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Research Article

Formulation and in Vitro Evaluation of Controlled Release Transdermal Drug Delivery System of Simvastatin A Model Hypocholesterolemia Drug

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ABSTRACT

The intention of this research work was to develop a matrix-type transdermal drug delivery system (TDDS) containing simvastatin an antilipidemic drug with different ratios of hydrophilic HPMC K100M and hydrophobic Eudragit RL100 & Eudragit RS100 polymers with surfactant Tween 80 and plasticizer glycerin by the solvent evaporation technique. The prepared films were evaluated for physicochemical properties. Matrix films were evaluated for their physicochemical characterization followed by *in-vitro* evaluation. The drug released rate was found to be increased when the concentration of the polymer decreases. The release rates by using three polymers are shown that the HPMC K100M showed faster release than Eudragit RL100 and Eudragit RS100 because due to hydrophilicity. Compared between Eudragit RL100 and Eudragit RS100, the release rate was slightly faster found in Eudragit RL100. The evaluation studies were carried out known as percentage moisture content, percentage moisture uptake, folding endurance, thickness, weight variation, physical appearance, UV-Visible spectrophotometer, FTIR study and quantitative estimation of the drug. It was shown by all the observations that the antilipidemic drug simvastatin could serve as an appropriate candidate for TDDS that can improve the bioavailability.

Keywords: Simvastatin, Transdermal, HPMC K100M, Eudragit RL100, Eudragit RS100.

INTRODUCTION

TDDS has been in survival for a long time. In the past, the most usually applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side effects with some of these formulations is investigative of absorption through the skin. For systemic treatment of the skin, a number of drugs have been applied. In reality, the word TDDS comprises all formulations having topically administered drug intended for the transport of active constituents into the systemic circulation. Transdermal therapeutic systems have been intended to provide controlled and continuous delivery of drugs via through the skin to the systemic circulation. The drug simvastatin is poor aqueous solubility; it becomes uncomfortable to grow in the market even though expressing the potential pharmacodynamic property. It is really useful to find suitable formulation approaches to improve aqueous solubility and thus bioavailability of poorly soluble drugs[1,2]. Simvastatin is usually used to treat hypercholesterolemia and a lipid lowering-agent and also a potent HMG-CoA reductase inhibitor. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, simvastatin inhibits this enzyme and decreases the cholesterol synthesis and decreases the blood cholesterol level, which would be an active step to treat hypercholesterolemia and mixed dyslipidemia patients and in the treatment of homozygous familial hypercholesterolemia[3-5]. The Simvastatin tablets are commercially available having different strengths 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg as immediate release dosage form. Due to extensive first-pass metabolism in the liver, the simvastatin bioavailability is only 5% after oral administration. The Ideal method of drug delivery is considered TDDS, which can bypass the first-pass metabolism and continue the stable drug level in plasma for an extended period and deliver drug at a predetermined rate[6]. In this study the suitable candidate was chosen is simvastatin because it possesses adjacent ideal characteristics that a drug must have formulated a TDDS due to the high lipid solubility, low molecular mass, effective in low plasma concentration as well as a high degree of first-pass metabolism. The purpose of this study was to improve and evaluate transdermal patches of simvastatin in order to prevent its first-pass metabolism and attain controlled release[7].

MATERIAL AND METHOD

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Table 1: Composition of all formulations F1 to F9.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	Category
Simvastatin	175 mg	175 mg	175 mg	175 mg	175 mg	175 mg	175 mg	175 mg	175 mg	Hypo lipidemic
HPMC K100M	1 g	750 mg	500 mg							Film former
Eudragit RL100				1 g	750 mg	500 mg				Film former, Plasticiser
Eudragit RS100							1 g	750 mg	500 mg	Film former, Plasticiser
Methanol	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	Solvent
Water	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	Vehicle
Tween 80	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml	0.4 ml	Surfactant
Glycerin	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	Plasticizer
Dissolution time	12 hr	12 hr	12 hr	12 hr	12 hr	12 hr	12 hr	12 hr	12 hr	

Materials

Simvastatin was collected as a gift sample from Unichem Pvt. Ltd, Mumba, India. Eudragit RS100, Eudragit RL100 was procured from Otto Chemicals Pvt. Ltd, Mumbai, India. HPMC K100M was purchased from Oxford Laboratories, Mumbai, India. In the study, used all other reagents and chemicals were contained analytical grade[7,15].

