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FORMULATION AND CHARACTERIZATION OF DRUG IN ADHESIVE TRANSDERMAL PATCHES OF BUFLOMEDIL HYDROCHLORIDE

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Keywords:

Pressure sensitive adhesive, penetration enhancers, solvent evaporation technique, transdermal patch.

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ABSTRACT: The purpose of this research was to develop a drug-in-adhesive type transdermal drug delivery system containing drug, buflomedil hydrochloride, pressure sensitive adhesive (PSA), Duro-Tak 387-2052 by the solvent evaporation technique. Different concentrations of penetration enhancers; oleic acid and isopropyl myristate (IPM) were used to enhance the transdermal permeation of buflomedil hydrochloride. 3M Scotchpak TM 9723 polyester film was used as a backing membrane and 3M Scotchpak TM 1022 - Fluoropolymer Coated Polyester film was used as a release liner for the preparation of transdermal patches. FTIR and DSC studies were done to know any possible interaction between drug and polymer. Prepared drug-in-adhesive transdermal patches were physically evaluated with regards to thickness, weight variation, surface pH, folding endurance, moisture content and moisture uptake. The adhesion properties of the patches were very satisfactory. Also, the prepared patches showed good uniformity with regard to drug content. In vitro drug permeation studies of formulations were performed by using Franz diffusion cell through dialysis membrane. It was observed that the formulation containing 95% adhesive solution and 10% IPM as permeation enhancer showed best in vitro drug permeation through dialysis membrane as compared to all other formulations. The results rate was found to follow zero order kinetics. These results indicate that the formulation F5 has shown optimum release in concentration independent manner. The mechanism of drug release from the PSA transdermal patches followed non-Fickian release mechanism.

INTRODUCTION: Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation.

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Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems. So, this transdermal drug delivery system has been great fields of interest in the recent times. Many drugs which can be injected directly into the blood stream via skin have been formulated.

The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin. A transdermal patch has several components including liners, adherents, drug reservoirs, drug release membrane which play a vital role in the release of the drug. A pressure sensitive adhesive (PSA) maintains an intimate

contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force.

Transdermal drug delivery system offers several advantages e.g. easy termination of the therapy, improves bioavailability, reduces toxic effects, suitability for unconscious patients. [1-5]

Buflomedil Hydrochloride is a synthetic origin drug belongs to pyrilidine group. It is a vasoactive drug used to treat claudication or the symptoms of peripheral arterial disease. It is metabolised hepatically with elimination half-life of 2-3 hr which nesscecates frequent dosing. Most of the adverse drug reactions associated with oral administration are mild upper gastrointestinal complaints such as nausea, dyspepsia or epigastric discomfort which could be eliminated by formulating transdermal drug delivery system.[6]

MATERIALS AND METHODS:

Materials:

Buflomedil HCl was obtained as a gift sample from Fresenius Kabi, Kolkata. Durotak 387-2052 was purchased from Henkel Ltd., United Kingdom. Isopropyl myristate, oleic acid, Potassium dihydrogen orthophosphate, sodium chloride, disodium hydrogen phosphate, potassium chloride, calcium chloride fused were purchased from CDH (P) Ltd., New Delhi. Dialysis membrane was purchased from Sigma Aldrich, Mumbai.

Preparation of Polymeric Solution:

Transdermal patches were prepared by solvent evaporation technique. Required amount of DuroTak 387-2052 was taken in beaker. Drug was dissolved in small quantity of methanol and this solution was added to the beaker containing Duro-Tak 387-2052. A homogeneous drug and pressure sensitive adhesive solution was made using a magnetic stirrer (Ikon Instruments, Delhi, India) and a magnetic bead at room temperature and covered with a laboratory film (Parafilm M, Chicago) for preventing solvent evaporation process. Then the required permeation enhancer was added and stirred until a homogeneous mixture was obtained. After that the homogeneous mixture was kept in an ultrasonic bath (Oscar Ultrasonics Pvt. Ltd, OU-23, Mumbai, India) for elimination of air bubbles.[7]

