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Development of matrix type transdermal Patches of Tizanidine HCl

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ABSTRACT

Transdermal drug delivery system (TDDS) was designed to sustain the release and improve the bioavailability of drug and patient compliance. Among the various types of transdermal patches, matrix dispersion type systems disperse the drug in the solvent along with the polymers and solvent is allowed to evaporate forming a homogeneous drug-polymer matrix. Tizanidine Hydrochloride, an imidazoline derivative, is α2-adrenergic agonist and centrally acting myotonolytic skeletal muscle relaxant with a structure unrelated to other muscle relaxants. Tizanidine hydrochloride having lower bioavailability (40%) due to first pass metabolism by the liver. So, bioavailability can be increased by transdermal route. The object of the study was to develop Matrix Type Transdermal Patch of Tizanidine HCl. Transdermal patches were prepared by solvent evaporation method using Eudragit RS 100 and PVP polymers by incorporating Polyethylene Glycol and Propylene Glycol as plasticizer. Standard procedures were used to analyze the prepared films for various physicochemical parameters(weight variation, thickness uniformity, % moisture content, %moisture uptake, Folding Endurance and drug content). drug release (Franz diffusion cell) and skin irritation test. The drug and polymer compatibility was studied by DSC. Among all the formulations, the F1 prepared by using Eudragit RS 100 and PEG 400 as plasticizer is the better formulation for control release of drug up to 6 hrs of time. Results of the present study encouraged that the Tizanidine HCl with Eudragit RS 100 transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized. The kinetic models used were Zero order, First order Higuchi's and Korsmeyer–Peppas model. Transdermal patches were successfully prepared for Tizanidine Hydrochloride and their evaluation suggested excellent quality and uniformity in patch characteristics. This can have potential applications in therapeutic area offering advantages in terms of reduced dosing frequency, improved patient compliance and bioavailability.

Keywords: Tizanidine Hydrochloride, Eudragit RS 100, Matrix type, polyvinylpyrrolidone, Transdermal patches

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INTRODUCTION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose[1].

The first transdermal patch, Transderm-Scop (scopolamine), developed by ALZA Corp (Mountain View, CA, USA) was approved by FDA in 1981 for the treatment of motion sickness and subsequently followed by nitroglycerine patch (Transderm-Nitro) for the management of angina pectoris. In the recent years, TDDS has become one of the most innovative topics for the delivery of drugs. The success of transdermal delivery system in pharmaceutical market is evident from the fact that currently, more than 35 transdermal drug delivery products are approved in the USA for wide variety of pathophysiological conditions including hypertension, angina pectoris, motion sickness, female menopause, and male hypogonadism, and approximately 40% of drugs are under investigations to validate the feasibility for transdermal drug delivery[2].

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. Transdermal route has advantages over conventional modes of drug administration[3]. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[4]. This mechanism of drug delivery route has many advantages, including steady drug plasma concentration, improved patient compliance, elimination of hepatic first pass, and degradation in the gastrointestinal tract, controlled release over extended period besides providing a convenient non-invasive and easily terminable means for systemic as well as topical drug delivery.

In recent times, transdermal patches are become most acceptable approach for patients. Several drugs were administered through transdermal route by matrix- type transdermal patches which include aceclofenac, dexamethasone, terbutaline sulphate, atenolol, diltiazem, etc.

Present day, transdermal patches are applied in several therapeutic regions like smoking cessation, pain management, hormone replacement and treatment of heart disease[5].

Tizanidine Hydrochloride, an imidazoline derivative, is α2-adrenergic agonist and centrally acting myotonolytic skeletal muscle relaxant with a structure unrelated to other muscle relaxants. It reduces spasticity by increasing presynaptic inhibition of motor neurons and also reduces increased muscle tone associated with spasticity in patients with multiple sclerosis or

spinal cord injury[6]. Tizanidine hydrochloride having lower bioavailability (40%) due to first pass metabolism by the liver. So, bioavailability can be increased by transdermal route. Transdermal permeability has linear dependency on partition coefficient. Drug with partition coefficient indicating an ability to dissolve in both lipid and water are favourably absorbed through the skin and would be ideal candidate for transdermal delivery. Tizanidine HCl has satisfactory log p value(1.4). The physicochemical and pharmacokinetic parameters of Tizanidine hydrochloride i.e. low MW of 290.2, low half life of 2.1-4.5 hrs, low oral bioavailability of 34-40%, low doses required orally for every 8hrs, low therapeutic drug concentration of 15.6ng/ml and high first pass hepatic metabolism suggests an ideal drug candidate for transdermal delivery system.[7] Very few studies were reported on transdermal patches using Tizanidine hydrochloride.

