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DEVELOPMENT AND EVALUATION OF ANTIHYPERTENSIVE TRANSDERMAL PATCH OF VALSARTAN

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ABSTRACT

The transdermal patch formulation was found to be efficacious, safe, stable and non-irritant to skin. IR spectra of the drug matches with standard functional group frequencies of drug. The pH of formulated transdermal patches was found to be in the range of 6.8, which lies in the normal pH range of the skin, which indicates the suitability of the formulations for application on the skin to avoid any irritation upon application. The formulation F1 (Gelatin and PVA using propylene glycol as a plasticizer) was optimized. The above formulation gave a maximum drug diffusion of 99.8 % over a period of 120 min. The Drug Content results indicated that the process employed to prepare transdermal patches formulations in this study was showed significant result of uniform drug content.

KEYWORDS: TDDS, In Vitro Drug Release Study, Patch, PVA, plasticizer, Gelatin.

INTRODUCTION

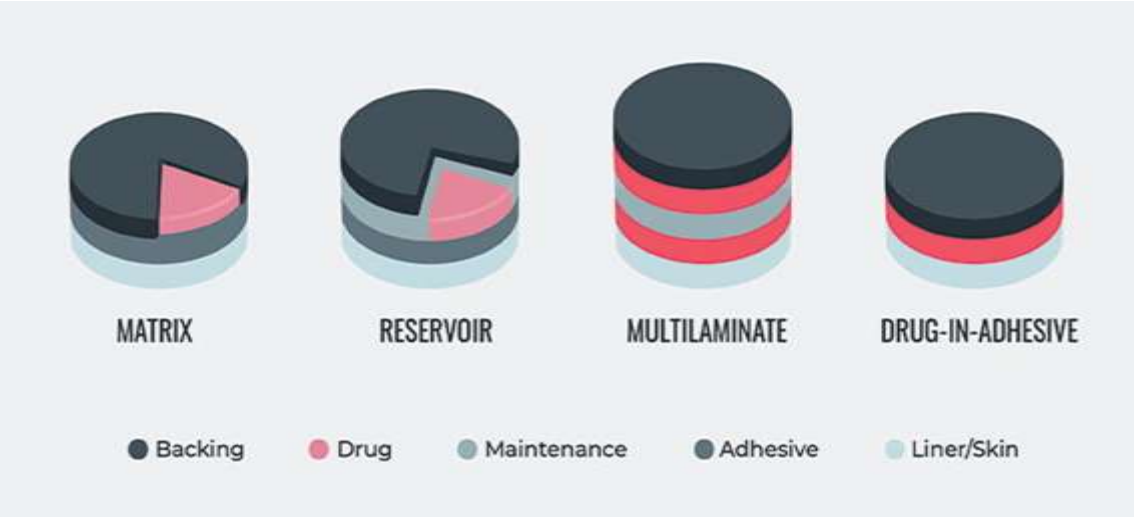
Transdermal drug delivery system is getting considerable attention for research. This route help in the delivery of the molecules through skin. This alternative route increases the safety and efficacy of the drug delivery. This method provides convenience to the patient, as discussed. Researches are going on for the development of new technologies and other routes of delivery of drugs.

The transdermal route has been viewed as a successful route for the delivery of drugs over oral delivery. During oral therapy, to maintain the therapeutic blood level, medicines have to be administered at regular intervals. This causes concentration of the drug to follow a peak and trough pattern in the body; it may also sometimes cause failure of the therapy. Large amount of drug is metabolized in the body due to first pass metabolism effect. The problems of oral route can be overcome by intravenous infusion that helps in refraining the first pass metabolism of the drug.

The largest organ on the body is skin. It provides an effective barrier to avoid the loss of water and entry of the external agents into the body.

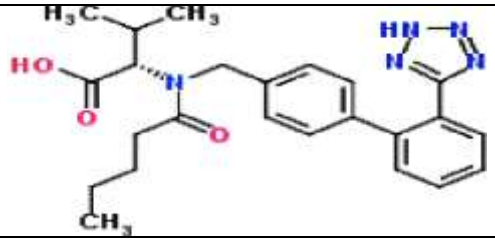
Types of Transdermal Patches

Preparation of new types of transdermal patches for better action is demand of present time. The patient with side effects like constipation and dysphagia may be treated with TDDS having effective dosing.



MATERIAL AND METHOD

VALSARTAN[35-38]	
IUPAC Name •	3-Methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol 5yl)phenyl]phenyl]methyl]amino]butanoic acid.
Description	A white hygroscopic crystalline powder
Molecular Formula	$C_{24}H_{29}N_5O_3$
Molecular weight	435.52
Melting point	116-117°c

Chemical Structure	
Solubility	Valsartan is practically insoluble in water, sparingly soluble in Methylene Chloride, and freely soluble in anhydrous ethanol and methanol.
Category	Angiotensin receptor type ll
Bioavailability	Bioavailability is 10-35%
Half Life	6-9hrs
Dissociation constant (Pka)	4.9 basic Pka
Mechanism of action	Valsartan is an antihypertensive drug which selectively inhibits angiotensin receptor type II.
Adverse effect	Nausea, vomiting, Bloody urine. decreased frequency or amount of urine. difficult breathing.

1. Chemical material and their Suppliers

Following material which was of analytical grade were gifted and purchased and used as supplied by the manufacturer, without further purification.

Table 2: Material used for the experimental purpose.