Methods

Drug-polymer compatibility study

The physicochemical interactions between simvastatin and the polymers used in the formulation of transdermal patches HPMC K100M, Eudragit RL100, and Eudragit RS100 were studied using Fourier transform infrared spectroscopy (FTIR). The infrared spectra were recorded in the FTIR (Shimadzu) instrument in the wavelength region between 4400 cm^{-1} and 500 cm^{-1} by KBr pellet method. The spectra obtained from the drug and the physical mixture of the drug and polymer were compared[7,18].

Preparation of pH 7.4 phosphate buffer

The disodium hydrogen phosphate 2.38 g and potassium dihydrogen phosphate 0.19 g were accurately weighed and into it, 250 ml of distilled water was added. Then sodium chloride 8.0 g was mixed in the above solution and with distilled water, the final volume was made up to 1000 ml. The pH adjusted to 7.4 if required[16,17].

Preparation of standard plot in pH 7.4 phosphate buffer

In a 100 ml volumetric flask the pure drug simvastatin 100 mg was taken and added 30 ml of methanol and then remaining volume was adjusted by adding a pH 7.4 phosphate buffer. The resultant concentration was 1 mg/ml. From the above solution, 10 ml was withdrawn into another 100 ml volumetric flask and volume is made up to 100 ml adding pH 7.4 phosphate buffer and the resultant stock solution was 100 µg/ml. From the stock solution 0.5, 1, 1.5, 2, 2.5 and 3 ml volumes were transferred into the 10 ml volumetric flask and volume are made up to 10 ml to produce concentration 5, 10, 15, 20, 25 and 30 µg/ml. At, 239 nm the six sample absorbance is measured against a blank using UV-Visible spectrophotometer[16,17].

Preparation of transdermal patches

The transdermal patches were prepared by a solvent evaporation method. Different polymers (HPMC K100M, Eudragit RL100, and Eudragit RS100) alone were accurately weighed and dissolved in 30 ml of solvent (9:1) Methanol: water. A known amount of glycerol was used as a plasticizer and Tween 80 used as a permeability enhancer and mixed thoroughly with the help of a magnetic stirrer. 175 mg of the drug was dissolved in the solution and mixed for 10 min. The resulted uniform solution was decanted into a petri dish having 6 cm diameter and for uniform evaporation, the funnel was kept in an inverted position on a petri dish and held for the evaporation in an oven. After, 24 hrs all the prepared dried films were brought out and packed in aluminum foils than stored in a desiccator[7,8,15,17].

Evaluation of transdermal patches.

Thickness

By applying a digital micrometer screw gauge the patch thickness was evaluated at three different places and the mean value was calculated[8,9,12].

Folding endurance

By repeatedly folding the strip at the same place of each film (2x2 cm) till it broke, the folding endurance of patches ware determined. The folding endurance value was defined as the number of times the film can be folded at the similar place without breaking[8,10,12].

Weight variation

The weights of 10 randomly selected patches are required for each formulation and the weight variation was estimated. The weights were taken in electronic digital balance[8,10,12].

Percent of moisture uptake

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hrs. The films were weighed individually and repeated until they show a constant weight. The moisture percentage of the patches were determined according to the difference between final and initial weight with respect to final weight[7,8,11,12].

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

Percentage moisture loss

Table 2: Characterization of transdermal patches.

S. no	Formulation Code	Percentage Moisture Uptake (mg)	Folding Endurance	Percentage Drug Content (%)	Thickness (mm)	Weight Uniformity (mg)	Percentage Moisture Content (mg)
1	F1	5.81	160.33	92.33	0.195	212	5.77
2	F2	4.75	136	91.6	0.164	201.3	4.64
3	F3	4.41	109.66	93.33	0.154	189	4.36
4	F4	3.26	196.66	94.33	0.161	194.3	3.24
5	F5	3.13	165.33	94.16	0.152	166.6	3.13
6	F6	3.11	129.66	93.23	0.146	100.3	3.09
7	F7	3.07	220.66	94.5	0.166	187.6	3.06
8	F8	3.09	186.33	93.66	0.150	161.3	3.06
9	F9	3.06	153.66	92.16	0.147	141.6	3.02

