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Formulation and Evaluation of Transdermal Drug Delivery System of Simvastatin

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ABSTRACT

The present investigation was aimed to evaluate the possibility of using different ratio of polymeric grades of hydroxypropyl methylcellulose (K15) and carbapol(400) and different ratio used in platsizer (PEG 400) for the development of transdermal delivery of simvastatin, an antilipedamic drug. Transdermal films of simvastatin were prepared by solvent casting method. Polymers were used such as HPMC: Corbopol (3:1) and polyethylene glycol (PEG) (1%,2%,3%).It was found that 1% of PEG helped as ideal concentration. The prepared films were evaluated for physicochemical properties. Matrix films were evaluated for their physicochemical characterization followed by *in vitro* evaluation. the *in vitro* release study from different transdermal patches across the goat abdominal skin Polymer concentration of 3:1 (HPMC:Carbopol) w/w in each type of as polymer film was found to be best. As the polymer concentration increase to be used 4:6 w/w, 1:3 w/w ratio. The drug released was found to be decreased.PEG in concentration of 1% showd best release as compared to other concentrations. The release pattern was found to be in the order of HPMC: Corbopol. Hence among all the formulation, HPMC: Carbopol (3:1), polymer concentration with 1%PEG concentration was showing the best release and r^2 is 9952.

Key words: Transdermal, antilipedamic, Matrix films and Simvastatin.

INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Simvastatin is poor aqueous solubility of many drug candidates; it becomes uneasy to drug to reach the market although exhibiting potential pharmacodynamic property. It is very useful to find appropriate formulation approaches to improve aqueous solubility and thus bioavailability of poorly soluble drugs [1, 4].

Simvastatin is selective hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, an enzyme which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of cholesterol synthesis, Inhibition of this enzyme by Simvastatin results into decrease in cholesterol synthesis and decreased blood cholesterol level which would be an effective step in the treatment of patients with hypercholesterolemia and mixed dyslipidemia and in the treatment of homozygous familial hypercholesterolemia. The main objective of the work is to enhance the oral bioavailability of Simvastatin using TDDS techniques by keeping particle Size as minimum as possible. to develop controlled release TDDS of simvastatin using polymer like HPMC and Carbopol, which will controlled the release of drug, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug, In the present study TDDS formulation was preferred over conventional tablet or capsule formulations, as it has several advantages like it controlled the release pattern thus decreasing the dosing frequency [5-7].

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MATERIAL AND METHOD

Chemicals and reagent

Simvastatin was obtained from Matrix pharma nasik and hydroxypropylmethyl cellulose, carbopol, methanol, glycerol, Tween 80, span 80, PEG and calcium chloride were obtained from central drug house (CDH). dimethylsulfoxide and Oleic acid were obtained from Loba chemicals.

OPTIMIZATION STUDY

I[st] phase

Firstly optimization of polymers, plasticizer and solvent system is done to

Table:I. Optimization studies for the I[st] phase.

Optn code	Polymeric ratio in (mg) HPMC	Carbopol	Solvent ratio in (ml) Methanol	Water	Plasticizer % w/v	Temp. in °C	Observation
C1	1	1	---	50	Glycerol 3%	60 °C	Polymeric film formed this show that HPMC has film forming property and has hydrophilic nature.
C2	3	7	25	25	Glycerol 2%	60 °C	Formulated patch was very sticky. Formulation was observed to be failed in complete drying; glycerol concentration was a reason for increased wetting property.
C3	7	3	25	25	Glycerol 1%	60 °C	Formulated patch was very sticky. Formulation was observed to be failed in complete drying; glycerol concentration was a reason for increased wetting property.
C4	4	6	25	25	Dibutyl phthalate 2%	60 °C	This composition was not dried and unable to form film
C5	5	7	25	25	Dibutyl phthalate 1%	60 °C	This composition was not dried and unable to form film
C6	1	2	25	25	PEG-400 2%	60 °C	Formulated patch was little sticky. Formulation was observed to be failed in complete drying; PEG-400 concentration was a reason for increased wetting property.
C7	1	3	25	25	PEG-400 3%	60 °C	Formulated patch was little sticky. Formulation was observed to be failed in complete drying; PEG-400 concentration was a reason for increased wetting property.
C8	3	1	25	25	PEG-400 1%	60 °C	Formulated patch was observed to have best properties as compared with other formulation. This patch was evaluated for thickness, folding endurance, moisture uptake, physical appearance and found to be suitable for further studies.