Sr. No.	Chemical /Material	Suppliers
1.	Valsartan	Bulk drugs and chemicals
2.	Gelatin	Loba Chemie Pvt.Ltd
3.	Polyvinyl alcohol (PVA)	Loba Chemie Pvt.Ltd
4.	PEG 400	Loba Chemie Pvt.Ltd
4.	Propylene glycol (PG)	Loba Chemie Pvt.Ltd
5.	DMSO	Loba Chemie Pvt.Ltd
6.	Tween 80	Loba Chemie Pvt.Ltd
7	Dibutyl phthalate	Loba Chemie Pvt.Ltd
8.	Methanol	Merck Ltd. Mumbai
9.	Phosphate Buffer	Loba Chemie Pvt.Ltd

FORMULATIONS AND DEVELOPMENT

The valsartan patches were formulated using solvent casting method, by dissolving weighed quantity of drug in required volume of methanol in a beaker. The selected concentrations of polymers were dissolved in 10 ml of distilled water in another beaker. To this beaker, add the methanol solution containing drug. Keep the beaker on thermostatically controlled magnetic stirrer which is maintained at 37±0.5ºC. The required quantity of plasticizer is added drop wise to the beaker while stirring is continued until the drug is dispersed with polymer. The

solution was poured into petridish; an inverted funnel was placed over the petridish to prevent fast evaporation of the solvent and the films were allowed to dry overnight at room temperature. Then the Patches were cut into 2×2 cm^2 and packed in an aluminum foil and stored in desiccators for further use.

Formulation table of Valsartan Patches

Composition (mg or ml)	F1	F2	F3	F4	F5	F6
Valsartan	361.72	361.72	361.72	361.72	361.72	361.72
Gelatin	500	600	700	500	500	500
Polyvinyl Alcohol (PVA)	100	100	100	100	100	100
Polyethylene glycol 400	4	4	4	4	4	4
Propylene glycol	2	2	2	-	-	-
Di-butyl phthalate	-	-	-	2	-	-
Tween 80	-	-	-	-	2	-
DMSO	-	-	-	-	-	2
Water: Methanol (ml)	15:10	15:10	15:10	15:10	15:10	15:10

EVALUATION OF TRANSDERMAL PATCHES

General Appearance

The general appearance of a transdermal patches, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are hydrogel, color, presence or absence of an odour, taste, physical appearance and consistency.

Thickness

Screw gauze was used for the determination of thickness of 10 selected patches. Thickness was measured at 5 different locations. And average was calculated.

Uniformity of weight

Uniformity of weight was calculated by weighing the patches on digital balance. The test was performed on 5 patches and average weight was calculated.

Moisture content

For moisture content, desiccator with fused calcium chloride was used. Patches to be evaluated were initially weighed and put in a desiccator for 24 h. After 24 h patches were reweighed and moisture content was calculated by subtracting the final weight from initial weight with respect to initial weight.

Folding endurance

Folding endurance was determined by folding the patch several numbers of time at same time and at same place till patch broke. The number at which patch fold without breaking will give the value of folding endurance.

Drug content determination

About 100 ml solution of Phosphate buffer with pH 7.4 was used to perform this test. A patch having dimension 4cm square was cut and added into buffer solution. Stirred the solution with magnetic stirrer for 5 h, filtered the solution and drug content analysis was done with dilution at 250 nm wavelength by using spectrophotometer.

In-Vitro drug Release Study

The Dialysis membrane is soaked in distilled water for 10 minutes and then used for drug release study. In vitro drug release study was performed through dialysis membrane by using Franz diffusion cell apparatus with a receptor compartment capacity of 15 ml and cross-sectional area 3.14 cm2. The prepared transdermal patch was fix between two compartments. It was then mounted in the donor compartment so that the membrane facing towards the receiver compartment. The phosphate buffer 7.4 was filled in the receiver compartment. The samples were withdrawn at different time intervals and analyzed for drug diffusion concentration. 3 ml of receptor solution was withdrawn and an equal volume of fresh buffer pH 7.4 was replaced. The sample were analyzed for drug content in spectrophotometer in UV – visible spectrophotometer at 250 nm.

Skin irritation study

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on healthy rabbits weighing 200-250 grams. Drug free polymeric film of diameter 2×2 cm^2 was used as control. The dorsal surface of rabbits was cleared well and the hair was removed by using a hair removal cream. The skin was cleared with rectified spirit. The patches were applied to the shaved skin of rabbits and secured using adhesive tape USP (Leucoplast TM). On one side of the back control patch (without any drug). The animals were observed for any irritation for a period of 24 hrs. All the experimental protocols involving laboratory animals were approved by the IAEC (Research Proposal No: - AVCOP/IAEC/2021-22/1153/26/08).

RESULTS AND DISCUSSION

Preformulation Studies

Preformulation study was carried out for Valsartan drug and excipients.

Identification and Characterization of Drug

The characterization of drug is necessary for identification and purity of drug. In characterization of drug different physical, chemical and spectroscopic tests were performed which are given below.

Organoleptic Characteristic

The Organoleptic evaluation of Valsartan such as colour, Odour, and texture were studied. The colour of drug was found to be A pale yellow to bright yellow Odour of drug identified as odorless and texture was found to be crystalline powder.

Table 5: Results of Organoleptic evaluation of Valsartan.

Properties	Standard	Observation
Colour	White	White
Odour	Odourless	Odourless
Taste	Bitter Taste	Bitter taste

Solubility

The drug was tested with different solvents for solubility testing the drug was found to be soluble in acetic acid, 0.1 N HCL and slightly soluble in distilled water.

