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Formulation and Evaluation of Valsartan Transferosomes Loaded Transdermal Patch

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Khan Sameer Jeelan[1], Dharashivkar Sanket*[1], Gaikwad Madhuri[2]

[1]Department of Pharmaceutics, Dr. L. H Hiranandani College of Pharmacy, Ulhasnagar, India

[2]Department of Pharmaceutics, AIKTC School of Pharmacy, Panvel. India

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ABSTRACT

In this work transferosome based transdermal patch was formulated, for reducing dosing frequency by developing sustained release formulation for the treatment of hypertension using Valsartan as a model drugs. The transferosomes were prepared by the diethyl ether injection method and characterized for entrapment efficiency and surface morphology. The optimized batch of trasfersomes was used to prepare the patch. The patch was evaluated for different parameters. The % Entrapment efficiency of the optimized batch of transferosome was found to be 90.18 %. Percent cumulative drug release from transferosomal patch was 71 % at the end of the 24 hours.

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INTRODUCTION

A recent approach to the transdermal drug delivery system is to deliver the drug via Transferosomes patch into systemic circulation at a predetermined rate using skin as a site of application. Transferosomes are novel drug carriers which are highly deformable vesicles composed of lipid and edge activator and can carry large molecules across intact skin. This property assists in their quick penetration through the intercellular lipid pathway of the subcutaneous tissue. Transferosomes provide sustained release delivery (1).

Traditional drug delivery system (DDS) has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need for a formulation with a controlled release that maintains a near-constant or uniform blood level. Therefore, nowadays the ideal system should have the advantage of single-dose for the whole duration of the treatment, and it should deliver the drug directly at a specific site in a controlled manner. The goal in designing sustained delivery systems is to reduce the frequency of the dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. So, sustained-release (SR) dosage form is a dosage form that releases drugs continuously in a predetermined pattern for a fixed period, either systemically or to a specified target organ. The goal of an SR dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtained zero-order release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). The transdermal drug delivery system can deliver the drugs through the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period (2).

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure typically does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Valsartan is an angiotensin 2 receptor antagonist that is used for the treatment of hypertension. Valsartan has poor water solubility and low bioavailability. It has a short half-life (nearly 5hrs). It is rapidly metabolized by first-pass metabolism. An oral side effect of the drug is headache, dizziness,

lightheadedness, tiredness, flu symptoms, an upper respiratory infection. These drawbacks of VLT can be overcome by the transdermal drug delivery system (TDDS). Transdermal route is ideal due to advantages such as non-invasive route, controlled release, reduced dosing frequency, improved patient compliance. Minimum fluctuations in plasma drug concentration and Maximum utilization of drugs and is therefore able to further therapeutic benefits to hypertensive patients (3).

MATERIAL AND METHODS:

MATERIAL:

Valsartan was purchased from Cipla Pharma, Mumbai. Phospholipon 90G was a gift sample from Lipoid, Germany. Methanol was purchased from Molychem Mumbai. All other chemicals and solvents used during the experiments were of analytical grade and procured from SD Fine Chemicals, Mumbai, India.

PREPARATION OF TRANSFEROSOMES:

Transferosomal formulation was composed of lipid Phospholipon90G and edge activator Span 40 transferosomes were prepared by the diethyl ether injection method. This method is essentially based on the slow injection of an ether solution of lipid or surfactants into an aqueous medium at high temperature. Typically a mixture of lipid or surfactant and cholesterol (150 μmol) is dissolved in ether (20 mL) and injected into an aqueous phase (4mL) using a 14-gauge needle syringe. The temperature of the system is maintained at 60°C during the process. (4,5)

OPTIMIZATION USING 2^3 FACTORIAL DESIGN

A 2^3 full factorial design (Table 1 and Table 2) was employed to study the effect of independent variables i.e Lipid concentration: Surfactant concentration, stirring speed (RPM), and temperature on dependent variable i.e entrapment efficiency.

