RESEARCH ARTICLE

Effect of penetration enhancers on the permeability characteristics of lisinopril transdermal delivery systems

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Lisinopril is an ACE inhibitor used in the treatment of hypertension and heart failure, prophylactically after myocardial infarction and in diabetic nephropathy. Lisinopril is slowly and incompletely absorbed following oral administration. On an average about 25% of the drug is absorbed after administration of a single dose. Thus, a controlled drug delivery formulation of lisinopril for transdermal absorption would be more advantageous and beneficial for improving the bioavailability and reducing the frequency of administration for long-term treatment. Matrix type transdermal films were prepared by solvent casting technique using a combination of ammonia methacrylate copolymer, type A. USP/NF(EudragitRL100) and poly vinyl pyrrolidone (PVP) as polymers. Propylene glycol was used as plasticizer. Glycerine, dimethyl sulphoxide (DMSO) and span-60 were used as penetration enhancers. The physicochemical parameters like thickness, folding endurance, drug content, tensile strength and stability were evaluated. In- vitro drug release and *in-vitro* skin permeation studies were carried out using modified Keshary-Chien permeation cell. Infra-red spectroscopy (IR) and differential scanning colorimetry (DSC) were performed to follow drug carrier interactions. In- vitro drug permeation profile of the formulated films showed that formulations containing span-60 as penetration enhancer (F4, F8, F12, F16, F20) showed highest drug permeation. From the results of this study it indicated that the permeation of lisinopril from films containing span-60 as penetration enhancer was the best at all polymer ratios as compared to the films containing DMSO and glycerine. The order of permeability enhancement from the films was found to be span-60 > DMSO > glycerine. There was no significant difference in the physicochemical characters and drug content for a period of 3 months.

Key words: *DMSO, ERL100, glycerine, lisinopril, PVP, span-60, transdermal films*

INTRODUCTION

The basic goal of drug therapy is to achieve a steady state blood or tissue level that is therapeutically effective for an extended period of time. The therapeutic efficacy and safety of the drugs administered by conventional methods can be improved by more precise, spatial and temporal placement within the body, thereby reducing both the size and number of doses through a controlled drug delivery system. Lisinopril is an ACE inhibitor used in the treatment of hypertension and heart failure, prophylactically after myocardial infarction and in diabetic nephropathy. Lisinopril is slowly and incompletely absorbed following oral administration.[1] Lisinopril has a molecular weight of 441.52, poor bioavailability after oral administration and has dose of 20 mg-80 mg once daily in treatment of hyper tension and at doses of 2.5 mg to 20 mg once daily improves cardiac function.[2] This makes it an ideal candidate for transdermal delivery. Thus, a controlled drug delivery formulation of lisinopril for transdermal absorption would be more advantageous and beneficial for improving the bioavailability and reducing the frequency of administration for long term treatment.

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A combination of hydrophobic (ERL100) and hydrophilic (PVP) polymers are used to formulate the transdermal films.

MATERIALS AND METHODS

Materials

Lisinopril was obtained as a gift sample from Dr. Reddy's Laboratories, (Hyderabad, India). EudragitRL100 was obtained as gift sample from Evonik Degussa Ltd (Mumbai, India). PVP was procured from Loba Chemie Pvt. Ltd. All other chemicals used in this study were of analytical grade.

Preparation of transdermal films

Matrix type transdermal films of lisinopril were prepared by solvent casting technique. A flat, petri dish having surface area of 4.9 cm^2 was used for casting the films. Twenty (20) formulations were prepared using ERL100 and PVP. All the formulations carried 0.5% v/w of propylene glycol as plasticizer. 0.5% v/w of glycerine, DMSO and span-60 were used as penetration enhancers [Table 1].

Polymer solution was prepared in methanol (10 ml). Weighed quantity of lisinopril (20 mg) was added to the polymer solution with stirring until it dissolved. Plasticiser and penetration enhancer was then added and the mixture was stirred at 500 rpm for 1 hour at room temperature using a magnetic stirrer. After stirring 3.5 ml of the resultant solution was poured in a petri-dish and a funnel was kept inverted over the petri-dish for air drying for 24 hrs. Circular films of 4.9 cm^2 were obtained which was then cut into films of 1 cm^2 size. The films were packed in aluminium foils and stored in a desiccator.[3-5]

Solubility measurement

The solubility of lisinopril was determined according to the method adopted by Krishnaiah.[6] An excess amount of drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. The solution was kept at room temperature for the attainment of equilibrium. The concentration of lisinopril in the filtrate was determined spectrophotometrically by measuring at 258 nm after 24 hours.