Table 6: Solubility Studies of Valsartan.

Sr.No.	Solvent	Solubility
1	Distilled water	Practically insoluble
1.	Methanol	Freely Soluble
2.	Ethanol	Freely Soluble
3.	Phosphate buffer (7.4)	Freely Soluble

8.1.1.3 Melting point determination

The Melting point of drug Valsartan was determined by capillary method. The temperature at which drug goes in the liquid state was consider as melting point. Practically it was found to be 116˚C.

Table 7: Melting Point of Valsartan.

Drug name	Standard	Observation
Valsartan	116-117 ° c	116°c

Ultra-Violet Absorption Maxima (λmax)

The λmax of Valsartan was found to be 250 nm in phosphate buffer 7.4 as solvent System as shown in Fig.

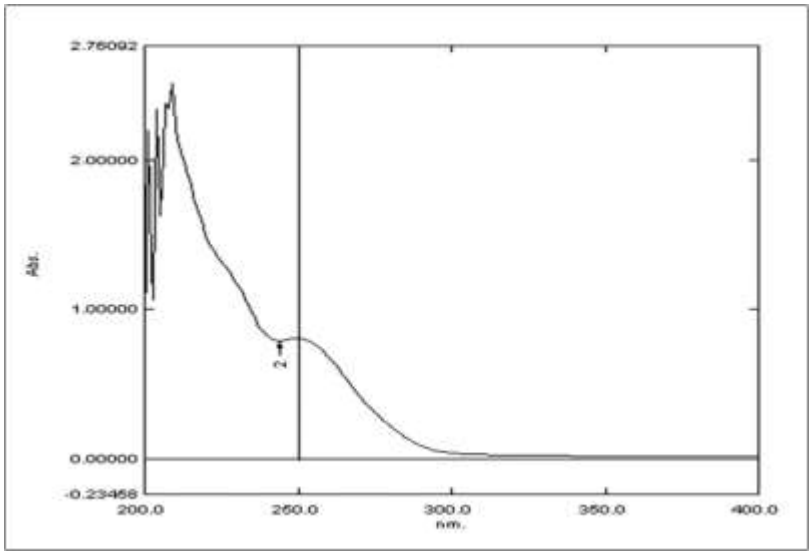


Figure 7: Ultraviolet Absorption Maxima of Valsartan.

Calibration curve of Valsartan

Table 8: Calibration of Valsartan at 250 nm.

Con. (µg/ml)	Absorbance
5	0.17758
10	0.34822
15	0.51974
20	0.68289
25	0.90685
30	1.07196

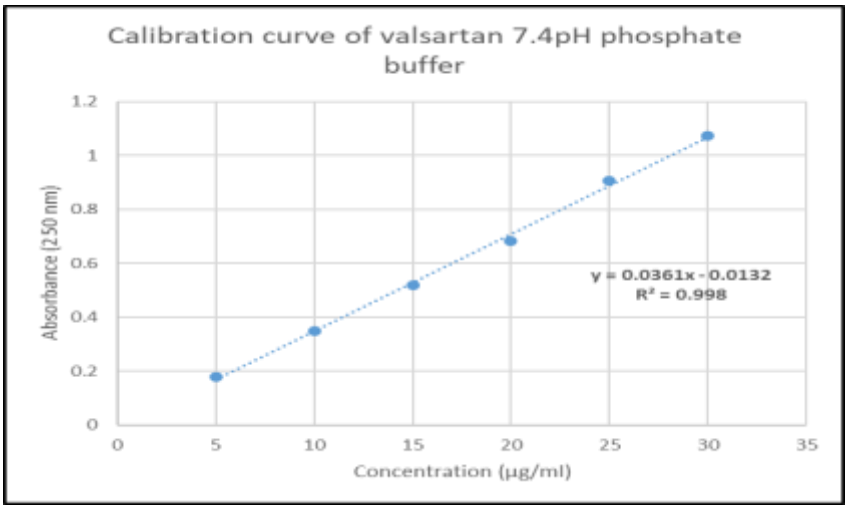


Figure 8: Calibration curve of valsartan in Phosphate buffer at 250 nm.

IR Spectroscopy

IR Spectra of Valsartan

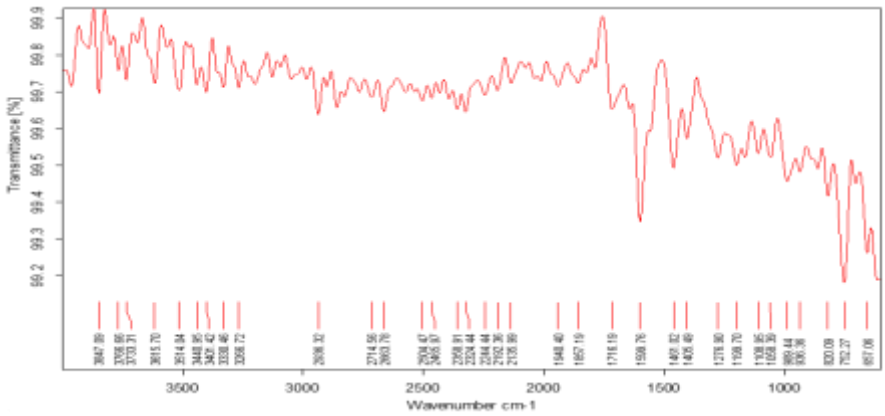


Table 9: Interpretation of IR spectra.