The objective of the present study was to develop and evaluate transdermal delivery systems of Tizanidine HCl for in vitro release studies, ex-vivo permeation studies and mechanical properties. Transdermal patch using different concentration of Eudragit RS100, PVP K30 singe, along with the combination of these two polymers. In these studies plasticizers PEG 400 and PG were used**.**

MATERIALS AND METHOD

Materials

Tizanidine HCl was obtained as gift sample from Endoc Pharma, Chennai. Eudragit RS 100 and PVP K30 were obtained as gift samples from Chemdyes Corporation and Propylene Glycol and Polyethylene Glycol was obtained from SD Fine chemicals, Mumbai.

Solvent casting method

Transdermal patches containing Tizanidine HCl were prepared by the Solvent casting method. The composition of Tizanidine HCl Transdermal Patch were shown in Table 1. The polymers in selected ratios were weighed and dissolved in specified solvent system. The plasticizers were added to the polymeric solution and mixed uniformly using magnetic stirrer. Finally the drug was incorporated with continuous agitation. The patches were prepared by casting the drug loaded polymeric solutions in a petri dish. The casting solution was dried at room temperature for a period of 12 hrs. The dried patches were packed in aluminum foil and stored in desiccators till further studies[8].

Table 1: Composition of Tizanidine HCl Transdermal Patch

Formulation	Polymer 2% (w/w)	PEG 400 %(w/w)*	PG % (w/w)*	Solvent	Drug (mg)
F1	Eudragit RS100	40	-	Methanol	4
F2	PVP K30	40	-	Methanol	4
F3	Eudragit RS100 :PVP K30	40	-	Methanol	4

F4	Eudragit RS100	-	40	Methanol	4
F5	PVP K30	-	40	Methanol	4
F6	Eudragit RS100 :PVP K30	-	40	Methanol	4

Physicochemical characteristics of patch[9] :

Physical appearance:

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Thickness[10]:

The thickness of patches was measured at three places using a digital micrometer and mean values were calculated.

Weight Variation[11]:

Weight of three individual patches 2 x 2 cm^2 from each batch was determined and average weight was calculated with standard deviation. The results were shown in Table 3.

Folding Endurance[12,13]:

It is expressed as number of times the patch is folded at the same place either to break the patch or to develop visible cracks. This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. A strip of specific area (2 cm*2 cm) was cut evenly and repeatedly folding one patch at the same place till it break. The number of times the patch could be folded at the same place without breaking/cracking gave the value of folding endurance.

Percentage Moisture content[14]:

The prepared films were weighed individually and kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24hrs the films were weighed again. The percent moisture content was calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

% Moisture Uptake[14]:

The weighed films were kept in desiccators at room temperature for 24hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the films were to be reweighed and determine the percentage moisture uptake from the below mentioned formula:

$$\% \text{ Moisture Uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content analysis:

The patches ($1cm^2$) were cut and added to a beaker containing 100 mL of Phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content.

***In-Vitro* Permeation study[15] :**

In-vitro Permeation study was carried out with the cellophane using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5^oC and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system.

Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, Franz type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. cellophane membrane.

The Cellophane membrane was kept between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the cellophane .The receptor compartment of the diffusion cell was filled with 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 50 rpm; the temperature was maintained at 32 ± 1°C .The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawn. The cumulative percentages of drug permeated per square centimeter of patches were plotted against time.

In vivo studies

The study was conducted as per the guidelines given by CPCSEA, Ministry of Fisheries, Animal Husbandry and Dairying, Department of Animal Husbandry and Dairying and approved by the Institutional Animal Ethics Committee (Approval no. 1209/ac/08/CPCSEA) Government of India.