Casting of polymeric solution over the Backing Membrane:

The release liner (3M Scotchpak^{TM} 1022 Release Liner-Fluoropolymer Coated Polyester film) was held in place on a flat surface, a sample of each polymeric adhesive mixture (5ml)was placed across the top edge of the release liner, the mixture was casted onto the release liner by drawing a multiple clearance film applicator AR 5315 (Pacific Scientific, Silver Spring, MD, U.S.A.). The wet adhesive film was dried at 75°C for 30min. The backing membrane (3M Scotchpak^{TM} 9723 backing polyester film) was placed on the top of the coatings. The film was laminated on to a backing film using a standard 2 kg roller. The transdermal films were cut into circular pieces having 1 cm diameter, stored in air tight container prior to the day of use. [7]

Evaluation of Transdermal Patches:

Thickness Uniformity of the Patches:

Thicknesses of the backing membranes (before casting the drug matrix) and of whole patches (adhesive matrix with the drug plus the backing membrane) were measured at six different points of the each patch in order to ensure uniform thickness using Screw gauge (Sterling Manufacturing Company, India). The average thicknesses of the backing membrane and of the drug matrix with the backing membrane were determined. The thickness of the drug-containing polymer matrix was determined by measuring the thickness of the whole patch (adhesive matrix with the drug plus the backing membrane) and subtracting the thickness of the backing membrane. The average thickness of the drug containing polymer matrix was determined: Thickness of the drug-containing adhesive matrix = Thickness of the whole patch - Thickness of the backing membrane.[8]

Weight Uniformity of the Patches:

For weight variation test, randomly selected six patches from each formulation were weighed individually on a digital single pan balance (Citizen, CX-220, India) and the average weight of patch was calculated, which determines the actual weight of the patches.[8]

Scanning Electron Microscopy:
The surface morphology of the optimized patch surface before and after in-vitro drug release study were analyzed by scanning electron microscopy (JEOL-JSM-6360, Jeol Datum Ltd, Tokyo, Japan). The experimental samples were cut into small parts, deposited onto stubs using one side of a double sided adhesive dried carbon tape (NEM Tape, Nisshin Em. Co. Ltd, Tokyo, Japan).

Then these experimental samples were mounted on the SEM instrument and scanning was performed. SEM photographs were taken at the required magnification at room temperature. The working distance of 39 mm was maintained and acceleration voltage used was 17 kV at a chamber pressure of 79.99 Pa with the secondary electron image (SEI) as a detector.

Drug Content Uniformity:
In order to determine amount of drug loaded in the transdermal patch, a small area (1cm^2) of prepared patch was taken in 10 ml phosphate buffer (pH7.4). With the help of a teflon coated magnetic bead the medium was stirred for 5 h followed by sonication. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content at 280 nm spectrophotometrically.[8]

Moisture Content:
The moisture content, which affects the rate of drug release from the patch, was determined. A small amount of moisture in drug in adhesive transdermal patch formulations helps maintain stability and prevents the formation of a dried and brittle film. A greater amount, can lead to microbial contamination during storage. The prepared patches were weighed individually and kept in a desiccators containing anhydrous calcium chloride for 24 h at room temperature. The patch was weighed repeatedly until it became constant. The percent moisture content was determined with the following equation.[8]

% Moisture Content =

$$\frac{(\text{Initial weight of the patch} - \text{Final weight of the patch}) \times 100}{(\text{Initial weight of the patch})}$$

Moisture Uptake:
This study can predict the moisture-absorbing capacity of a particular type of patch at various humidity levels. Little moisture uptake indicates the stability of the formulation. A good amount of moisture uptake indicates bulkiness of the formulation and the chance of microbial growth. The weighed patch was kept in a dessicator at room temperature, exposed to relative humidity of 79.5% using a 100 ml of saturated solution of aluminum chloride in a dessicator. The patch was weighed until it showed a constant weight. Percent moisture uptake was determined as follows.[8]

% Moisture Uptake =

$$\frac{(\text{Final weight of the patch} - \text{Initial weight of the patch}) \times 100}{\text{Initial weight of the patch}}$$

