Final wt}} \times 100.
\]

In-vitro drug diffusion studies
A modified Franz diffusion cell.\cite{25} with a 50 ml receptor compartment capacity is used for these research. The artificial cellophane membrane was attached to the diffusion cell's donor and receptor compartments. The prepared patches were divided into 1 cm2 squares, applied over adhesive taps, secured to cellophane membranes, and connected to glass tubes using rubber bands. Phosphate buffer pH 7.4 was poured into the receptor compartment of the
diffusion cell as well as the drug-releasing membrane. 32°C was kept as the temperature. The 3ml samples were taken out at intervals of 10, 20, 30, 60, 120, 180, and 720 minutes, and the drug concentration was measured spectrophotometrically at a maximum wavelength of 270 nm against a blank. At each sample removal, an equivalent volume of phosphate buffer was added to the receptor phase to refill it.

![Franz Diffusion Cell](image)

**Figure: Franz Diffusion Cell.**

1.8. RESULT AND DISCUSSIONS

**Preformulation study of Buclizine Dihydrochloride**

**Detailed Description of Buclizine Dihydrochloride**

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White or almost white, crystalline powder</td>
<td>Almost white, crystalline powder.</td>
<td></td>
</tr>
</tbody>
</table>

**Solubility of Buclizine Dihydrochloride**

It was discovered that the buclizine dihydrochloride is not dissolved in phosphate Buffer & water. Very little soluble in methanol and sparingly soluble in water.

**Solubility of Buclizine Dihydrochloride**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Descriptive terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distilled water</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Phosphate buffer pH 7.4</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Very slightly soluble</td>
</tr>
</tbody>
</table>
Melting point
Melting point of Buclizine Dihydrochloride was found to be 230 to 240°C. Result are shown as follows

Partition coefficient
Partition coefficient of Buclizine Dihydrochloride was found to be 3.5 to 4.5, Result are shown as follows

Melting point and partition coefficient Buclizine Dihydrochloride

<table>
<thead>
<tr>
<th>Studies</th>
<th>Melting point (°C)</th>
<th>Partition coefficient (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>231 (±0.05)</td>
<td>3.7 (±0.02)</td>
</tr>
<tr>
<td>Limits</td>
<td>230-240°C</td>
<td>4-5</td>
</tr>
</tbody>
</table>

Evaluation Tests

- Physical Appearance
The various batches of patches were all found to be opaque, non-sticky, flexible, smooth, and of a homogenous character.

Physical appearance of patches of Buclizine Dihydrochloride

<table>
<thead>
<tr>
<th>Formulation Batch</th>
<th>Stickiness</th>
<th>Smoothness</th>
<th>Flexibility</th>
<th>Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Non-sticky</td>
<td>Smooth</td>
<td>Flexible</td>
<td>Opaque</td>
</tr>
<tr>
<td>F2</td>
<td>Non-sticky</td>
<td>Smooth</td>
<td>Flexible</td>
<td>Opaque</td>
</tr>
<tr>
<td>F3</td>
<td>Non-sticky</td>
<td>Smooth</td>
<td>Flexible</td>
<td>Opaque</td>
</tr>
<tr>
<td>F4</td>
<td>Non-sticky</td>
<td>Smooth</td>
<td>Flexible</td>
<td>Opaque</td>
</tr>
<tr>
<td>F5</td>
<td>Non-sticky</td>
<td>Smooth</td>
<td>Flexible</td>
<td>Opaque</td>
</tr>
</tbody>
</table>

Weight uniformity, Folding Endurance, Thickness and Drug content of films of Buclizine Hydrochloride
The weight of patch, its folding endurance, thickness of patch & drug content of different batches of formulation of Buclizine dihydrochloride are given in the following table as follows:-

Weight, Folding Endurance, Thickness and Drug content of films of Buclizine Dihydrochloride

<table>
<thead>
<tr>
<th>Formulation Batch</th>
<th>Weight* (mg)</th>
<th>Thickness* (mm)</th>
<th>Folding Endurance</th>
<th>Drug content (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>360.5(±0.50)</td>
<td>0.065(±0.005)</td>
<td>&gt;300</td>
<td>96.02(±0.62)</td>
</tr>
<tr>
<td>F2</td>
<td>494.8(±0.82)</td>
<td>0.15(±0.008)</td>
<td>&gt;200</td>
<td>97.25(±0.95)</td>
</tr>
<tr>
<td>F3</td>
<td>365.5(±0.87)</td>
<td>0.066(±0.006)</td>
<td>&gt;300</td>
<td>99.20(±0.70)</td>
</tr>
</tbody>
</table>
Evaluation of % Moisture absorption, % Moisture loss

Percentage moisture absorption and percentage moisture loss was found to be acceptable. The results are shown as follows.