II phase

The result outcomes after first phase study have been used to optimize enhancer with the polymeric composition mentioned in table no. II. Enhancer's ratio was optimized using different ratio of DMSO, Glycerol, Tween-80, and Span-80 in different concentration.

Table:-II Optimization Studies for the phase II.

Form. Code	Polymeric Ratio HPMC :Carbopol	Solvent ratio MeOH :Water	Plasticezer ratio	Enhancer ratio Glycrol	Tween -20	Span -80	DMSO
TDPI	3:1	1:1	1%	0.1%			
TDPII	3:1	1:1	1%	0.2%			
TDPIII	3:1	1:1	1%	0.3%			
TDPIV	3:1	1:1	1%	0.5%			
TDPV	3:1	1:1	1%		0.1%		
TDPVI	3:1	1:1	1%		0.2%		
TDPVII	3:1	1:1	1%		0.3%		
TDPVIII	3:1	1:1	1%			0.1%	
TDPIX	3:1	1:1	1%			0.2%	
TDPX	3:1	1:1	1%			0.3%	
TDPXI	3:1	1:1	1%			0.5%	
TDPXII	3:1	1:1	1%				0.1%
TDPXIII	3:1	1:1	1%				0.2%
TDPXIV	3:1	1:1	1%				0.3%
TDPXV	3:1	1:1	1%				0.5%

Preparation of TDDS

Method used for the preparation of film is by solvent casting technique. Composition of transdermal film containing Simvastatin along with polymers such as HPMC and Carbopol. Polymer was dissolved in the mixture of alcohol:water (1:1) with help of magnetic stirrer. Drug was separately dissolved in the mixture of alcohol:water, PEG was added to the polymer solution and stirred for 30 min using magnetic stirrer. The prepared solution was casted in Petridis and dried at room temperature by covering Petridis with inverted funnel for 48 hrs.

EVALUATION PARAMETER OF TRANSDERMAL PATCHE

Basis physical appearance, weight & thickness

The weight, thickness and physical consistency of the films were observed immediately after formulation. On achieving the desired characteristics of the film, the same was also subjected for storage for one month at normal room temperature conditions. This was done to determine the effect of storage conditions on the physical nature of the prepared films [8-10].

Thickness of the film

The thickness of the drug-loaded polymeric films were measured at three different places using a Vernier caliper and mean values were calculated show in table no III.[11]

Percent elongation:

It would be defined as the ratio of the length of film/patch in normal position to stress condition. Here, stress conditions would be stated as stretching the film/patch to the point till it breaks down and measuring the largest length of the intact patch before breaking. This was performed at CIPET (Central Institute of Plastic Engineering & Technology), a central government undertaking institute.

Moisture content:

The prepared films weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content was calculted by following formula:

% Moisture content = [Intitial weight – Final weight / Final weight] x 100

Moisture uptake:

Weighed films were kept in desiccators at room temperature for 24 hrs. These were then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccators until a constant weight is achieved % moisture uptake is calculated as given below :

% Moisture uptake = [Final weight –Initial weight/ Initial weight] x 100

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the subjected to frequent extreme conditions of folding. Folding endurance was determined by repeatedly folding the film at the same place until it break. The number of time the films could be folded at the same place without breaking is folding endurance value.

Tensile strength:

To determine tensile strength, polymeric films were sandwiched separately by corked linear iron plates. One end of the films was sandwiched separately by corked linear iron plates. One end of the films kept fixed with the help of an iron screen and other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. A pointer on the thread was used to measure the elongation of the film. The weight just sufficient to break the film was noted. These tests were carried out at CIPET (Central Institute of Plastic Engineering & Technology), a central government undertaking institute. The tensile strength was calculated using the following equation:

Tensile strength = F/a.b (1+L/I)

Where F is the force required to break; a is width of film; b is thickness of film; L is length of film; I is elongation of film at break point.

