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PERMEATION ENHANCEMENT OF MODEL ANTI-HYAPERTENSIVE DRUG FROM TRANSDERMAL PATCHES USING ESSENTIAL OILS

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Abstract

The main objective of this study was to develop transdermal Patch of Valsartan using various essential oils which act as permeation enhancer. valsartan is the most widely used antihypertensive drug in the treatment of hypertention and based on physicochemical properties. It is a potential drug candidate for developing a transdermal patch for controlled release. Patches were prepared by solvent evaporation method using different concentrations of linseed oil, pumpkin seed oil, peppermint oil, oleic acid and rose oil. The initial compatibility studies were carried out using FTIR spectroscopy. Patches were evaluated for various physicochemical parameters like thickness, weight variation, folding endurance, tensile strength and % elongation. *In vitro* study was carried out using cellophane membrane and *ex-vivo* drug release study was drug carried out using wister rat skin. An optimized formulation P9 containing 30% w/w of linseed oil having excellent appearance, transparency, % elongation (170±0.08 kg/cm^2), tensile strength (4.43±0.09 kg/cm^2), folding endurance (608±1.6) and *ex vivo* maximum drug release (93.65±0.12%) within 16 hours. Propylene glycol and linseed oil was used as the plasticizer and penetration enhancer which gave good elasticity to the patch. Presence of linseed oil increased the drug permeation rate from the transdermal patch. Stability studies of optimized batch were carried out according to ICH guideline. There was no significant change in folding endurance appearance, elasticity and *ex vivo* drug release after storage at 40±2^{0}C,75±5%RH and 30±2^{0}C and 65±5% RH for a period of six month. This approach suggested that the transdermal patch of Valsartan using HPMC K15M, Eudragit RL 100 and linseed oil gave controlled release up to 16 hrs.

***Key words*:** Transdermal patch, solvent evaporation method, valsartan, linseed oil, controlled drug release

Introduction

Hypertension is the most common cardiovascular disease worldwide; hypertension is cited as the leading cause of non-communicable disease mortality worldwide. It is a progressive disorder, which if not effectively managed results in a greatly increased probability of coronary thrombosis, strokes and renal failure, moreover, it required long-term treatment that may result in poor patient compliance with conventional dosage forms due to greater frequency of drug administration. Gi side effects and extensive hepatic metabolism. These finding suggest that despite the availability of a plethora of therapeutically effective antihypertensive molecules, inadequate patient welfare is observed; this arguably presents an opportunity to deliver antihypertensive agents through a different route.

Transdermal drug delivery system are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate periods of time. Currently transdermal drug delivery is one of the most promising methods for drug application through the skin to the systemic circulation. Transdermal drug delivery system avoidance the first-pass metabolism and gastro intestinal incompatibility. This single application has capacity for multi day therapy, thereby improving patient compliance and self medication is possible with this systems. This is provides utilization of drugs with short biological half life, narrow therapeutic window and avoiding the fluctuations in drug levels.

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Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. It acts selectively at the AT_1 receptor subtype. Valsartan is a potent and highly selective type I antagonist that lowers blood pressure in hypertensive patients. Valsartan is available as a white, microcrystalline powder. Valsartan is considered as a class II compound, *i.e.* water insoluble and highly permeable.

The essential oils are nontoxic, non allergic, and compatible with drug and excipients. Penetration enhancer that exhibit low toxicity while maintaining their enhancing activity. They have been reported to use for permeation enhancement of both hydrophilic and lipophilic drugs. They cause no skin toxicity or if any, only mild irritation. In the present study, pumpkinseed oil, linseed oil, rose oil and peppermint oil were selected as essential oils.

Material and Method

Valsartan was purchased from chemdyes corporation rajkot, Eudragit RL 100 was supplied from Sulab laboratories, Baroda, India and HPMC K15M was supplied from LOBA Chemie Pvt. Ltd., Mumbai, India, Essential oils was supplied from Hamdard Laboratories, Ghaziabad, India and Propylene glycol was supplied from Chemdyes Corporation, Vadodara.

