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RESEARCH ARTICLE

OPTIMIZATION OF TRANSDERMAL DELIVERY OF SELECTED ANTIHYPERLIPIDAEMIC AGENTS-STATIN

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ABSTRACT

A transdermal dosage form of Simvastatin has been developed using various polymers like Eudragit L100, Eudragit S-100, HPMC, Ethyl cellulose, SCMC, Sodium alginate, Guar gum and Carbomer. Polymers like Eudragit L-100 Eudragit S-100, Ethyl cellulose and HPMC exhibited good film forming properties. Propylene glycol, Tween 80, Oleic acid and 4N- dibutyl phthalate were used as plasticizers to improve the film forming properties of the polymer film. Among these 4N- dibutyl phthalate exhibited excellent results. The formulations H_{20} and E_{20} containing HPMC and Ethyl cellulose showed excellent physico-chemical properties, drug content, uniform content uniformity, but the permeability was not sufficient enough. Permeability enhancers such as Tween 80, Oleic acid, Eucalyptus oil and DMSO were used to enhance the permeability. The final formulations E_{20} and H_{20} were evaluated for their permeability coefficient, flux, and mechanism of drug release and kinetics of drug release. The permeability coefficient and flux were found to be satisfactory. The mechanism of drug release may be by diffusion and kinetics of drug release was first order. Finally the stability studies for one month were studied at different temperatures.

Key words: Folding endurance, Transdermal, Permeability Coefficient, Plasticizer.

INTRODUCTION:

Cardiovascular diseases are the major concern of death in India. Cardiovascular diseases (CVD) are the cause of more than 30% of deaths, not only in the developed countries. The World Health Organization (WHO) estimates that low- and middle income countries are disproportionately affected. 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women. The WHO projects that by 2030, almost 23.6 million people will die from CVDs. One of the major causes of cardiovascular disease is hyperlipidaemia an increased serum level of total cholesterol (low density lipoprotein, cholesterol, triglycerides or both cholesterol and triglycerides).In the management of hyperipidaemia, statins are more effective than other classes of drugs. [1]

The HMG-CoA reductase inhibitors (statins) are most affective and well known drugs for the management of hyperlipidaemia. These efficiently act by competitively inhibiting the HMG-CoA reductase, leading to inhibition of cholesterogenesis in the liver[2]. However the statins administered in conventional dosage forms have certain disadvantages such as low oral bioavailability due to extensive first pass metabolism. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed

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to the corresponding β-hydroxyacid form. This is an inhibitor of HMG-CoA reductase. Simvastain, because of its short biological half life($t_{1/2}$, 2 hours) only 5% of its dose reaches to the systemic circulation of the blood on oral administration. Hence Simvastatin is a suitable candidate for transdermal dosage form .[3]

The skin is the most extensive and readily accessible organ of the human body. The medication through the skin can be used for dermatological local action within the skin and circulating into blood stream for systemic action. The skin layers act as permeation barrier for the absorption of drugs into the systemic circulation. The transdermal route of administration has various advantages over oral route of administration; major one is bypassing the first pass metabolism in the liver, and thus extends the activity of drugs having short half life. It also provides capacity to terminate drug effect rapidly by removal of drug application from the surface of skin. Therefore transdermal drug delivery system was chosen as an ideal dosage form for Simvastatin.[4,5]

In this project a transdermal drug delivery system for Simvastatin was formulated with optimization of polymer, plasticizer, permeation enhancer and their concentrations. Such prepared formulations were evaluated for their physico-chemical characters, water vapor transmission, stability, drug interaction and permeation study through rat abdominal skin.

MATERIALS AND METHODOLOGY

MATERIALS

Simvastatin was obtained as a generous gift from Biocon India Ltd, Bangalore. Hydroxyl propyl methyl cellulose, Carbomer, Sodium alginate, Guar gum, 2N- Dibutyl Phthalate and Dimethyl sulfoxide were obtained from NR chemicals, Mumbai. Eudragit L-100, Eudragit S-100, Ethyl cellulose were purchased from BDH Laboratory Mumbai.

METHODS

1.DETERMINATION OF PARTITION CO-EFFICIENT OF SIMVASTATIN[6]

For the determination of partition co-efficient of Simvastatin, octanol/water system was used. Equal volumes of distilled water (10ml) and n-octanol (10ml) were taken in a separating funnel and shaken for 1 hour. 10mg of the Simvastatin was added to the separating funnel and shaken for 2 hours. Then the aqueous and n-octanol layers were separated. From the aqueous layer 0.1mL solution was pipetted out and diluted to 100mL and absorbance was determined by UV spectrophotometer at a λmax of 247.5nm. The residue obtained after evaporation of n-octanol was dissolved in methanol and after appropriate dilution with distilled water the concentration of the solute was determined by UV spectrophotometric method. The partition co-efficient was calculated using the following equation.

$P_{o/w} = (C_{oil}/C_{water})$ equilibrium.

2. PERMEATION STUDIES OF SATURATED SOLUTION OF SIMVASTATIN THROUGH CELLOPHANE MEMBRANE AND RAT ABDOMINAL SKIN

Simvastatin is classified as a Biopharmaceutics Classification System (BCS) Class-II compound with a poor aqueous solubility and an acceptable permeability through membranes. Permeation studies of the pure simvastatin were carried out using cellophane membrane and rat abdominal skin. The abdominal skin was isolated from the body of rat and was treated with dilute ammonia solution to remove the hairs and subcutaneous fat. The cellophane membrane or rat skin was washed with plenty of distilled water and trimmed into

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a circular section about 3 cm diameters. The modified Franz diffusion cell assembly having 100 ml capacity in receptor chamber was used. Throughout the study the assembly was kept at temperature 37 ± 2^0C. The studies were carried out using three different media, phosphate buffer (pH 7.4), distilled water and 20 % alcohol respectively with continuous stirring on magnetic stirrer at 70 RPM. The samples were withdrawn at pre determined, regular time intervals for a period of 24 hours and an equal amount of fresh respecter medium was replaced. Amount of drug in withdrawn samples was determined spectrophotometrically at 247.5 nm after suitable dilution.

3. PREPARATION OF POLYMER FILMS WITHOUT DRUG

Different polymers like Eudragit L-100, Eudragit S-100, HPMC, Carbomer, Ethyl cellulose, Guar gum, SCMC, Sodium alginate were studied for their film forming property. Films were prepared using the above polymers in the concentration of 1%, 2%, 3%, 4% and 5% w/v.

The polymer film with various polymers in different concentrations was then checked for desired characteristics like physical appearance, tensile strength, folding endurance by a set of experiments.

4. SELECTION OF PLASTICIZER

For proposed formulation of polymer film, the plasticizers used were Propylene glycol, 4N-Dibutyl phthalate, Oleic acid and Tween 80. The optimum concentration of plasticizers was determined by formulating transdermal patches with three different polymer concentrations 2%, 3%, 4% with plasticizer concentrations at 10%, 20%, 30%, 40%, and 50% respectively.