Skin Irritation studies[16,17,18]:

Transdermal patch should be free from skin irritation and it is also an ideal property of transdermal drug delivery system. So, designed transdermal patch should not irritate the skin and hence skin irritation study was performed. Skin irritation potential of the patches was assessed on Wistar rats by Draize score method. The hair from the dorsal area of the rats was removed with the help of clipper, 24 h before the test. The skin irritation test was performed on six healthy albino rabbits weighing between 1.8 to 2.2 kg. Aqueous solution of formalin

0.8% was used as standard irritant. Drug free polymeric patches were used as test patches. 0.8% of formalin is applied on the left dorsal surface of each rabbit, whereas the test patch was placed on identical site, on the right dorsal surface of the rabbit. Matrices were applied to the shaved skin on the back of 4 albino rabbits and secured using adhesive tape. On one side of back, a control patch (without any drug) and on another side an experimental patch were secured. The animals were observed for any sign of erythema or edema for a period of 7 days. The patches were removed after a period of 24 hours with the help of alcohol swab. The skin was examined for erythema/edema. Erythema and edema observed using Draize scoring method the code was shown in Table 2.

Table 2: Draize Method

Code	Erythema scale	Edema scale
0	None	None
1	Slight	Slight
2	Well defined	Well defined
3	Moderate	Moderate
4	Scare formation	Severe

Kinetic modeling of drug release[19]:

To analyze the mechanism of drug release from the patches, the release data were fitted to the following equations:

Zero-order equation:

$Q = K\,0t$

Where Q is the amount of drug released at time t, and *K0* is the release rate.

First-order equation:

$\ln (100\text{-}Q) = \ln 100 - K1t$

Where Q is the percent of drug release at time t, and *K1* is the release rate constant.

Higuchi's equation:

$Q = K2\ t$

Where Q is the percent of drug release at time t, and *K2* is the diffusion rate constant.

Stability Studies[20,21]:

The stability studies of the optimized batch of the transdermal patches were conducted according to the ICH guidelines by storing the patches at 40°C ± 2°C and 75 % ± 5 % RH for 1 months. The samples were withdrawn at 30 days and evaluated for physical appearance, thickness, and drug content. The In-vitro permeation study was performed after 30 days and compared with fresh batch. The results were given in Table 8.

RESULTS AND DISCUSSION:

Investigation of physicochemical compatibility of drug and polymer:

Drug polymer interaction was checked by DSC study.

