Development and evaluation of matrix diffusion controlled Transdermal patches of Donepezil

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ABSTRACT

Background study: Transdermal drug delivery systems (TDDS) are a class of novel drug delivery systems, which are gaining worldwide accolade, as evidenced by researchers. Objective: The present work was aimed at developing a matrix dispersion type transdermal drug delivery of donepezil, an alzheimer drug to ensure satisfactory drug release with the use of optimum polymers and thereby to avoid first pass metabolism and prolong duration of action. Methods: Donepezil transdermal patches were prepared by solvent casting method using aluminium foil as the backing membrane with different concentrations of hydrophobic polymeric system (eudragit L 100 & pvp) and 30% w/ w of dibutyl phthalate (DBT) as plasticizer. Different concentrations of propylene glycol were used to increase the transdermal permeation of donepezil. The drug and polymers physicochemical compatibility were studied by means of Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC). Formulated transdermal patches were evaluated for thickness, tensile strength, hardness, weight variation, swellability, flatness, folding endurance & water vapour transmission rate. Results: The physicochemical evaluation study reveals that all formulations measured weight and thickness with low standard deviation values. The results of flatness study showed that none of the formulations had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied onto the skin. The cumulative percentage drug permeation was higher in case of eudragit containing polymer matrix. Conclusion: From the evaluation studies of the transdermal patches, it may be concluded that transdermal drug delivery system of donepezil can be formulated, which provides better compliance than conventional drug delivery system.

KEY WORDS: Donepezil, transdermal patches, eudragit L 100, PVP

1. INTRODUCTION:

Transdermal drug delivery systems (TDDS) are a class of novel drug delivery systems, which are gaining worldwide accolade, as evidenced by researchers. TDDS as many advantages such as reduced side effects, less frequent administration to produce the desired plasma concentration with improved patient compliance, sustained drug delivery and interruption of treatment when necessary [1,2].

Alzheimer’s disease (AD) is the most common type of dementia, more than 100 years ago the alzheimer’s disease was first identified, but research into its risk factors, causes, symptoms, and treatment has gained momentum only in the last 30 years. The cholinesterase inhibitors (ChEIs) were the first anti-Alzheimer drugs approved by the Food and Drug Administration (FDA), by inhibiting acetylcholinesterase these are capable of improving cholinergic neurotransmission. Rivastigmine, galantamine, and donepezil these are the most common ChEIs used to treat cognitive symptoms in mild to moderate AD [3,4]. It affecting 30% of people older than 85 years and nearly 6–8% of people over the age of 65 years. In fact, it has been confirmed that the number of people over 60 years old affected by AD doubles every 5 years. The common signs and symptoms of AD include apathy, agitation, irritability, disinhibition, delusions, mood disturbances, and aberrant motor behavior, as well as sleeping and eating abnormalities. Since this disease may progress in different ways, it has become difficult to make a precise diagnosis. AD is associated with decreased levels of a number of cerebral neurotransmitters such as noradrenaline, somatostatin, serotonin,
acetylcholine (ACh), and corticotrophin releasing factors, whereas the levels of glutamate raise [5].

Donepezil is a small and lipophilic molecule, (Molecular weight: 379.5, Log P value: 3.08 - 4.11) is considered to be physicochemically well-suited for transdermal delivery. Donepezil (DNZ) is a centrally acting reversible acetyl cholinesterase inhibitor. It is mainly used in the treatment of alzheimer’s disease where it is used to increase cortical acetylcholine [6].

The main aim of the present study is to eliminating the risk that confused patients forget to take their medicine twice a day.

2. MATERIALS AND METHODS:
Donepezil was gifted by Jubilant life sciences LTD, nanjangud, mysuru, India. eudragit L 100 was obtained from degussa, India Pvt. Ltd, mumbai, India. PVP obtained as a gift sample from SRL, mumbai, India. All the other chemicals used were of analytical grade.

2.1. Formulation of patches
In the present study, matrix type transdermal patches of donepezil were prepared by solvent casting techniques. Circular, petridish coated with aluminum foil having surface area of 9 cm² were fabricated for casting the patches.

2.2. Selection of polymers
From the literature review and based on the characteristics of eudragit L 100, it was selected as parent polymer. The further need was to select polymer which can retard the drug release for or near to 24 hrs. pvp was selected as co-polymer [7-9].

2.3. Method of preparation of transdermal patch
Transdermal patches containing donepezil were prepared by solvent casting method using aluminum foil as the backing membrane. Transdermal patches were prepared according to the formula shown in Table 1. poly vinyl pyrrolidone (PVP), eudragit L 100 were weighed in requisite ratios and PVP dissolved in water and eudragit L100 dissolved in ethanol as solvent using magnetic stirrer. Donepezil (10mg) was added into homogenous dispersion under slow stirring with a magnetic stirrer. Dibutyl phthalate 30% w/w of polymer composition was used as plasticizer, added to the above dispersion under continuous stirring [10-12].

