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FORMULATION AND DEVELOPMENT OF CARBAMAZEPINE TRANSDERMAL PATCHES: IN VITRO AND EX VIVO

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Abstract*:* **Objective**: The aim of the investigation was to develop and evaluate matrix type transdermal drug delivery systems (TDDS) of Carbamazepine (CBZ).

Experimental: The matrix type TDDS of CBZ were prepared by solvent evaporation technique. Ten formulations (composed of Eudragit RL 100 and Hydroxypropyl methyl cellulose in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4 in formulations A1, A2, A3, A4, A5 and Eudragit RS 100 and Hydroxypropyl methyl cellulose in the same ratios in formulation B1, B2, B3, B4, B5 respectively) were prepared. All formulations carried 6 % v/w of carvone as penetration enhancer and 15% v/w of propylene glycol as plasticizer in dichloromethane and methanol as solvent system. The prepared TDDS were evaluated for *in vitro* release, *ex vivo* permeation, moisture absorption, and moisture content and mechanical properties. The physicochemical interactions between Carbamazepine and polymers were investigated by Fourier Transform Infrared (FTIR) Spectroscopy.

Results: The maximum drug release in 24 hrs for A series formulations were 89.29% (A4) and 86.17% for B series (B5), which are significantly ($p < 0.01$) different to the lowest values (57.58 for A1 and 50.64 for B1). Again formulations A4 (flux 23.51 µg/hr/cm^2) and B5 (flux 22.98 µg/hr/cm^2) showed maximum skin permeation in the respective series. The flux obtained with formulation A4 and B5 meets the required flux (19.10 µg/hr/cm^2). The mechanical properties, tensile strength, elastic modulus (3.42 kg/mm^2 for A4 and 4.25 kg/mm^2 for B5) reveal that the formulations were found to be strong but not brittle. FTIR studies did not show any evidence of interaction between the drug and the polymers.

Conclusion: Carbamazepine matrix type transdermal therapeutic systems could be prepared with the required flux having suitable mechanical properties.

Keywords: Carbamazepine, Transdermal, Drug Release, Skin Permeation, Transdermal Patches, Mechanical Properties.

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1. Introduction*:* 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 as it avoids hepatic first pass metabolism and improves patient compliance [1]. However, the highly organized structure of *stratum corneum* forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery [2].

Carbamazepine is a tricyclic compound chemically related to tricyclic antidepressants (TCA) with anticonvulsant and analgesic properties. Carbamazepine exerts its anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation [3]. Its analgesic activity is not understood; however, carbamazepine is commonly used to treat pain associated with trigeminal neuralgia [4].

Carbamazepine is a dibenzoazepine that is 5H-dibenzo [b, f] azepine carrying a carbamoyl substituent at the azepine nitrogen, used as an anticonvulsant. It has a role as an anticonvulsant, an EC 3.5.1.98 (histone

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deacetylase) inhibitor, a mitogen, a glutamate transporter activator, an antimanic drug, an analgesic, a non-narcotic analgesic, an environmental contaminant, a xenobiotic, a drug allergen and a sodium channel blocker. It is a dibenzoazepine and a member of ureas [5].

Previous studies, reported Carbamazepine transdermal therapeutic systems based on fabrication of Carbamazepine patches in a polyisobutylene matrix using azone as a penetration enhancer [6] and acrylate based pressure sensitive adhesive using d-limonene as a penetration enhancer [7]. The flux and diffusion coefficient can be increased with transdermal permeation enhancer due to their ability to change the structure of lipophilic and/or keratinized domains in *stratum corneum* [8]. Terpenes present in naturally occurring volatile oils appear to be clinically acceptable enhancers [9]. Moreover, a wide variety of terpenes have been shown to increase the percutaneous absorption of number of drugs [10]. In the present study carvone was used as penetration enhancer, as reported earlier for some other drugs [11-13].