5. FORMULATION OF TRASNSDERMAL FILMS WITH DRUG

The transdermal patch of Simvastatin was prepared by simple solvent evaporation method. The polymer and drug Simvastatin was dissolved in methanol separately and both were mixed together with vigorous stirring then the determined quantity of plasticizers and permeation enhancers were added. Prepared mixture was cast in a petri dish shaped alupoly of a definite radius. After complete evaporation of the solvent the patch was removed and stored properly.The area of petri dish shaped alupoly was calculated as follows.

Diameter of alupoli was 5.14 cm. therefore radius r = 2.57 cm.

Area of alupoli = πr^2

= $3.142 \times (2.57)^2$ = 20.752 cm^2

Formulation composition of films made using ethyl cellulose and HPMC are given in Table No: 1.

6. EVALUATION PARAMETERS FOR THE POLYMER FILM

The polymer films without drug were evaluated for physico-chemical characteristics which include physical appearance, weight variation, thickness, folding endurance and tensile strength.

Appearance

The physical appearance of the polymer film was observed.

Weight variation

The polymer film with the surface area 6cm^2 was cut at 3 different places in the cast film. The weight of each film strip was taken and average weight variation was calculated.

Thickness

The thickness of the polymer film was determined by using screw gauge at different positions and mean values were calculated.

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ix. **Folding endurance**

The folding endurance is expressed as the number of folds (number of times a film is folded at the same plane) required to break the film or to develop visible cracks. This gives an indication of brittleness of the film. A strip of 6 cm^2 was subjected to this test by folding the film at the same place repeatedly several times until a visible crack was observed.

x. **Tensile strength**

Tensile strength was measured using modified analytical two pan balance method. The film of 6 cm^2 wide was clamped between two clamps on one side; weights were added to the pan on other side until the patch breaks. The weight required for breaking the patch was taken as a measure of tensile strength of the patch.

xi. **Percentage elongation** [7]

Percentage elongation was calculated by measuring the increase in length of the film after tensile measurement by using the following formulae.

Percent elongation = $[L - L_0] \times 100 / L_0$

Where, L = Final Length,

L_0 = initial Length.

Further the selected formulations were subjected for permeation studies, drug content, content uniformity and water vapor transmission as follows.

xii. **Permeation studies of formulation through rat abdominal skin**

Permeation studies of the transdermal patches which exhibited satisfactory physico chemical parameters were carried out using rat abdominal skin (treated with dilute ammonia and distilled water). The modified Franz diffusion cell assembly having 100ml capacity receptor chamber was used. The media used in acceptor compartment was 20% alcohol and distilled water, where as phosphate buffer (pH 7.4), solution was not used because; the drug release profile in this media was found negligible. The study was carried out at room temperature i.e. 37 ± 2^0C with continuous stirring on magnetic stirrer at 70 rpm. The sample was withdrawn at predetermined regular time intervals and an equal amount of respective fresh medium was replaced. The amount of drug in the withdrawan sample was determined spectrophotometrically at 237.5nm after suitable dilution.

xiii. Selection of permeation enhancers

As the release rate of Simvastatin from the formulations was not satisfactory, permeation enhancers like Dimethyl sulfoxide, Tween 80, Oleic acid and Eucalyptus oil in a concentrations of 1ml, 2ml, 3ml and 4ml were used. The release profile of the drug through the selected transdermal patch with different enhancers of varying concentrations was used as a tool for optimizing the permeation enhancer.

xiv. Drug content

The films were tested for drug content. Films of area 6 cm^2 were cut, placed in 10 ml volumetric flask and dissolved in methanol; volume was made up to 10 ml with methanol. 3ml of above solution was withdrawn and diluted up to 25 ml with 50% v/v of methanol. Form the above solution 2 ml was diluted to 10 ml with methanol in 10 ml volumetric flask. The absorbance of the solution was measured at 237.5 nm.

xv. Content uniformity

The film was tested for content uniformity. Films of area 6 cm^2 were cut from three different places from the cast film. Each film was placed in 10 ml volumetric flask and dissolved in methanol and the volume was made up to 10 ml with methanol. 3ml of above solution was withdrawn and diluted up to 25 ml with 50% v/v of methanol. From the above solution 2ml was diluted to 10 ml with methanol in 10

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ml volumetric flask. The absorbance of the solution was measured at 237.5 nm.

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xx. **Water vapor transmission studies**

The water vapor transmission was determined by placing films in open 5 ml glass vials containing 2 gm of desiccant (silica gel) and sealed with cellotape. The vials were conditioned in desiccators containing silica gel for 12 hours. The vials were then placed in a Newtronic humidity control oven (75% RH, 22^0 C). The moisture transmitted through films was determined gravimetrically by weighing the vials initially and over 72 hours period (2,10,24 and 36 and 72 hours).

xxi. **Flux calculation** [8]

The flux was calculated by Fick`s law of Diffusion. Flux is defined as the amount (in mg) of the drug passing through a unit cross sectional area S (in cm^2) in unit time t (in hours). The equation for calculating the flux is

$$J=dm/S.dt$$

Where, m=Amount of drug passing through the rat abdominal skin

S=Surface area of rat abdominal skin

t = total time of diffusion through the rat abdominal skin.

xxii. **Permeability coefficient** [9]

Permeability coefficient is defined as the amount of drug that would pass through unit cross section area of rat abdominal skin if the concentration in the donor compartment remains relatively constant through the time.

If the concentration changes appreciably with time the permeability coefficient may be calculated according to following equation by calculating slope of log C v/s time as follows,

$$\text{permeation coefficient} = \frac{\text{slope } 2.303 * \text{vol. of compartment}}{\text{surface area}}$$

xxiii. **Kinetics of drug release** [8]

The kinetics of drug release was estimated by comparing R^2 values of first order release kinetics (Wagner's graph of log amount of drug remained in the dosage form (AR v/s Time) and zero order release kinetics (zero order of CR v/s Time) graphs.

xxiv. **Mechanism of drug release** [10]

The mechanism of drug release of the final formulations were determined by comparing the slope values of log CR Vs log time (Peppas Plot) with the standard values and by plotting a graph of CR v/s √t (Higuchi plot)

xxv.

xxvi. **Compatibility studies**

Compatibility studies of drug with different excipients were evaluated by following methods.

a) **Fourier Transform Infra Red Spectroscopy (FTIR)**

Instrument used was Shimadzu FTIR-8700 spectrophotometer. In this studies potassium bromide disc method was employed. Both pure drug and its formulations were subjected to IR studies. TDDS formulation was powdered and intimately mixed with dry powdered potassium bromide. The mixture was the compressed in to transparent disc under high pressure using special dies. The disc was then placed in IR spectrophotometer using sample holder and the spectrum was recorded.

b) **Differential scanning calorimetric analysis (DSC)**

Differential scanning colorimeter was employed as a tool to investigate the compatibility between the drug and number of commonly used excipients which may affect the solubility of drug by chemical or physical interaction thus posing a threat to the drugs stability and bioavailability. DSC is a fast and reliable method to screen any drug excipient

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interaction as compared to the time consuming method of accelerated stability studies.

Procedure: The instrument used was Perkin-Elmer DSC-7. Thermograms of formulations, excipients used and pure simvastatin were obtained. Samples were sealed hermetically in flat bottomed aluminum cells (pans). These samples were then heated over a temperature range 320K to 420K in an atmosphere of nitrogen (20 mm/min) at a constant rate of 10K/min with alumina being reference standard.