Selection of ingredients for preparing Transdermal Patchs

Selection of ingredients for transdermal patch was done on the bases of literature review different permeation enhancers like Linseed oil, pumpkinseed oil, rose oil, eucalyptus oil, oleic acid, peppermint oil and plasticizers like PG, PEG-400, dibutyalpthalate and glycerine were screened for their permeation ability.

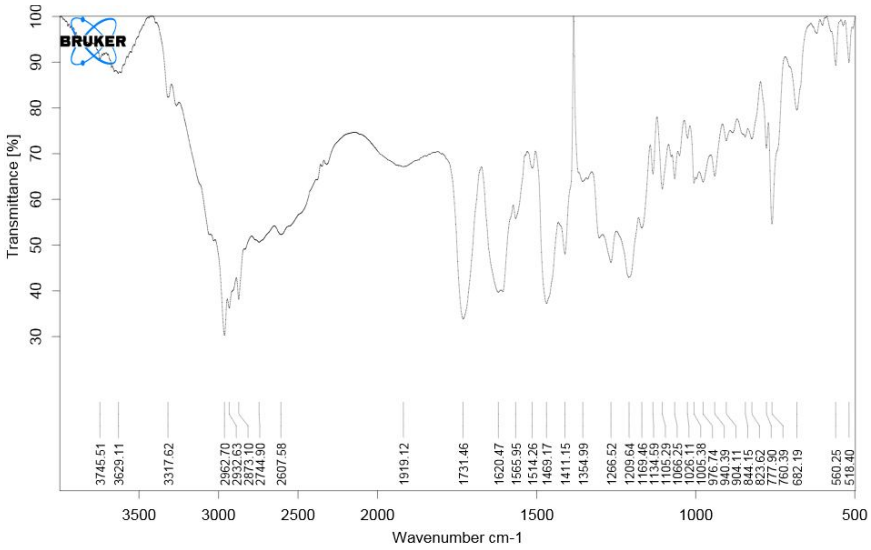

Fig. 1 : FTIR Spectra of drug

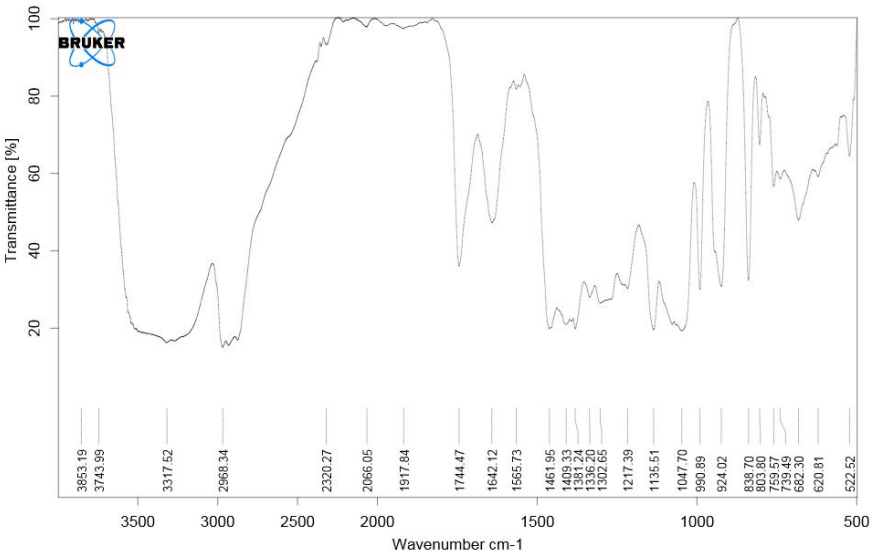

Fig. 2 : FTIR Spectra of drug + pumpkinseed oil

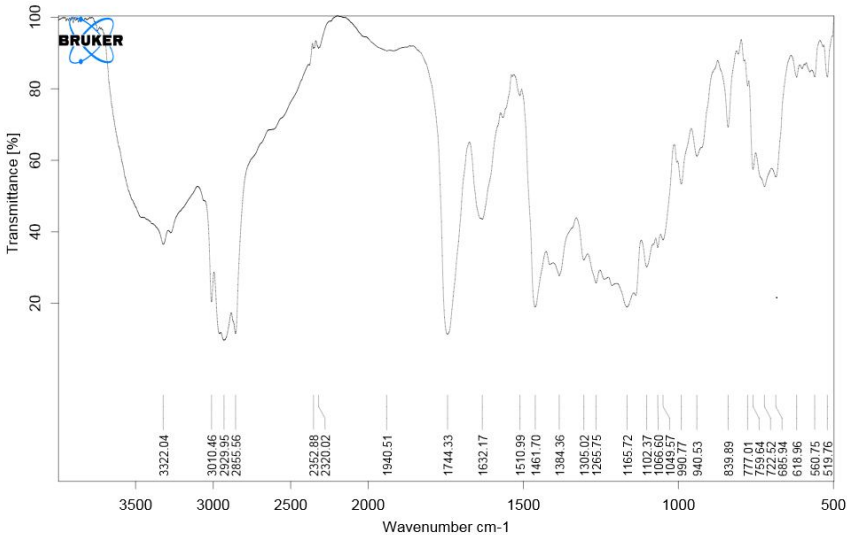

Fig. 3: FTIR Spectra of drug + linseed oil

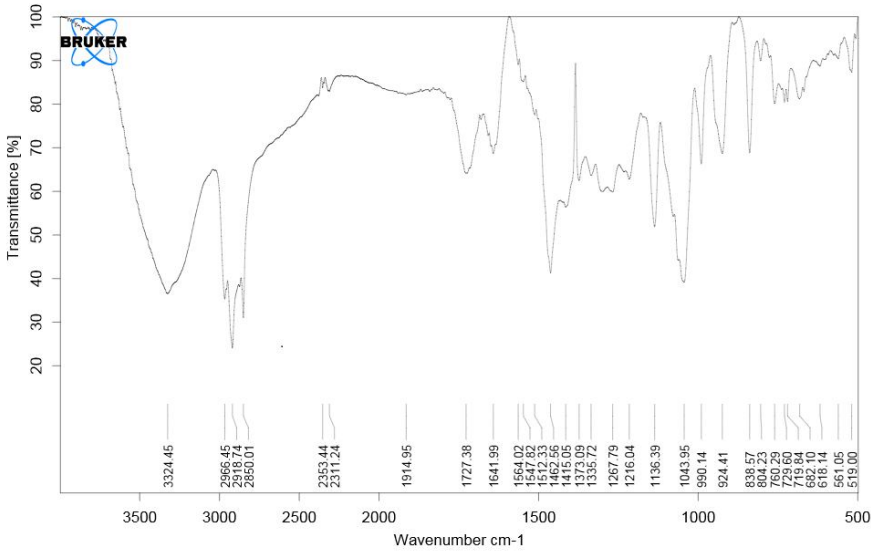

Fig. 4: FTIR Spectra of drug + rose oil

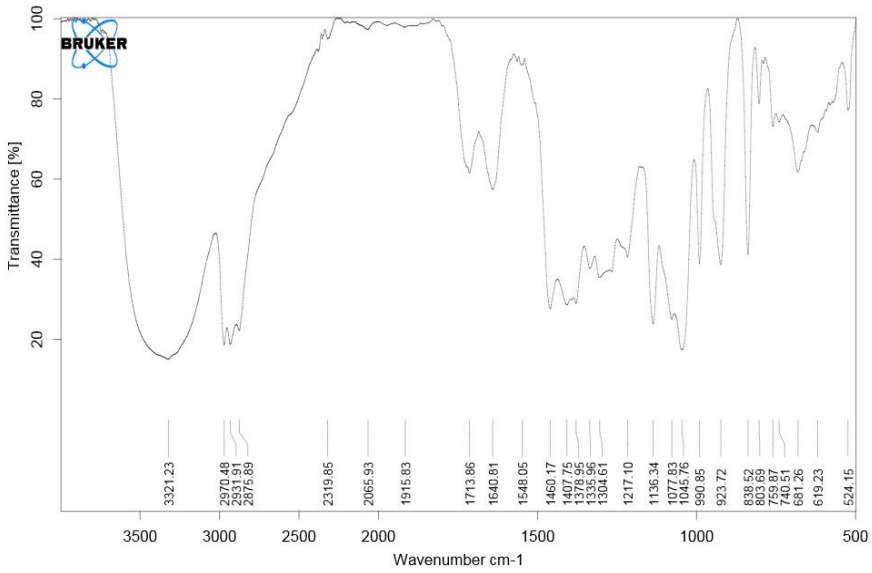

Fig. 5: drug + oleic acid