The objective of the present work was to develop and characterize the Carbamazepine monolithic transdermal therapeutic systems for *in vitro* release, *ex vivo* permeation and mechanical properties.

2. Materials and Methods

2.1. Materials: Carbamazepine was gift sample from M/s US Vitamins, India. Carvone was procured from Merk-Schuchardt, Hohenbrunn, Germany. Eudragit RL 100(ERL 100), Eudragit RS 100(ERS 100) and Hydroxypropyl Methyl Cellulose (HPMC) were gift samples from Zydus Cadila, Ahmedabad, India. All other chemicals used were of analytical grade.

2.2. Development of Transdermal Systems: Matrix type transdermal patches containing Carbamazepine were prepared by solvent evaporation technique, using different ratios of ERL 100 (or ERS 100) and HPMC E 15 (Table 1). The polymers were weighed in requisite ratios by keeping the total polymer weight 2.50 gm and allowed for swelling for about 6 hrs in solvent mixture (1:1 ratio of dichloromethane, methanol). Propylene glycol was incorporated as plasticizer and carvone as penetration enhancer. Then the drug solution was added to the polymeric solution, casted on to anumbra petriplate of surface area about 70 sq.cm, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 3.14 cm^2 i.e. with a diameter of 2 cm. About 10 patches were obtained from each sheet.

2.3. *In vitro* Release Studies: The drug release studies from Carbamazepine transdermal patches were performed using Labindia dissolution rate test apparatus (USP-II). Commercially available water impermeable adhesive backup membrane was placed over the patches (3.14 cm^2), it was further fixed to a glass slide (2.1x2.1 cm) with the help of cyanoacrylate adhesive. Then the transdermal patch was placed in a dialysis membrane (Himedia Mol. Wt 5000). It was further placed in dissolution vessel and samples (5 ml) were collected up to 24 hrs. Analysis was carried out using UV-Vis spectrophotometer. Phosphate buffer pH 5.6 (500 ml) containing 0.5% w/v of Tween 80 was used as release media. The study was conducted at 32 ± 0.5°C and paddle speed was kept 25 rpm. The analysis was done at 340 nm against phosphate buffer pH 5.6 containing 0.5 % w/v Tween 80 as reference. At λ max of 238 nm for Carbamazepine, Tween 80 has absorbance and interferes in Carbamazepine detection, therefore analysis carried at 340 nm. At 340 nm maximum absorbance without interference was observed and therefore this was used.

Mathematical expressions, zero order [14], First order [15] and Higuchi model [16] were applied to analyze the release mechanism from the transdermal patches.

2.4. Preparation of Rat Abdominal Skin: Albino rats weighing 150-200 gm were sacrificed using anaesthetic ether. The hair of test animals was carefully trimmed short (< 2 mm) with a pair of scissors and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique [17], which involved soaking the entire abdominal skin in water at 60° C for 45 sec, followed by careful removal of the epidermis. The epidermis was washed with water and used for *ex vivo* permeability studies.

2.5. *Ex vivo* Permeation Studies: Franz diffusion cell with a surface area of 3.56 cm^2 was used for *ex vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with *stratum corneum* facing the donor compartment. The *stratum corneum* side of the skin was kept in intimate contact with the release surface of the TDDS under test. A dialysis membrane (Himedia) with molecular weight cut off of 5000 was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receiver phase is 12 ml of phosphate buffer saline (PBS) pH 7.4 containing 40 % v/v of PEG 400, stirred at 500 rpm on a magnetic stirrer; the whole assembly was kept at 37 ±

0.5° C. The amount of drug permeated was determined by removing 1 ml of sample at appropriate time intervals up to 24 hr, the volume was replenished with an equal volume of PBS pH 7.4 containing 40 % v/v PEG 400. The absorbance was measured at 238 nm spectrophotometrically. Cumulative amounts of drug permeated in µg/cm^2 were calculated and plotted against time (Figs. 3 and 4). Drug flux (µg/hr/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (3.14 cm^2) [18] and the permeability coefficient was deduced by dividing the flux by initial drug load as shown in Table 2. The target flux is calculated using the following equation [19].

