PREPARATION AND CHARACTERIZATION OF POLYMERIC MATRIX DIFFUSIONAL TRANSDERMAL DRUG DELIVERY DEVICE OF DILTIAZEM

B.Venkateswara Reddy*, S.Satyanandam

Department of Pharmaceutics, School of Pharmacy, Monad University, Hapur, U.P, India.

ABSTRACT

In an attempt to reduce the cost of drug development process and advantageously reap the benefits of patient regime, health care firms are now investing strategically in the development of new drug delivery system. One of such drug delivery system is transdermal drug delivery system. In the present research work diltiazem is formulated into a transdermal patch by using various polymers such as Ethylene vinyl acetate copolymer, Eudragit RS 100 (ERS 100), Eudragit RL 100 (ERL 100) and ethyl cellulose as polymers and plastisizers such as Diethyl Phathalate, Di-n-butyl Phalate, and glycerin. A diffusion mediated matrix controlled transdermal drug delivery system for Diltiazem base was successfully prepared using different polymers using mercury subtract method and all matrices were evaluated using different physiochemical parameters. Among different polymers evaluated EVA (VA 40%) copolymer gave good results and is more stable, non irritant and non sensitizing to skin and was safe.

Keywords: Drug development; Patient regime; Transdermal drug delivery system; Matrix controlled.

INTRODUCTION

Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several difficulties. In an attempt to reduce the cost of drug development process and advantageously reap the benefits of patient regime, health care firms are now investing strategically in the development of new drug delivery system.\(^1\)
Globally, cardiovascular diseases are the number one cause of death and are projected to remain so. An estimated 17.5 million people died from cardiovascular disease in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million due to stroke. About 80% of these deaths occurred in low- and middle-income countries. If current trends are allowed to continue, by 2015 an estimated 20 million people will die from cardiovascular disease (mainly from heart attacks and strokes).\(^2\)

Diltiazem, a calcium channel blocker, has been shown to be safe and effective in the treatment of patients in atrial fibrillation and/or atrial flutter. It has a mean plasma half-life of 3.5 hrs and only 40-67% of the orally administered drug reaches the circulation due to hepatic metabolism. The model predicts that mean plasma Diltiazem concentration of 79, 172, and 294 ng/ml are required to produce a 20%, 30%, and 40% reduction in heart rate, respectively.\(^3\) This concentration can be achieved by preparing matrix diffusion controlled transdermal drug delivery system. The transdermal controlled drug delivery is a newer approach to deliver drug in to systemic circulation at a predetermined rate. Matrix diffusion controlled release transdermal drug delivery systems are monolithic systems which are the simplest and least expensive means of controlling the release of an active agent. Here the active agent is physically blended with the polymer agent. The release rate is governed by Higuchi equation. Parameter influencing the release characteristics of monolithic devices can be classified as solute dependent factors like solubility, partition co-efficient and diffusion coefficient of drug in the polymer matrix.\(^4\) The solute independent parameters are system variables like geometry, tortuosity, pores, concentration, volume fraction and diffusion layer etc. In the present investigation solute related factors were considered to fabricate the devices using different polymer matrix. Polymer matrices employed were of non polar and hydrophobic nature.

With perception to above objective, it is necessary to modify current solid dosage forms in to controlled transdermal drug delivery system. A first step in this process is to illustrate how formulation and process variables could give drug release through skin. The aim of present investigation is to formulate and optimize the Diltiazem matrix diffusion controlled transdermal drug delivery system. In the present investigation, the influence of various grades and concentration of polymers were studied. Study was carried out to
formulate an elegant product exhibiting desired therapeutic performance, from a small and cute dosage form.

In order to achieve this goal, following criteria were set

- The dosage form should remain intact for a period of 24 hr.
- Drug should be delivered in a controlled manner.
- The size of dosage form should be small with a view to enhance convenience of patient as well as compliance to therapy.
- Plasma concentration should be achieved within short period of time.