Water vapour transmission studies (WVT):

For the determination of WVT weighed one gram of calcium chloride and placed it in previously dried empty vial having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then vial were again weighed at the end in humidity chamber maintained at 68% RH described in table no.III. The vial were again weighed at end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. WVT =W/ST. [12-16]

Table: - III Characterization of transdermal patches

S.No.	Parameter	F1	F2	F3
1.	Thickness(mm)	0.2±0.3	0.2±0.5	0.23±0.18
2.	Folding endurance test	++	++	++
3.	Percent moisture uptake	4.453	3.637	3.761
4.	Percent moisture content	1.08	0.83	0.164
5.	Water vapor transmission study (gm/cm²/hours)	5.87×10^{-3}	4.3×10^{-3}	12.4×10^{-3}
6.	Tensile strength (N/mm²)	4.56±0.243	3.56±1.12	5.14±0.134

Calibration curve

Weighed quantity of Simvastatin 10 mg each was dissolved in phosphate buffer, pH 7.4 and volume made up to 100 ml with phosphate buffer, pH 7.4 to give a concentration of 100 µg/ml from this stock solution, different volume 1,2,3,4 and 5ml were transferred into 100 ml volumetric flask and the volume were made up to 5 ml with the phosphate buffer,pH 7.4 to gate the different concentration of 5,10,15,20 and 25 µg/ml. the absorbance's were measured at 238 nm for Simvastatin against a blank using UV spectrophotometer and regression coefficient (r^2) 0.9946 is find out shown in figure no. I.

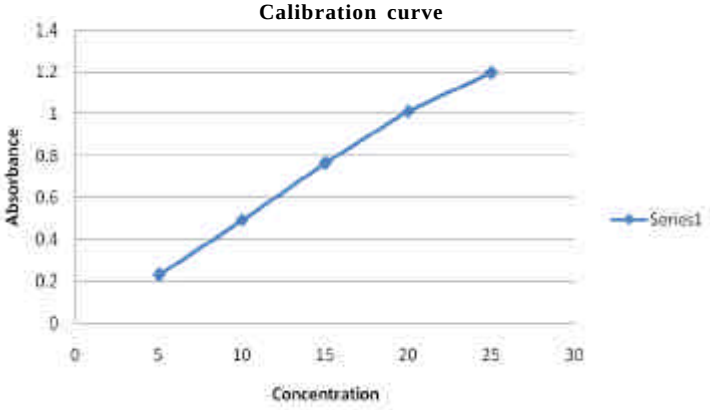

Fig:-I Statistical parameters related to calibration curve of Simvastatin

Drug content uniformity

Transdermal system of specified area (2 cm^2) was cutted into small pieces and taken into a 100 ml volumetric flask and 100 ml of phosphate buffer pH 7.4 was added, and kept for 24 hours with occasional shaking. Then, the suitable dilution was made with phosphate buffer of pH 7.4 similarly; a blank was carried out using a drug –free patch. The solutions were filtered and the absorbance was measured at 238 nm for Simvastatin.[17]

***IN VITRO* SKIN PERMEATION STUDIES**

Preparation of the skin barrier:

Fresh full-thickness goat skin was used for the study. The skin was immersed in water at 60°C for a period of 5 minutes. The epidermis was peeled from the dermis. The *in vitro* skin permeation studies were carried out using keshary-chain diffusion cell. A 2 cm^2 patch is placed in intimate contact with stratum corneum side of the skin; the top side was covered with the aluminum foil as a backing membrane. Magnetic bead was placed in the receptor compartment filled with 200 ml of phosphate buffer, the whole assembly was kept on the magnetic stirrer, at a speed of 100 rpm and the temperature conditions controlled at 37±5^0 C. The cell contents were stirred with a magnetic stirrer. Sample of 5ml was withdrawn at interval of 1, 2,3,4,5 and 6 hour simultaneously replaced with equal volume of phosphate buffer. The samples were withdrawn and filtered through whatman filter paper and diluted up to 10 ml with phosphate buffer of pH 7.4.[18-21]

RESULT AND DISCUSSION

Firstly optimization of polymers, plasticizer and solvent system is done to obtain a polymeric film which can fulfill the criteria of suitability required for the transdermal formulation is show in table No I. The result outcomes after first phase study have been used to optimize enhancer with the polymeric composition. Enhancer's ratio was optimized using different ratio of DMSO, Glycerol, Tween-80, and Span-80 in different concentration is show in table no. II. The result come out in first and second phase study to help in selection of polymers, plasticizer and solvent system is used to prepare transdermal patch.