A represents the surface area of the transdermal patch (i.e 3.14 cm^2) BW, the standard human body weight of 60 kg, Css the CBZ concentration at the therapeutic level (50 µg/L) and the CLT the total clearance (20 ml/min/kg) [4], the calculated target flux value for CBZ was 19.10 µg/hr/cm^2.

2.6. Moisture Absorption Study: The films were weighed accurately and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride (79.50% RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [20].

2.7. Moisture Content: The patches were weighed and kept in a desiccator containing calcium chloride at 40° C for 24 hr. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight [21].

2.8. Measurement of Mechanical Properties: Mechanical properties of the films were evaluated using a microprocessor based advanced force guaze (Ultra Test, Mecmesin, UK) equipped with a 25 kg load cell. Film strip with dimensions 60 x 10 mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm/s pulled the strips to a distance till the film broke. The force and elongation were measured when the film broke. The mechanical properties were calculated according to the following formulae [22]. Measurements were run in four replicates for each formulation.

2.9. Drug- Polymer Interaction Study: To study the possible interaction between Carbamazepine and polymeric materials of the patches, infrared (IR) spectroscopy was carried out on pure substances and their physical mixtures. The IR spectra was recorded using IRSpectrophotometer (Perkin Elmer FT-IR, Perkin Elmer Inst. USA) by KBr pellet method.

3. Results and Discussions

3.1. *In vitro* Release Studies: Figs. (1) and (2) show the release profiles of Carbamazepine from transdermal patches. Formulations A4 and B5 exhibited greatest (89.29 ± 6.88 and 86.17 ± 7.70 % respectively) percentage of drug release values, which are significantly ($p<0.01$) different compared to the lowest values observed with the formulations containing ERL 100 and ERS 100 (57.58 ± 3.70 and 50.64 ± 1.20 % respectively). In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially, however with a very nominal decrease in formulation A5. The addition of hydrophilic component to an insoluble film former tends to enhance the release rates [23].

The description of dissolution profiles by a model function has been attempted using different kinetics (zero order. first order and Higuchi square-root model) and using the following equation derived by Korsmeyer et al. [24].

$$Mt/ M\alpha = K.t^n$$

Where Mt/ Mα is the fractional release of drug, Mt is the amount released at time t, Mα is the total amount of drug contained in the TDDS, t is the release time, K is the kinetic constant and n is the diffusional release exponent indicative of the operating release mechanism. Higuchi square route seemed to be the most appropriate model describing release kinetics from all patches (correlation coefficient between 0.9651 and 0.9923). On the other hand, n values ($1.02 \leq n \geq 1.37$) indicated that amount of released drug was by non Fickian diffusion, super case II transport [25].

$$\text{Tensile strength (Kg.mm}^{-2}\text{)} = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation at break (\% mm}^{-2}\text{)} = \frac{\text{Increase in length (mm)}}{\text{(\% mm}^{-2}\text{ Original length (mm)}} \times \frac{100}{\text{Cross sectional area (mm}^2\text{)}}$$

$$\text{Elastic Modulus (Kg.mm}^{-2}\text{)} = \frac{\text{Force at corresponding strain (kg)}}{\text{Cross-sectional area (mm}^2\text{)}} \times \frac{1}{\text{Corresponding strain}}$$