Partition coefficient (Kp)

The partition coefficient of the drug was determined by shaking equal volumes of organic phase (n-octanol) and the aqueous phase in a separating funnel.[7] A drug solution of 1 mg/ml was prepared in phosphate buffer pH 7.4 and 50 ml of this solution was taken in a separating funnel and shaken with an equal volume of n-octanol for 10 minutes and allowed to stand for 24 hours with intermittent shaking. Then, the concentration of lisinopril in the aqueous phase was determined using a UV spectrophotometer at 258 nm to get the partition coefficient value. The partition coefficient (K_p) was calculated using the following equation,

$$K_p = \frac{\text{concentration of drug in organic phase}}{\text{concentration of drug in aqueous phase}} \quad (1)$$

Drug - Excipient interaction studies

In order to find out the possible interactions between lisinopril and the polymers used in the formulation of the transdermal films, Fourier transform infra-red spectroscopy (FT-IR) and differential scanning calorimetry (DSC) analysis were carried out on the pure substance, their physical mixtures.[8-10]

Table 1: Formulation Composition

Formulation code	Drug (mg)	Polymer ratio ERL100/PVP	ERL100 (mg)	PVP (mg)	Propylene glycol (ml)	Penetration enhancer (ml)		
						Glycerine	DMSO	Span-60
F1	20	5:0	100	-	0.5	-	-	-
F2	"	"	"	"	"	0.5	-	-
F3	"	"	"	"	"	-	0.5	-
F4	"	"	"	"	"	-	-	0.5
F5	20	4:1	80	20	0.5	-	-	-
F6	"	"	"	"	"	0.5	-	-
F7	"	"	"	"	"	-	0.5	-
F8	"	"	"	"	"	-	-	0.5
F9	20	3:2	60	40	0.5	-	-	-
F10	"	"	"	"	"	0.5	-	-
F11	"	"	"	"	"	-	0.5	-
F12	"	"	"	"	"	-	-	0.5
F13	20	2:3	40	60	0.5	-	-	-
F14	"	"	"	"	"	0.5	-	-
F15	"	"	"	"	"	-	0.5	-
F16	"	"	"	"	"	-	-	0.5
F17	20	1:4	20	80	0.5	-	-	-
F18	"	"	"	"	"	0.5	-	-
F19	"	"	"	"	"	-	0.5	-
F20	"	"	"	"	"	-	-	0.5

Characterization of the transdermal films

Physical appearance:

All the prepared transdermal films were observed for colour, clarity, flexibility, and smoothness.[11]

Thickness of the film:

The thickness of patches was measured at three different places using a micrometer and mean values were calculated.[5]

Weight variation:

Three films of size 1 cm^2 from each batch were weighed individually and average weight determined.[12]

Moisture content

3 films were weighed individually and kept in a desiccator containing calcium chloride at 37°C for 24 hrs. The final weight was noted. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.[11,13,14]

Moisture uptake

A weighed film was kept in a desiccator at room temperature and exposed to 2 different relative humidity's 75% and 93% in 2 different desiccators for a period of 3 days. The percentage moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[11,13,14]

Folding endurance

A small strip of the film (1 cm^2) was folded repeatedly at the same place till it broke. The number of times the film could be folded at the same place without breaking is the folding endurance.[14,15] This was repeated six times and the mean values plus standard deviation was calculated.

Tensile strength and % elongation

A strip of the film of 1*0.5 cm was selected and attached to a clip at one end of a flat wooden surface and was pulled by means of a pulley system. Weights were added to the pan to increase the pulling force till the film was broken. The elongation of the film at the point of break up was measured.[12]

The tensile strength was calculated as per the formula given below,

$$\text{Tensile strength} = \left(\frac{\text{break force}}{a \times b}\right)\left(\frac{1+\Delta L}{L}\right) \quad (2)$$

Where a = thickness of the film b= width of the film, ΔL = length at breaking point L = length of the film.