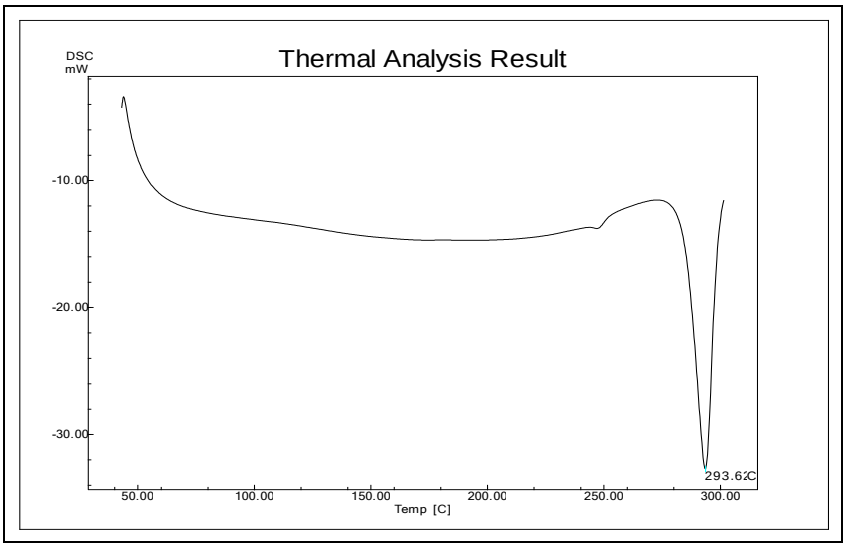

Figure 1: DSC thermogram of Tizanidine HCl

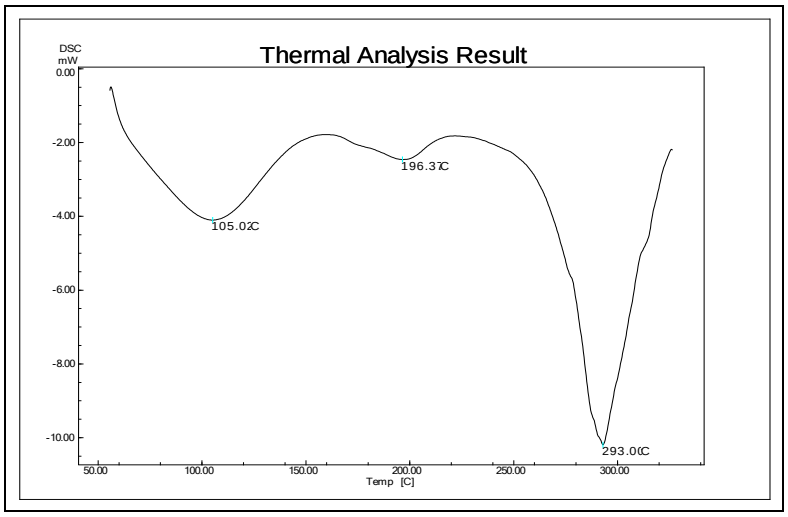

Figure 2: DSC thermogram of Tizanidine HCl +PVP K30+Eudragit RS 100

Differential Scanning Calorimeter allows the possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. DSC thermograms of Tizanidine HCl and mixture with Polymers are shown in Figure 1 and 2. The DSC curve of tizanidine hydrochloride showed a single sharp endothermic peak at 293ºC corresponding to its melting point. In optimized formulation, endothermic peak of drug was well preserved with slight changes in terms of shifting towards the lower temperature, 293ºC There was no interaction between drug and excipients found from thermograms.

Physicochemical evaluation of patches:

Thickness of all Formulation was ranged from 0.2233±0.824 to 0.2933±0.0152. Percent flatness data of the prepared patches were shown in Table 3. It was evident that was no much deviation in the flatness reveals uniform patches.

The Weight variation of all Formulation ranged from 0.3766±0.015275 to 0.48±0.005774. Weight variation data of all the patches shown that there were no significant differences among the patches, and the deviation was within limits.

The Folding Endurance of all formulations varied from 265.333 ±2.0538 to 293 ± 2.0866. The highest folding endurance was noted for formulation F1.

The moisture content and moisture uptake of all the formulations was shown in Table 3 and the moisture content is increased as hydrophilic polymer concentration increased and similarly decreased as hydrophobic concentration increased. The moisture uptake and content was found to be low in formulation F1, F2 and F6. F2 was found to show the lowest moisture uptake among all. The moisture absorbed the patch did not affect adversely the patch strength and integrity. The small moisture content helps them to remain stable and from being a completely dried and brittle patches.

Table 3: Physicochemical Evaluation

Formulation	Average Thickness (mm)±SD	Weight Variation (g)±SD	Folding Endurance	%Moisture Content	% Moisture Uptake
F1	0.2233±0.824	0.47±0.01	293±2.0866	2.04±0.045826	2.13±0.026458
F2	0.2533±0.0152	0.43±0.015275	287.333±4.5095	1.87±0.02	1.936667±0.05
F3	0.2933±0.0152	0.48±0.005774	249.666±2.08127	2.386667±0.020	2.46±0.036056
F4	0.2333±0.0124	0.41±0.011547	292±5.2447	3.08±0.026458	3.133333±0.01
F5	0.23±0.0264	0.39±0.01	265.333±2.0538	3.466667±0.057	3.8±0.1
F6	0.2566±0.0152	0.3766±0.0152	275.666±6.8067	2.133333±0.057	2.7±0.264575

Note: All values expressed in mean ±SD, n=3

Table 4: % Drug Content of Patches

Formulation	%Drug Content
F1	98.427±0.605
F2	97.153±1.525
F3	96.477±1.385
F4	98.223±0.673
F5	96.910±2.069
F6	97.857±0.384

Note: All values expressed in mean ±SD, n=3

The percentage of drug content was found in the range of 96.47 to 98.42; It indicates there was no significant loss of the drug during the formulation and handling of the material and also indicates fit for giving the proper therapeutic effect. Formulation F1 shows highest % Drug content of about 98.42%.