$$\text{Strain} = \frac{\text{Tensile strength}}{\text{Elastic modulus}}$$

3.2. *Ex vivo* Permeation Studies: The results of *in vitro* skin permeation of Carbamazepine from patches were shown in Figs. (3) and (4). The formulations (area of 3.14 cm^2) A4 and B5 exhibited the greatest (2300 ± 39.26 and 1911.60 ± 35.71 µg respectively) cumulative amount of drug permeation, which were significantly ($P < 0.01$) different compared to the lowest values observed with the formulations containing ERL 100 (Formulation A1) and ERS 100 (Formulation B1) (307.90 ± 16.81 and 237.50 ± 10.02 µg respectively) in 24 hr. The cumulative amounts of drug permeated per square centimeter of patches through the rat abdominal skin when plotted against time, the permeation profiles of drug seem to follow zero order kinetics as it is evidenced by correlation coefficients (0.9387 to 0.9975) better than first order (r^2 = 0.8317 to 0.8904) and Higuchi's equation (Higuchi square-root model) (r^2 = 0.9311 to 0.9864).

As the proportion of HPMC increased in all the formulations, increased drug release and permeation in both series were observed. In case of formulation A5, more rigid films were formed, that could substantially retard the release of drug from formulation. The required flux was obtained with formulation A4 (23.51 µg/cm^2 /hr) and B5 (22.98 µg/cm^2/hr). The results of drug permeation from transdermal patches of CBZ through the rat abdominal skin confirmed that CBZ was released from the formulation and permeated through the rat skin and hence could possibly permeate through the human skin.

3.3. Moisture Content and Moisture Absorption Studies: The results of moisture content and moisture absorption studies were shown in Fig. (5). The moisture content in the patches is ranged from 1.37 ± 0.24 to 4.02 ± 0.84% and 1.36 ± 0.27 to 4.33 ± 1.34% (for formulation A series and formulation B series respectively). The moisture absorption in the formulations is ranged from 1.45 ± 0.50 to 15.90 ± 2.68% and 0.83 ± 0.32 to 14.10 ± 4.01% (for formulation A series and formulation B series respectively). The results revealed that the moisture absorption and moisture content was found to increase with increasing concentration of hydrophilic polymer (HPMC). The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle film [26].

3.4. Mechanical Properties: The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength (TS) and elastic modulus (EM) and elongation at break (E/B). A soft and weak polymer is characterized by a low TS, EM and E/B; a hard and brittle polymer is defined by a moderate TS, high EM and low E/B; a soft and tough polymer is characterized by a moderate TS, low EM and high E/B; where as a hard and tough polymer is characterized by a high TS, EM and E/B [27]. Another parameter strain has been used as an indicator of the overall mechanical quality of the film [28]. A high strain value indicates that the film is strong and elastic. Hence, it is suggested that a suitable transdermal film should have a relatively high TS, E/B and strain but low EM.

The results of mechanical properties (tensile strength, elongation at break, elastic modulus and strain) are shown in Table 3. Formulation A5 and B5 exhibited greater values of tensile strength and elastic modulus (2.15 ± 0.077 kg/mm^2 and 5.35 ± 0.654 kg/mm^2 for A5; 2.20 ± 0.091 kg/mm^2 4.25 ± 0.599 kg/mm2 respectively). The results revealed that as the concentration of HPMC increased, the tensile strength and elastic modulus were found to be increased but elongation at break values decreased. An inverse relation was observed between tensile strength and elongation at break. These observations indicate that formulation A4 and B5 patches were found to be strong, not brittle and flexible.

3.5. Drug - Polymer Interaction Study: The IR spectral analysis of CBZ alone showed that the principal peaks were observed at wave numbers of 1701.87, 1649.86, 1537.76, 1212.19 and 1095.94. In the IR spectra of the physical mixture of CBZ, ERL and HPMC were 1701.73, 1650.55, 1531.84, 1212.32 and 1095.98; 1701.66, 1650.51, 1531.78, 1212.32 and 1095.96 wave numbers were observed for the mixture of CBZ ERS and HPMC. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the present study. It is already well known that the common polymers such as HPMC, ERL and ERS are popular in controlled/sustained release matrix type patches because of their compatibility with a number of drugs [29].