RESULTS AND DISCUSSIONS

Partition coefficient of Simvastatin

Partition coefficient of simvastatin was found to be 4.68

Permeation studies of Simvastatin through cellophane membrane and Rat abdominal skin

Permeation study of saturated solution of Simvastatin across cellophane membrane and rat skin using distilled water, 20% alcohol and phosphate buffer (pH 7.4) solution were carried out. The results showed, the permeation of saturated solution of simvastatin via rat abdominal skin in distilled water as recipient vehicle was satisfactory for further study of permeation of Simvastatin. The results of permeation study of pure simvastatin is given in Table Nos : 2 and 3 respectively.

Selection of the polymer

The polymer film without drug using different polymers of varying concentrations was formulated. Such prepared polymeric films were subjected to evaluation of their physico-chemical parameters in order to select the best polymer.

Selection of best formula

Polymer films without drug were prepared using the polymers in a concentration of 1%, 2%, 3%, 4% and 5% w/v. Polymer films formulated using carbomer, guar gum, SCMC, and sodium alginate were tacky and sticky even after 48 hours, hence these polymers were not used for further formulations of transdermal patch. Polymer film formulated using eudragit L 100, eudragit S 100, HPMC and ethyl cellulose in concentrations of 1%and 2% were not possible to peel out from the alupoly without breaking the film. Polymer films formulated using eudragit L 100, eudragit S 100, HPMC and ethyl cellulose in a concentration of 3% were very thin and broken during handling. Polymer film formulated using eudragit L 100, eudragit S 100, HPMC and ethyl cellulose in a concentration of 5% were thick and brittle. Finally polymers eudragit L 100, eudragit S 100, HPMC and ethyl cellulose in a concentration of 4% were selected for formulation of transdermal patch. Results of different physical evaluation parameters like appearance, weight variation, folding endurance, tensile strength of films with and without drug are given in Table Nos: 4 and 5 respectively.

Selection of plasticizer:

For the formulation of polymer film without drug with selected polymers, the plasticizers used were propylene glycol, 4N-Dibutyl phthalate, Oleic acid and Tween 80. Polymer film without drug using 4N-Dibutyl phthalate as the plasticizer was found to exhibit ease of peeling and good appearance. The Optimum concentration of plasticizers was determined by formulating the film with a polymer concentration 4% w/v and plasticizer concentrations of 10%, 20%, 30%, 40%, and 50% of the polymer respectively. It was found that 4N-Dibutyl phthalate in a concentration of 30% was found to be best platicizer.

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Dose calculation

The total dose of drug (Dt), in a prolonged action preparation comprises of the normal (prompt) dose (Dn), and the sustaining dose (Ds) i.e. Dt = Dn+Ds

If the first order elimination rate constant is K

Then **$Dt = Dn(1+Kt)$, $Kt = t_{1/2}$** where $t_{1/2}$ is biological half life.

In case of Simvastatin the Normal dose Dn is 10mg and its biological Half life Kt $_{1/2}$ is 2 Hours

Therefore, **Dt = 10(1+2) = 30mg**

Permeation study of E_{20} and H_{20} formulation.

The best two formulations E_{20} and H_{20} were subjected to permeation studies through rat abdominal skin in distilled water. 1cm^2 of the prepared patch of 6cm^2 was subjected to permeability studies. Therefore the amount of drug available for permeation through rat abdominal skin was only 17.33mg. It was found that the release of Simvastatin from the formulation H_{20} and E_{20} was very less, 1.34% and 1.190% respectively at the end of 27 hours. The results are shown in Table no:6.

Selection of permeation enhancers.

As the release rates of simvastatin from the formulations were not satisfactory, permeation enhancers like Dimethyl sulfoxide (DMSO), Tween 80, Oleic acid and Eucalyptus oil were used. In order to select a best permeation enhancer 2ml of above permeation enhancers were incorporated into E_{20} and H_{20} formulations and the resultant films were subjected to permeation studies through the rat abdominal skin using distilled water as receptor medium. As shown in Table No: 7 the formulations E_{20} and H_{20} with DMSO as the permeation enhancer show a good release profile. Hence the formulations E_{20} and H_{20} prepared with different concentrations of DMSO (1ml, 3ml and 4ml) were subjected to permeation studies through rat abdominal skin using distilled water as receptor medium. It was found that the formulations H_{20} and E_{20} with 3ml DMSO showed highest drug release, 3.258% and 3.73% respectively at the end of the 27th hour. Results are shown in Table No: 7, 8 and 9 respectively.

The formulations H_{20} and E_{20} were subjected for drug content, content uniformity and water vapor transmission studies as follows.

Drug content:

The drug content was determined in formulations H_{20} and E_{20}. Simvastatin content in H_{20} and E_{20} was found to be 99%± 0.08and 99%± 0.06 respectively.

Content uniformity:

The drug content in each formulation of H_{20} and E_{20} was found uniform within each film respectively.

Water vapor transmission studies:

The water vapor transmission was determined by placing films in an open 5 ml glass vials containing 2 gm of desiccant (silica gel) and sealed with cello tape. The vials were conditioned in desiccators containing silica gel for 12 hours. The vials were then placed in a Newtonic humidity control oven (75% RH, 22^0 C). The moisture transmitted through films was determined gravimetrically by weighing the vials initially and over a period of 72 hours. The water vapor transmission was found to be negligible. The data is tabulated in Table No: 10.

Kinetics and Mechanism of drug release of drug release

The results of *in-vitro* release profile obtained for all the formulations were plotted in kinetic models as follows,

1. Cumulative percent drug released versus time (zero order kinetic model).

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2. Log cumulative percent drug remaining to be absorbed versus time (First order model)

3. Amount of drug release or cumulative amount of drug release versus square root of
time (Higuchi model)

4. Log Mt / M∞ versus log time (Korsmeyer-Peppas model).

The kinetics of drug release can be estimated by comparing R^2 values of first order release kinetics and zero order release kinetics graphs. From the estimation as given in table no:17 it is clear that the R^2 (0.991and 0.975) values of Wagner's graph was higher than the R^2 (0.987 and 0.967 respectively) values of Zero order graph; hence the release kinetic follows First order for both the formulations H_{20} and E_{20}. The Higuchi plot shows a straight line with R^2 values0.967 and 0.967, which indicates diffusion as drug release from both H_{20} and E_{20} formulations respectively.

The mechanism of drug release of the final formulations were determined by comparing the slope values of log CR v/s log time (Peppas Plot) with the standard values of korsmeyer peppas model and by plotting a graph of CR v/s √t (Higuchi plot).

COMPATIBILITY STUDIES

FTIR SPECTRAL STUDIES:

The FTIR studies were carried out to study the possible drug excipient interaction. By comparing the FTIR spectra of pure drugs and physical mixture, it was observed that there was no significant difference in the characteristic peaks of pure drug and physical mixture revealing absence of any interaction.

DSC STUDIES:

The DSC spectrum for pure drug shows that the drug Simvastatin is in an amorphous form. The DSC spectra for drug and polymer shows no change in the spectrum which clearly indicating that the drug remain in its original form i.e. amorphous form, after incorporating it into polymer.