**METHODS AND METHODOLOGY**

**Preparation of polymeric matrix device**

Matrix – type transdermal patches containing Diltiazem were prepared using different ratios of drug to polymers (Table 1). The polymers were weighed in requisites ratios keeping the total polymer weight 800mg, and dissolved in a given solvent. Diethyl Phathalate (2% w/w of polymer composition), Di-n-butyl Phalate (30% w/w of polymer composition) and glycerin (40% w/w of polymer composition) were used as a plasticizer for EVA, ERL100, ERS100 and EC respectively. Diltiazem (533.33mg) was added and mixed using a mechanical stirrer. The uniform dispersion of polymeric solution of drug (10 ml) was poured on the mercury surface (73.86 cm²), and dried at room temperature. After 24h, the films were cut into a 3.14 cm² area and backing membrane (biaxial oriented polyethylene film) was then glued. A glossy paper having a smooth surface was used as a release liner. The devices were stored in desiccators until used.

**Table 1: Composition of polymeric matrix diffusional patches of Diltiazem**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Polymers</th>
<th>Plasticizers (%w/w of polymer composition)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>EVA (VA 40%) copolymer</td>
<td>DEP (2 %)</td>
<td>Toluene</td>
</tr>
<tr>
<td>F2</td>
<td>EC</td>
<td>Glycerin (40 %)</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F3</td>
<td>ERS100</td>
<td>DBP (30%)</td>
<td>Chloroform</td>
</tr>
<tr>
<td>F4</td>
<td>ERL100: ERS100 (1:4)</td>
<td>DBP (30 %)</td>
<td>Chloroform</td>
</tr>
</tbody>
</table>
Physiochemical Evaluation Of Polymeric Matrix Device

a) **Thickness:** The thickness of the laminate was assessed at six different points of the prepared medicated film using thickness gauge micrometer (0.001mm, Mitutoyo, Japan). For each formulation, three randomly selected laminated were used.

b) **Weight variation:** The weight variation for each batch was determined using Sartorius electronic balance (Model CP-224 S), Shimadzu, Japan. Six patch from each batch (3.14 cm²), were weighed individually and the average weight was calculated.

c) **Drug content:** The Diltiazem content of each prepared film was measured in triplicate and analyzed by UV-VIS spectrophotometer and expressed as the percentage of nominal lode. Patches (n=3) of specified area (3.14 cm²), were cut and weighed accurately. The pieces were taken into 100 ml volumetric flask and dissolved in respective solvent. The solution was filtered through whatman filter paper (Nylge Nune, UK). This stock solution was diluted 100 times using respective solvent and the absorbance of the resulting solution was measured at specific wavelength. The content of Diltiazem was calculated at 281.5 nm for toluene and 259 nm for chloroform using calibration curve prepared using respective solvent system. [5,6]

d) **Flatness:** The flatness was measured manually for the prepared films. Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in the length because of non uniformity in flatness was measured by determining percentage constriction, considering 0% constriction is equivalent to 100 % flatness. [7] Flatness was determined using below given formula:

\[
\text{% Constriction} = \left[ \frac{l_1 - l_2}{l_2} \right] \times 100
\]
Where, \( l_1 \) = Initial length of each strip \( l_2 \) = Final length of each strip

The flatness for Diltiazem matrices was measured in triplicate and average reading was considered.

e) **Folding endurance**: The folding endurance was measured manually for the prepared films. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm size at same place till it break.\[^8\] The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

f) **Moisture content (Loss on drying)**:\[^9\] The inherent moisture presents in material may influence the stability of dosage forms, especially if it contains a drug that is sensitive to water. The absolute method is employed to determine the moisture content which gives a weight loss registered during process.

Three patch from each batch (3.14 cm\(^2\)), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. Then all the patches were kept in a desiccators containing activated Silica at normal room temperature for 24hr. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between initial and final weight with respect to final weight.

\[
\text{% Moisture content} = \left\{ \left[ \left( \text{Initial weight} - \text{Final weight} \right) / \text{Final weight} \right] \times 100 \right\}.
\]

g) **Moisture absorption**:\[^10\] Moisture uptake also influences the stability of dosage form. Low moisture uptake protects the material from microbial contamination. So for transdermal drug delivery system it is necessary to determine % Moisture absorption of matrices.