4. Conclusion: Matrix type transdermal therapeutic systems of CBZ could be prepared with the required flux having suitable mechanical properties. Further work is recommended in support of its efficacy claims by long

term pharmacokinetic and pharmacodynamic studies on human beings.

Table 1. Composition of CBZ Transdermal patches

Formulation	Drug (mg)	Polymers	
	CBZ	ERL 100 : HPMC E 15	ERS 100 : HPMC E 15
A1	240	5 : 0	-
A2	240	4 : 1	-
A3	240	3 : 2	-
A4	240	2 : 3	-
A5	240	1 : 4	-
B1	240	-	5 : 0
B2	240	-	4 : 1
B3	240	-	3 : 2
B4	240	-	2 : 3
B5	240	-	1 : 4

Note: 15% v/w propylene glycol to the total polymer weight, incorporated as Plasticizer.
6% v/w of carvone to the total polymer weight, as penetration enhancer.
Each patch (3.14 cm^2) contains 10 mg of Carbamazepine.

Table 2. *In vitro* Drug Release, *Ex vivo* Skin Permeation, Transdermal Flux, Permeability Coefficient and Lag Time of Carbamazepine Transdermal Patches

Formulation	Q24 release [a]	Q24 permeation [b]	Jss[c] (µg/cm^2 /hr)	Kpd (cm hr^{-1} X102)	LTe (hr)
A1	57.58 ± 3.70	307.9 ± 16.81	3.28 ± 0.19	0.103 ± 0.014	3.92 ± 1.89
A2	68.11± 5.16	692.01 ± 27.16	7.15 ± 0.45	0.225 ± 0.023	1.24 ±0.01
A3	87.91± 1.97	1273.57± 43.60	12.68 ± 0.80	0.398 ± 0.051	0.36 ± 0.05
A4	89.29 ± 6.88	2300.00 ± 39.26	23.51 ± 3.83	0.738 ± 0.112	0.15 ± 0.01
A5	83.59 ± 5.64	1315.73 ± 42.13	15.25 ± 1.20	0.479 ± 0.094	1.83 ± 0.03
B1	50.64 ± 1.20	237.5 ± 10.02	2.58 ± 0.61	0.081 ± 0.012	1.54 ± 0.11
B2	60.76 ± 5.28	589.32 ± 23.93	6.82 ± 1.02	0.214 ± 0.033	0.39 ± 0.04
B3	69.56 ± 4.09	981.26 ± 24.83	12.28 ± 1.76	0.386 ± 0.131	0.38 ± 0.09
B4	82.35 ± 6.97	1418.65 ± 36.12	17.02 ± 2.31	0.534 ± 0.115	0.10 ± 0.01
B5	86.17 ± 7.70	1911.6 ± 35.71	22.98 ± 2.50	0.722 ± 0.150	0.03 ± 0.00

[a]Cumulative % drug released, results are the mean ± SD of six observations.
[b]Cumulative amount (µg) of drug permeated per cm^2, results are mean ± SD of triplicate observations.
Jss[c] Transdermal flux, values represent mean ± SD (n=3).
Kp[d] Permeability Coefficient, values represent mean ± SD (n=3).
LT[e] Lag Time, values represent mean ± SD (n=3).

Table 3. Tensile Strength, Elongation at Break, Elastic Modulus and Strain values of Carbamazepine Transdermal Patches