The physicochemical characteristics of prepared patches are showed Table III. The Tensile strength (N/mm^2) is ranged from 3.56±1.12 to 5.14±0.134. Thickness (mm) ranged from 0.2±0.3 to 0.23±0.18mm. Good uniformity in drug content was observed and it ranged from 90.5±0.7% to 91.3±0.5% in all the formulation. The percentage moisture uptake in the range of 3.637 to 4.453 and moisture content to be found is the range of 0.83 to 1.08. Water vapor transmission (gm/cm^2/hours) observed is $4.3\times10\times^{-3}$ to 12.4×10^{-3}. The folding endurance was found to be satisfactory. The results of the *in vitro* release study from different transdermal patches across the goat abdominal skin Polymer concentration of 3:1 (HPMC:Carbopol) w/w in each type of as polymer film was found to be best. As the polymer concentration increase to 4:6 w/w, 1:3 w/w. The drug released was found to be decreased. PEG in concentration of 1% showed best release as compared to other concentrations. The release pattern was found to be in the order of HPMC: Carbopol.

Hence among all the formulation, HPMC: Carbopol (3:1), polymer concentration with 1%PEG concentration was showing the best % drug release is 89%.

The in vitro drug releases were subjected to zero, first, Higuchi's and korshmeyer's model. The kinetic treatment revealed that the drug release from the patch F1 followed Higuchi's model as the correlation coefficient of linear relationship between the cumulative percent drug release and the square root of time was found to be 0.9794. The data fitment of the drug release profile done using korshmeyer's drug model showed values of diffusion coefficient as 0.0.6546 (fig no. II).

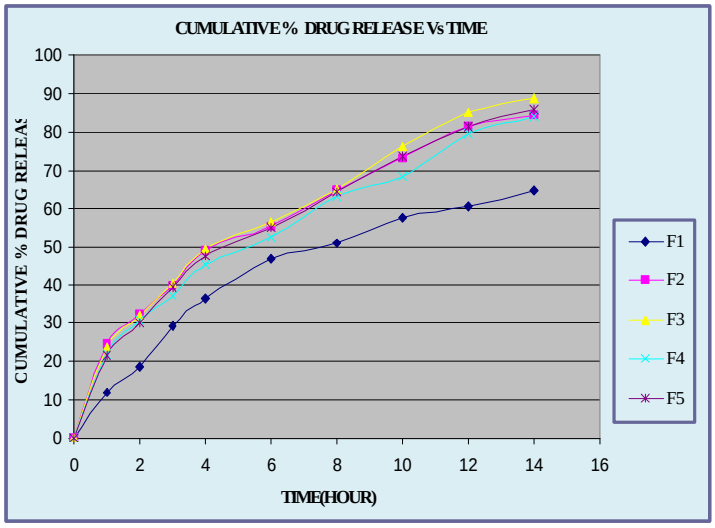

Fig: - II Zero order plot (cumulative % drug release Vs time)

The mechanism of drug release in this case was known to anomalous transport mechanism. i.e drug was release by initial swelling and followed by anomalous transport. The 'n' values can be used to characterize different release mechanisms. If the value of release exponent is 0.5 than the drug is assumed to follow fickian diffusion transport mechanism, value more than 0.5 and less than 1.0 it follows anomalous transport.

Higuchi's model as the correlation coefficient of linear relationship between the cumulative percent drug release and the square root of time was found to be 0.9958. The data fitment of the drug release profile done using korshmeyer's drug model showed values of diffusion coefficient as 0.4906 (fig no.III). The mechanism of drug release in this case was known to anomalous transport mechanism.