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Table No: 1 Simvastatin transdermal patch of different concentrations of Ethyl cellulose and HPMC

SI NO	FORMULATION CODE	DRUG: POLYMER RATIO
1	E_{10}	1:1
2	E_{20}	1:2
3	E_{30}	1:3
4	E_{40}	1:4
5	E_{50}	2:1
6	E_{60}	2:3
7	H_{10}	1:1
8	H_{20}	1:2
9	H_{30}	1:3
10	H_{40}	1:4
11	H_{50}	2:1
12	H_{60}	2:3

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Table No: 2 Permeation study of a saturated solution of Simvastatin through cellophane membrane using different receptor media

SI NO	Time(hrs)	%CPR		
		Water	Alcohol 20%	Phosphate buffer pH 7.4
1	½	0.2808	0.1872	0.2247
2	1	0.6367	0.4681	0.4494
3	2	1.3483	1.0486	1.1610
4	3	1.8539	1.6666	1.5916
5	4	2.2471	2.5093	2.0599
6	5	3.1460	2.9775	2.3970
7	10	3.6516	3.7078	3.0711
8	15	4.7003	3.9325	3.5393
9	27	6.4606	4.8314	3.9325

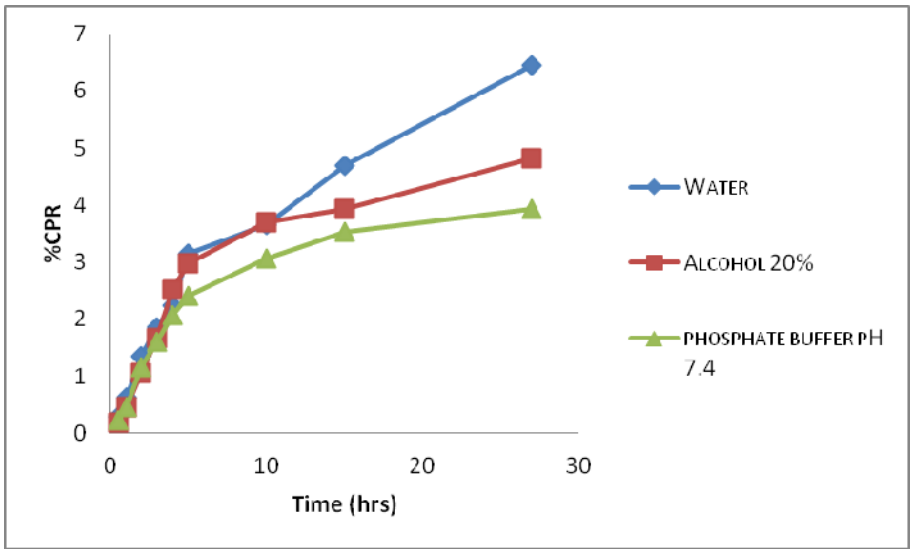

Fig No:1 Permeation study of saturated solution of simvastatin through cellophane membrane using different receptor media

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Table No:3 Permeation study of a saturated solution of Simvastatin through rat abdominal skin using different receptor media

SI NO	Time(hrs)	%CPR		
		Water	Alcohol 20%	Phosphate buffer pH 7.4
1	½	2.883895	2.41573	2.509363
2	1	3.707865	3.146067	3.2397
3	2	4.138577	3.40824	3.614232
4	3	5.486891	3.764045	4.007491
5	4	5.82397	4.382022	5.262172
6	5	7.172285	5.355805	5.842697
7	10	7.696629	6.554307	6.966292
8	15	9.213483	7.303371	7.921348
9	27	9.76779	7.883895	9.588015

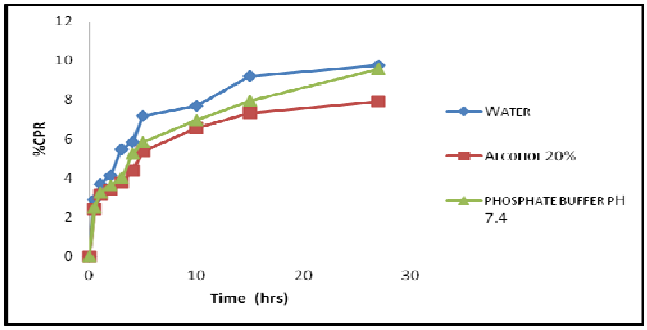

Fig No:2 Permeation study of saturated solution of Simvastatin through rat abdominal skin using different receptor media

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Table No: 4 Physical evaluation of polymer films containing different concentrations of plasticizer

POLYMER	PLASTICI-ZER	WEIGHT (mg)	APPEARENCE	THICKNESS (mm)	FOLDING ENDURANCE	TENSILE STRENGHT (Kg/cm^2)
Eudragit L-100	10%	98±2	Transparent	20±0.73	10	0.1±0. 01
Eudragit S-100		95±1	Transparent	19±0.3	15	0.2±0. 09
HPMC		114±3	Transparent	25±0.01	98	0.335±0.04
Ethyl cellulose		113±5	Transparent	26±0.43	99	0.361±0.02
Eudragit L-100	20%	194±2	Transparent	39±0.29	10	0.1±0.03
Eudragit S-100		192±5	Transparent	35±0.38	14	0.2±0.02
HPMC		227±3	Transparent	49±0.6	94	0.337±0.04
Ethyl cellulose		229±4	Transparent	50±0.02	98	0.363±0.03
Eudragit L-100	30%	294**±2**	Transparent	55±0.03	8	0.1±0.02
Eudragit S-100		289**±5**	Transparent	49±0.043	10	0.2±0.02
HPMC		**341±1**	**Transparent**	**71±0.83**	**89**	**0.347±0.41**
Ethyl cellulose		**338±2**	**Transparent**	**74±0.04**	**93**	**0.364±0.03**
Eudragit L-100	40%	401±5	Transparent	74	2	0.1± 0.02
Eudragit S-100		389±3	Transparent	70±0.75	6	0.2±0.01
HPMC		421±4	Transparent	89±0.49	80	0.333±0.02
Ethyl cellulose		419±2	Transparent	93±0.53	83	0.342±0.04
Eudragit L-100	50%	485±5	Transparent	97±0.43	Unable to fold	0. ±0.01
Eudragit S-100		475±3	Transparent	100±0.53	3	0.1±0.04
HPMC		561±2	Transparent	119±0.03	79	0.325±0.05
Ethyl cellulose		560±4	Transparent	124±0.57	80	0.338±0.08

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EVALUATION PARAMETERS OF TRANSDERMAL PATCHES

TABLE NO:5 Physical evaluation of drug loaded formulations

Formulation code	Weight (mg)	Appearance	Thickness (mm)	Folding endurance	Tensile strength (Kg/cm^2)	% elongation
E_{10}	680± 3	Transparent	84±0.4	73	0.364±0.03	26±0.07
E_{20}	**1034±6**	**Transparent**	**91±0.8**	**73**	**0.347±0.41**	**25±0.08**
E_{30}	1652 ±3	Transparent	92±0.3	67	0.324±0.05	18±0.05
E_{40}	1989 ±5	Transparent	102±0.3	38	0.287±0.41	12±0.02
E_{50}	996±4	Transparent	93±0.4	65	0.332±0.05	26±0.04
E_{60}	2065± 6	Transparent	103±0.1	28	0.265±0.03	13±0.09
H_{10}	690± 4	Transparent	86±0.3	69	0.362±0.08	24±0.09
H_{20}	**1124±5**	**Transparent**	**95±0.5**	**67**	**0.346±0.03**	**24±0.08**
H_{30}	1451 ±2	Transparent	99±0.4	56	0.313±0.02	17±0.06
H_{40}	1985 ±9	Transparent	112±0.4	32	0.277±0.03	12±0.09
H_{50}	1023±1	Transparent	96±0.5	55	0.318±0.02	25±0.07
H_{60}	2195± 8	Transparent	111±0.2	25	0.256±0.03	12±0.09