Formulation	Tensile Strength (kg/mm^2)	Elongation at Break (% mm^{-2})	Elastic Modulus (kg/mm^2)	Strain
A1	0.31± 0.038	107.34 ± 19.346	0.49 ± 0.109	0.63 ± 0.021
A2	0.66 ± 0.208	64.78 ± 11.072	1.25 ± 0.236	0.52 ± 0.018
A3	1.31 ± 0.311	26.75 ± 8.371	1.89 ± 0.358	0.69 ± 0.024
A4	1.58 ± 0.052	15.26 ± 1.231	3.42 ± 0.407	0.46 ± 0.016
A5	2.15 ± 0.077	12.02 ± 0.862	5.35 ± 0.654	0.40 ± 0.014
B1	0.13 ± 0.021	172.63 ± 23.024	0.41 ± 0.091	0.31 ± 0.011
B2	0.56 ± 0.014	73.34 ± 10.828	0.91 ± 0.102	0.61 ± 0.021
B3	0.83 ± 0.047	31.70 ± 3.611	2.40 ± 0.190	0.34 ± 0.012
B4	1.47 ± 0.051	18.48 ± 3.490	3.15 ± 0.410	0.46 ± 0.016
B5	2.20 ± 0.091	11.53 ± 1.876	4.25 ± 0.599	0.51 ± 0.018

Values represent mean ± SD (n=4).

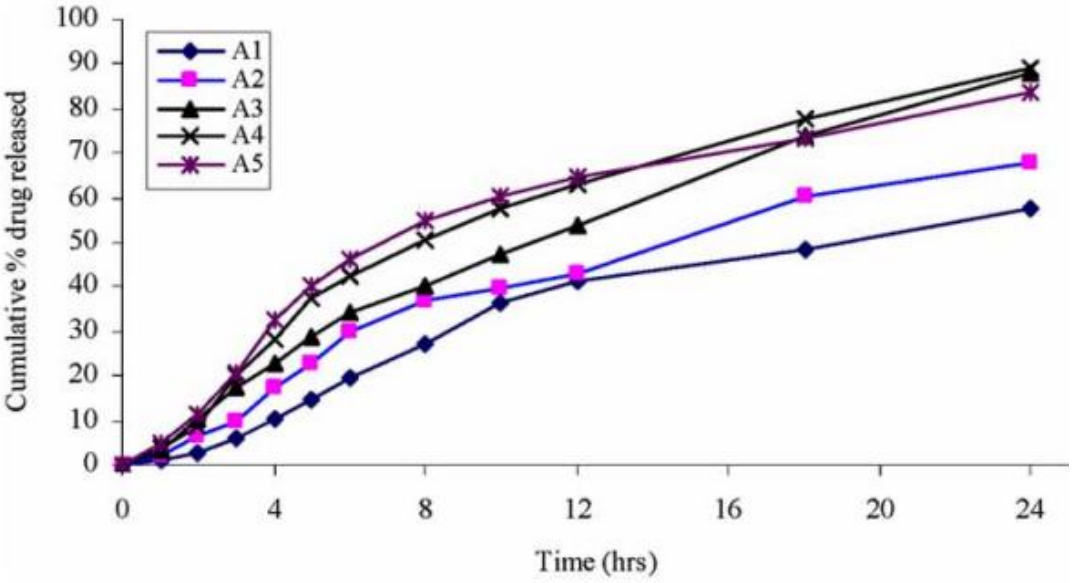

Fig. (1). Release of Carbamazepine from transdermal patches (A Series), mean ± SD (n=6) are presented