Three patch from each batch (3.14 cm\(^2\)), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. Then all the patches were kept in a desiccators containing 200 ml saturated solution of Sodium chloride (Relative humidity of 75%) at normal room temperature for 72h. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between final and initial weight with respect to initial weight. The % Moisture absorption was determined using below formula:

\[
\text{% Moisture absorption} = \left\{ \left[ \left( \text{Final weight} - \text{Initial weight} \right) / \text{Initial weight} \right] \times 100 \right\}.
\]
h) **Water vapor transmission rate (%WVTR):** [11, 12] In this study vials of equal diameters were used as transmission cells. These cells were washed thoroughly and dried in oven, about 1 gm of activated silica was taken in cells and the polymeric films measuring 3.14cm² were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing 200 ml saturated solution of potassium chloride. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hr of storage. The amount and rate of water vapor transmitted was calculated by the difference in weight using below given formula:

\[
\text{% Water vapor transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{time}} \times \text{Area}.
\]

i) **In Vitro Diffusion Study:** The release rate determination is one of the most important study to be conducted for all controlled release delivery systems. The diffusion studies of patches are very crucial, because one needs to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in the body to achieve a constant rate of drug permeation. [13]

**Experimental**

In vitro diffusion studies of Diltiazem from various transdermal patches were studied using modified Keshary-Chien diffusion cell (Figure 2 and experimental setup in figure 3). The diffusion cell consists of two parts: the upper parts i.e. The donor compartment and contains the active ingredients and the carrier adhesive/patch; the bottom part contains the receptor solution, the water jacket for temperature control, and the sampling port. The effective permeation area of the diffusion cell and receptor cell volume was 3.14cm² and 40 ml, respectively. The temperature was maintained at 37±0.5°C. The receptor compartment contained 40 ml of 0.01N HCl stirred by magnetic stirrer. Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at different time intervals. The absorbance of the withdrawn samples were measured using UV VIS spectrophotometer at 237.8 nm using 0.01N HCl as a blank. The experiments were done in triplicate. Amount of drug released per square centimeter of patch were plotted against function of square root of time for different formulations. The release rate \(Q/\sqrt{T}\) was determined by simple regression analysis of steady state data.
Figure 2: Modified Keshary-Chien diffusion cell

Figure 3: Experimental setup

J) In Vitro Permeation Study of Matrix Diffusional Transdermal Drug Delivery Device Of Diltiazem Across Human Live Skin: Human live skin was collected from unused portion of human male patients from private hospital with consent of plastic surgeon and patient, who have no problem regarding reactions to medicines or problems of breathing. Healthy skin is taken from a place on patient’s body called the donor site.

Common sites for the collection of skin graft include the upper anterior and lateral thighs. Most people having a skin graft have a split-thickness skin graft (STSG). STSGs are categorized further as thin (0.005-0.012 in), intermediate (0.012-0.018 in), or thick (0.018-0.030 in), based on the thickness of the harvested graft. For study of controlled transdermal drug delivery system skin site is required.
k) **In vitro permeation study through human live skin:** Permeation study was performed in a modified Keshary-Chien diffusion cell. The permeation study was performed using human live skin. The skin was used after fulfilling all the ethical requirements. Skin was kept at room temperature in saline and then washed with soap solution to remove adhering matter. A section of skin was cut having thickness 140µm and placed on the brim of diffusion cell in such a way that the dermal side of the skin was in the donor compartment and patch was affixed on the skin so that aluminum backing was upward. The receiver compartment was filled with 40 ml 0.01 N HCl. The transdermal patch containing Diltiazem: EVA (40:60) with backing membrane was firmly pressed on the human skin. To perfectly fix the release face of patch on the skin, the release face was covered with a very thin layer (10µm) of natural rubber solution. Once the adhesion to the skin surface was confirmed, flange of the diffusion cell mounted in such a way that the patch was...
situated precisely over the flange aperture. The whole assembly was kept on a magnetic stirrer and diffusion medium in the receiver compartment was constantly and continuously stirred using a magnetic bead. Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at different time intervals till 24 hrs. The absorbance of the withdrawn samples were measured using UV VIS spectrophotometer at 236.0 nm using 0.01N HCl as a blank. Cumulative amount of drug released per square centimeter of patch were plotted as function of time. The release rate was determined by simple regression analysis of steady state data. The experiments were triplicated and mean release rate was recorded.