Table no: 6 Permeation studies of the best formulations through rat abdominal skin

Si No	Time	%CPR (Cumulative percentage drug release)	
		H_{20}	E_{20}
1	1/2	0.303	0.368
2	1	0.346	0.519
3	2	0.443	0.368
4	3	0.454	0.617
5	4	0.606	0.801
6	5	0.768	0.887
7	10	1.071	1.125
8	15	1.114	1.309
9	27	1.190	1.342

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TABLE NO.7 Permeation study of H_{20} with different permeation enhancers

Si No	Time	H20	%CPR(Cumulative percentage drug release)			
			H20 with 2ml eucalyptus oil	H20 with 2ml oleic acid	H20 with 2ml tween 80	H20 with 2ml DMSO
1	1/2	0.303	0.476	0.519	0.432	0.692
2	1	0.346	0.606	0.638	0.584	0.887
3	2	0.443	0.909	0.952	0.887	1.071
4	3	0.454	1.136	1.147	1.234	1.331
5	4	0.606	1.331	1.298	1.450	1.602
6	5	0.768	1.418	1.428	1.645	2.089
7	10	1.071	1.710	1.731	2.045	2.652
8	15	1.114	2.045	2.078	2.273	2.749
9	27	1.190	2.435	2.554	2.630	3.171

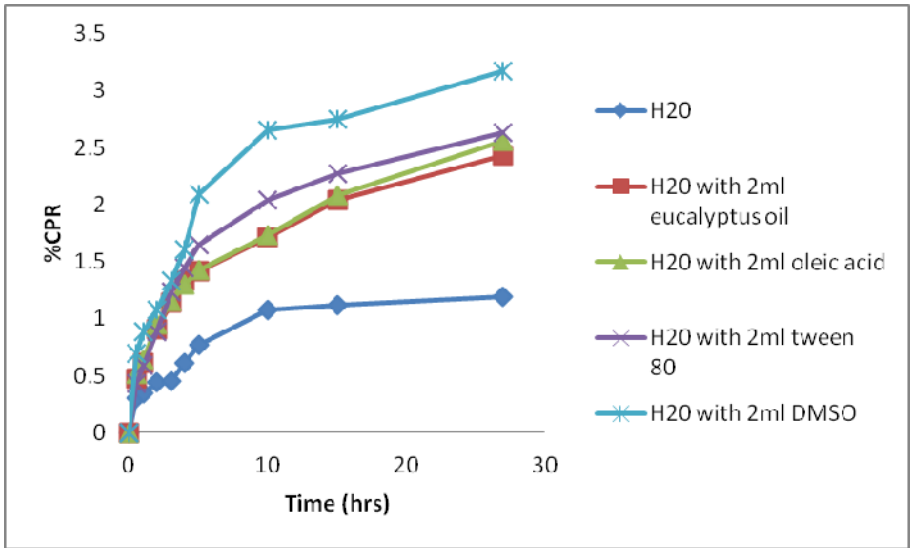

FIGURE NO.3 Permeation study of H_{20} with different permeation enhancers

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TABLE NO.8 Permeation study of E_{20} with different permeation enhancers

Si No	Time	%CPR(Cumulative percentage drug release)				
		E_{20}	E_{20} with 2ml eucalyptus oil	E_{20} with 2ml oleic acid	E_{20} with 2ml tween 80	E_{20} with 2ml DMSO
1	1/2	0.368	0.368	5.520	0.443	0.627
2	1	0.519	0.519	6.711	0.606	0.887
3	2	0.368	0.801	9.742	0.909	1.017
4	3	0.617	1.104	1.298	1.277	1.212
5	4	0.801	1.190	1.504	1.515	1.537
6	5	0.887	1.331	1.721	1.764	2.035
7	10	1.125	1.656	2.110	2.110	2.338
8	15	1.309	2.002	2.392	2.327	2.684
9	27	1.342	2.435	2.771	2.781	2.944

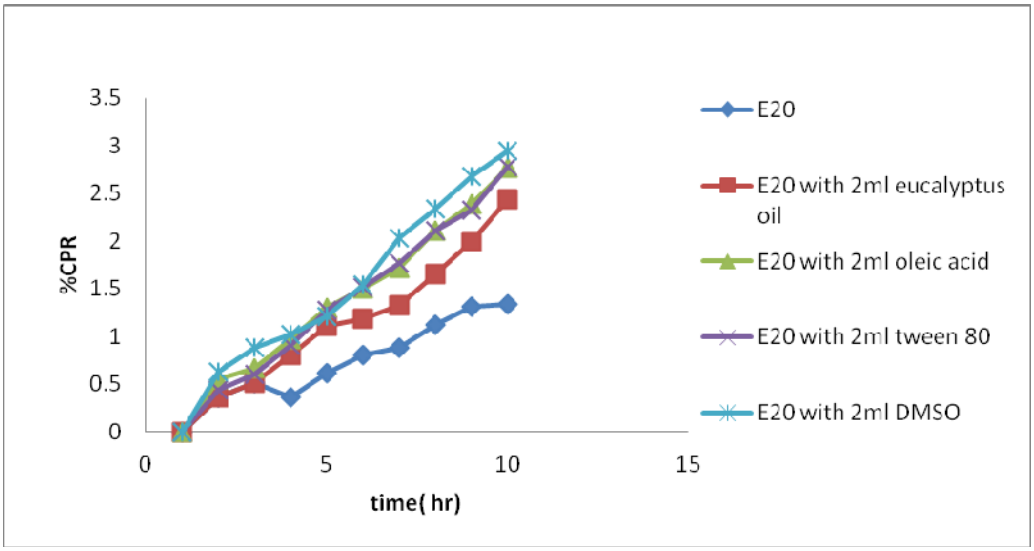

FIGURE NO.4 Permeation study of E_{20} with different permeation enhancers

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TABLE NO. 9 Permeation study of E_{20} and H_{20} formulations with different concentrations of DMSO through rat abdominal skin using distilled water as receptor medium

Si No	Time	%CPR(Cumulative percentage drug release)					
		H_{20} with 1ml DMSO	H_{20} with 3ml DMSO	H_{20} with 4ml DMSO	E_{20} with 1ml DMSO	E_{20} with 3ml DMSO	E_{20} with 4ml DMSO
1		0.627	0.573	0.368	0.562	0.790	0.562
2	1	0.811	0.811	0.552	0.736	0.974	0.844
3	2	0.985	1.093	0.898	0.985	1.309	0.865
4	3	1.212	1.428	1.190	1.309	1.537	1.071
5	4	1.428	1.872	1.504	1.537	1.970	1.331
6	5	1.786	2.089	1.775	1.818	2.175	1.656
7	10	2.154	2.359	2.110	2.154	2.944	2.143
8	15	2.359	2.857	2.532	2.413	3.236	2.608
9	27	2.836	3.258	2.857	2.836	3.734	3.128