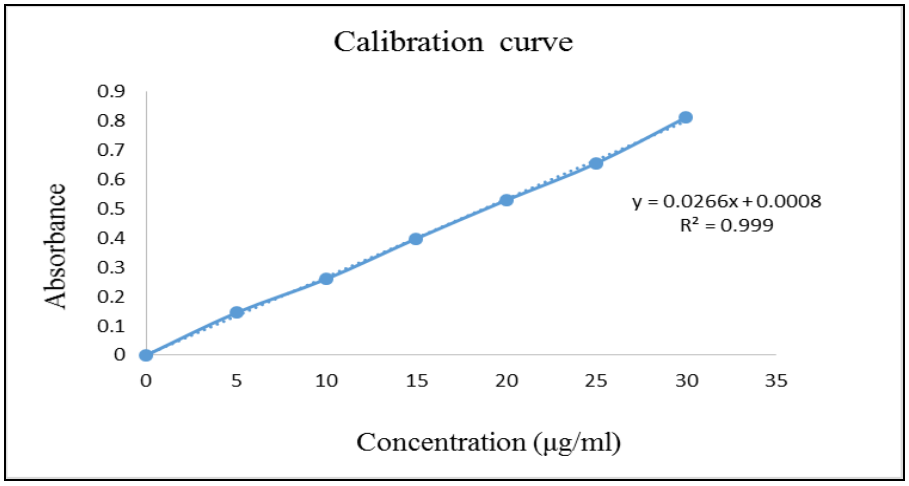

Figure 1: Standard curve of simvastatin

The desiccators which contain anhydrous calcium chloride, the films were weighed accurately and held back. After 3 days, the films were taken out and weighed. The moisture loss was estimated by using below-given formula[7, 8,11,12].

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

Drug content uniformity of films

The patches (2x2 cm) were cut and added to a beaker containing 100 ml of phosphate buffer saline of pH 7.4. The medium was stirred with the help of a magnetic bead. By using Whatman No. 1 filter paper the contents were filtered, and the filtrated drug content was examined against the reference solution containing placebo films (containing no drug) spectrophotometrically at 239 nm. The experiment was repeated to validate the result[7,8,13].

In-vitro drug release studies

From the fabricated patch, a (2x2 cm) film was removed and placed in the semi-permeable membrane and attached to the modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with 100 ml phosphate buffer solution of pH 7.4 at 37±0.5 ^{0}C. The elution medium was stirred magnetically. At a predetermined time intervals (1 hr) the aliquots (5 ml) samples were withdrawn and replaced with the similar volume of pH 7.4 phosphate buffer. The samples were analyzed for drug content using UV-Visible spectrophotometer at 239 nm[7,9,14].

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero-order (total percentage of drug release versus time), first-order (log total percentage of drug remaining vs. time), Higuchi (total percentage of drug release versus the square root of time), Hixon-Crowell (cube root of drug percentage remaining in matrix versus time) and Korsmeyer-Peppas (log total percentage of drug release versus log time) respectively[9,17,18].

RESULT AND DISCUSSION

FTIR spectra of simvastatin alone and its combination with excipients are shown in Figure 2 & 3. An FTIR spectrum of pure simvastatin shows prominent peaks at 1658.70 cm^{-1}, 1592.90 cm^{-1}, 1520.07 cm^{-1}, 1433.76 cm^{-1}, 1224.03 cm^{-1}, 1155.65 cm^{-1}, 844.59 cm^{-1}, and 696.07 cm^{-1}. These peaks can be regarded as characteristic peaks of simvastatin were not affected and prominently observed in the FTIR spectra of simvastatin along with excipients as shown in Figure 3, which indicated that there was no interaction between drug and excipients. Transdermal patches of simvastatin were prepared by using polymers, like HPMC K100M, and Eudragit RL100 and Eudragit RS100. The patches were transparent, smooth and elastic. The physicochemical characteristics of prepared patches are shown in Table 2. Thickness was found from 0.146