Table No. 1: Factors and factor levels investigated in 2^3 factorial design

FACTORS	LEVEL	
	-1	+1
(X1), Concentration of Lipid: Surfactant	225/650	325/650
(X2), Stirring speed	650 rpm	750 rpm
(X3), Temperature	50 ^{0}C	60 ^{0}C

CHARACTERIZATION OF TRANSFEROSOMES:

Transferosome were characterized based on various parameters such as surface morphology, entrapment efficiency, particle size, and zeta potential.

(A) Morphology

The morphological appearance of transferosomes was observed by Cryo- Scanning electron microscopy (6, 7).

(B) Determination of drug entrapment efficiency

The entrapment efficiency of the transferosome was determined by centrifugation method Transferosomal dispersion was subjected to centrifugation at 20,000 rpm at -4^{0}C for 20 minutes. The sediment was analyzed for the entrapment efficiency after suitable dilution with Methanol by measuring absorbance at 250 nm using UV Spectrophotometer. (8,9)

Entrapment efficiency was calculated according to the equation below:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of Entrapment drug}}{\text{Total drug added}} \times 100$$

FORMULATION OF TRANSFEROSOME LOADED TRANSDERMAL FILM:

Transferosomes equivalent to 100 mg of Valsartan was weighed and Dispersed in 8ml of water. After uniform dispersion of transferosomes in water, film-forming agents were added to form viscous solutions. Then Propylene glycol and Methylparaben were added to the above viscous solution and uniformly mixed using a magnetic stirrer. A glass mold of area 30.6 cm^2 was used for casting the film. The film was dried for 24 hours then packed in aluminum foil and stored in a desiccator till further use. (10)

EVALUATION OF TRANSFEROSOME LOADED TRANSDERMAL FILM:

Evaluation of Physio-Chemical Properties of Transdermal Film

1) Thickness

The thickness of each film was measured at different sites using a screw gauge and the average thickness was calculated. The percentage deviation from mean thickness was determined. (10)

2) Weight variation

Films from each batch having an area of 2cm x 2cm (4 cm^2) were weighed individually on a digital balance and average weight was calculated. (10)

3) Percentage of moisture content

Films were weighed individually. Then it was kept in a desiccator containing calcium chloride at room temperature for 24hrs. After 24hrs it was taken out and weighed and percentage moisture content was calculated by the following formula: (10)

$$\text{Moisture content (\%)} = \frac{\text{(Initial weight – Final weight)}}{\text{Final weight}} \times 100$$

4) Percentage moisture uptake

Films were weighed individually. Then it was kept in a desiccator containing potassium chloride to maintain 84 % RH for 24 hours it was taken out and reweighed and percentage moisture uptake was calculated by the following formula: (10)

$$\text{Moisture uptake (\%)} = (\text{Final weight} - \text{Initial weight}) \times 100$$

5) Folding endurance

This was determined by repeatedly folding the films until it shows signs of cracking or breaking. The number of times the film could be folded without breaking or cracking gave the value of folding endurance. (10)

6) Drug content

Film of 1cm x 1cm (2 cm^2) was cut into small pieces and dissolved in methanol, sonicated, and the volume was adjusted up to 10 ml with Methanol. The solution was filtered through a 0.45 µm membrane filter, diluted suitably and the absorbance of the resultant solution was measured spectrophotometrically at 250 nm using methanol as blank. The drug content of the prepared formulation was determined by the formula: (10)

Drug content (%) = (Amount drug in formulation/ total amount of drug taken) x 100

7) Tensile strength

Tensile strength is the maximum stress applied to a point at which the patch breaks. The tensile strength of the film was evaluated by using the tensile strength apparatus. A film with a dimension of 2 cm x 2 cm (4 cm^2) was fixed between the jaws of the instrument. The load on the film was gradually increased until the film broke. The tensile strength was taken directly from the dial reading in Kg. (11)