***In-vitro* permeation studies:**

The purpose of this study was to investigate the *In-vitro* release studies of all formulations made of polymers such as Eudragit RS100 and PVP K30. The *in-vitro* permeation of drug from the patches was carried out using Modified Franz diffusion cell apparatus for 6 hrs and showing drug release of 90.56%, 71.52%, 82.63%, 87.31%, 72.6%, 80.26%, for F1, F2, F3,

F4, F5, F6 respectively at the end of 6 hrs. The results of in-vitro permeation studies of Tizanidine hydrochloride from transdermal patches are shown in Figure 3, F1 and F4 shows good release.

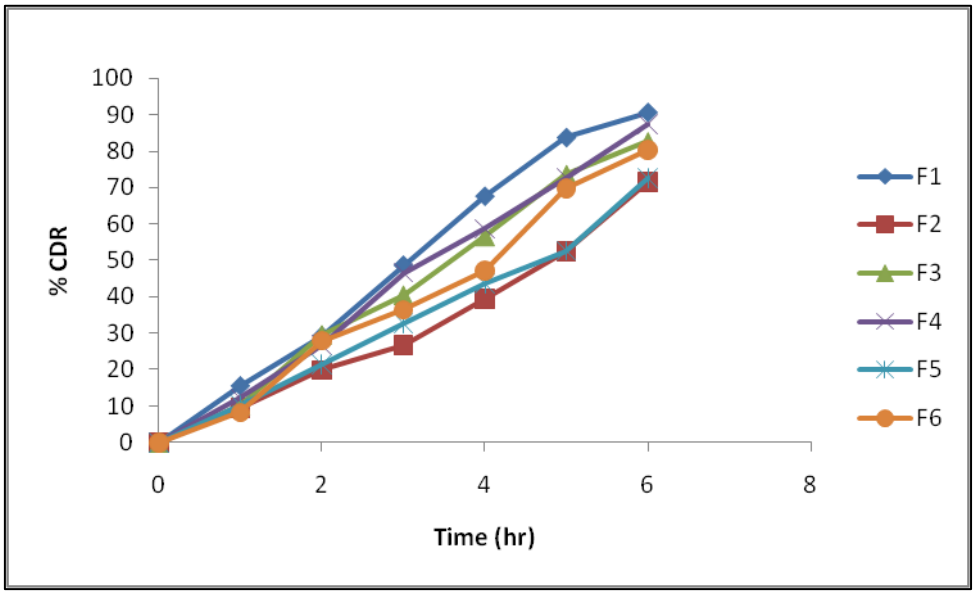

Figure 3: *In-vitro* permeation for formulation F1 to F6

Table 5: *In-vitro* Permeation

Time (hr)	%CDR					
	F1	F2	F3	F4	F5	F6
1	15.67	9.63	10.23	12.23	10.23	8.36
2	29.36	19.96	29.69	26.79	21.63	27.95
3	48.72	26.89	40.56	46.61	32.85	36.48
4	67.62	39.42	56.69	58.63	43.76	47.19
5	83.69	52.36	73.65	72.63	52.63	69.56
6	90.56	71.52	82.63	87.31	72.6	80.26

Kinetics of drug release:

The cumulative amount of drug permeated per square centimeter of patches through cellophane membrane was plotted against time was fitted to Zero, First, Higuchi and Korsmeyer–Peppas Kinetic model. As indicated in Table 6, the release profile followed mixed zero-order and Higuchi kinetics in different formulation. However, the release profile of the optimized formulation F1 (R^2 = 0.985 for Zero) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

Table 6: Kinetic Model

Formulation	Correlation Co-efficient			
	Zero Order	First Order	Higuchi	Korsmeyer–Peppas
F1	0.985	0.856	0.984	0.981
F2	0.975	0.871	0.928	0.983
F3	0.992	0.904	0.989	0.993
F4	0.996	0.852	0.99	0.979
F5	0.985	0.926	0.956	0.998
F6	0.984	0.874	0.967	0.988

Skin irritation study:

The main objective of the skin irritation study was to evaluate the skin irritation potential of the optimized patch Skin irritation test of the transdermal formulation F1 showed a skin irritation score (erythema and edema) of less than 2. Results were shown in table 7. According to Draize *et al*, compound producing score of 2 or less are considered negative (no skin irritation). Hence the developed transdermal formulation is free of skin irritation[22,23,24].

