FORMULATION AND DEVELOPMENT OF TRANSDERMAL PATCH OF TIZANIDINE HYDROCHLORIDE

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ABSTRACT
Tizanidine Hydrochloride, is an centrally acting myotonolytic skeletal muscle relaxant. It undergoes first pass metabolism on oral administration resulting in less bioavailability (40%). Present research work was carried out to formulate and develop transdermal patch of Tizanidine hydrochloride which will overcome the limitation of bioavailability. In the present study transdermal patches were prepared by solvent-casting method using hydrophilic polymer HPMC E-5 LV, chitosan, Moringa oleifera gum and Propylene Glycol as plasticizer. The six formulations were prepared and evaluated. Accelerated stability studies of drug containing films, were performed according to ICH guidelines. It was found that, Moringa oleifera gum has potential to modify drug release rate and posses good film former and adhesive property. The transdermal patch has shown promising drug release within 12 hr (84.36%), good stability and no irritancy.

KEYWORDS
Tizanidine Hydrochloride, Transdermal patch and Moringa oleifera gum.

INTRODUCTION
Today about two third of drugs (available in market) are taken orally, but these are not as effective as required¹. Conventional oral dosage forms are required to be administered in multiple doses at a specific time interval in aspecific amount for an effective therapy. Administration of the drugs in multiple dosage has several drawbacks such as inconvenient administration, chances of overdose if administered prior to time interval, lack of patient compliance, skip of dose by the patient, fluctuation of drug plasma level, first pass metabolism, to avoid such complications transdermal drug delivery
systems are designed. Transdermal therapeutic systems are self-contained, discrete dosage forms which, when applied to the intact skin deliver the drug, through the skin at a controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system deliver drug at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drug.

Tizanidine Hydrochloride, is an centrally acting myotonolytic skeletal muscle relaxant. It undergoes first pass metabolism on oral administration resulting in less bioavailability (40%) hence there is need to develop formulation to overcome limitation of bioavailability. Thus the main objective of the present study was to formulate and develop transdermal patch of tizanidine hydrochloride.

**Anatomy of skin**

Human skin comprises of three distinct but mutually dependent tissues, the stratified, vascular, cellular epidermis, underlying dermis of connective tissues and Hypodermis.

**Principles of transdermal permeation**

The various steps involved in transport of drug from patch into systemic circulation are as follows:

- Diffusion of drug from drug reservoir to the rate controlling membrane.
- Diffusion of drug from rate limiting membrane to stratum corneum.
- Sorption by stratum corneum and penetration through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.

**Transdermal patches**

A transdermal patch is also known as skin patch which is used to deliver the specific amount of dose through skin and it directly goes into the blood stream.

**MATERIAL AND METHODS**

**Material**

Tizanidine Hydrochloride was gifted by Blue cross, Nashik. *Moringa oleifera* gum was naturally collected from stem of plant of *Moringa oleifera*.

HydoxyPropyl Methyl Cellulose and Chitosan were purchased from local market.

**Moringa oleifera gum**

**Collection and authentication**

The *Moringa oleifera* tree was identified. The tree trunk was incised working from the base up towards the branches. The incisions were 10-15 mm long and 4-5 mm deep. The gum then started seeping out from the incisions and coagulated in 10-20 days. The gum was collected after drying and authenticated by Ayurved Seva Sangh’s Ayurved Mahavidyalaya, Ganeshwadi, Panchvati, Nashik

**Isolation and purification of gum**

The dried gum was ground, and passed through sieve no 80 and (10 g) was stirred in distilled water (250 ml) for 6-8 hr at room temperature. The supernatant was obtained by centrifugation. The washing of residue was done with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with distilled water and dried at 50-60°C under vacuum.

**Evaluation of Moringa oleifera gum**

The gum was evaluated for loss on drying, pH determination, test for Tannin, test for Starch, test for Sucrose and fructose, Swelling power test as per official procedure in IP.