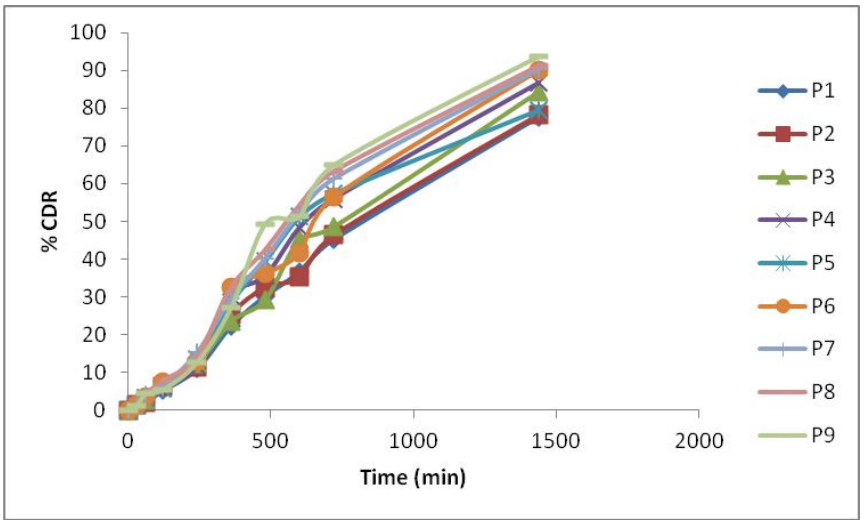

Fig. 6: Comparative drug release profile of batches P1-P9

Solvent was fixed based on literature review.

Method for manufacture of transdermal patch

Transdermal patch was prepared by solvent evaporation method. Accurately weight polymer was dissolved in suitable solvent using magnetic stirrer for prepared a clear solution. Then add plasticizer and permeation enhancer into it. Clear solution was casted on petriplate previously lubricated with plasticizer. Put inverted funnel on petriplate for uniform evaporation of the solvent. Transdermal patch dried at room temperature for 24 hrs. An after 24 hrs, the dried patch was taken out and stored in desiccators for further studies.

Preformulation Study

FTIR study was done for the identification of the drug and excipients and to study drug-excipients and excipient-excipient compatibility. FTIR spectra of drug, HPMC K15M, Pumpkinseed oil, Propylene Glycol mixture are shown in fig. 1 to 4 respectively. The spectral elucidations for drug alone and with powder mixture are shown in table

Evaluation of Transdermal Patches

Physical appearance: All the prepared patches were visually inspected for colour, clarity, flexibility and smoothness.

Thickness: thickness was determined by micrometer at five random points on the patches.

Uniformity of Weight: weight variation was studied by individually weighing 10 randomly selected patches and calculating the average weight. The individually weight should not deviate significantly from the average weight.