% Elongation was calculated using the formula,

$$\% \text{ Elongation} = \left(\frac{Lb - L0}{L0}\right) \times 100 \quad (3)$$

L0 = original length of the film, Lb = length of the film when stress is applied.

Hardness:

Hardness was determined using an apparatus designed in our laboratory as per literature report. The film was placed between the metal and sharp end of the rod of the apparatus. Weights were added gradually at an interval of 10 seconds for the stabilization of the force till the bulb glows. The final weight was considered as the measure of hardness.[12]

Drug content

The transdermal films (1 cm^2) were added to beaker containing 100 ml of phosphate buffer (pH 7.4). This was then stirred with Teflon coated magnetic bead at 200 rpm for 2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 258 nm. Similarly a blank was prepared from transdermal films without the drug.[13,14]

Stability studies

The transdermal films were sealed in polyethylene coated aluminium foils and kept at 10°C, room temperature, and 45°C for a period of 3 months. During this period the films were tested for any change in colour, texture and analysed periodically for its drug content.[16]

In-vitro drug release studies

Modified Keshary-Chien apparatus was fabricated in our laboratory and used for the release study. The transdermal film was placed on cellophane membrane which was mounted on the donor compartment of the diffusion cell having a surface area of 1.76 cm^2. The donor compartment was kept in contact with the receptor compartment which was filled with 100 ml phosphate buffer solution pH 7.4 at a temperature of 37°C ± 1°C, in such a way that the membrane just touches the solution. The elution medium was stirred magnetically at 50 rpm. The aliquots (5 ml) were withdrawn at predetermined time intervals for 12 hours and replaced with the same volume of the buffer. The samples were analysed for drug content using UV spectrophotometer at 258 nm.[14-16]

In-vitro skin permeation studies

Preparation of the skin barrier: Fresh full-thickness (75-80 μm) goat ear skin was used for the study. The skin was immersed in water at 60°C for a period of 5 minutes. The epidermis was peeled from the dermis. The isolated epidermis (25 ± 5 μm thick) was rapidly rinsed with hexane to remove surface lipids and then rinsed with water and used immediately. The *in vitro* skin permeation from the prepared polymeric films across the goat ear skin barrier was studied using a modified Keshary Chien diffusion cell. 100 millilitres of phosphate buffer of pH 7.4 was used as an elution medium. The transdermal films to be studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The elution medium was magnetically stirred for uniform drug distribution at a speed of 50 rpm. The temperature of the whole assembly was maintained at 37°C ± 1°C by thermostatic arrangements.[17-19]

An aliquot of 5 ml was withdrawn at a suitable interval and an equivalent volume of fresh buffer was replaced. The amount of drug permeated across the skin was determined on a UV spectrophotometer at 258 nm.

To examine the drug permeation kinetics and mechanism, the data were tabulated and fitted to models representing zero-order, first-order, Higuchi diffusion model and Korsmeyer-Peppas.

RESULTS AND DISCUSSION

Matrix-type transdermal films of lisinopril were prepared using different ratios of ERL100 and PVP and also by using different penetration enhancers. The prepared films were found to be uniform, smooth, flexible and homogenous. The films were subjected to test for thickness of the film, weight uniformity, folding endurance, tensile strength, drug content, percentage moisture uptake, percentage moisture content, and stability studies at different temperature [Tables 2].

Partition coefficient of lisinopril in the octanol/water system was found to be 10.125. Solubility and permeability of lisinopril were evaluated at various values of pH with phosphate buffer. It was seen that solubility increased with increase in the pH. FT-IR spectral analysis showed that there were no physical and chemical interactions between the drug and the polymer [Figures 1 and 2].

The DSC thermo grams of lisinopril and physical mixture of the drug with the polymers are represented in [Figures 3 and 4]. The DSC thermo gram of lisinopril displayed the characteristic peak at 180°C corresponding to its melting point. The drug peak appeared in the thermo gram for the physical mixture of the drug and polymers, confirming the chemical integrity of the drug.

The polymers used for the fabrication of the transdermal system showed good film forming properties. The method adopted for casting the film was found to be satisfactory. All the patches showed good folding endurance properties.