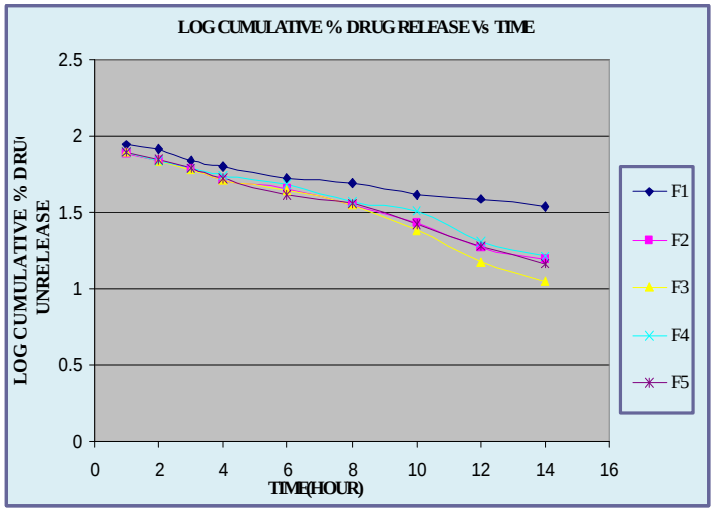

Fig: III First order plot (log cumulative % drug unreleased Vs time)

Higuchi's model as the correlation coefficient of linear relationship between the cumulative percent drug release and the square root of time was found to be 0.9952. The data fitment of the drug release profile done using korshmeyer's drug model showed values of diffusion coefficient as 0.5063 (fig no. IV). the mechanism of drug release in this case was known to anomalous transport mechanism.

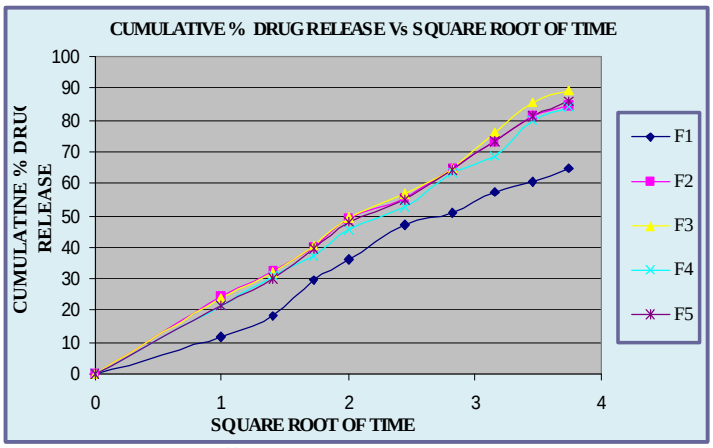

Fig: - IV Higuchi's diffusion equation (cumulative % drug release Vs square root of time)

The kinetic treatment revealed that the drug release from the patch F4 & F5 followed Higuchi's model as the correlation coefficient of linear relationship between the cumulative percent drug release and the square root of time was found to be 0.9956 & 0.9973. The data fitment of the drug release profile done using korshmeyer's drug model showed values of diffusion coefficient as 0.5252 & 0.5293 (fig no. V). the mechanism of drug release in this case was known to anomalous transport mechanism. i.e drug was release by initial swelling and followed by anomalous transport. The 'n' values can be used to characterize different release mechanisms.

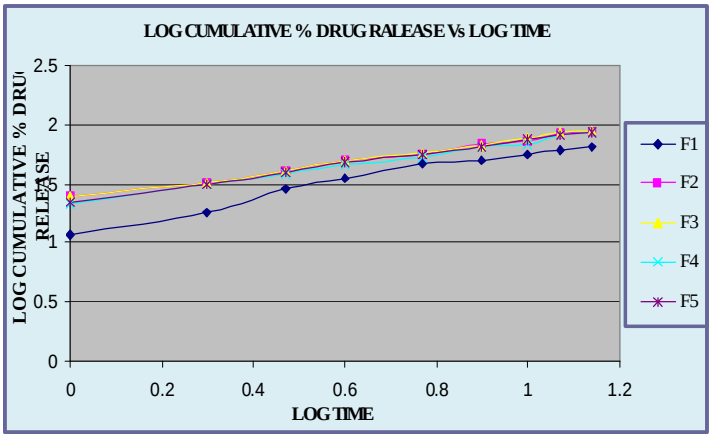

Fig: - V Korsmeyer's equation (Log % Cumulative drug release Vs log time)

CONCLUSION:

All eight formulations were evaluated for thickness, folding endurance, moisture uptake, physical appearance and results found for all satisfactory. By the study of all parameters it was concluded that C8 is better formulation among all the prepared formulation of transdermal patch.

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