Drug content determination: An accurately weighted portion of the patch was dissolved in 100 ml of phosphate buffer pH 6.8 and then the

Table 1: FTIR spectra Interpretation:

Principal pecks(cm^{-1})						
Functional group	**C-H bending**	**C=C starching**	**C=O starching**	**O-H bending**	**C-O starching**	**N-H bending**
Drug	823	1565	2873	1134	1266.52 1354	1514.26
Drug with pumpkinseed oil	838.7	1461	1744	1135	1336	1565.73
Drug with linseed oil	839.89	1461.7	1744.33	1102	1305.02	1510.99
Drug with rose oil	838.57	1462.56	1727.38	1136.39	1335.72	1547.82
Drug with oleic acid	838	1460	1713.86	1136	1335.96	1548.05

Evaluation of physic-chemical parameters of 3^2 full factorial design Batches P1 to P9

Table 2: Evaluation of weight variation, thickness, % drug content, flatness, folding endurance, tensile strength and % elongation of transdermal patch

Batch code	**Weight variation (mg)**	**Thickness (mm)**	**% Drug content(%)**	**Flatness (%)**	**Folding endurance**	**Tensile Strength (Kg/cm^2)**	**% Elongation (% cm^{-2})**
P1	36 5±1.73	0.14 ±0.01	85.59± 0.21	96.7±0.17	617 ±2.3	3.35± 0.01	159 ±0.02
P2	375±2.41	0.15 ±0.02	94.22±0.875	97.2±0.39	608 ±4.5	3.41 ±0.02	162 ±0.02
P3	384 ±1.5	0.16 ±0.03	95.23±0.805	98.3±0.13	602 ±3.6	3.53 ±0.03	163 ±0.03
P4	398±1.52	0.17 ±0.04	96.54±0.402	97.5±0.60	605 ±2.0	3.67 ±0.04	164 ±0.03
P5	452±2.082	0.18 ±0.03	97.65±0.234	98.4±0.23	610± 4	3.79 ±0.05	165 ±0.04
P6	465±1.524	0.19 ±0.02	97.74±0.237	98.6±0.22	600 ± 5.4	3.86 ±0.06	166 ±0.05
P7	478±2.01	0.21 ±0.01	97.90±0.478	97.6±0.31	619± 3.5	4.09 ±0.07	168 ±0.06
P8	488±1.527	0.22 ±0.02	98.21±0.349	98.2±0.46	601 ±2.8	4.16 ±0.08	169 ±0.07
P9	531±2.654	0.23 ±0.01	98.87±0.324	98.8±0.12	608 ±1.6	4.43 ±0.09	170± 0.08

Mean ± SD; n=3

Table 3: Evaluation of Moisture uptake, moisture loss, Water vapour transmission rate and surface pH of transdermal patch

Batch	**% Moisture Content**		**Surface pH**	**Content uniformity(%)**
	Uptake	**Loss**		
P1	1.60± 0.04	0.81±0.02	6.69±0.08	89.57
P2	1.78 ±0.06	0.94±0.01	6.72±0.03	90.12
P3	1.83 ±0.05	1.03±0.02	6.80±0.08	91.25
P4	1.99 ±0.03	1.12±0.01	6.75±0.03	91.56
P5	2.10 ±0.05	1.15±0.03	6.75±0.04	92.01
P6	2.32 ±0.06	1.23±0.04	6.74±0.06	92.45
P7	2.45 ±0.03	1.37±0.06	6.79±0.05	94.23
P8	2.90 ±0.04	1.45±0.04	6.81±0.06	95.65
P9	3.14 ±0.02	1.58±0.03	6.82±0.04	95.78

Mean ± SD; n=3

solution was shaken continuously for 24 h in shaker incubator. After sonicating and filtering, concentration of drug was estimated specrophotometrically (at 250nm) by appropriate dilution.

Content uniformity test: 10 patches were selected and content was determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, than transdermal patches was pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, than addition 20 patches was tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content: the prepared patches were weighted individually and kept in desiccators containing calcium chloride at room temperature for 24 hrs.. The patches were weighed again and again after specified interval until they show a constant weight.

Moisture uptake: weighted patches were taken and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators until a constant weight is achieved.