Table 7: Skin Irritation study

Rabbit No.	Control		Formulation (F1)	
	Erythema	Edema	Erythema	Edema
1	0	0	0	0
2	0	0	0	1
3	0	0	0	0
4	0	0	1	0
5	0	0	0	0
6	0	0	0	0

Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; 4, scare formation

Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; 4, severe

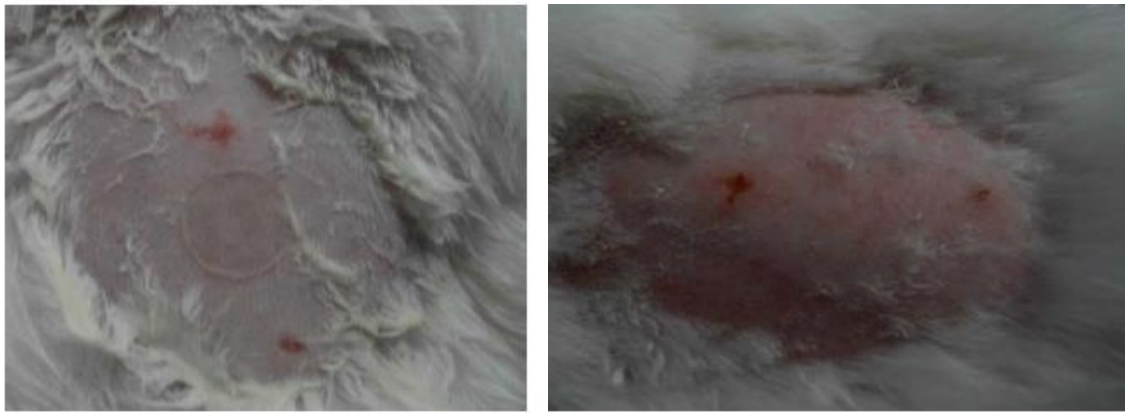

Figure 4: skin irritation studies on rabbit with applied transdermal patch F1.

Stability studies:

Stability is the essential factor for quality, safety and efficacy of product. The drug product is with insufficient stability result in altering of their physical as well as chemical characteristics. The selected formulations namely F1 was subjected for stability studies and observed for all evaluation parameters as per ICH guidelines by storing the patches at 40°C ± 2°C and 75 % ± 5 % RH for 1 months. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed. Table 8 was showing the Data of optimized formulation F1 at 0 and 30 days.

Table 8: Physicochemical evaluation of formulation F1 during stability studies

Parameter	0 Day*	30 Days*
Thickness	0.2233±0.82	0.2212±0.32
Weight Variation	0.47±0.01	0.46±0.05
Folding Endurance	293±2.086	291±1.25
%Moisture Content	2.04±0.045	2.00±1.23

%Moisture Uptake	2.13±0.0264	2.10±0.25
%Drug Content	98.427±0.605	98.12±0.086

*****All values are the mean of three readings ± SD, 40 ± 2°C/ 75 ± 5% RH

CONCLUSION:

From the Results obtained so far it can be concluded that Eudragit RS 100 with PEG 400 as plasticizer (F1) is controlled release transdermal drug delivery system for Tizanidine hydrochloride. Prepared patches exhibited zero order and Higuchi kinetics permeation of the drug from the patches was governed by a diffusion mechanism. The result of *In-Vitro* study showed the feasibility of formulating rate-controlled transdermal patch of Tizanidine hydrochloride for effective management of generalized Muscle Pain. The transdermal drug delivery system F1 is having greater % drug release. So, it was concluded that the formulation F1 prepared by using Eudragit RS 100 is the better formulation for control release of drug up to 6 hrs of time and minimized the frequency of administration. The stability studies were carried out on the most satisfactory formulations F1 40 ± 2°C/ 75 ± 5% RH for one month to assess their stability as per ICH guidelines. At fixed time intervals of 30 days, the formulation was evaluated for *In vitro* drug release and other evaluation parameters. There was no significant difference in the physicochemical parameters, *In vitro* drug release profiles were found to be super impossible with the initial readings at zero day results. From the above studies, it was clearly indicated that Tizanidine HCl transdermal patches containing Eudragit RS 100 alone was the best formulation among the prepared patches.

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