Required quantity of the prepared solution was cast on a petridish lined with aluminum foil. The cast film was dried in oven at 38±2 °C for first 8 hours and later at 60±2°C for next 48 hours. The patches were removed by peeling and cut into square dimension of 2 x 2 cm (4 cm²). These patches were kept in desiccator for 24 hrs for further drying and wrapped in aluminum foil, packed in self-sealing covers.

Table 1: Detailed formulas of transdermal patch containing donepezil

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Polymers</th>
<th>Polymer ratio</th>
<th>Plasticizer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>E. L 100</td>
<td>PVP 100</td>
<td>15</td>
</tr>
<tr>
<td>K2</td>
<td>E. L 100</td>
<td>PVP 100</td>
<td>10</td>
</tr>
<tr>
<td>K3</td>
<td>E. L 100</td>
<td>PVP 50</td>
<td>15</td>
</tr>
<tr>
<td>K4</td>
<td>E. L 100</td>
<td>PVP 150</td>
<td>10</td>
</tr>
<tr>
<td>K5</td>
<td>E. L 100</td>
<td>PVP 50</td>
<td>10</td>
</tr>
<tr>
<td>K6</td>
<td>E. L 100</td>
<td>PVP 150</td>
<td>5</td>
</tr>
<tr>
<td>K7</td>
<td>E. L 100</td>
<td>PVP 50</td>
<td>15</td>
</tr>
<tr>
<td>K8</td>
<td>E. L 100</td>
<td>PVP 50</td>
<td>10</td>
</tr>
<tr>
<td>K9</td>
<td>E. L 100</td>
<td>PVP 150</td>
<td>15</td>
</tr>
</tbody>
</table>

2.4. Screening of formulation
Total nine formulations were studied for drug release characteristics by in vitro diffusion across franz diffusion, in order to select the optimum formulation which can retard the drug for desired period of time.

2.5. Evaluation of transdermal patches:

2.5.1. Drug content and content uniformity
The patch was transferred into a graduated glass stopper flask containing 100 ml of phosphate buffer 7.4. The flask was shaken for 4 hrs in a mechanical shaker. Then the solution was filtered and 1 ml was diluted to 10 ml with phosphate buffer and the absorbance was measured at 268 nm using a placebo patch solution as blank and the drug content and content uniformity were calculated.

2.5.2. Physical characterization
The following physical evaluation studies were conducted on the prepared patches.

2.5.3. Drug excipients compatibility study
The pure drug and its formulation were subjected to IR studies. In the present study, the Potassium bromide disc (pellet) method was employed. Instrument used was Shimadzu FTIR-8400 spectrophotometer. In this study, potassium bromide disc method was employed. IR studies of pure drug and physical mixture were done. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded.

2.5.4. Thickness
The prepared 4 cm² patch was divided into four equal quadrants of (1 x 1 cm) using a marker and the thickness was measured in each
2.5.5. Weight variation
Three patches (4 cm²) from three different batches were selected randomly, were cut and weighed on digital balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.

2.5.6. Moisture uptake
The patches were dried at 40°C for 24 h and then weighed accurately up to three decimal points in gram unit and were exposed to two different relative humidity conditions of 75% RH in humidity oven (Thermolab, India) at 27±2°C. Then the weight was measured periodically to constant weight. The moisture uptake by the patches was calculated as a difference between final constant weight and initial dried weight.

\[
\text{% Moisture uptake} = \frac{(\text{Final weight of patch})-(\text{Initial weight of patch})}{\text{(Initial weight of patch)}} \times 100
\]

2.5.7. Moisture loss
The patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride (CaCl₂). After 72 hours the patches were taken out and weighed. The moisture loss was calculated using the formula.

\[
\text{% Moisture loss} = \frac{(\text{Initial weight of patch})-(\text{Final weight of patch})}{\text{(Initial weight of patch)}} \times 100
\]

2.5.8. Moisture content
In order to determine the moisture content of the patches, the patches were weighed accurately. The patches were kept in a desiccator containing calcium chloride (CaCl₂) at 40°C until it showed a constant weight. The moisture content was determined by calculating the difference between initial weight taken and the constant weight. The moisture content was reported in terms of percent moisture content.

\[
\text{% Moisture content} = \frac{(\text{Initial weight of patch})-(\text{Final weight of patch})}{\text{(Initial weight of patch)}} \times 100
\]

2.5.9. Tensile strength
Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength. The tensile strength of the patches was determined by using a tensile strength instrument as described by Agarwal GP, et al. Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

\[
\text{T.S.} = \text{break force/ a.b (1+ΔL/L)}
\]