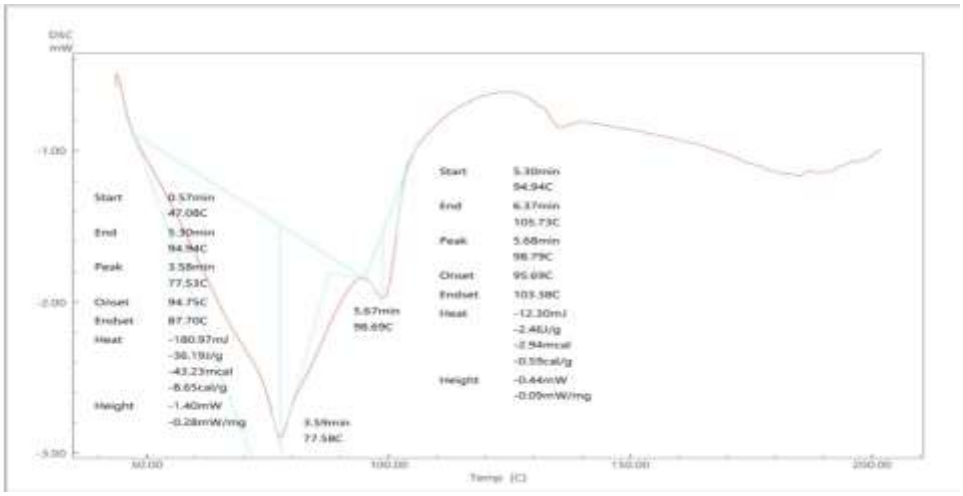
Sr. No	Functional group	Observed Wavenumber(cm-1)	Standard wavenumber(cm-1)
1	N-H (Stretching)	3514.04	3400-3600
2	CH=CH Aromatic	2906.32	2910-2990
3	C=N (Stretching)	2324.44	2310-2380
4	C=O (Bending)	1716.19	1650-1760
5	C-N (Bending) Aromatic amine	1461.02	1380-1570

CONCLUSION: The IR spectrum of the pure Valsartan sample was recorded by FT-IR spectrometer as shown which was compared with standard functional group frequencies of Valsartan. The major peaks observed and corresponding functional groups are given.

Compatibility Study

DSC (Differential Scanning Calorimetry) Studies:

DSC of Valsartan



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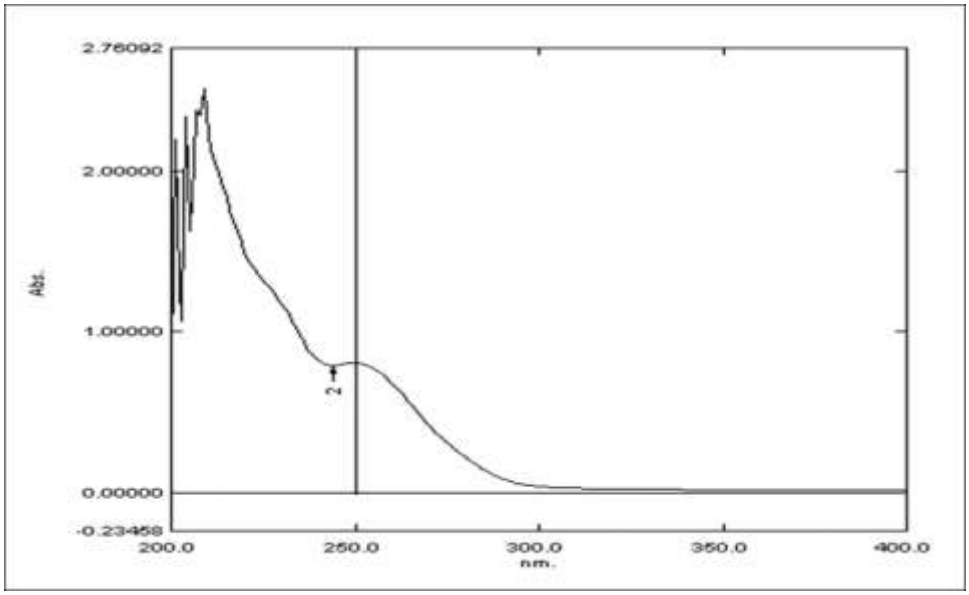

Fig: Calibration curve of Valsartan.

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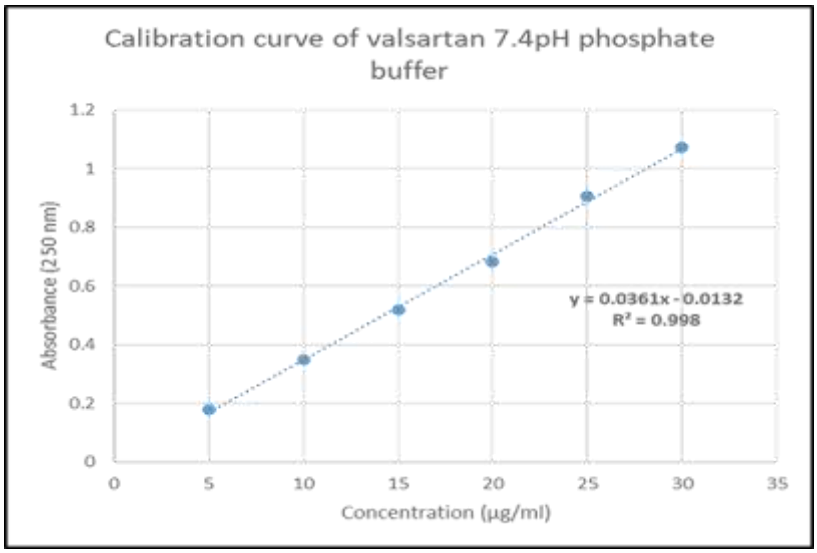