There was no significant difference in the thickness and average weight of the prepared films. The thickness of the prepared films ranged from 0.118 mm to 0.242 mm. The average weight of the films ranged from 23 mg to 28 mg. The low standard deviation values show the uniformity of the films prepared.

The drug content analysis of the prepared formulations have shown that the process employed to prepare the films was capable of giving uniform drug content, with minimum batch variability. All the films were found to have drug content in the range between 89.5 to 94.11% of the labelled amount.

The mechanical properties i.e., tensile strength of the patches revealed that the formulations were found to be strong but

Table 2: Physicochemical evaluation of the transdermal films of Lisinopril

Formulation	Weight (mg), SD	Thickness (mm), SD	Tensile strength (kg/cm^2), SD	Folding endurance, SD	% Elongation, SD	Drug Content, SD	% moisture content	% moisture uptake	
								75% RHRT	93% RHRT
F1	23±0.035	0.138±0.005	0.44±0.045	198±6.021	60.5±0.120	95.09±0.025	0.95	3.84	8.45
F2	24±0.022	0.136±0.002	0.45±0.038	200±5.130	62.5±0.313	90.09±0.0375	0.98	3.85	8.86
F3	25±0.030	0.202±0.004	0.45±0.208	210±6.250	63.05±0.145	91.66±0.0345	1.05	3.86	8.66
F4	24±0.025	0.140±0.007	0.46±0.311	224±6.114	62.0±0.063	91.91±0.0144	1.04	3.85	8.75
F5	25±0.018	0.242±0.006	0.52±0.052	228±5.035	70.24±0.182	91.17±0.0275	1.21	4.12	10.87
F6	27±0.042	0.125±0.003	0.54±0.077	290±5.105	73.06±0.274	94.11±0.025	1.22	4.29	10.86
F7	26±0.035	0.108±0.003	0.53±0.021	185±6.018	74.8±0.132	91.42±0.0344	1.28	4.18	10.94
F8	27±0.022	0.232±0.005	0.53±0.014	203±4.055	73.65±0.893	92.64±0.0365	1.28	4.17	11.09
F9	25±0.025	0.145±0.004	0.62±0.047	231±6.550	76.58±0.675	91.66±0.0375	1.60	4.73	13.15
F10	26±0.015	0.195±0.004	0.65±0.051	245±4.810	79.15±0.205	91.05±0.045	1.62	4.75	13.45
F11	27±0.008	0.155±0.005	0.64±0.091	284±5.624	77.76±0.143	95.30±0.055	1.68	4.80	13.60
F12	27±0.024	0.118±0.008	0.65±0.050	248±5.112	78.05±0.506	91.15±0.015	1.69	4.82	13.55
F13	26±0.045	0.154±0.010	0.72±0.045	204±4.505	81.06±0.452	91.70±0.024	1.86	5.12	14.86
F14	28±0.032	0.176±0.005	0.72±0.125	196±6.213	81.75±0.146	92.02±0.0142	1.88	5.08	15.10.
F15	28±0.005	0.204±0.006	0.75±0.005	215±5.152	83.02±0.351	89.5±0.015	1.90	5.15	15.18
F16	27±0.015	0.210±0.004	0.73±0.012	224±4.382	84.06±0.254	90.1±0.005	1.90	5.18	15.60
F17	26±0.020	0.198±0.012	0.81±0.005	218±5.241	89.76±0.185	90.45±0.014	2.04	5.72	16.80
F18	27±0.018	0.148±0.005	0.79±0.026	235±4.450	92.04±0.234	91.02±0.008	2.1	5.85	16.86
F19	28±0.025	0.182±0.007	0.80±0.035	204±4.028	91.65±0.156	89.0±0.024	2.08	6.02	16.94
F20	27±0.030	0.165±0.012	0.81±0.044	227±5.055	92.86±0.345	91.66±0.038	2.14	5.95	16.91