**Compatibility Studies**

A compatibility study for Tizanidine Hydrochloride was carried out with potential formulation excipients i.e.Chitosan, *Moringa oleifera* gum, PG and HPMC. These samples were mixed together as per formula, stored for 30 days at elevated temperature and humidity conditions of 40 ± 2°C / 75 ± 5 % RH. After30days IR spectra of these stored samples was obtained.DSC was performed to check if any large shift of exothermic peak of drug in mixture. Mettler DSC 820 (SHIMADZU60).The assay of drug was performed using U.V. Spectrophotometer.

**Formulation of Transdermal patch of Tizanidine Hydrochloride**

The composition of Tizanidine Hydrochloride transdermal patches is given in Table No.1

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Preparation of transdermal patches
Solvent casting technique
The transdermal patches prepared by solvent casting technique are of matrix diffusion controlled systems.

Procedure for patches containing Chitosan and HPMC
For (F1 to F3): The polymer was weighed and stirred in distilled water for 2 hrs. Then Propylene glycol was added to the polymeric solution, mixed thoroughly by means of Magnetic stirrer. Tizanidine Hydrochloride 6mg was added prior dissolving in sufficient of water then the resulting solution was poured in to petri plate. This petri plate were kept into hot air oven for 12hrs at 45° C, the patches were removed and stored in desiccator for further use.

Procedure for patches containing Moringa oleifera gum and HPMC
For (F4 to F6): The drug reservoir was prepared by dissolving Moringa oleifera gum and HPMC in distilled water. Propylene glycol and Tizanidine Hydrochloride6mg dissolved in sufficient amount of water was added under slow stirring. It was poured in petri plate. Which was kept in hot air oven for 1 hrs at 45°C, and then the patches were removed and stored in desiccator.

Physicochemical evaluation of transdermal patches
The transdermal patches were evaluated for.
Uniformity of weight
Three different patches from individual batch were weighed average weight was calculated.

Thickness of the patch
It was measured by using vernier caliper at different points and average value was calculated.

Percentage Moisture loss
It was calculated for three different patches from individual batches by keeping them in desiccators containing calcium chloride at 37°c for 24 hrs.

Folding Endurance
This was determined by repeatedly folding one film at the same place till it broke.

Drug content determination
It was determined by cutting patch of size 1cm² diameter and dissolving it in Phosphate buffer of pH 7.4. The medium was stirred, filtered and analyzed for drug content at 318nm by UV spectrophotometer.

In-vitro drug release studies
Preparation of rat Abdominal Skin
The male rats were sacrificed by excess Diethyl ether inhalation and hair on the abdominal skin was removed with a razor. The shaved skin was excised from the animal and kept in the beaker containing distilled water covered with Aluminum foil.

In-vitro Drug Release
The fabricated film was placed on the rat skin and attached to the diffusion cell such that the cell’s drug releasing surface was towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±1°C. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 318 nm.

Kinetics of drug release
The cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q0-Q) v/s t], Higuchi’s square root of time (Q v/s t1/2) and KorsemeyerPeppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

Skin irritation study
The skin irritation study was conducted with prior permission of Institutional Animal Ethical committee (IPEC) under the purview of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), on male Wistar rats. The dorsal side of rat was applied with hair remover cream, under anesthesia, 24 hr. before the beginning of experiment. The animals were divided into 4 groups. Each group was consisting of 5 rat: Group I served as control, Group II was applied 0.5 ml of a 0.8% V/V aqueous formalin solution topically as a standard irritant. Group III was applied with diclofenac transdermal patch as standard, Group IV was treated with medicated Patch. The application site was examined for edema
and erythema after 24 and 72 hr, and graded (0-4) according to visual scoring scale always by the same investigator, the final score represents the average of 24 and 72 hr. reading. The erythema scale was: 0- none, 1- slight, 2- well define, 3- moderate, 4- scare formation. Edema scale was: 0- none, 1- slight, 2- well define, 3- moderate, 4- severe.

**Stability study for F4**

Stability studies of formulation F4 was done as per ICH guidelines. In which the formulation was stored at 45°C and 75%RH for 90 days and evaluated for physical changes, hardness, friability, drug content and percentage drug release.

**RESULTS AND DISCUSSION**

**Evaluation of isolated and purified *Moringa oleifera* gum**

The evaluation of *Moringa oleifera* gum was carried out, the evaluation test results are shown in Table No.2.