1) Stability study of matrix diffusional transdermal drug delivery device: Stability is defined as the ability of particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic and toxicological specification. Drug decomposition or degradation occurs during stability, because of chemical alteration of the active ingredients or due to the product instability, lowering the concentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated by accelerated stability studies. The objective of accelerated stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature. Finally selected and optimized matrix diffusional transdermal drug delivery system of Diltiazem was subjected to stability study.

The accelerated stability study was carried out according to ICH guideline by storing the samples at 25 °C / 60% RH, 30 °C/ 65% RH and 40 °C/ 75% RH for 90 days in a stability chamber (Thermo Lab., Mumbai, India). These samples were analyzed UV Spectrophotometrically and checked for changes in physical appearance and drug content at an interval of 15 days.

RESULT AND DISCUSSION
The present investigation deals with the development of Diltiazem base loaded polymeric matrix using different polymers. The preliminary screening was carried out for the selection of best polymer. A diffusion mediated matrix controlled transdermal drug delivery system for Diltiazem base was successfully prepared using different polymers using mercury subtract method and all matrices were evaluated using different physiochemical parameters.
**Thickness:** The thickness results are given in Table 2. The results indicate that there was no much difference in the thickness within the formulations. Maximum thickness was found in formulation F1, while minimum found in formulation F4. These results revealed that thickness was found to increase as hydrophobic portion of polymer increases. The results of thickness also indicate uniform distribution of the drug and polymer over the mercury surface. The rank order of thickness of Diltiazem loaded polymeric matrices was EVA (40% vinyl acetate)> EC> ERS 100> ERL100:ERS100 (1:4)

**Weight variation:** All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Diltiazem in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with acceptable deviation.

**Drug content:** The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for content uniformity as per official requirements. All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Diltiazem in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with acceptable deviation.

The drug content analyses of prepared formulation showed that the process employed to prepared patches was capable of giving uniform drug content, with minimum batch variability.

**Flatness:** The results of the flatness study showed that none of the formulations had the differences in the strip length before and after their cuts. It indicates 100% flatness observed in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches and thus they could maintain a smooth surface when applied on to the skin.

**Folding endurance:** The results of folding endurance are given in Table 2. Here formulation F1 and formulation F2 shows good folding endurance as compare to formulation F3 and F4.
Moisture content (Loss on drying): The moisture content in all the formulations was found to be low and ranged from 0.681 ± 0.019 to 3.181 ± 0.024%. The result revealed that the moisture content was found to increase with increasing concentration of hydrophilic polymers. The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle film. The rank order of % moisture content of Diltiazem loaded polymeric matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

Moisture absorption: The moisture absorption in all the formulations was found to be low and ranged from 0.7584 ± 0.0276 to 3.2617 ± 0.05696%. The result revealed that the moisture absorption was found to increase with increasing concentration of hydrophilic polymers. The small moisture absorption in the formulations helps them to remain stable and protects the material from microbial contamination and bulkiness of the patches. The rank order of % moisture absorption for Diltiazem loaded matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

Water vapor transmission rate (%WVTR): The water vapor transmission rates of different formulation were evaluated. Diltiazem films containing ERL100 showed higher % WVTR as compared to other polymers. This may be due to the hydrophilic nature of ERL 100. Formulation F1 and F2 showed less % WVTR as compared to F3 and F4. The rank order of % water vapor transmission rate for Diltiazem loaded polymeric matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

In Vitro Diffusion Study: Diffusion studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release. In vitro release profile is an important tool that predicts in advance how the drug will behave in vivo. The results of in vitro drug diffusion studies of transdermal patches are depicted in Table 6.