IR Spectroscopy

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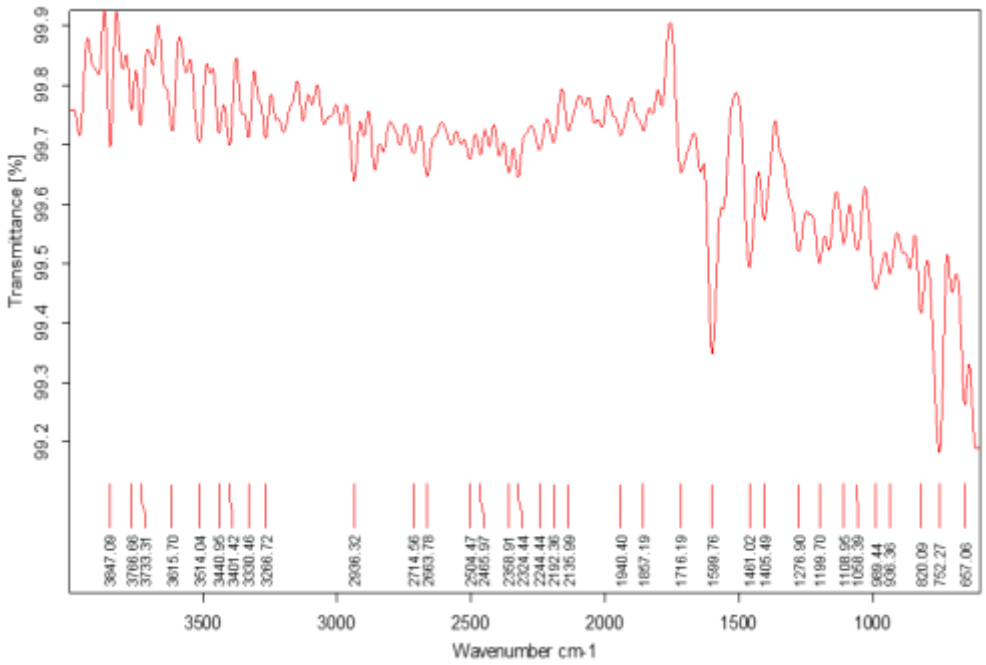

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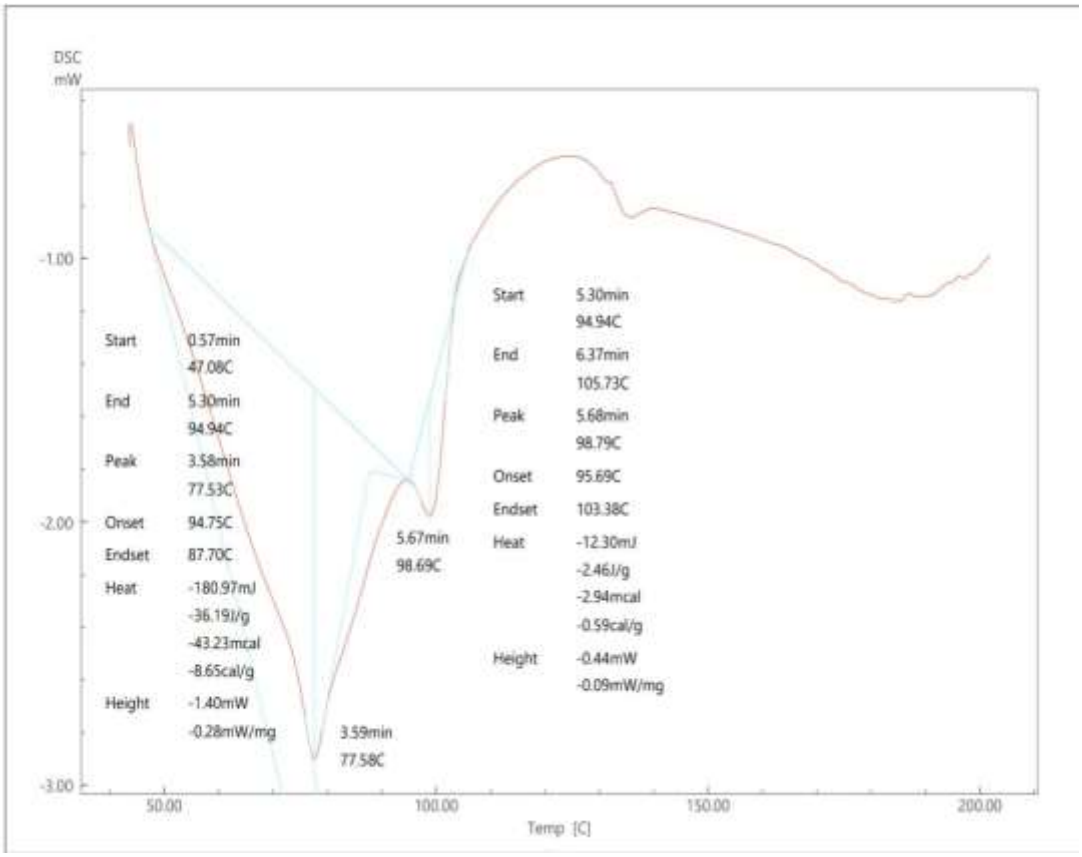
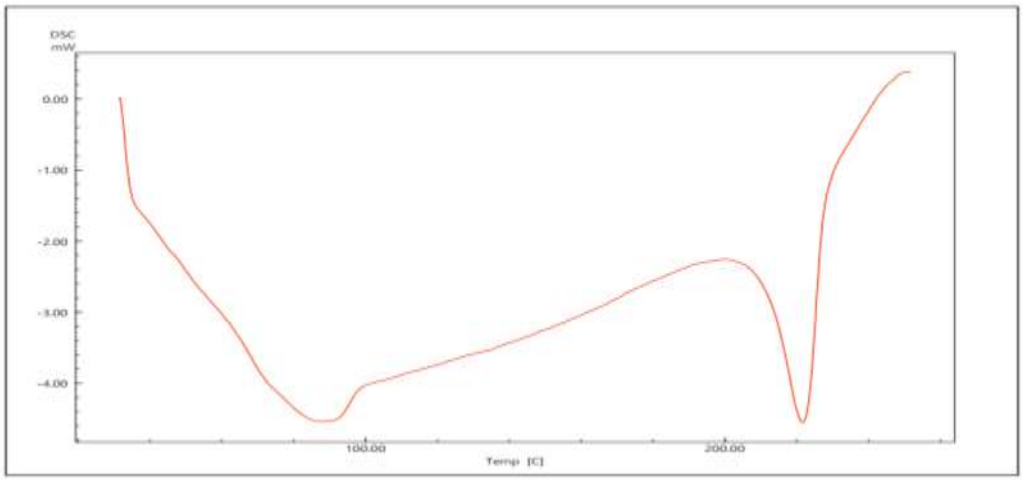