**Drug-Polymers Interaction Studies**

**Infrared Spectroscopy**

Drug-excipients interaction study showed no interaction between Tizanidine Hydrochloride and selected polymers as there was no significant shift of peaks in IR spectrum.

**Differential Scanning Calorimetry**

DSC analysis was performed by taking 2 to 5 mg sample. Results have shown that the sharp exothermic peak was observed of the drug individually at 282°C, corresponding to its melting point (282°C -290°C). Thus the Tizanidine Hydrochloride was found to be compatible with the selected excipients.

**Evaluation of transdermal patches**

**Physical appearance**

All patches from F1-F6 were found to be smooth in nature and had good appearance.

**Weight Uniformity**

The average weight and thickness of all the films is given in Table No.3. Weight variation values (mg) of different Tizanidine Hydrochloride films were found to be in the range of 625± 0.0247 to 734± 0.0433 mg.

**Thickness**

The average thickness of all the films is given in Table No.3 the average thickness of all the transdermal patch ranged from 0.99± 0.0212 to 2.36± 0.04716 mm.

**% Moisture loss**

The value of % moisture loss was found to be between 0.99-2.36 for all formulations.

**Drug content uniformity**

Tizanidine HCl has shown maximum absorbance at 319nm in phosphate buffer pH 7.4 hence percentage drug content was determined by UV spectrophotometer in phosphate buffer.

**Folding endurance**

The number of folding required to break or crack a film was taken as the folding endurance. The folding endurance was found to be increased with an increasing concentration of chitosan and *Moringa oleifera* gum.

**Ex Vivo Drug Release Studies**

**Ex Vivo** skin permeation study shows a drug release profiles are shown in Figure No.1 and Figure No.2. And drug release was successfully observed for all patches. The drug release profile shown in Table No.4

**Kinetics of Drug Release**

The kinetic Drug release study was performed for all batches of transdermal patches. From this, drug release profile of optimised batch F4 is given below. The release data of formulation F4 was fitted into release rate equations such as zero-order, first order, Higuchi’s square root time dependent diffusion and Korsmeyer-peppas exponential equation. It was found it follows Zero-order with diffusion controlled mechanism. By fitting in the Korsmeyer–Peppas equation the release kinetics follows Fickian and non-fickian kinetics. As the range of ‘n’ value for Korsmeyer–Peppas’s equation is 0.726.

**h. Accelerated Stability Studies**

In the results of stability studies performed on batch F4, after the 90 days, it was found that there was no change in appearance of the films and negligible change in thickness.
i. Skin irritation study
Skin irritation test was performed on Wistar Rats for F4 formulation and there were no signs of redness or erythema observed for 72hrs after application of patch.

Table No.1: Composition of Tizanidine Hydrochloride transdermal patches

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Tizanidine HCl(mg)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>HPMC(mg)</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>Chitosan(mg)</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td><em>Moringa oleifera</em> gum</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Propylene Glycol(ml)</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>Distilled water(ml)</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>Acetic acid(ml)</td>
<td>q.s</td>
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</table>

Table No.2: Evaluation of isolated and purified *Moringa oleifera* gum

<table>
<thead>
<tr>
<th>S.No</th>
<th>TEST</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH</td>
<td>4.7(Acidic)</td>
</tr>
<tr>
<td>2</td>
<td>LOD</td>
<td>47.5%</td>
</tr>
<tr>
<td>3</td>
<td>Test for Tannin</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>Test for Starch</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>Test for Sucrose and Fructose</td>
<td>Absent</td>
</tr>
<tr>
<td>6</td>
<td>Swelling power</td>
<td>30.28 ml</td>
</tr>
</tbody>
</table>

Table No.3: Physicochemical evaluation parameters of Tizanidine Hydrochloride transdermal patch