Flatness: For flatness determination, one strip was cut from the center and two from each side of patches. The length of each strip was measured and variation in length was measured by determining percent constriction. Zero percent constriction is equal to 100% flatness.

Folding Endurance: folding endurance of the patch was determined repeatedly folding the patch at the same place until it break. The number of times the patch was folded at the same place without breaking was the folding endurance value.

Table 4: Evaluation of *ex-vivo*% cumulative drug release studies of batches P1-P9 using wister rat skin

Time (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0
30	1.33±0.20	1.29±0.21	1.37±0.11	1.28±0.12	1.45±0.11	1.29±0.21	1.19±0.12	1.04±0.16	1.21±0.19
60	2.16±0.19	2.15±0.25	2.54±0.15	3.24±0.15	3.15±0.21	3.45±0.25	4.25±0.15	4.36±0.15	4.51±0.18
120	5.21±0.15	6.35±0.36	7.58±0.14	6.23±0.18	5.53±0.36	7.56±0.65	6.35±0.16	7.85±0.46	5.45±0.17
240	10.95±0.14	11.24±0.45	12.35±0.56	11.65±0.19	13.54±0.25	12.89±0.85	15.24±0.25	14.25±0.54	12.65±0.16
360	22.32±0.16	25.35±0.57	23.56±0.45	30.24±0.17	28.56±0.54	32.51±0.71	29.65±0.45	32.56±0.21	27.21±0.12
480	30.25±0.19	32.56±0.68	29.35±0.36	35.65±0.15	39.56±0.45	36.23±0.21	40.25±0.12	42.56±0.51	49.35±0.13
600	36.65±0.11	35.26±0.12	45.28±0.21	48.36±0.18	51.25±0.46	41.65±0.25	52.26±0.12	54.32±0.12	51.28±0.14
720	45.23±0.12	46.35±0.11	48.59±0.12	55.96±0.22	57.35±0.55	56.35±0.45	61.23±0.11	63.25±0.15	64.85±0.15
1440	77.65±0.31	78.25±0.14	84.35±0.15	86.59±0.12	79.56±0.18	89.95±0.91	90.21±0.51	91.23±0.11	93.65±0.12

Mean ± SD; n=3

Table 5: Results of Transdermal Flux, Steady state flux, Permeability coefficient Diffusion Coefficient and Enhancement Ratio of batches P1-P9

Batch code	Transdermal Flux (µg/cm²/hr)	Steady State Flux (µg/cm²/hr)	Lag Time (hours)	Permeability Coefficient (Kp) (cm/hr)	Diffusion coefficient (cm/h×10⁸)	ER
P1	136±0.10	0.0140±0.12	0.281±0.12	2.46×10^{-6}±0.20	0.0181±0.11	1.10±0.01
P2	139±0.11	0.0142±0.11	0.290±0.11	2.48×10^{-6}±0.21	0.0231±0.12	1.11±0.02
P3	140.12±0.09	0.015143±0.14	0.301±0.14	2.50×10^{-6}±0.22	0.0254±0.13	1.12±0.03
P4	141.23±0.12	0.0145±0.12	0.304±0.15	2.56×10^{-6}±0.21	0.0265±0.15	1.14±0.04
P5	143.52±0.14	0.0146±0.11	0.321±0.11	2.65×10^{-6}±0.23	0.0272±0.11	1.15±0.05
P6	145.84±0.15	0.0148±0.15	0.345±0.12	2.69×10^{-6}±0.25	0.0276±0.14	1.17±0.06
P7	148.32±0.13	0.0150±0.16	0.365±0.13	2.78×10^{-6}±0.24	0.0279±0.15	1.21±0.07
P8	149.56±0.12	0.0151±0.14	0.378±0.14	2.81×10^{-6}±0.26	0.028±0.12	1.25±0.08
P9	149.89±0.15	0.0155±0.16	0.395±0.11	2.85×10^{-6}±0.22	0.0285±0.18	1.28±0.09