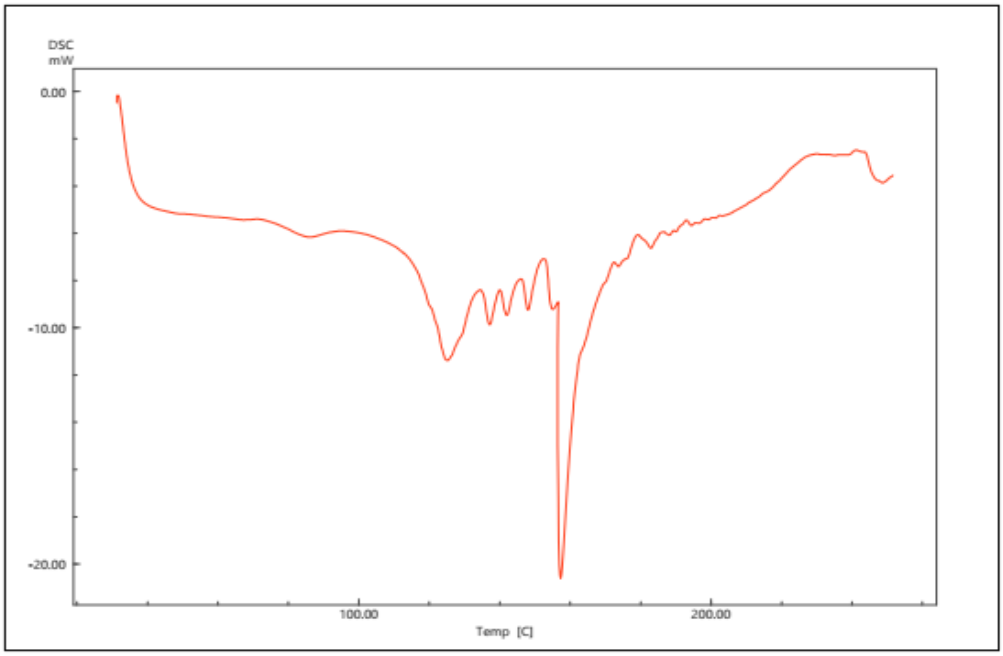
RESULT

The Thermogram of Valsartan showed peak indicating the 77.85˚C. which is identify due to evaporation and moisture.

DSC of Thermogram of Valsartan: Gelatin: PVA



Result: DSC Thermogram of PM showed a endothermic peak at 221.60˚C



Result: In Thermogram of optimize batch show a endothermic peak at 125.42˚C. Represents melting point of excipient and endothermic peak at 157.38˚C shows melting point of Valsartan.

CONCLUSION

Valsartan does not show peak in physical mixture and show low intensity, it making molecular dispersion. There is no extra peak observed hence drug is compatible with the excipient.

Compatibility by FT-IR Study

IR spectroscopy has been employed as a useful to identify the drug excipients interaction. IR spectroscopy of pure Valsartan and excipients were taken before starting a compatibility study and after completion of compatibility study the IR of all samples were taken and compared with IR graph of before compatibility Study.