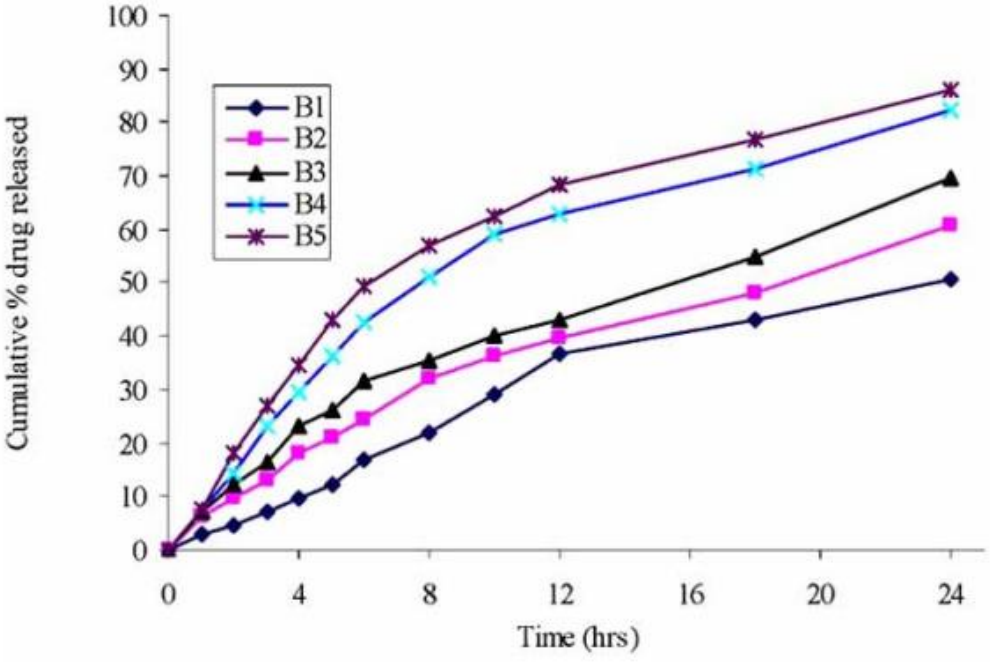

Fig. (2). Release of Carbamazepine from transdermal patches (B Series), mean ± SD (n=6) are presented

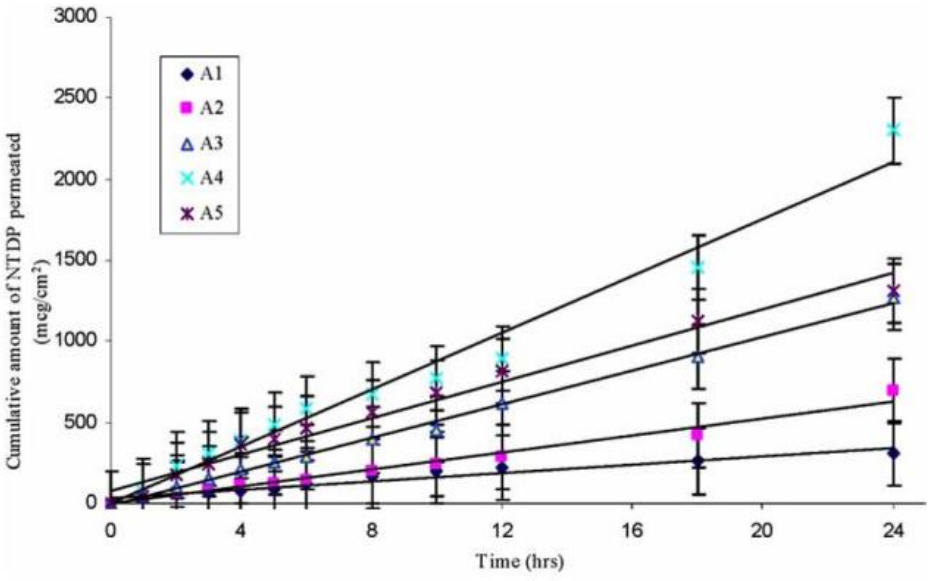

Fig. (3). Permeation of Carbamazepine from transdermal patches (A Series) through rat abdominal skin, mean ± S.D (n=3) are presented