Where a, b and L are width, thickness and length of the patch respectively. ΔL is the elongation of patch at break point. Break force = Weight required to break the patch (Kg)

2.5.10. Flatness
Three longitudinal strips are to be cut from each film at different portion like one from the left side, another one from the right side and other one from the center. The length of each strip was measured and because of non uniformity variation in the length in flatness was measured by determining percent constriction, with 0%constriction equivalent to 100% flatness.

\[
\text{% Construction} = \frac{(\text{Average thickness of patch})-(\text{Thickness at sampling point of patch})}{\text{(Average thickness of patch)}} \times 100
\]

2.5.11. Folding endurance
This was determined by repeatedly folding the patches at the same place until it broke. The number of times the patches can be folded at the same place without breaking or cracking gave the value of folding endurance.

2.5.12. In vitro drug release study
In vitro drug release studies were performed by a franz diffusion cell with a receptor compartment capacity of 7 ml. Cellophane membrane having pore size 0.45 μm and dialysis membrane having pore size 2.4 nm was employed for the determination of drug from plain donepezil transdermal films. The receptor compartment of the diffusion cell was filled with saline phosphate buffer pH 7.4. The whole assembly was fixed on the three station diffusion cell apparatus, and the solution in the receptor compartment was constantly and continuously stirred at 1000 rpm using magnetic beads and the temperature was maintained at 37 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically.

2.5.13. Ex vivo skin permeation study
Ex vivo skin permeation studies were performed by the franz diffusion cell with a receptor compartment capacity of 7 ml and effective diffusion area 3.14 cm². The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin. The receptor compartment of the diffusion cell was filled with saline phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 1000 rpm; the temperature was maintained at 37 ± 0.5°C. The samples were withdrawn at pre-determined time intervals (1, 2, 4, 6, 8, 16, 20 and 24 h) and analyzed for drug content spectrophotometrically at 268 nm. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.
2.5.14. Primary skin irritation study
The hair on the dorsal side of Wistar albino rats was removed by clipping 1 day prior to this portion of the experiment. Rats were divided into three groups (n = 6). Group I served as the control, Group II received plain piroxicam containing patch, and Group III received pirox-SLN containing the patch. After 24 h, application site was graded according to visual erythema scoring method.

3. RESULTS AND DISCUSSION:
3.1. Drug excipients compatibility study
IR studies were performed on DNZ, and a physical mixture of DNZ with EL 100 and PVP to understand the interaction between drug and polymers. From these spectras, it was observed that there was no significant change in the original peak of the drug Figure (1), when compared with the spectra of physical mixture Figure (2) and this indicates that there is no interaction between drug and polymers selected for film formation.

Fig 1: FTIR spectra of Donepezil

Fig 2: FT-IR spectra of physical mixture of Donepezil with polymers.
3.2. Characterization of transdermal patches

Matrix type transdermal patches of donepezil were prepared using eudragit L 100 and PVP as film formers by solvent casting method. Incorporation of dibutyl phthalate at a concentration of 30% w/w of dry polymers yielded smooth and flexible patches. Decreasing or increasing the concentration of dibutyl phthalate from the above mentioned value resulted in the formation of brittle or soft patches respectively. The physicochemical evaluation study reveals that all formulations measured weight and thickness with low standard deviation values. The results of flatness study showed that none of the formulations had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied onto the skin.

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three dimensional network of polymer chains. The cumulative percent drug permeation was higher in case of Eudragit containing polymer matrix.

The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. Polymer combination Eudragit L 100: PVP possessed high tensile strength. Patches require certain amount of hardness to withstand the mechanical shocks in handling, packaging and at the time of application. The hardness of the patch varied from 237 gm. to 261 gm. Homogeneous uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible sustained release of the drug from the patch. Estimation of drug content indicated that the drug is uniformly distributed throughout the patches, evidenced by the low values of the SD.

The study of the hydration of polymers used in sustained release applications has been an area of interest because it is believed that it affects drug release from controlled release matrix. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses. It varied between 15.67 to 37.35 % the swellability varied with nature and composition of patches. Hydrophilic polymer showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix. Tensile strength and swellability (%) profiles of donepezil patches sown in figure 3 & 4 respectively below.

Eudragit L 100 patch showed good water vapour permeation. The enhancement of water vapour permeation with increase of PVP is due to the irregular arrangement of molecules in the amorphous state, which usually causes the molecules to be spaced further apart than in a crystal. Hence, the specific volume is increased and the density is decreased compared to that of crystal, which leads to the absorption of vapour into their interstices. All the formulations were permeable to water vapour. Characterization of transdermal patches shown in Table 2 below.