Mean ± SD; n=3

Ex-vivo permeation studies: Franz diffusion cell with a surface area of 2.64 cm^2 was used for *ex-vivo* permeation studies. Excised 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 transdermal patch under the test. The receiver compartment contained 21 ml of PBS of pH 6.8, stirred with a magnetic stirrer at a speed of 400 rpm. The whole assembly was kept on a magnetic stirrer and study was conducted at 37 ± 0.5°C. The amount of the permeated drug was determined by removing 2 ml at preset time points up to 16 hrs. and replenishing with an equal volume of fresh medium. The absorbance was measured at 250 nm specrophotometrically. The cumulative amount of drug permeated was calculated and plotted against time.

Statistical Analysis:-

Transdermal Flux:-

$$\text{Transdermal flux} = \frac{\%\ \text{cumulative drug release}}{\text{Area of patch}}$$

Diffusion Coefficient:- $T_L = \frac{h^2}{6D}$

Where T_L = lag time

h = Thickness of patch (mm)

D = Diffusion coefficient

Permeability Coefficient:- $K_p = J_{ss}/C$

Where K_p = permeability coefficient

J_{ss} = steady state flux

C = oral dose (µg/ml)

Partition coefficient: $K = K_p \cdot D/h$

Where, K_p = Permeability co-efficient

D = Diffusion coefficient

h= Thickness of patch

Enhancement ratio:-

$$E_R = \frac{\text{Permeability co- efficient of drug with penetration enhancer}}{\text{Permeability co-efficient of drug without permeation enhancer}}$$

Table 6: Kinetic modelling and mechanism of drug release of P9

Time (min)	Log t	SQRT t	% Cumulative release	Log % Cumulative release
10	1	3.162	1.19	0.075
20	1.301	4.472	4.25	0.628
30	1.477	5.477	6.35	0.802
60	1.778	7.745	15.24	1.182
120	2.079	10.954	40.25	1.604
180	2.255	13.416	52.26	1.718
240	2.380	15.499	61.23	1.786
360	2.556	18.973	71.25	1.852
720	2.857	26.832	90.21	1.955

Table 7: Results of kinetic model fitted for P9

Sr. No.	Equation	Regression coefficient (r)
1	Zero order	0.823
2	Higuchi	0.959

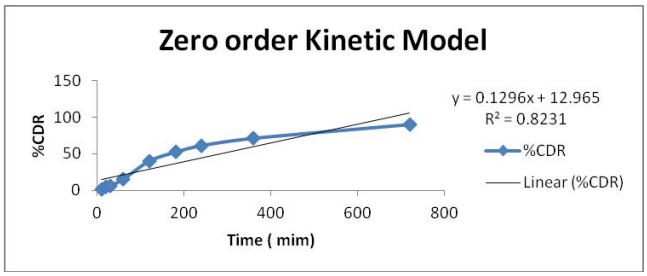

Fig. 7: Zero order Kinetic Model

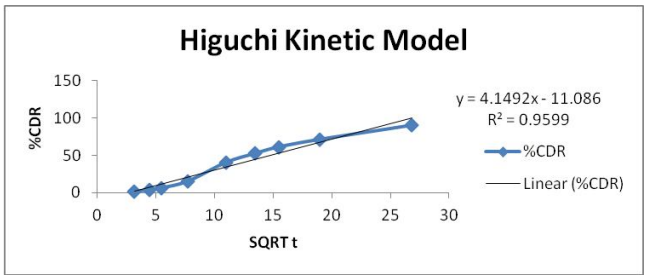

Fig. 8: Higuchi Kinetic Model

Drug Release Kinetic

In order to investigate the mechanism of drug release from Valsartan patch, the release data was analyzed with the following mathematical models.

Zero order equation : $Qt=Qt_0+ k_0$

Where, Qt is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0=0$) and k_0 is the zero-order release rate.

Higuchi's equation : $Q=kH\ t^{1/2}$

Where, Q is the amount of drug release at time t, and kH is the Higuchi diffusion rate constant.