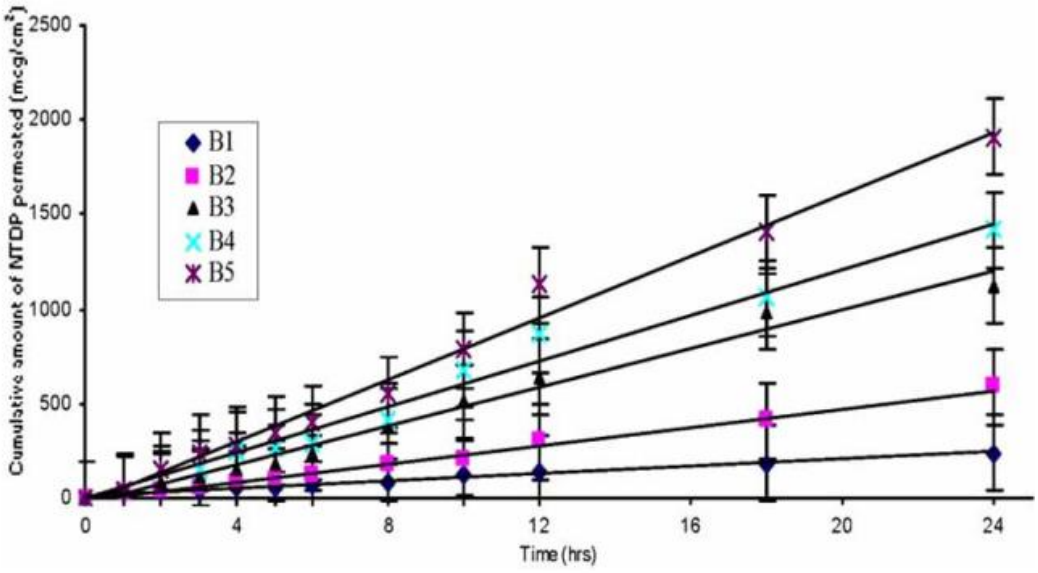

Fig. (4). Permeation of Carbamazepine from transdermal patches (B Series) through rat abdominal skin, mean ± S.D (n=3) are presented

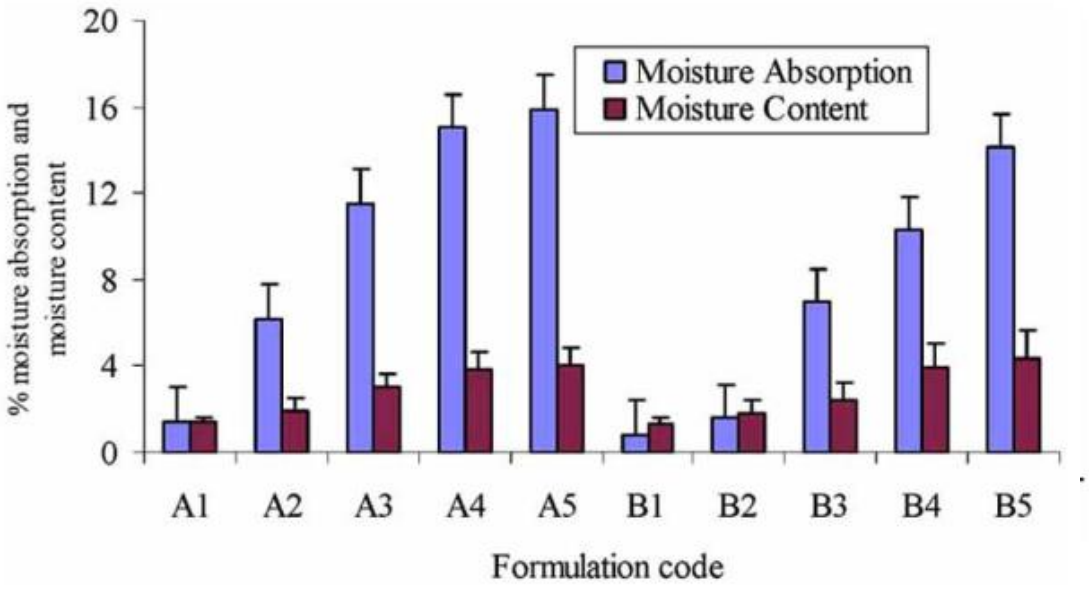

Fig. (5). Moisture absorption and moisture content of CBZ transdermal patches, mean ± S.D (n=3) are presented

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