***In-vitro* Diffusion Study**

The aqueous dispersion of Valsartan and Valsartan loaded transdermal film was subjected to an *in-vitro* diffusion study using modified Franz diffusion cell. The dialysis membrane was soaked in pH 7.4 phosphate buffer for 24 hrs before activation. The dialysis membrane mixed with phosphate buffer pH 7.4 and maintained at 32± 0.5ºC. The magnetic bar was placed in the receptor compartment and driven at 100 rpm. At time intervals of 1, 2, 3, 4, 5, 6, 7, and 24 hrs. 1ml of an aliquot from the receptor compartment was withdrawn, and the same volume of fresh medium was added back into the compartment. The samples were analyzed spectrophotometrically for drug content at a wavelength of 250nm. (11)

RESULTS AND DISCUSSION:

Optimization of transfersomes using 2^3 factorial design

A 2^3 factorial design (Table 2 and Fig.1) was employed for further study. Percent entrapment efficiency was performed and the results were fed into the design expert software. The data were analyzed by ANOVA and were reported to be significant.

Table No. 2: Design and responses for 2^3factorial design batches

Batch	Lipid/Surfactant	Temp (°C)	RPM	Entrapment (%)
F1	225/650	50	650	71.423
F2	325/650	50	650	85.41
F3	225/650	60	650	79.96
F4	325/650	60	650	89.94
F5	225/650	50	750	80.51
F6	325/650	50	750	90.43
F7	225/650	60	750	80.69
F8	325/650	60	750	91.63

Effect of formulation variable on the entrapment efficiency

In percent entrapment efficiency polynomial equation in terms of the coded factor was obtained as percent entrapment efficiency y= +64.09500 +64.09500 * X2 -24.12000 X1 * X2. R^2 was found to be 0.9962 which implies that 99.62 of the variation in the responses was attributed to independent variables. There is only a 1.53% chance that an F-value this large could occur due to noise. There are only 0.06% chances that an F value (Table 3) this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant.

Table No. 3: Annova table for percentage entrapment efficiency

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	156.24	4	39.06	16.54	0.0220	significant
A-Surf:lipid	74.91	1	74.91	31.72	0.0111	
B-Temp	37.07	1	37.07	15.69	0.0287	
C-RPM	2.86	1	2.86	1.21	0.3518	
AB	41.40	1	41.40	17.53	0.0248	
Residual	7.09	3	2.36			
Cor Total	163.32	7				

The **Model F-value** of 16.54 implies the model is significant. There is only a 2.20% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, A, B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