Stability studies: The Transdermal patch of optimized batch was wrapped in aluminium foil and place in poly bags. Then it was kept in stability chamber at 40±2°C and 75±5 % RH and 30±2°C and 65±5 % RH for a period of one month. The patches were evaluated for the drug content, dissolution study and folding endurance at the end of the month.

Results

FTIR study was done for the identification of the drug and excipients and to study drug-excipients and excipient-excipient compatibility. FTIR spectra of drug, HPMC K15M, Pumpkin seed oil, Propylene Glycol mixture are shown in fig. 1 to 4 respectively. The spectral elucidations for drug alone and with all formulation exicipiants are shown below:

Discussion : Frequencies of principle peaks in FTIR spectra of physical mixture of drug with other excipients were nearly similar to the frequency of principle peaks present in FTIR spectra of pure drug. So, these results revealed that the drug was compatible with excipients and neither drug decomposition nor drug-excipients and excipient-excipient interactions occurred in the formulation.

Formulation optimization of transdermal patch of valsartan using 3^2 factorial design

It is desirable to develop acceptable pharmaceutical formulation in shortest possible time using minimum number of man hours and raw material. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. This method was time consuming and it may be difficult to develop an ideal formulation using this classical technique since the joints effect of independent variables are not considered. It

Table 8: Results of Stability study

Stability condition	Sampling time	Folding endurance	Drug content uniformity (%)	*Ex-vivo* drug release (%)	Visual appearance of patches
Room storage (30±2°C and 65±5% RH)	Initial (0 day)	619	86.62	88.03	Clear homogeneous appearance
	After 7 days	618	86.61	88.02	Clear homogeneous appearance
	After 14 days	618	86.60	88.01	Clear homogeneous appearance
	After 21 days	616	86.59	88.00	Clear homogeneous appearance
	After 30 days	615	86.58	87.99	Clear homogeneous appearance

was therefore essential to understand the complexity of pharmaceutical formulation using established statistical tools such as factorial design in addition to art of formulation; this technique was effective method of indicating the relative significance of a number of variables and their interactions.

The correlation coefficient (R^2) of the zero order model was found to be 0.823 that indicated controlled release of drug, Higuchi's model was found to be 0.959 that indicated diffusion occur through the transdermal patch.

Results of Stability Study

The Transdermal patch of optimized batch was wrapped in aluminium foil and place in poly bags. Then it was kept in stability chamber at 40±2°C and 75±5% RH and 30±2°C and 65±5% RH for a period of one month. The patches were evaluated for the drug content, dissolution study and folding endurance at the end of the month. Observed results indicated that transdermal patch was stable and maintain its mechanical integrity during storage period. Results of stability data are shown in table for the optimized batch (P9).

Conclusion

The objective of the present study was to formulate transdermal patch of Valsartan by solvent evaporation method using essential oils as penetration enhancer for the treatment of hypertension. Controlled release of drug is the primary concern for the treatment of hypertension. The formulated patch of valsartan were evaluated for their mechanical parameters like thickness, folding endurance, % elongation, drug content and *ex-vivo* drug release. The optimized formulation P9 was selected by using 3^2 factorial design which have 267mg HPMCK15M and 133mg Eudragit RL100 and 30% penetration enhancer. Optimized batch had shown 4.43±0.09 Kg/cm^2 tensile strength,170±0.08 Kg/cm^2 % elongation, 608±1.6 folding endurance, 98.87±0.324 %drug content, 0.23±0.01mm thickness as well as gives 93.65±0.12 % maximum drug release for 24 hrs which is highest amongst P1-P9 batches. The stability study was performed in accelerated condition (40°C and 75% RH) and room temperature for optimized batch P9. Results showed that patch were susceptible to high temperature and humidity due to presence of water soluble polymer and other excipients. From the above all results it was concluded that the transdermal patch of Valsartan was developed with good *in vitro* and *ex-vivo* charecteristics on laboratory scale and enhanced skin permeation as well as patient compliance.

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