**Evaluation of % Moisture absorption, % Moisture loss of Buclizine Dihydrochloride**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% Moisture absorption</th>
<th>% Moisture loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.02(±0.057)</td>
<td>1.22(±0.98)</td>
</tr>
<tr>
<td>F2</td>
<td>1.52(±0.042)</td>
<td>2.22(±0.92)</td>
</tr>
<tr>
<td>F3</td>
<td>1.34(±0.022)</td>
<td>2.34(±0.72)</td>
</tr>
<tr>
<td>F4</td>
<td>1.45(±0.036)</td>
<td>1.99(±0.68)</td>
</tr>
<tr>
<td>F5</td>
<td>2.44(±0.065)</td>
<td>1.85(±0.42)</td>
</tr>
</tbody>
</table>

**In-Vitro Drug Diffusion Studies**

The cumulative percentage release of Buclizine Dihydrochloride from films F1, F2, F3, F4 & F5 were 89.04, 93.80, 96.98, 87.46 & 86.46 respectively at the end of 12 h. The batch F3 containing concentration of and DMSO was optimized, here DMSO act as a penetration enhancer. The results are given in below table.

**In – Vitro Drug Release of Buclizine Dihydrochloride of batches F1 to F5**

<table>
<thead>
<tr>
<th>Time in Hrs.</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Cumulative drug release *</td>
<td>% Cumulative drug release *</td>
<td>% Cumulative drug release *</td>
<td>% Cumulative drug release *</td>
<td>% Cumulative drug release *</td>
</tr>
<tr>
<td>1</td>
<td>39.76</td>
<td>39.84</td>
<td>39.84</td>
<td>38.65</td>
<td>40.23</td>
</tr>
<tr>
<td>2</td>
<td>43.41</td>
<td>45.07</td>
<td>45.15</td>
<td>44.60</td>
<td>43.80</td>
</tr>
<tr>
<td>3</td>
<td>47.69</td>
<td>48.60</td>
<td>49.76</td>
<td>49.12</td>
<td>47.77</td>
</tr>
<tr>
<td>4</td>
<td>51.34</td>
<td>55.63</td>
<td>56.90</td>
<td>55.71</td>
<td>52.93</td>
</tr>
<tr>
<td>5</td>
<td>55.71</td>
<td>60.87</td>
<td>61.66</td>
<td>59.68</td>
<td>55.63</td>
</tr>
<tr>
<td>6</td>
<td>59.28</td>
<td>63.65</td>
<td>65.23</td>
<td>63.65</td>
<td>57.69</td>
</tr>
<tr>
<td>7</td>
<td>63.8</td>
<td>67.31</td>
<td>71.58</td>
<td>68.80</td>
<td>63.65</td>
</tr>
<tr>
<td>8</td>
<td>69.12</td>
<td>72.69</td>
<td>74.74</td>
<td>71.58</td>
<td>68.80</td>
</tr>
<tr>
<td>9</td>
<td>73.17</td>
<td>77.75</td>
<td>79.52</td>
<td>74.44</td>
<td>71.58</td>
</tr>
<tr>
<td>10</td>
<td>78.49</td>
<td>83.49</td>
<td>85.77</td>
<td>79.52</td>
<td>75.71</td>
</tr>
<tr>
<td>11</td>
<td>82.69</td>
<td>88.45</td>
<td>90.63</td>
<td>83.49</td>
<td>79.52</td>
</tr>
<tr>
<td>12</td>
<td>89.04</td>
<td>93.80</td>
<td>96.98</td>
<td>87.46</td>
<td>86.46</td>
</tr>
</tbody>
</table>

**1.9. CONCLUSION**

Transdermal drug delivery has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood.
stream. The Transdermal Patch Of Buclizine Dihydrochloride was prepared and evaluated. Total Five Patches of buclizine dihydrochloride were prepared.

Different Evaluation Tests were carried out like Physical appearance, % Moisture absorption, % Moisture loss, Weight uniformity, Folding Endurance, Thickness and Drug content And Diffusion study of formulation F1 to F5 were found to be satisfactory. The Evaluation studies show that the Formulation F3 having less thickness, high folding endurance, less moisture content, and have optimum uniformity of weight characteristic as compared to other formulations. They also have more drug content than other formulations.

REFERENCES