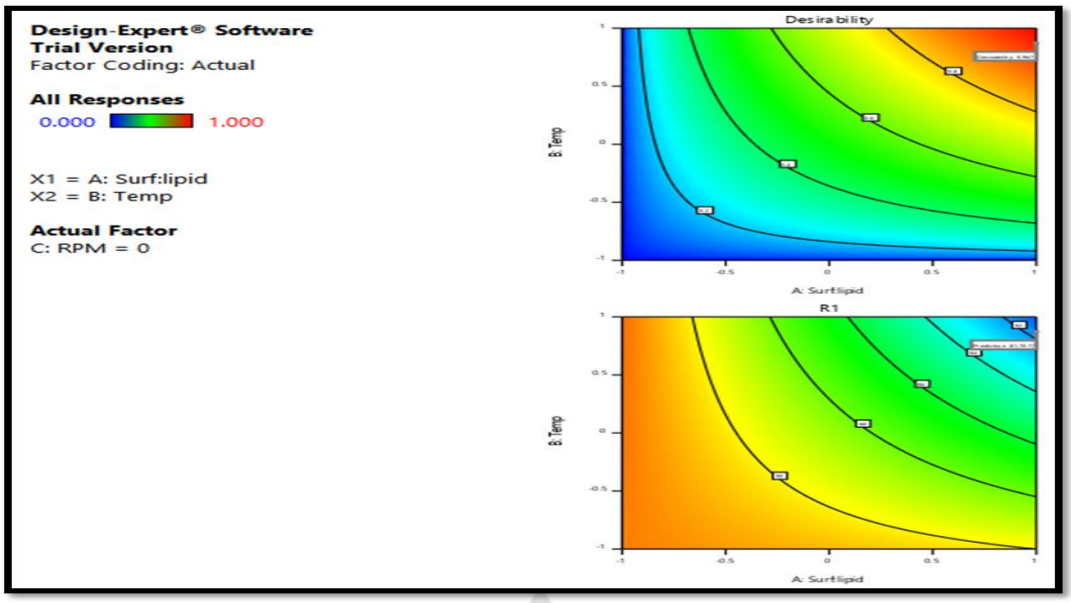

Figure No. 1: Counter plot of percentage entrapment efficiency

Selection of optimized batch

There is no significant difference between in percent entrapment efficiency predicted batch and actual batch. This indicates that the concentration of surfactant, RPM, and temperature is optimized. This optimized batch was further selected (Table 4) and studied for the drug release profile.

Table No. 4: Selection of optimized batch

Batch	Lipid/ Surfactant	Temperature (ºC)	RPM	Entrapment efficiency (%)
Predicted	325/650	60	750	92.739
Actual value	325/650	60	750	90.18

Morphology

CRYO-scanning electron microscopy (CRYO-SEM) analysis of transfersomes (Fig.2) was done to find out the morphology. Perfect spears were observed.

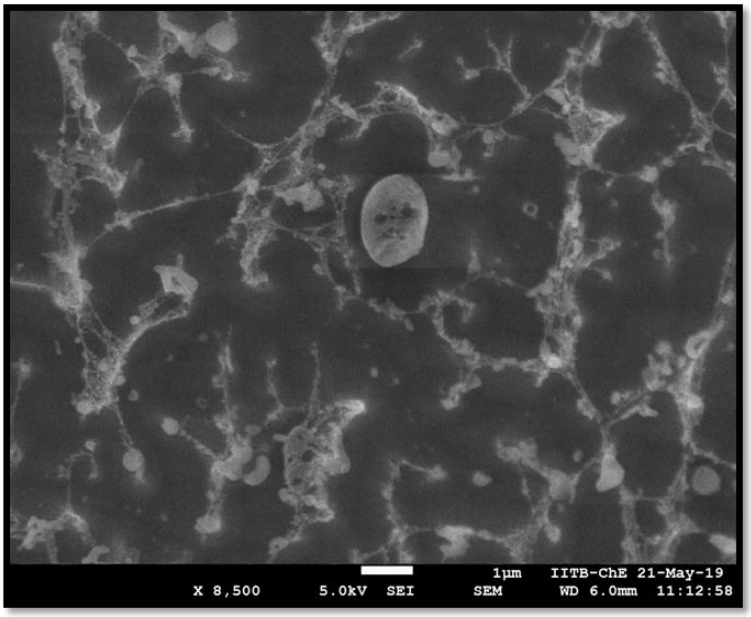

Figure No. 2: Cryo-SEM analysis of optimized transferosomes

FORMULATION OF TRANSFEROSOME LOADED TRANSDERMAL FILM

Selection of polymer for preparation of the transdermal film

For the preparation of transdermal film polymers PVA, PVPK30, and HPMCK4 were used and polymers were evaluated for casting, ability to dry, and formation of an intact film. Table 5 indicates the results for the selection of polymers.

Table No. 5: Selection of polymer for the formulation of the transdermal film

Sr. No.	Polymer	Nature
1	PVA	No film formation
2	PVPK-30	Discontinuous film formation
3	PVPK-30+ HPMC K4M	Formation of intact film

Optimization of concentration of plasticizer for the formulation of the transdermal film

Plasticizer plays an important role in the formulation of Transdermal film as it provides flexibility to the film. A high concentration of plasticizer results in the formation of highly viscous dispersion difficult to cast whereas low concentration results in the formation of the brittle film, therefore the concentration of plasticizer was optimized as shown in the below table 6.