Surface pH:
The patches were kept in contact with casting solvent for 30 min. The surface pH was measured by means of pH paper placed on the surface of the patch.[9]

Folding Endurance:
The folding endurance is defined as the number of folds required to break any polymeric film. The folds on the patch have to be made at the same point, till it breaks. It was measured manually by cutting a strip of patch of uniform size (2 x 2 cm) and repeatedly folded at the same place till it broke. The number of folds a patch can sustain will dictate its folding endurance.[10]

Adhesive Property: Thumb tack test:
Tackiness is the ability of pressure sensitive adhesives to bond under conditions of light contact pressure and a short contact time. This test is used to quantify or realize the sticky feel of the material. Pressure sensitive adhesives adhere to the skin surface with no more force then applied finger pressure, have a strong holding force, and are tacky in nature. Tackiness is taken in to consideration when these adhesives are used for the drug matrix or other transdermal patches to adhere on to the skin surface. With a little pressure, a liquid like flow in the adhesive wets the skin surface and founds a strong bond to the skin. Upon removal of pressure, the adhesive layer remains adhered to the skin because of its viscoelastic characteristics. One week after the preparation of patches, a thumb tack

test was performed by lightly pressing a thumb on the patch for 5 sec and then quickly removing it. By varying the pressure, time of contact, and considering the difficulty of pulling the thumb from the adhesive, it was possible to guess how easily, quickly, and strongly the adhesive formed a bond with the skin. The test was performed blindly on different patches to determine the proper formulation for further studies. The adhesive properties of the patches were expressed by the following value range: good adhesion, poor adhesion, and no adhesion.[11]

***In Vitro* Drug Permeation Studies:**

In-vitro drug release studies were performed by using a Franz diffusion cell. The diffusion cell was fabricated from borosilicate glass and consists of two compartments receptor and donor compartment. The receptor compartment was filled with phosphate buffer saline pH 7.4. The dialysis membrane soaked in phosphate buffer pH 7.4 for 2 hours before the study. A circular patch of 1cm diameter was taken, release liner was removed and fixed over the dialysis membrane. The membrane with the attached patch was mounted and clamped carefully between the receiver and donor compartment of diffusion cells with the patch facing the donor side.

The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using Teflon coated magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The amount of drug permeated in to the receptor compartment was determined by removing sample (1 ml) at hourly intervals and replaced with the same amount of phosphate buffer saline (pH 7.4*)* to maintain the sink condition. After suitable dilution the samples were analyzed for drug content using UV spectrophotometer at λ max 280nm.[12]

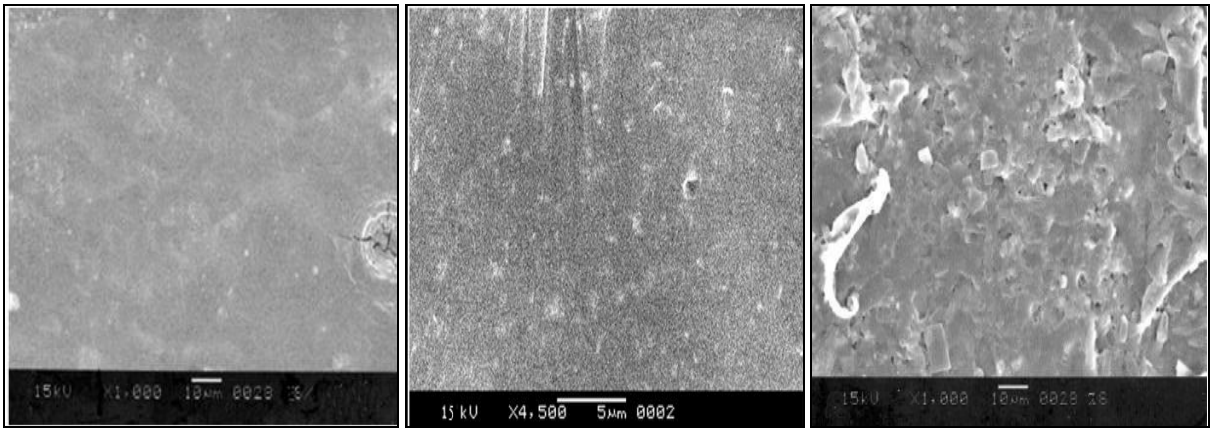
Kinetics of Drug Release:

The suitability of several equations to identify the mechanisms for the release of drug was tested with respect to the release data. The drug release data of the *in vitro* dissolution study was analyzed with various kinetic equations like zero-order (% release v/s time), first order (Log % retained v/s time), Higuchi model and korsmeyer peppas equation. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots and are shown in **Table 5**. The value of 'n' gives an indication of the release mechanism; when n = 1, the release rate is independent of time (zero-order) (case II transport), n = 0.5 for Fickian diffusion and when 0.5 < n <1.0, diffusion and non-Fickian transport are implicated. Lastly, when n > 1.0 super case II transport is apparent.[12]

RESULTS AND DISCUSSION:

Scanning Electron Microscopy (SEM):

SEM studies were conducted to visualize drug distribution in the matrix patch. It was clear from SEM studies that drug distribution in the matrix patches was a uniform distribution (**Fig. 1**). The SEM of the drug loaded patch clearly indicates that the Buflomedil Hydrochloride is homogenously dissolved in the polymer matrix. SEM photographs of the patch showed that it is rigid and free from bubbles.



A. Blank Patch **B. Drug Loaded Patch** **C. After Diffusion of Drug**

FIG. 1: SCANNING ELECTRON MICROGRAPH OF TRANSDERMAL PATCHES

Determination of Weight Variation: The weights ranged between 25.3±0.020 mg to 28.4±0.015 mg, which indicates that all the formulations exhibited uniform weight with low standard deviation values indicating the uniformity of the patches (**Table 1**).

Determination of Thickness: The thickness of the patches varied from 0.17±0.005 to 0.19±0.008 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent casting technique (**Table 1**).

TABLE 1: RESULTS OF WEIGHT VARIATION AND THICKNESS TEST

S.No	Formulation	Weight Variation (mg)	Thickness (mm)
1	F1	26.2±0.015	0.17±0.005
2	F2	25.3±0.020	0.19±0.008
3	F3	25.4±0.018	0.19±0.006
4	F4	28.4±0.015	0.18±0.005
5	F5	26.2±0.018	0.18±0.008

Determination of Percent Drug Content:
The percentage drug content was determined for all the formulations (n=3) by UV Spectrophotometric method. The result of percentage drug content was found in range between 95.6±0.96 to 92.8±1.52. It was considered that the drug was dispersed uniformly throughout the film. The results indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability (**Table 2**).

TABLE 2: RESULTS OF PERCENT DRUG CONTENT

S. No	Formulation	Drug Content (%)
1.	F1	92.8±1.87
2.	F2	92.8±1.52
3.	F3	95.6±0.96
4.	F4	94.8±0.87
5.	F5	93.0±1.56

Surface pH:
The surface pH of all formulations was found about to 7.0, that comes to pH range of skin and hence no skin irritation was expected (**Table 3**).

Determination of Folding Endurance: From the results it can be concluded that the patches would not break and would maintain their integrity with general skin folding when used (**Table 3**).

TABLE 3: RESULTS OF FOLDING ENDURANCE AND SURFACE pH

S.No	Formulation	Folding Endurance	Surface pH
1.	F1	>250	7.0
2.	F2	>250	7.0
3.	F3	>250	7.0
4.	F4	>250	7.0
5.	F5	>250	7.0

Determination of Moisture Content: A small amount of moisture in drug in adhesive transdermal patch formulations helps maintain stability and prevents the formation of a dried and brittle film. A greater amount, can lead to microbial contamination during storage. The % moisture content of all the patches was determined and was found in range of 0.50±0.71 to 1.0±0.62 (**Table 4**) (**Fig. 2).**

Determination of Moisture Uptake: This study can predict the moisture-absorbing capacity of a particular type of patch at various humidity levels. Little moisture uptake indicates the stability of the formulation. A good amount of moisture uptake indicates bulkiness of the formulation and the chance of microbial growth.