<table>
<thead>
<tr>
<th>Code</th>
<th>Code</th>
<th>Wt. Variation</th>
<th>Thickness (mm)</th>
<th>Tensile Strength (Kg/mm²)</th>
<th>Folding Endurance</th>
<th>Hardness (%)</th>
<th>Swellability (%)</th>
<th>Water Vapour transmission (gm/cm²/24 hr)</th>
<th>Flatness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>152.8±1.23 0.323±0.0028</td>
<td>0.469±0.0046</td>
<td>245±4.54</td>
<td>259±2.62</td>
<td>15.67±0.44</td>
<td>4.55×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2</td>
<td>157.1±1.76 0.319±0.0018</td>
<td>0.459±0.0056</td>
<td>257±3.45</td>
<td>261±4.35</td>
<td>18.75±0.56</td>
<td>4.86×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K3</td>
<td>166.9±2.47 0.327±0.0019</td>
<td>0.445±0.0072</td>
<td>277±5.84</td>
<td>258±3.61</td>
<td>21.46±0.85</td>
<td>4.49×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K4</td>
<td>152.2±1.68 0.354±0.0026</td>
<td>0.439±0.0046</td>
<td>236±3.35</td>
<td>248±3.12</td>
<td>24.85±0.34</td>
<td>5.86×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K5</td>
<td>168.6±1.35 0.336±0.0039</td>
<td>0.424±0.0073</td>
<td>273±4.63</td>
<td>256±4.24</td>
<td>26.53±0.96</td>
<td>5.45×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K6</td>
<td>174.1±2.73 0.224±0.0003</td>
<td>0.419±0.0047</td>
<td>346±4.24</td>
<td>237±3.58</td>
<td>28.46±0.67</td>
<td>5.96×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K7</td>
<td>154.7±2.36 0.242±0.0039</td>
<td>0.411±0.0085</td>
<td>384±3.94</td>
<td>243±4.18</td>
<td>33.43±0.64</td>
<td>6.56×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K8</td>
<td>169.8±1.73 0.257±0.0035</td>
<td>0.398±0.0064</td>
<td>336±4.35</td>
<td>238±5.38</td>
<td>34.74±0.78</td>
<td>6.85×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K9</td>
<td>172.7±2.63 0.264±0.0039</td>
<td>0.378±0.0035</td>
<td>225±5.67</td>
<td>242±4.39</td>
<td>37.35±0.49</td>
<td>6.46×10⁴</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3. In vitro drug release study

For any drug to absorb across a biological membrane, it should release quickly and completely from the dosage form. The cumulative percentage release of donepezil from prepared transdermal films was investigated for 24 h shown in Figure 5 below. Percent drug release at the end of 24 h for formulation K-5 was found to be 90.46% which is higher as compared to other formulations. This can be explained by virtue of the higher content of hydrophilic polymer, i.e., polyvinyl pyrrolidone.

![Figure 5: In vitro drug release study profile](image)

3.4. Ex-vivo skin permeation study

The ex-vivo skin permeation of plain donepezil transdermal patches (formulation K-5) was investigated through the rat abdominal skin as shown in Figure 6. The cumulative amount of drug permeated at the end of 24 h was found to be (398.37 ± 2.19 μg/cm²) for transdermal patches which was significantly ($P < 0.05$) high. Results of the permeation parameters, such as steady state flux, lag time ($L_t$), permeability coefficient ($P$), and enhancement ratio ($E$), are as shown in Table 3.

![Figure 6: Ex-vivo skin permeation of donepezil from donepezil transdermal patch through rat abdominal skin](image)

3.5. Skin irritation testing

Skin irritation testing of donepezil transdermal patch showed skin irritation score (erythema) of ≤2 [Table 4]. According to Draize and Woodward, compounds producing scores of 2 or less are considered negative (no skin irritation). Hence, the developed transdermal formulations were free of skin irritation.

![Table 4: Skin irritation studies](image)

3.6. Preliminary testing of trial formulations

Table 5: Preliminary testing of trial formulations.

<table>
<thead>
<tr>
<th>Trial Batches</th>
<th>Polymer</th>
<th>Film forming ability</th>
<th>Film separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB 1</td>
<td>Eu L 100</td>
<td>Poor (Brittle)</td>
<td>Poor (Brittle)</td>
</tr>
<tr>
<td>TB 2</td>
<td>PVP</td>
<td>Good</td>
<td>Poor (More Brittle)</td>
</tr>
<tr>
<td>TB 3</td>
<td>Eu L 100:PVP</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

4. CONCLUSION:

From the evaluation studies of the transdermal patches, it may be concluded that transdermal drug delivery system of donepezil can be formulated, which provides better compliance than conventional drug delivery system.
ACKNOWLEDGMENT:
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REFERENCES:

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