<table>
<thead>
<tr>
<th>FC</th>
<th>Weight Uniformity (mg)</th>
<th>Thickness (mm)</th>
<th>% moisture loss</th>
<th>Drug content uniformity (mg)</th>
<th>Folding endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>633± 0.1071</td>
<td>0.260± 0.01</td>
<td>2.36± 0.04716</td>
<td>105.8 ± 7.07</td>
<td>152 ± 2</td>
</tr>
<tr>
<td>F2</td>
<td>634± 0.0240</td>
<td>0.271± 0.00854</td>
<td>1.466± 0.0387</td>
<td>109.5 ± 6.30</td>
<td>158 ± 1.595</td>
</tr>
<tr>
<td>F3</td>
<td>625± 0.0247</td>
<td>0.279± 0.0524</td>
<td>1.116± 0.1587</td>
<td>102.59 ± 8.70</td>
<td>165.3 ± 2.38</td>
</tr>
<tr>
<td>F4</td>
<td>664±0.00552</td>
<td>0.0733± 0.00067</td>
<td>2.25± 0.02</td>
<td>105.82 ± 4.85</td>
<td>208 ± 1.581</td>
</tr>
<tr>
<td>F5</td>
<td>697±0.01977</td>
<td>0.0783± 0.00735</td>
<td>1.286± 0.0360</td>
<td>110.33 ± 10.41</td>
<td>210.6 ± 2.310</td>
</tr>
<tr>
<td>F6</td>
<td>734± 0.0433</td>
<td>0.0887±0.00961</td>
<td>0.99± 0.0212</td>
<td>105.30 ± 8.847</td>
<td>217 ± 3.08</td>
</tr>
</tbody>
</table>

Table No.4: drug release profile of F1- F6 for Ex Vivo skin permeation study

<table>
<thead>
<tr>
<th>S.No</th>
<th>Time in hrs</th>
<th>F1 (%)</th>
<th>F2 (%)</th>
<th>F3 (%)</th>
<th>F4 (%)</th>
<th>F5 (%)</th>
<th>F6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>28.51238</td>
<td>26.01543</td>
<td>22.32496</td>
<td>38.70435</td>
<td>27.33457</td>
<td>25.9055</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>40.59512</td>
<td>36.2922</td>
<td>32.53891</td>
<td>48.98112</td>
<td>43.15489</td>
<td>33.52827</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>50.76196</td>
<td>48.73613</td>
<td>45.72094</td>
<td>57.34199</td>
<td>55.41038</td>
<td>41.60647</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>65.04328</td>
<td>56.46884</td>
<td>55.46377</td>
<td>70.74387</td>
<td>68.60811</td>
<td>61.3057</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>83.98872</td>
<td>74.34639</td>
<td>70.98572</td>
<td>84.36562</td>
<td>77.59715</td>
<td>76.41934</td>
</tr>
</tbody>
</table>

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**Table No.5: Kinetic parameters of Tizanidine HCl transdermal patch**

<table>
<thead>
<tr>
<th>FC</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.987</td>
<td>0.977</td>
<td>0.987</td>
<td>0.987</td>
</tr>
<tr>
<td>F2</td>
<td>0.988</td>
<td>0.975</td>
<td>0.988</td>
<td>0.985</td>
</tr>
<tr>
<td>F3</td>
<td>0.988</td>
<td>0.987</td>
<td>0.988</td>
<td>0.974</td>
</tr>
<tr>
<td>F4</td>
<td>0.991</td>
<td>0.934</td>
<td>0.991</td>
<td>0.993</td>
</tr>
<tr>
<td>F5</td>
<td>0.994</td>
<td>0.955</td>
<td>0.994</td>
<td>0.988</td>
</tr>
<tr>
<td>F6</td>
<td>0.963</td>
<td>0.990</td>
<td>0.963</td>
<td>0.956</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The six formulations transdermal patches were prepared by solvent-casting method and evaluated for physical parameters along with Ex vivo skin permeation studies and skin irritation studies. It was found that, folding endurance was increased with an increase in chitosan and *Moringa oleifera* gum concentration. Optimized batch F4 showed good folding endurance i.e. 208. Ex Vivo skin permeation study has shown drug release 84.36% within 12 hr, it has shown no irritancy in skin irritation studies. There was no significant change in the physical parameters when stored at temperature and humidity conditions of 40 ± 2°C / 75 ± 5% RH in stability studies carried out as per ICH guidelines. Thus, *Moringa oleifera* gum has potential to modify drug release rate and posses good film former and adhesive property.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

BIBLIOGRAPHY