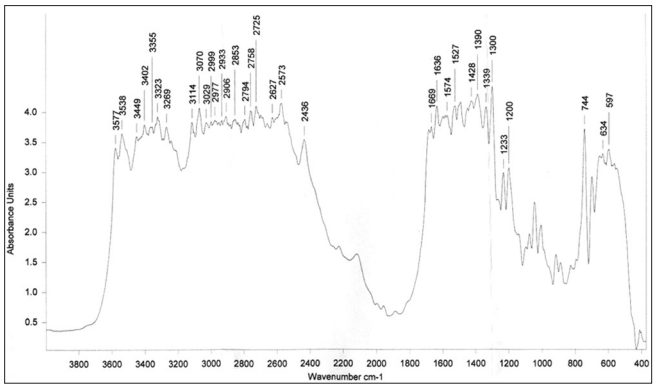

Figure 1: IR Spectrum of Pure Drug

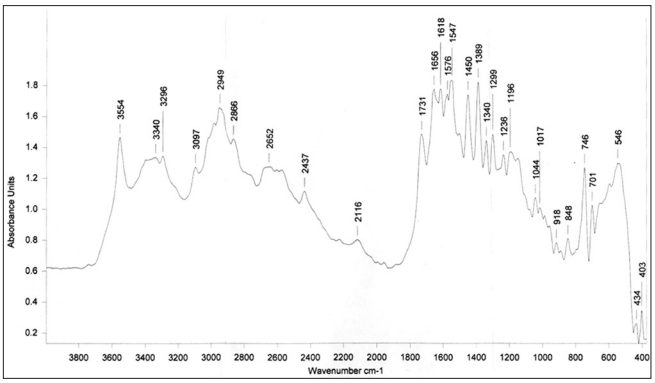

Figure 2: IR Spectrum of physical mixture of drug and polymers

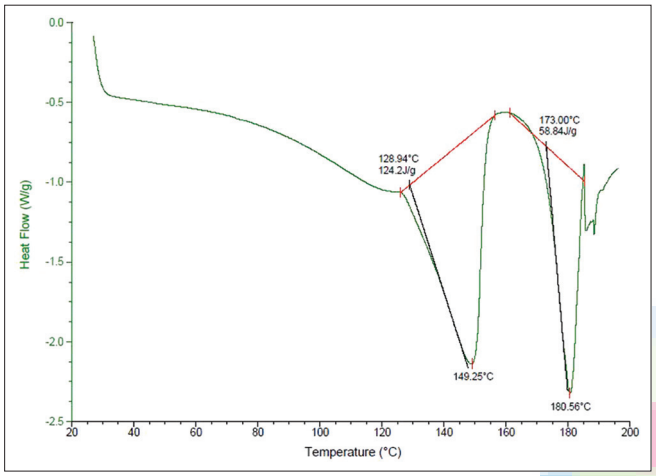

Figure 3: DSC of Pure Drug

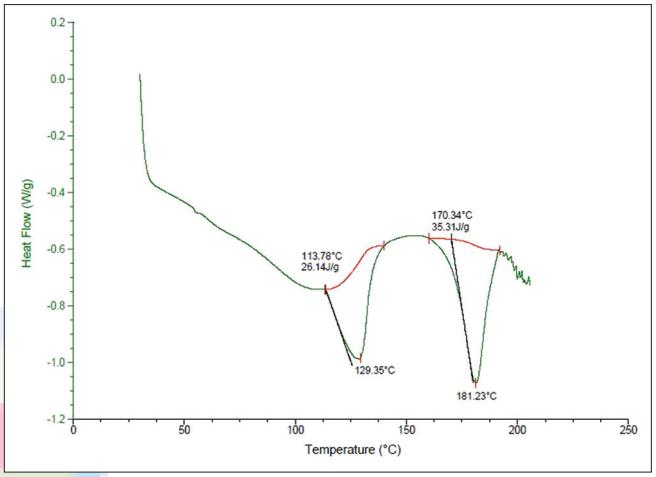

Figure 4: DSC of physical mixture of drug and polymers

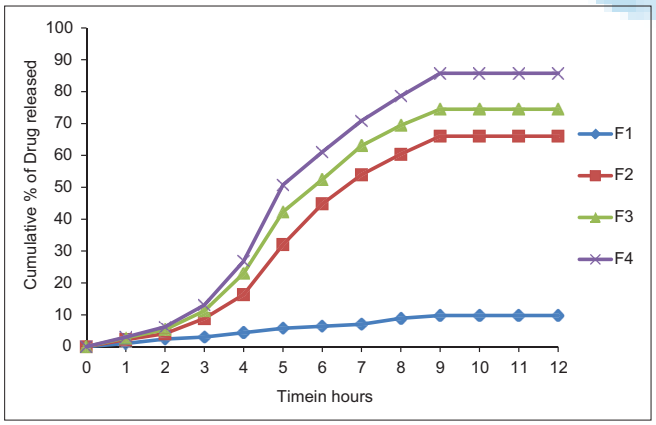

Figure 5: *In-vitro* drug release profile of films (F1-F4)