Table 2: Physicochemical evaluation of the formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness</th>
<th>Weight variations (mg)</th>
<th>Drug content (mg)</th>
<th>Folding endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>173.33 ± 1.443</td>
<td>53.00 ± 0.100</td>
<td>97.87 ± 1.172</td>
<td>248.33 ± 1.527</td>
</tr>
<tr>
<td>F2</td>
<td>116.66 ± 1.443</td>
<td>52.46 ± 0.152</td>
<td>100.82 ± 0.672</td>
<td>245.33 ± 1.527</td>
</tr>
<tr>
<td>F3</td>
<td>150.83 ± 1.443</td>
<td>58.00 ± 0.500</td>
<td>98.57 ± 0.672</td>
<td>16.66 ± 1.527</td>
</tr>
<tr>
<td>F4</td>
<td>85.00 ± 2.500</td>
<td>50.30 ± 0.100</td>
<td>101.23 ± 0.251</td>
<td>18.00 ± 1.000</td>
</tr>
</tbody>
</table>
Table 3: In vitro diffusion profiles of Diltiazem from F1 to F4 formulations

<table>
<thead>
<tr>
<th>Time (hr&lt;sup&gt;1/2&lt;/sup&gt;)</th>
<th>Cumulative amount of drug release from device (µg/cm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
<td>F2</td>
</tr>
<tr>
<td>0.707</td>
<td>1105.51 ± 15.20</td>
<td>486.25 ± 5.39</td>
</tr>
<tr>
<td>1.000</td>
<td>1499.85 ± 20.33</td>
<td>750.17 ± 10.34</td>
</tr>
<tr>
<td>1.414</td>
<td>2099.63 ± 25.46</td>
<td>1164.70 ± 15.34</td>
</tr>
<tr>
<td>1.732</td>
<td>2470.25 ± 26.59</td>
<td>1520.00 ± 18.45</td>
</tr>
<tr>
<td>2.000</td>
<td>2985.46 ± 32.46</td>
<td>1775.24 ± 20.58</td>
</tr>
<tr>
<td>2.236</td>
<td>3231.56 ± 30.29</td>
<td>1920.56 ± 22.59</td>
</tr>
<tr>
<td>2.449</td>
<td>3500.23 ± 45.38</td>
<td>2100.36 ± 25.79</td>
</tr>
<tr>
<td>Q/&lt;sqrt&gt;T (µg/cm&lt;sup&gt;2&lt;/sup&gt;/√hr)</td>
<td>1488.10</td>
<td>946.30</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.9976</td>
<td>0.9959</td>
</tr>
</tbody>
</table>

*Standard deviation, n=3

The results of diffusion study of Diltiazem loaded polymeric matrix formulated using various polymers are presented in Table 6. The release of Diltiazem from all the matrices followed square root law. The rank order of release was EVA (40% vinyl acetate) > EC > ERL100:ERS100 (1:4) > ERS 100. Release rate Q/<sqrt>T increased with increasing concentration of Diltiazem base in EVA (VA 40%) matrix. The rank order of release rate observed was C1 < C2 < C3 < C4 < C5.

The formulation C5 exhibited the maximum Q/<sqrt>T (3749.10 µg/cm<sup>2</sup>h<sup>1/2</sup>) release rate, which were significantly different, compared to the lowest values in the formulation C1 (310.95 µg/cm<sup>2</sup>h<sup>1/2</sup>). Based on physiochemical characteristics and in vitro release experiments, formulation C4 may be chosen for further in vitro permeability study through human live skin.
Table 4: Data of various parameters of model fitting of C1 to C5 formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order equation</th>
<th>First order equation</th>
<th>Higuchi’s equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.9897</td>
<td>0.9400</td>
<td>0.9987</td>
</tr>
<tr>
<td>C2</td>
<td>0.9720</td>
<td>0.8904</td>
<td>0.9979</td>
</tr>
<tr>
<td>C3</td>
<td>0.9877</td>
<td>0.9334</td>
<td>0.9979</td>
</tr>
<tr>
<td>C4</td>
<td>0.9785</td>
<td>0.9308</td>
<td>0.9988</td>
</tr>
<tr>
<td>C5</td>
<td>0.9904</td>
<td>0.9486</td>
<td>0.9985</td>
</tr>
</tbody>
</table>

In our experiment, the in vitro permeation profiles of all formulations could be best expressed by Higuchi’s equation ($R^2 = 0.9979$ to 0.9988) for the permeation of drug from a homogeneous-polymer matrix type delivery system that depends mostly on diffusion characteristics.