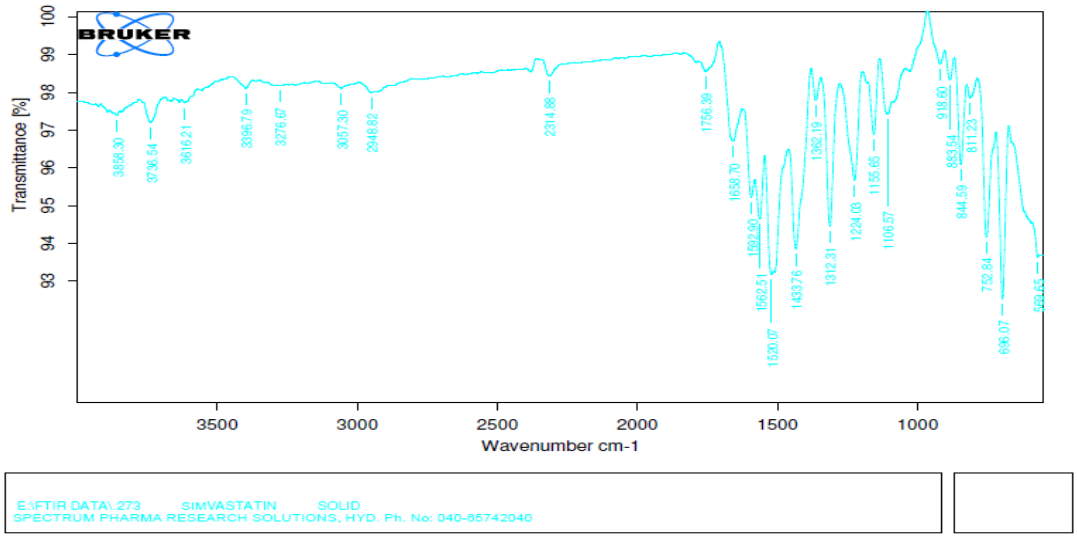

Figure 2: FTIR spectrum of simvastatin.

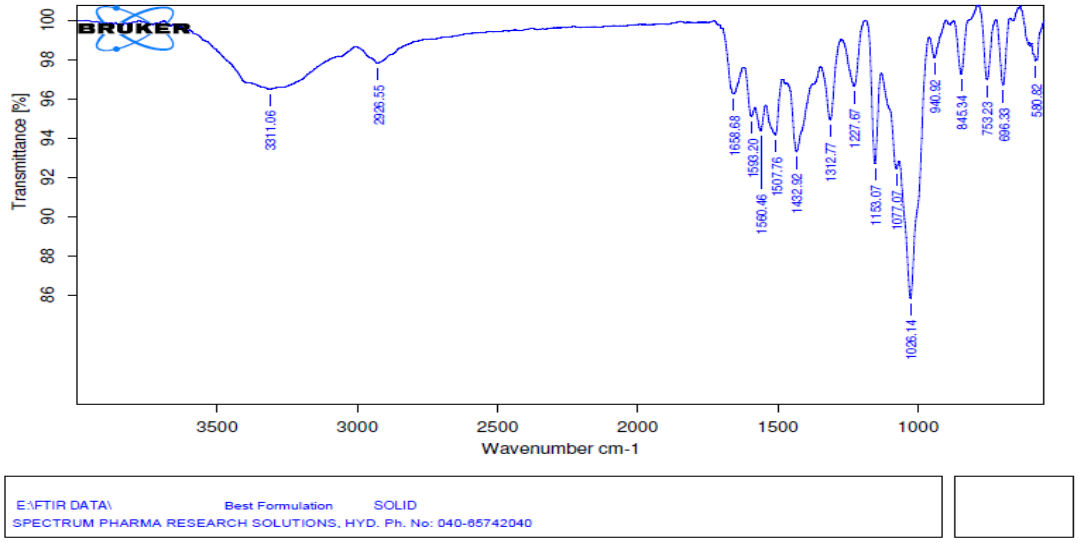

Figure 3: FTIR spectrum of best formulation.

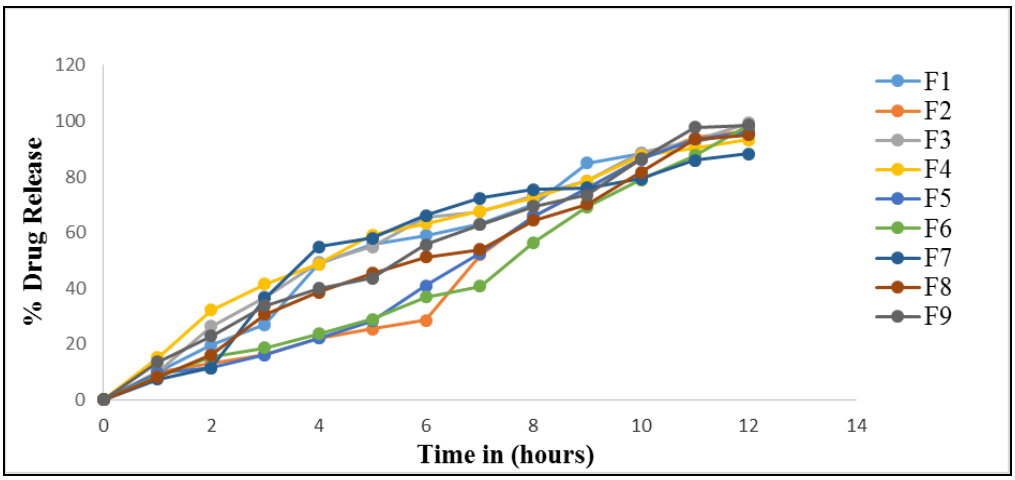

Figure 4: *In-vitro* drug release comparative profile of simvastatin patches.