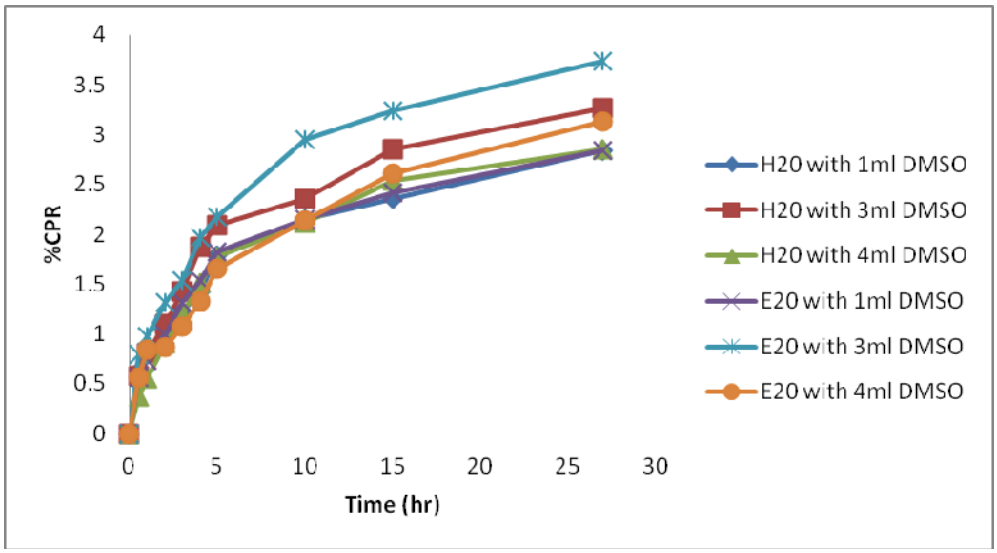

FIGURE NO.5 Permeation study of E_{20} and H_{20} formulation with different concentration of DMSO through rat abdominal skin using distilled water as receptor medium

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Table No:10 Water vapor transmission study for formulation H_{20} and E_{20}

Sl .No.	Time (hours)	Amount of water vapor transmission rate ($gm/cm^2/h$)	
		E_{20}	H_{20}
1	1	0.01512	0.01612
2	2	0.026548	0.03124
3	4	0.032154	0.03978
4	8	0.044125	0.04983
5	12	0.055421	0.05876
6	18	0.068745	0.07654
7	24	0.084512	0.08875
8	36	0.098457	0.15634
9	48	0.167981	0.19754
10	72	0.2987630	0.36487

FIGURE NO. 11 Flux and Permeability coefficient of H_{20} and E_{20}

Si No	H_{20} formulation		E_{20} formulation	
	Flux (in mg)	Permeability Coefficient(in mg)	Flux (in mg)	Permeability Coefficient (in mg)
1	5.3×10^{-2}	0.4×10^{-2}	3.8	0.29
2	6.6×10^{-2}	0.26	5.7	0.21
3	8.9×10^{-2}	0.172	5.8	0.11
4	10.4×10^{-2}	0. 12	7.2	0.09
5	13.4×10^{-2}	0.128	9	0.089
6	14.8×10^{-2}	0.113	11.2	0.086
7	20×10^{-2}	0.072	14.5	0.055
8	22×10^{-2}	0.056	17.7	0.045
9	25.4×10^{-2}	0.035	21.3	0.030

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TABLE NO. 12 Determination of release kinetics and mechanism of drug release of E_{20} and H_{20} formulation

Formulation	Zero order		First order		Higuchi		Korsemeyer-Peppas		Best fit Model
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	
E_{20}	0.070	0.967	-0.001	0.975	0.070	0.967	0.070	0.967	First order
H_{20}	0.061	0.987	-0.001	0.991	0.070	0.967	0.070	0.967	First order