A) Before **B) After**

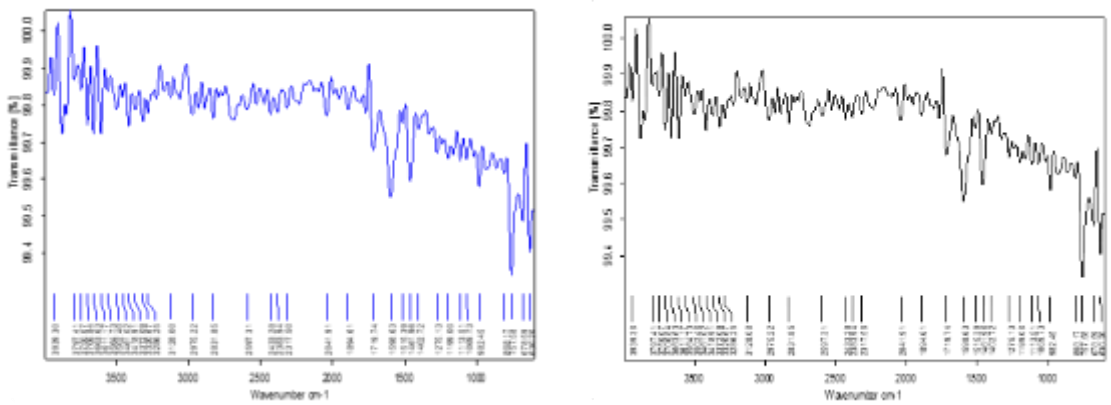


Figure 13: Valsartan + Gelatin before and after compatibility study.

A) Before **B) After**

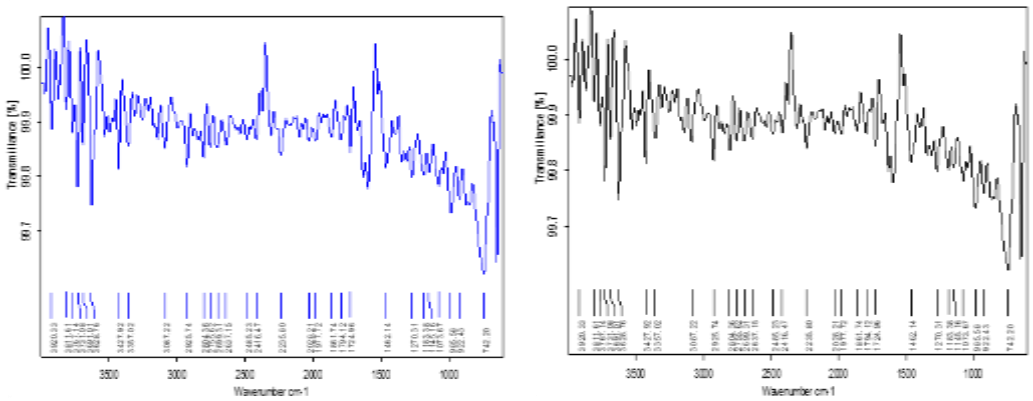


Figure 14: Valsartan + PVA before and after compatibility study.

CONCLUSION

It shows that all the characteristic peaks of Valsartan were present in FTIR spectra before and after compatibility study. Hence from IR study it can be concluded that the drug Valsartan was compatible with all excipients which was used in the formulation and development.

Compatibility study

The daily observations of compatibility study for 14 days were taken for colour changes, cake formation and liquefaction.

Excipients + Valsartan Compatibility Study

Sr. No.	Drug + Excipients	Ratio	Observation		
			Colour change	Cake formation	Liquefication
1	Valsartan + Gelatin	1:1	No	No	No
2	Valsartan + PVA	1:1	No	No	No
3	Valsartan +Gelatin + PVA	1:1:1	No	No	No

Formulation development

General Appearance

Formulation is transparent, clear and homogeneous in texture.

pH

The pH of formulated transdermal patches was found to be in the range of 3.9 to 6.9 which lies in the normal pH range of the skin, which indicates the suitability of the formulations for application on the skin to avoid any irritation upon application.

Table 11: Results of thickness, Uniformity of weight, Moisture content, folding endurance and Drug content.

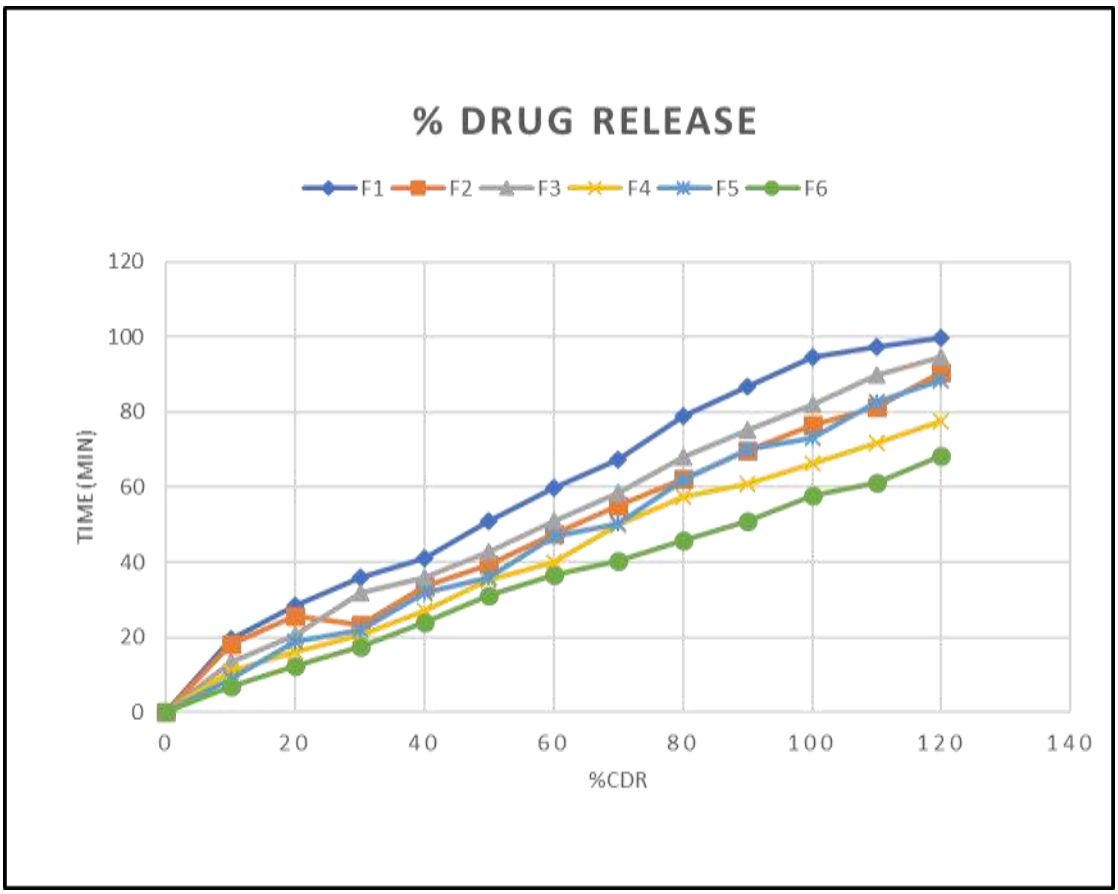
Sr.No.	Thickness (mm)	Uniformity of weight (mg)	Moisture content (%)	Folding Endurance	Drug Content (%)
F1	0.090±0.0057	218.33±14.71	4.696±0.28	243.33±15.24	98.10%
F2	0.096±0.0051	260±10.95	3.958±0.27	247.66±20.05	95.40%
F3	0.098±0.0040	261.66±20.41	4.113±0.42	238.66±15.95	97.15%
F4	0.095±0.0054	376.66±22.50	2.791±0.25	206.66±22.60	91.98%
F5	0.096±0.004	350±26.07	2.975±0.15	204.33±18.60	93.27%
F6	0.096±0.005	175±12.24	6.233±0.62	98.66±10.34	91.08%