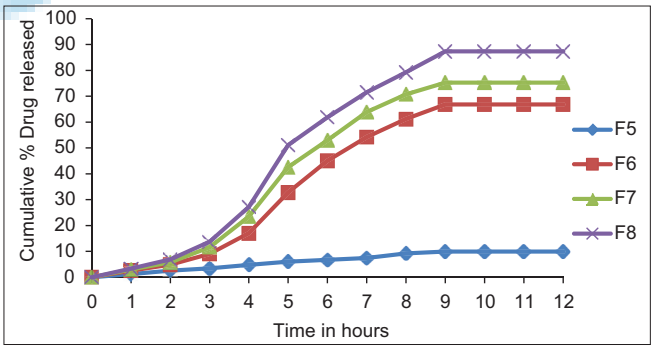

Figure 6: *In-vitro* drug release profile of films (F5-F8)

not brittle. The tensile strength of the films was ranging from to 0.44 to 0.83 kg/cm^2.

Moisture absorption studies showed strong water absorbing capacity. Moisture content was found to increase with increase in the concentration of PVP. The results of moisture content have indicated that all transdermal films have a specific amount of moisture content in them which prevents the films from becoming dry and brittle. All the formulations were permeable to water vapor.

All the formulations were selected for stability studies and observed for changes in color, appearance, flexibility, and drug content. Temperature and humidity values selected were as per the ICH guidelines and the tests were carried out in a stability chamber. Patches were analyzed at an interval of 30 days for a period of 3 months. No physical changes were observed but decrease in drug content was observed at higher temperatures (45°C ± 5°C).

In-vitro drug release profiles indicated that the drug release increased with the increase in concentration of PVP. The rate of drug permeation was lowest in case of films prepared from ERL100 (F1-F4) alone. It was also observed that as the concentration of hydrophilic polymer PVP increased in the formulations, the drug permeation rate increased substantially, with a nominal decrease in formulations F17-F20. Addition of PVP increased the amount of drug permeated. The burst effect due to incorporation of PVP was because of the rapid dissolution of the surface hydrophilic polymer. The rapid leaching of hydrophilic fraction of film former result in the formation of pores and thus lead to decrease of mean diffusional path length of drug molecules to permeate into dissolution medium and hence, higher permeation rates. *In-vitro* drug release profiles [Figures 5-9] indicated that films (F13-F16) exhibited maximum percentage of drug release.

From the *in-vitro* drug release profiles it can be seen that the

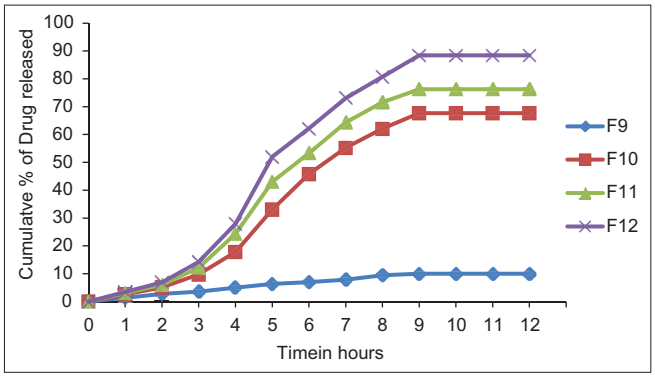

Figure 7: *In-vitro* drug release profile of films (F9-F12)