**In vitro permeation study:** In vitro permeation study is predictive of in vivo performance of a drug. Various parameters of diffusion kinetics of Diltiazem (Diltiazem from selected formulation C4) released from device across human live skin are presented in Table 8. The parameters listed in this table are useful for biopharmaceutics and pharmacokinetics of the matrix diffusional system evaluated.

Table 5: Parameters of diffusion kinetics of Diltiazem from Diltiazem:EVA (VA 40%) co-polymer(40:60) matrix patch through human live skin

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin flux (Jss)</td>
<td>16.26 µg/cm² hr</td>
</tr>
<tr>
<td>2</td>
<td>Time lag ($t_L$)</td>
<td>1.63 hr</td>
</tr>
<tr>
<td>3</td>
<td>Skin thickness (µm)</td>
<td>140 µm</td>
</tr>
<tr>
<td>4</td>
<td>Diffusion coefficient</td>
<td>$2.004 \times 10^{-5}$ cm²/sec</td>
</tr>
<tr>
<td>5</td>
<td>Solubility of drug in skin (Cs)</td>
<td>11.36 mg/cm³</td>
</tr>
</tbody>
</table>

The time lag ($t_L$) for devices is presented in Table 8. The average diffusion coefficient, $D$ of Diltiazem was determined using $D = h^2/6 t_L$ relationship, where Skin thickness $h$ was $140 \times 10^{-4}$ cm. The amount of Diltiazem retained by skin area used for permeation was calculated by dividing steady state flux with gradient of diffusivity and it was found to be $11.36 \text{ mg/cm}^3$ of skin.
Stability study of matrix diffusional transdermal drug delivery device

Formulation F4 was selected for stability study and observed for change in color, appearance, flexibility and drug content. Temperature and humidity values selected were as per the ICH guidelines and the test was carried out in a stability chamber. The stability study was carried out at 25\(^0\)C / 60% RH, 30\(^0\)C/ 65% RH and 40\(^0\)C/ 75% RH for 90 days. Diffusion study was carried out and it was observed that formulation stored at 40\(^0\)C exhibited higher Q/\sqrt{T} release rate as compared to those stored at 25\(^0\)C and 30\(^0\)C. The release rate at 30\(^0\)C was altered but it was in order. The product stored at 25\(^0\)C exhibited no change in release rate.

Drug degradation study was carried out as per ICH guideline at above mentioned physical condition of temperature and humidity. Periodic samples were subjected to drug content analysis. The % retained in device was worked out and from the plot of log % retained versus time degradation rate constant was computed for 25\(^0\)C, 30\(^0\)C and 40\(^0\)C temperatures. The degradation was higher at an elevated temperature. The first order rate constant of degradation for room temperature was 1.105 x 10\(^{-3}\) week\(^{-1}\). The self life calculated was 95 week. Results of stability study indicated a good stability for laminate (matrix) containing drug delivery device. The results of stability study indicated that the products should not be stored at an elevated temperature and also should not be refrigerated as at lower temperature transdermal patches lost overall flexibility and turned rigid loosing elegancy. The product should be stored at room temperature.

**CONCLUSION**

EVA (VA 40%) copolymer matrix modulated transdermal drug delivery system of Diltiazem has been prepared successfully. Among different polymers evaluated EVA (VA 40%) copolymer gave a medicated matrix, which was stable, non irritant and non sensitizing to skin and was safe. It also complied with official and non official pharmacotechnical specification. The matrix device evaluated for Diltiazem release in vitro into infinite sink and across human live skin, enabled to provide adequate rate of Diltiazem, meeting requisite pharmacokinetic requirement of steady state plasma concentration for 24 hours, giving once a day drug delivery system.
REFERENCES


2. WWW. WHO Cardiovascular disease.htm