In Vitro Drug Release Study

Table 12: Drug Release study of formulation.

Time (Min)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
10	19.58	18.24	13.50	10.95	9.10	6.83
20	28.34	25.56	20.41	16.24	18.70	12.24
30	35.78	23.14	31.78	20.71	22.06	17.43
40	41.20	33.61	36.04	27.03	31.78	24.09
50	51.06	39.21	42.90	35.27	35.98	31.22
60	59.77	47.42	51.10	40.05	46.69	36.69
70	67.27	54.98	58.60	49.85	50.23	40.42
80	78.83	62.04	67.86	57.57	61.73	45.69
90	86.67	69.65	75.27	60.81	69.99	51.09
100	94.60	76.55	81.95	66.42	73.22	57.71

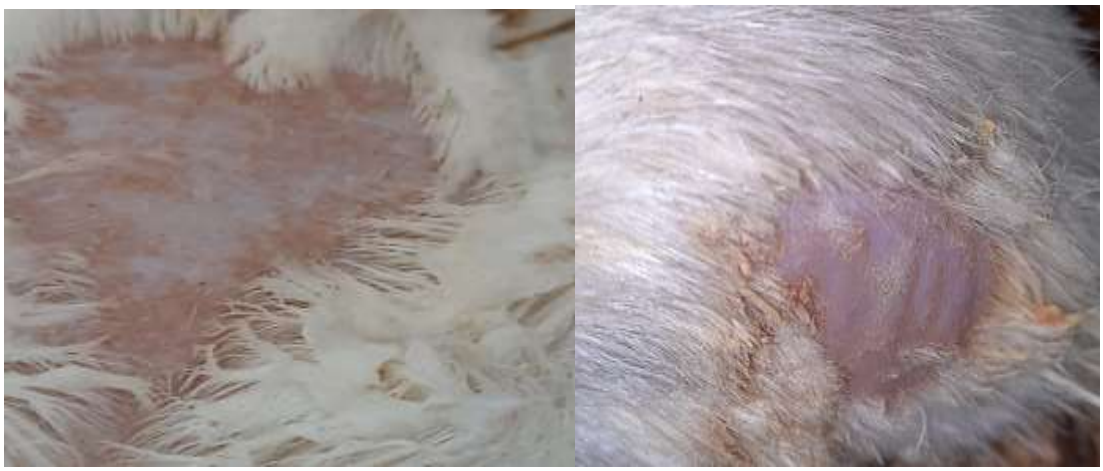
110	97.22	81.34	89.90	71.79	82.73	61.01
120	99.89	90.54	94.58	77.60	88.39	68.43



cumulative Drug Release Study

Results of Skin irritation test

Before **After**



Formulation patch

RESULT

Skin irritation test of all 3 groups on rats No signs of erythema and oedema or ulceration were observed on the skin of albino male Wistar rats after 24 hours.

SUMMARY AND CONCLUSION

The present study was to prepare valsartan loaded transdermal patches

Based on the above study following conclusions were drawn.

- ✓ The transdermal patch formulation was found to be efficacious, safe, stable and non-irritant to skin.
- ✓ IR spectra of the drug matches with standard functional group frequencies of drug
- ✓ The pH of formulated transdermal patches was found to be in the range of 6.8, which lies in the normal pH range of the skin, which indicates the suitability of the formulations for application on the skin to avoid any irritation upon application.
- ✓ The formulation F1 (Gelatin and PVA using propylene glycol as a plasticizer) was optimized. The above formulation gave a maximum drug diffusion of 99.8 % over a period of 120 min.
- ✓ The Drug Content results indicated that the process employed to prepare transdermal patches formulations in this study was showed significant result of uniform drug content.

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