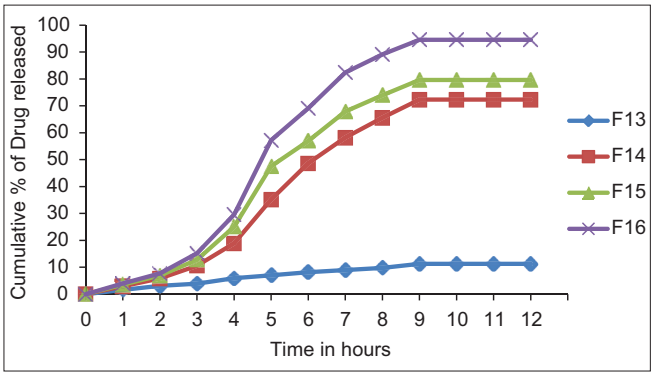

Figure 8: *In-vitro* drug release profile of films (F13-F16)

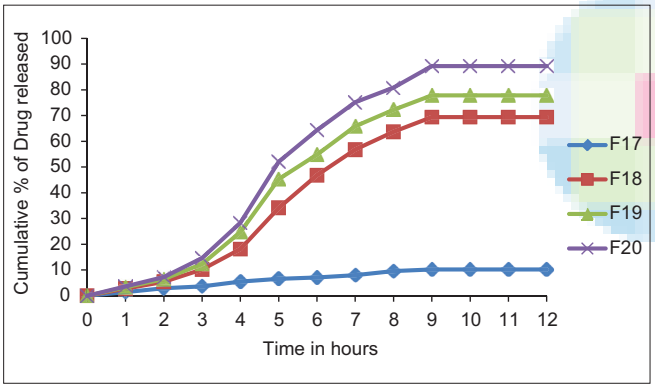

Figure 9: *In-vitro* drug release profile of films (F17-F20)

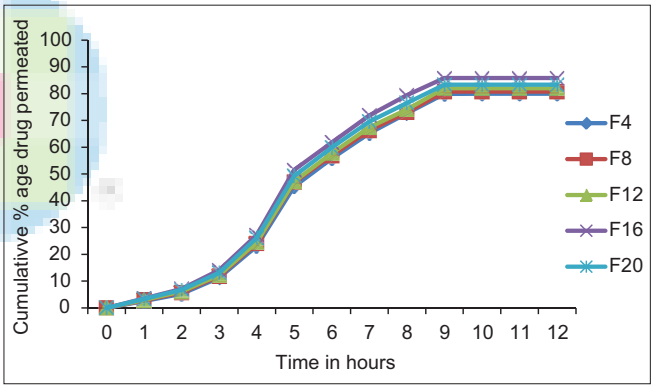

Figure 10: *In-vitro* drug permeation profile of the optimized formulations (series 1-F4, series 2-F8, series 3-F12, and series 4-F16 and series 5-F20)

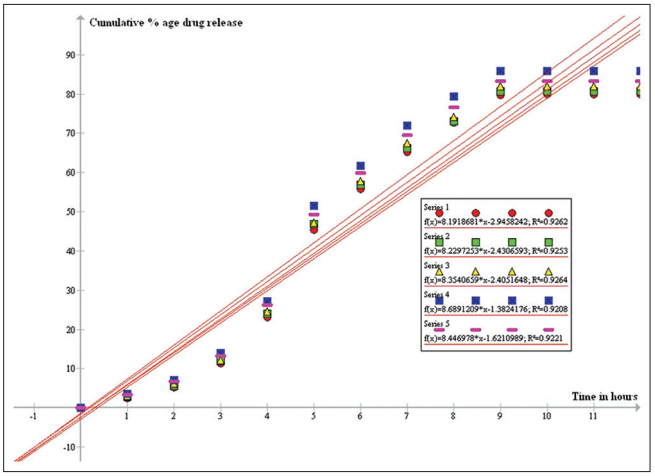

Figure 11: Zero order Plot of the optimized films (series 1-F4, series 2-F8, series 3-F12, series 4-F16 and series 5-F20)