mm to 0.195 mm in range. The F1 formulation was more thickness due to its high swellability when compared to other polymers and when the concentration increases the thickness also increases. Uniformity of drug content was

Table 3: *In-vitro* drug release kinetic studies of different formulations.

Formulation	Zero-order	First-order	Higuchi	Hixon Crowell	Release Exponent (n)
	Regression coefficient (R^2)				
F1	0.965	0.918	0.982	0.971	1.049
F2	0.95	0.838	0.884	0.9	0.738
F3	0.969	0.771	0.995	0.931	1.058
F4	0.964	0.953	0.994	0.985	0.82
F5	0.976	0.858	0.922	0.924	0.868
F6	0.967	0.698	0.899	0.841	0.847
F7	0.87	0.977	0.941	0.957	1.42
F8	0.987	0.847	0.975	0.925	1.004
F9	0.992	0.771	0.972	0.892	0.762

observed and varies from 91.6% to 94.5% range in all the formulations. The percentage of moisture uptake in the range of 3.06% to 5.81% and moisture uptake of the hydrophilic polymer is more when compared to hydrophobic polymers and by increasing the concentration of the polymer, moisture uptake also increased. Moisture content to be found in the range of 3.02% to 5.77% and formulation F1 containing HPMC K100M (1 g) in which moisture content is more when compared to other formulations due to its more hydrophilic nature. The percentage moisture content of F9 is less than other formulations due to its hydrophobic nature. The folding endurance was found to be satisfactory.

The percentage of drug diffusion rate for the formulations F1 to F9 was shown in Figure 4. The drug release data obtained were fitted to zero-order, first-order, Higuchi plot, Hixson-Crowell and Korsmeyer-Peppas equation plots to understand the mechanism of drug diffusion from the simvastatin transdermal patches and shown in Table 3. The in-vitro permeation studies of patches using cellophane membrane barrier were carried out utilizing a modified diffusion cell. From the graph, it is evident that the drug release rate was decreased with the increase in the concentration of the polymer. HPMC K100M (in F1, F2 & F3) have likewise demonstrated that decreased drug release rate was found as compared to Eudragit RL100 (in F4, F5 & F6) and Eudragit RS100 (in F7, F8 & F9) patches. From the above data, it is evident that the promising formulation F7 gives better-extended drug release, i.e. 88.26% at 12 hr.

The drug releases through the transdermal patches F2, F5, F6, F8, and F9 follows zero-order kinetics and, F7 follows first-order kinetics with the diffusion-controlled mechanism. F1, F3, and F4 follow Higuchi diffusion kinetics. The 'n' values obtained from Korsmeyer-Peppas plots indicated that the F1, F3, F7, and F8 formulations value ware above 1 it indicates super case II transport i.e., the formulation is following more than one type of release profiles possibly owing to chain disentanglement and swelling of hydrophilic polymers. The 'n' values obtained from Korsmeyer-Peppas plots showing that F2, F4, F5, F6, and F9 formulations value was above 0.5 it indicates that they follow non-Fickian release mechanism and simvastatin release from the patches F1, F3 and F4 followed diffusion and controlled mechanism because release occurs through the pores of the matrix.

CONCLUSION

All nine formulations were evaluated for thickness, folding endurance, moisture uptake, physical appearance and results found for all is satisfactory. By the study of all parameters, it was concluded that the transdermal patch F7 is a better formulation among all the prepared formulations. Drug-polymer compatibility studies by FTIR gave confirmation about their purity and showed no interaction between the drug and polymers. Various formulations were developed by using hydrophilic polymer like HPMC K100M and hydrophobic polymers like Eudragit RS100 and Eudragit RL100 respectively by the solvent evaporation technique with the incorporation of penetration enhancer such as Tween 80 and glycerol as plasticizer.

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