The results of moisture uptake study were found in range of 1.046±0.742 to 1.90±1.029. It was found that formulations containing higher percentage of penetration enhancer absorb more moisture compared to formulations containing lower amount of penetration enhancers (**Table 4) (Fig.2**).

TABLE 4: RESULTS OF MOISTURE CONTENT AND MOISTURE UPTAKE

S.No	Formulation	Moisture Content (%)	Moisture Uptake (%)
1.	F1	0.65±0.59	1.08±1.071
2.	F2	1.0±0.62	1.198±0.971
3.	F3	0.60±0.49	1.892±0.957
4.	F4	0.75±0.55	1.046±0.742
5.	F5	0.50±0.71	1.90±1.029

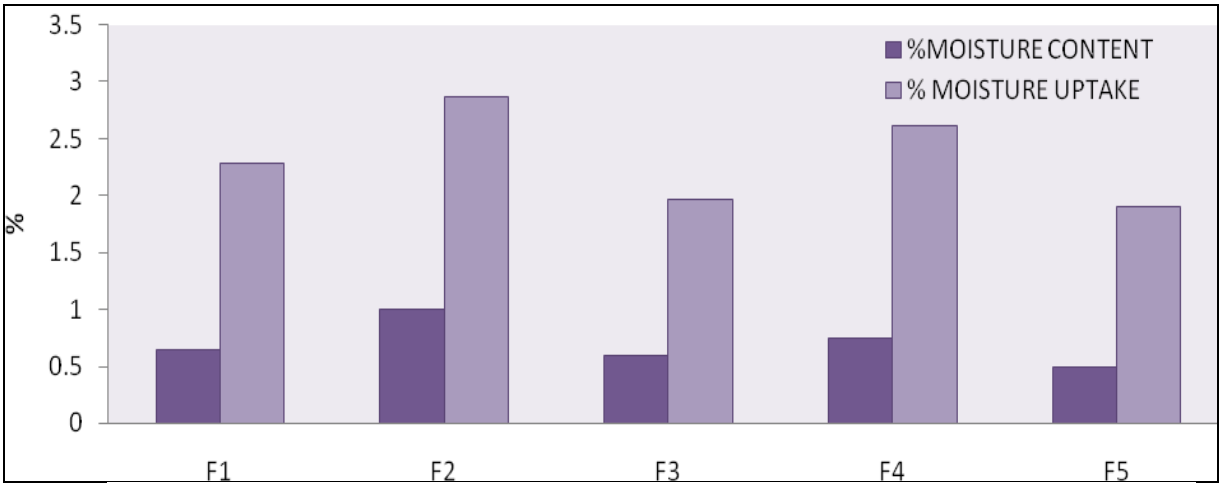


FIG. 2: COMPARISION OF MOISTURE CONTENT AND MOISTURE UPTAKE OF FORMULATIONS F1-F5

Evaluation of Adhesion: Thumb tack test:

Tackiness is the ability of a polymer to adhere to the substance with low contact pressure. These measurements are used to quantify or realize the sticky feel of the material. A good transdermal pressure sensitive adhesive should be removed from the skin surface without leaving a residue. From the results it was observed that the formulation without penetration enhancer was less tacky but other formulations were tackier compared to F1 formulation. All the formulation had acceptable tackiness (**Table 5**).