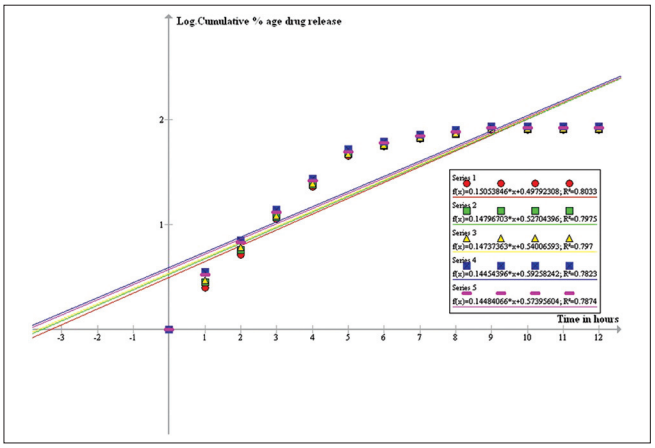

Figure 12: First order Plot of the optimized films (series 1-F4, series 2-F8, series 3-F12, series 4-F16, series 5-F20)

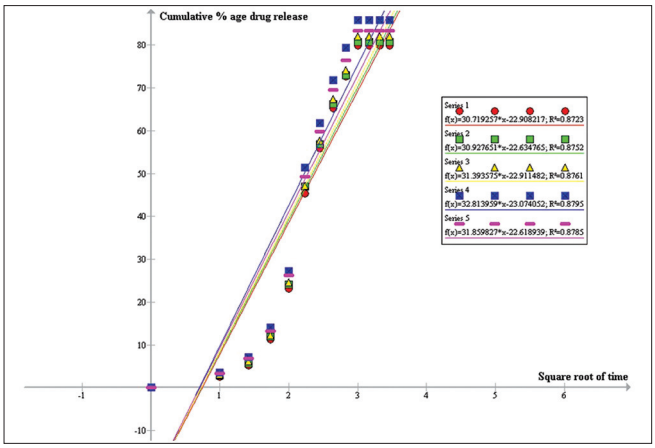

Figure 13: Higuchi Plot of the optimized films (series 1-F4, series 2-F8, series 3-F12, series 4-F16 and series 5-F20)

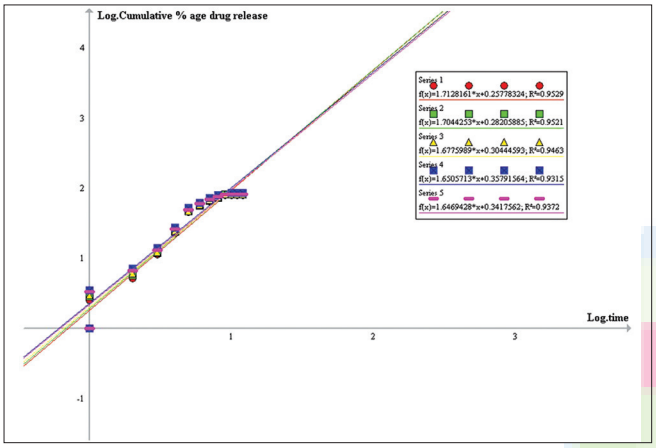

Figure 14: Korsenmeyers-Peppas Plot of the optimized films (series 1-F4, series 2-F8, series 3-F12, series 4-F16 and series 5-F20)

films which do not contain any penetration enhancers (F1, F5, F9, F13 and F17) showed the least drug release. This explains the fact that penetration enhancement was required for drug release. The films containing span-60 as penetration enhancer showed maximum drug release (above 95% drug release) at all polymer ratios (F4, F8. F12. F16 and F20) when compared to films containing glycerine (F2, F6, F10 and F18) and DMSO (F3, F7, F11 and F19) as penetration enhancers. The order of drug permeation enhancement is as follows, span-60 > DMSO > glycerine.

The data from the *in-vitro* skin permeation studies conducted on films F4, F8, F12, F16 and F20 was fitted to various kinetic models to determine the kinetics of drug release [Figures 10-14]. Higuchi's plot and zero order plots were found to be linear indicating matrix diffusion mechanism with regression coefficient of 0.87 and 0.92 respectively.

CONCLUSION

From the present study it can be concluded that matrix type transdermal films of lisinopril could be prepared by solvent casting technique having suitable mechanical properties and *in-vitro* permeation profiles. Drug release is best with transdermal films containing span-60 as penetration enhancer (F4, F8, F12, F16 and F20). Order of drug release enhancement is span-60 > DMSO > glycerine.

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