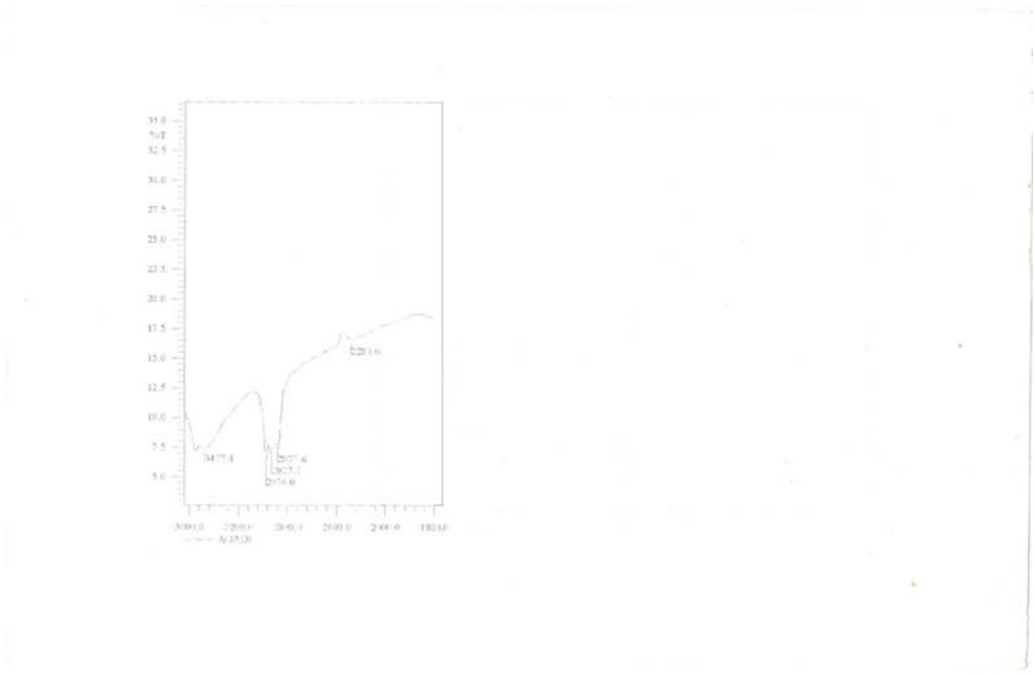

Figure No: 6 Infra-red spectra of pure drug

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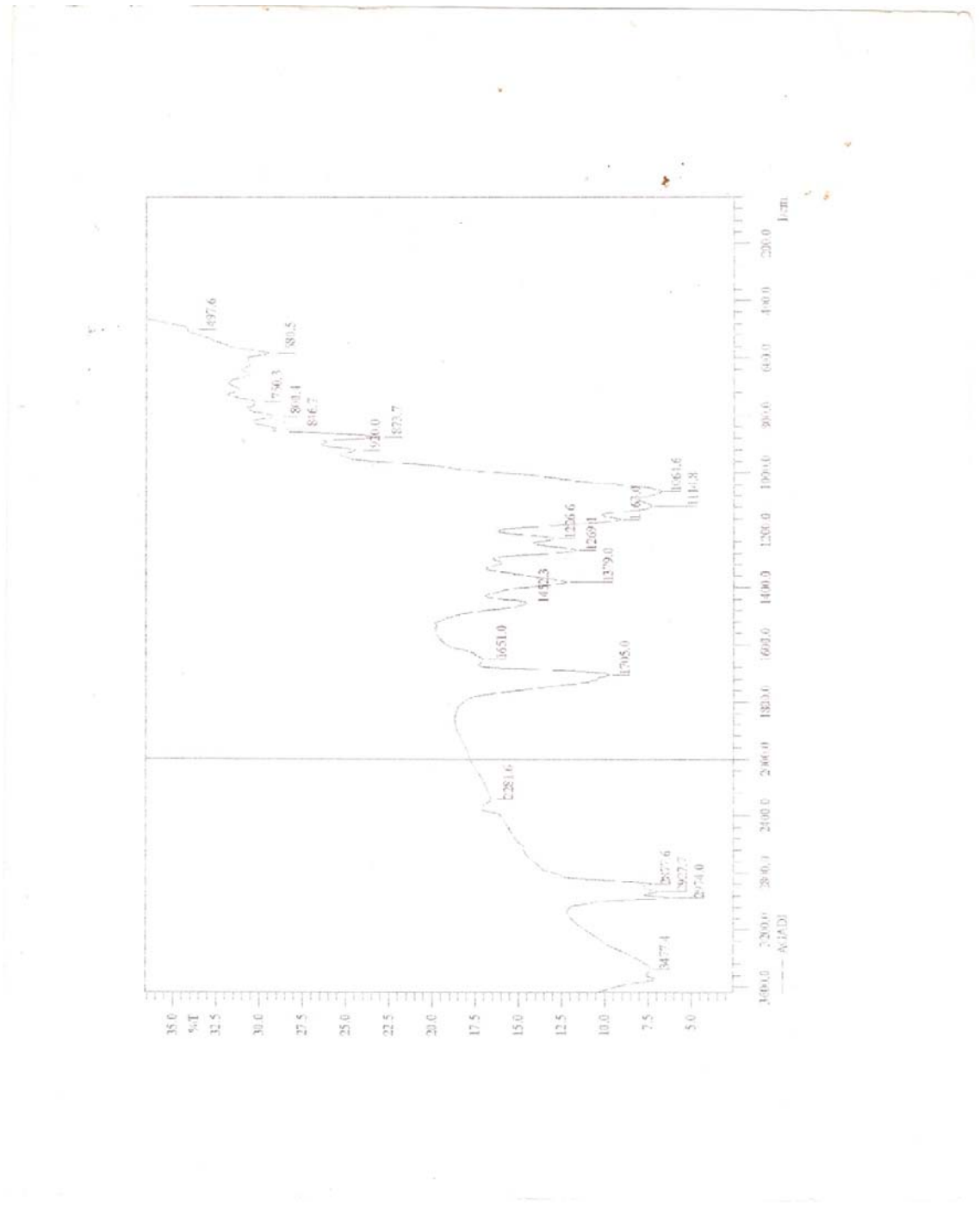

Figure No: 7 Infra- red spectra of formulation E20

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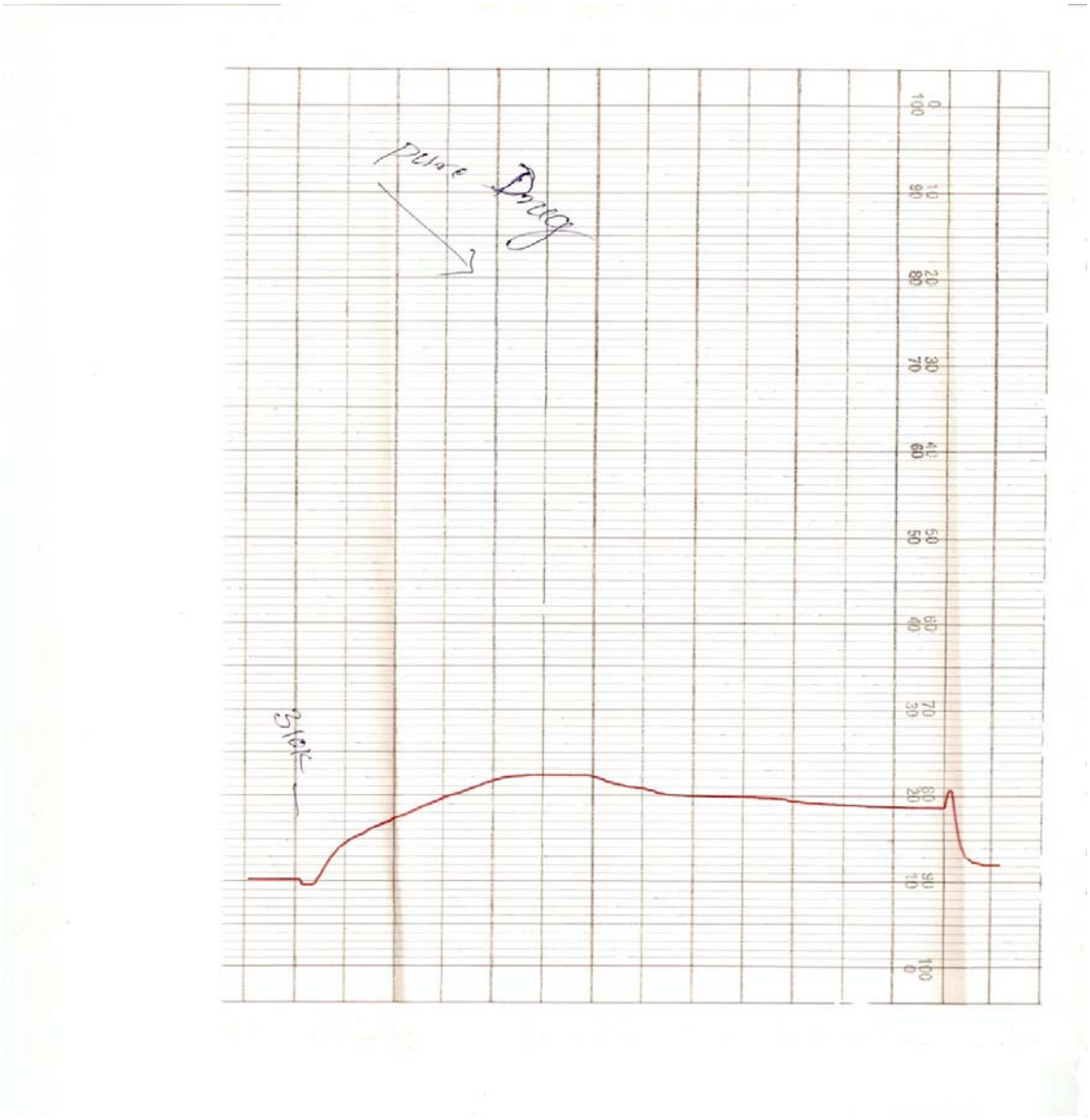