TABLE 5: RESULTS OF THUMB TACK TEST

S.No	Formulation Code	Tackiness
1.	F1	++
2.	F2	+++
3.	F3	+++
4.	F4	+++
5.	F5	+++

++ indicates medium corresponding property
+++ indicates highest corresponding property

***In Vitro* Permeation Studies:**

In-vitro release profile is an important tool that predicts in advance how the drug will behave *in vivo*. Franz Diffusion cell was used for *in-vitro* permeation study of transdermal patches. *In-vitro* drug release study was carried out across Dialysis membrane (Sigma Aldrich, Mumbai) membrane (soaked in phosphate buffer pH 7.4) and using phosphate buffer (pH 7.4) as an *in vitro* fluid in the receptor compartments of Franz's diffusion cell at 37 ± 0.5 °C. From the in-vitro drug release results of it was observed that the drug release was higher with formulations containing penetration enhancers compared to the formulation without penetration enhancer (**Table 6**). It was observed that on increasing the concentration of Oleic acid & Isopropyl myristate from 5 % to 10 %, permeation of drug through dialysis membrane also increased. It was observed that the drug permeation was highly affected by the enhancer employed. Out of the two, if analyzed individually, Isopropyl myristate has proved to be the better candidate in increasing rate of drug permeation.

TABLE 6: *IN-VITRO* DRUG RELEASE DATA

S.No	Time	Cumulative % drug release				
	Hrs	F1	F2	F3	F4	F5
1.	1	6.87	8.78	10.6	12.27	15.18
2.	2	13.86	18.265	21.81	24.28	25.41
3.	3	20.98	25.58	28.41	28.64	31.38
4.	4	28.07	32.95	35.33	35.23	38.63
5.	5	32.87	37.56	42.5	39.89	45.48
6.	6	38.68	41.52	46.65	43.17	49.99
7.	7	42.12	45.48	50.82	46.465	54.16
8.	8	46.87	49.76	56.33	52.1	57.62
9.	9	49.56	54.08	60.82	56.73	64.16
10.	10	53.98	58.65	65.61	60.96	70.78
11.	11	55.62	65.66	70.04	68.06	76.42
12.	12	58.01	72.31	76.84	74.23	82.03

Zero Order Drug Release:

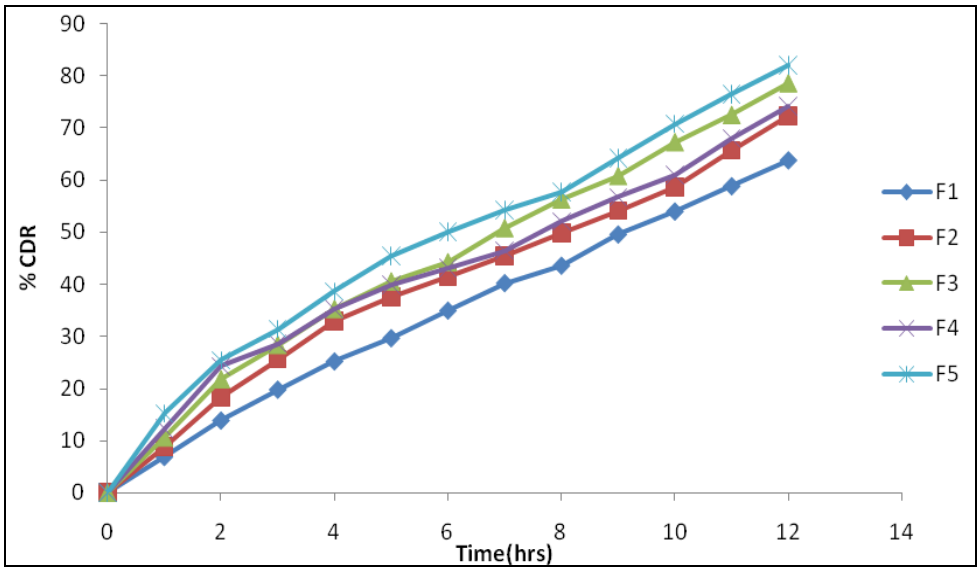


FIG. 3: PLOT OF CUMULATIVE PERCENT DRUG RELEASED VERSUS TIME FOR FORMULATION F1-F5

First Order Drug Release:

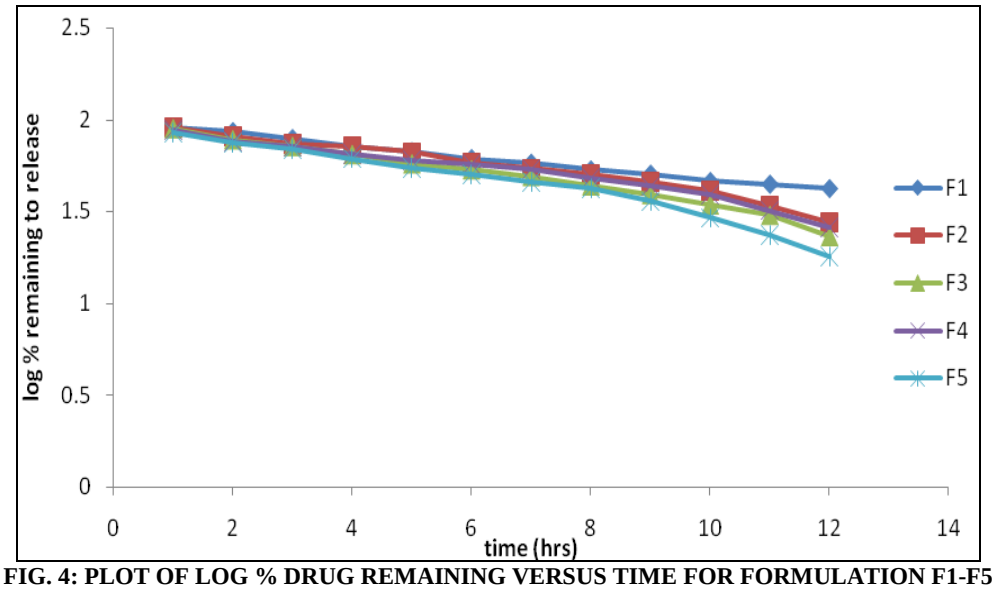


FIG. 4: PLOT OF LOG % DRUG REMAINING VERSUS TIME FOR FORMULATION F1-F5

Higuchi Drug Release:

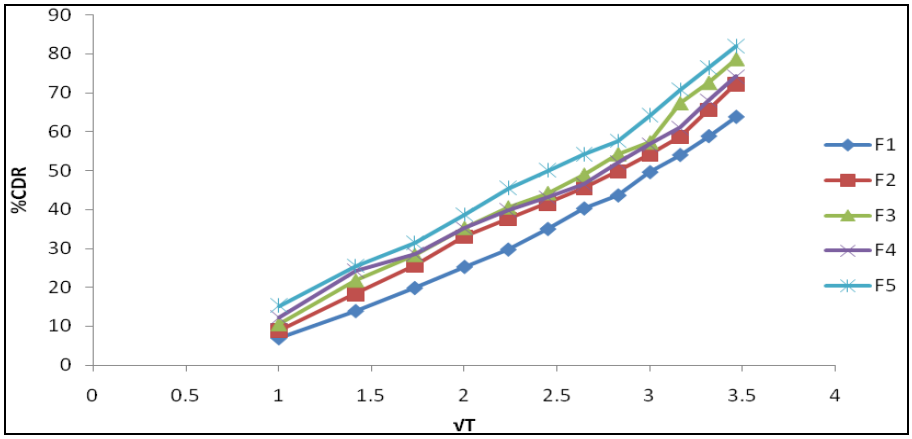


FIG. 5: PLOT OF CUMULATIVE PERCENT DRUG RELEASED VERSUS SQUARE ROOT OF TIME FOR FORMULATION F1-F5

Hixson-Crowell Drug Release:

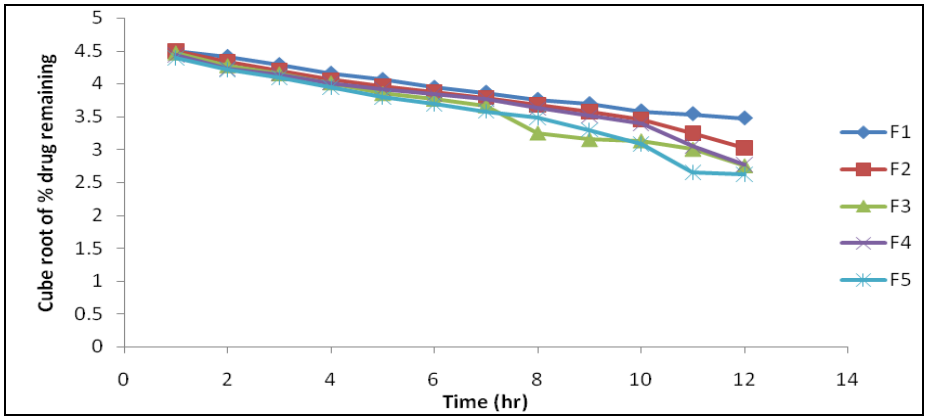


FIG. 6: PLOT OF CUBE ROOT OF % DRUG REMAINING TO RELEASE VERSUS TIME FOR FORMULATION F1-

Korsmeyer-Peppas Drug Release:

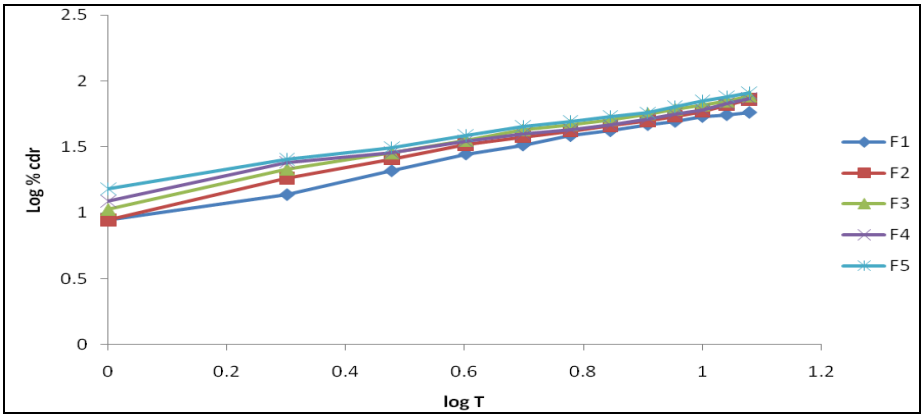


FIG. 7: PLOT OF LOG CUMULATIVE PERCENT DRUG RELEASED AS A FUNCTION OF LOG TIME FOR FORMULATION F1-F5

Kinetic Modelling of Drug Release Data:

From the kinetic modelling of drug release data it was found that the formulations showed zero order release kinetic (**Table7**), this suggest that the release rate was independent of the concentration of dissolved species. In case of Korsemeyer–Peppas equation the calculated value of 'n' was in range from 0.657 to 0.792 indicating that the mechanism of drug release from the PSA transdermal patch followed non-Fickian release kinetic.

TABLE 7: RELEASE KINETIC DATA OF FORMULATIONS F1-F5

Formulation	Zero order	First order	Higuchi kinetic	Hixson Crowell	Korsemeyer–Peppas	
					n	R^2
F1	0.995	0.994	0.987	0.989	0.786	0.992
F2	0.980	0.969	0.978	0.979	0.792	0.978
F3	0.984	0.982	0.981	0.983	0.756	0.982
F4	0.971	0.963	0.968	0.952	0.666	0.966
F5	0.975	0.961	0.973	0.970	0.657	0.975

CONCLUSION: Pressure sensitive drug in adhesive type transdermal patches of buflomedil hydrochloride were prepared and effects of various penetration enhancers on the permeation of buflomedil hydrochloride were studied. For this, oleic acid and isopropyl myristate were the permeation enhancers of the choice for the percutaneous absorption of buflomedil hydrochloride.

The adhesion properties of the patches were very satisfactory. Also, the prepared patches showed good uniformity with regard to drug content. *In vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation containing 95% adhesive solution and 10% IPM as permeation enhancer showed best in vitro permeation through dialysis membrane as compared to all other formulations. The results rate was found to follow zero order kinetics.

In conclusion, the present data confirms the feasibility of developing pressure sensitive drug in adhesive type transdermal patches of buflomedil hydrochloride. Further study in respect to *in vivo* performance after transdermal administration is required to establish the therapeutic utility of this system.

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