Table No. 6: Selection of concentration of plasticizer for the formulation of a transdermal patch

Batch	Conc of PVPK-30 (mg)	Concentration of HPMC K4M (mg)	Concentration of plasticizer (%)	Volume of solvent (ml)	Nature
1	200	300	5	10	Poor flexibility
2	200	300	10	10	Poor flexibility
3	200	300	20	10	Poor flexibility
4	200	300	30	10	Good flexibility

From Table 6 it was observed that a total weight of 500 mg using a combination of polymers PVPK-30 and HPMC K4M as well as plasticizer concentration of 30% produced the intact film with good flexibility.

EVALUATION OF TRANSFEROSOME LOADED TRANSDERMAL FILM

Evaluation of Physio-Chemical Properties of Transdermal Film

The results of the evaluation of the physio-chemical properties of the transdermal film are shown in table 7.

Table No. 7: Evaluation of transferosome loaded transdermal film

Test	Results
Thickness	0.81±0.04571mm
Weight variation	35.58±1.07mg
Percentage of Moisture content	9.45±0.51%
Percentage Moisture Uptake	6.3±0.65%
Drug content	92 %
Folding Endurance	245±6.02 times
Tensile strength	0.54±0.0195 kg/cm^2

***In-vitro* diffusion study**

Cumulative release (%) of drug form transferosomes incorporated transdermal patch (Fig. 3) was 71% at the end of the 24 hours. Thus the optimized batch of transferosome incorporated transdermal patch was able to sustain the release of VLT up to 24 hours.

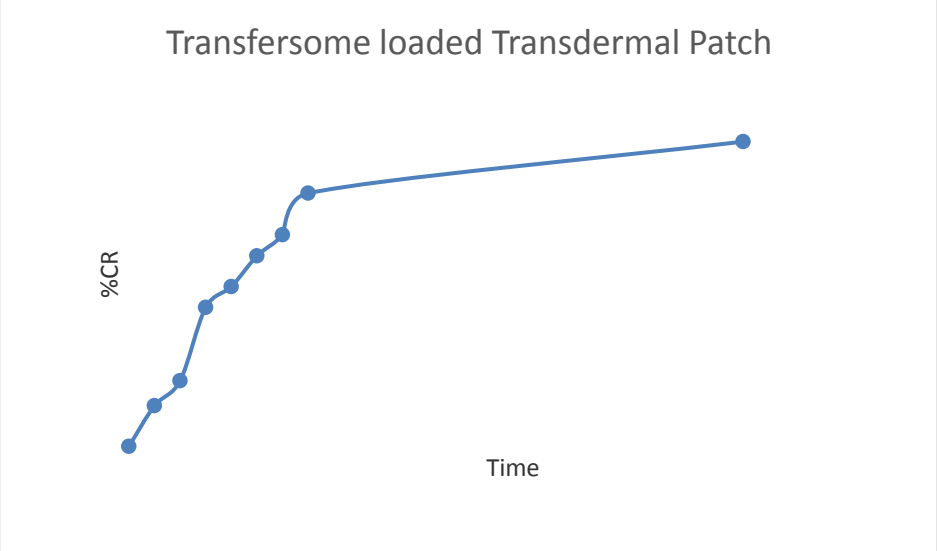

Figure No. 3: *In-vitro* diffusion study of transfersome loaded transdermal patch

CONCLUSION:

Percent cumulative release of drug form transferosome loaded patch was 79 % at the end of the 24 hours. Hence, valsartan transferosome loaded transdermal patch will be effective to reduce the dosing frequency and have sustained release patterns. This will surely help to improve patient compliance.

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