Figure No: 8 DSC Spectra for pure Drug

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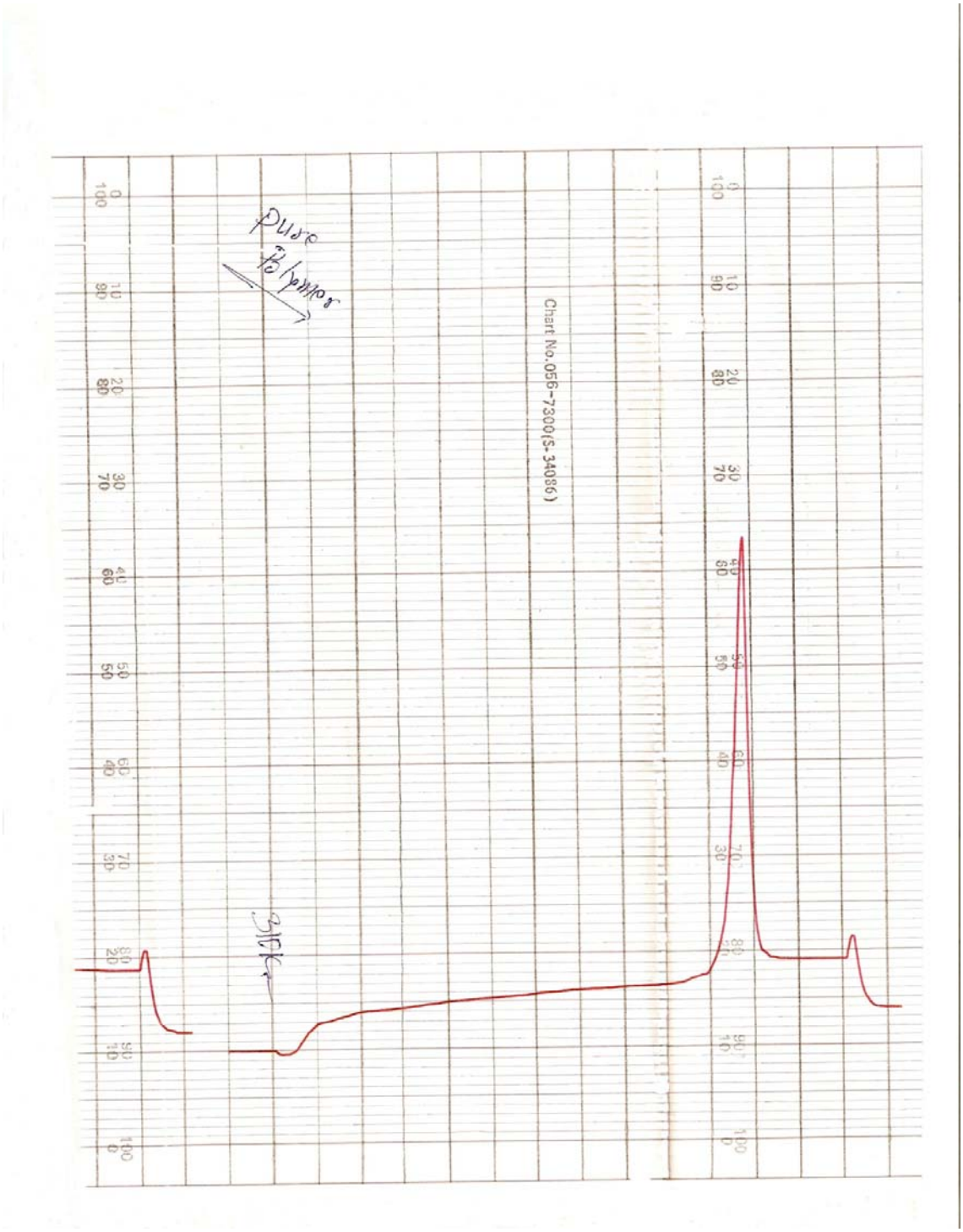

Figure No: 9 DSC Spectra for pure Polymer

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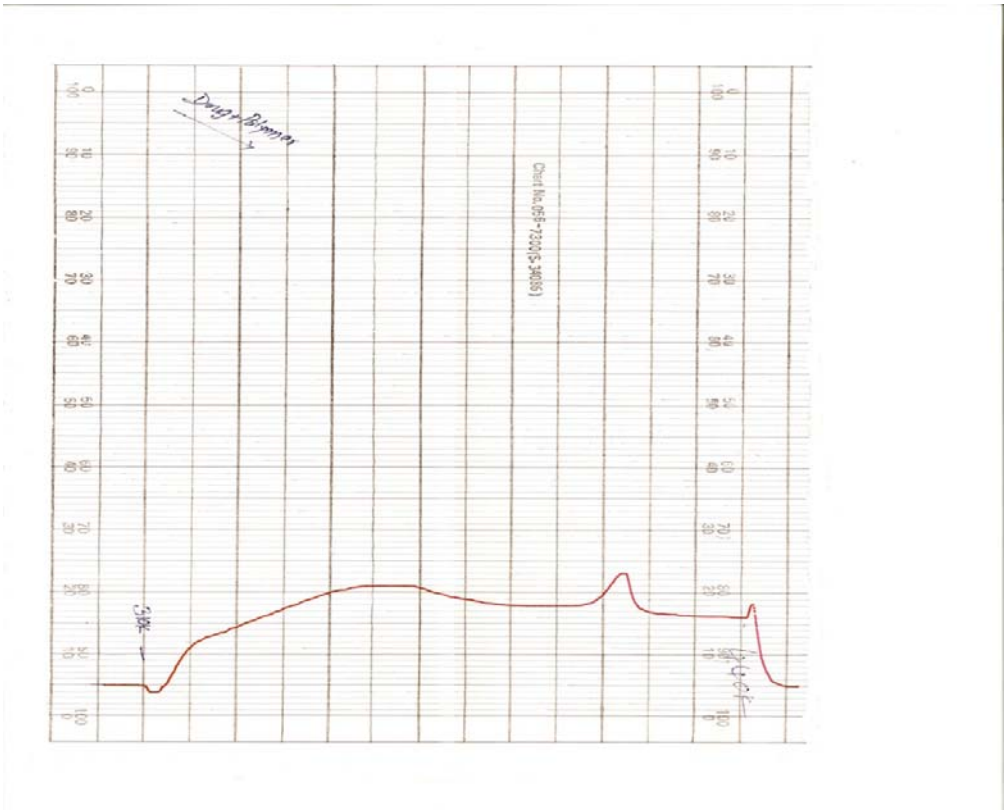

Figure No:10 DSC Spectra for Drug and Polymer

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CONCLUSION

Simvastatin is currently available as conventional tablets in strength of 10mg/20mg. It has to be administered two to three times a day. Simvastatin and its metabolites have a half life of around 2 hours and their oral bioavailability is less than 5% of the dose administered. In order to overcome the above problems associated with simvastatin, Transdermal drug delivery system of Simvastatin was developed.

Out of the polymers investigated, HPMC and Ethyl Cellulose in a concentration of 4% with DMSO as permeation enhancer in a concentration 30% of polymer weight gave the most satisfactory results.

In view of the results obtained we could conclude that a transdermal patch of the drug of area of 3.5cm^2 would achieve the minimum effective concentration required for drug action in one hour time. Thus it is possible to make a transdermal drug delivery system of Simvastatin which could overcome the problems associated with conventional dosage forms primarly overcoming the first pass metabolism and thus decreasing its dosage and the dose related side effects.

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