Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

HPMC & EC Based Formulation and *In Vitro* & *Ex Vivo* Evaluation of Atorvastatin Transdermal Patch

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ARTICLE DETAILS

Article history:
Received on 27 June 2019
Modified on 25 November 2019
Accepted on 5 December 2019

Keywords:
Transdermal Drug Delivery,
Atorvastatin Calcium,
HPMC,
EC,
Eudragit,
PEG 400.

ABSTRACT

Abstract

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Advantages of transdermal delivery include convenience, comfort, by-pass the first phase hepatic metabolism, and control over drug absorption. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability (30%). Food has been shown to reduce the rate and extent of atorvastatin absorption. Administration of atorvastatin with food produces a 25% reduction in C_{max} (rate of absorption) and a 9% reduction in AUC (extent of absorption). In present work was designed to develop suitable transdermal matrix type of Atorvastatin calcium, using Hydroxypropyl methylcellulose (HPMC), Eudragit RS 100 and ethyl cellulose (EC) with PEG 400 (as plasticizer) and propylene glycol (as penetration enhancer). The solvent casting technique was employed for the preparation of Atorvastatin calcium transdermal patches. The dry films were evaluated for weight variation, thickness uniformity, moisture content, moisture uptake, folding endurance and % drug content. *In-vitro* release studies were performed using Franz's diffusion cell and permeation studies were carried out by using rat skin. The concentration of diffused drug was measured using UV-visible spectrophotometer at λ max 246.2 nm. FT-IR studies revealed that the drug and polymer were compatible with each other and all the batches prepared and evaluated, F1, F4 and F5 showed promising results. It was concluded that HPMC and ethyl cellulose are useful in formulating sustained release Atorvastatin transdermal patches.

INTRODUCTION

A transdermal patch is a medicated adhesive patch placed on skin to deliver a time released dose of medication through the skin for treating topical or systematic illness. A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed minimum toxic dose. Such a system offers variety of significant clinical benefits over other systems, such as tablet and injections. For example, it provides controlled release of the drug and produces a steady blood-level profile leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage form. In addition transdermal dosage form is user-friendly, convenient, painless, and offers multi-day dosing, it generally leads to improved patient compliance.

It offers many important advantages over oral drug delivery, e.g., gastrointestinal and hepatic first pass metabolism, reduces variation in delivery rates, avoids interference due to presence of food, controls absorption rate, suitable for unconscious patients, and enables fast termination of drug delivery, if needed. Hyperlipidemia involves abnormally elevated levels of any or all lipids and or lipoproteins in the blood or when the concentration of triglycerides, cholesterol in our blood is too high. Antihyperlipidemic agents promote reduction of lipid levels in the blood. Some antihyperlipidemic agents aim to lower the levels of low-density

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lipoprotein (LDL) cholesterol some reduce triglyceride levels, some help raise the high-density lipoprotein (HDL) cholesterol. By reducing the LDL cholesterol, they can prevent both the primary and secondary symptoms of coronary heart disease.

Some antihyperlipidemic agents produce their maximum effect at night time when given orally. It is not possible to handle a drug during night time due to various reasons. Here we found an alternate way like transdermal patches to deliver the drug effectively.

In present study, attempt was made to prepare transdermal patches containing antihyperlipidemic agent Atorvastatin calcium along with various polymers for controlled release action [1].

MATERIALS

Atorvastatin Calcium was purchased from Ronak pharmaceuticals Pvt Ltd., Patan. EC, HPMC and Propylene glycol were purchased from SD Fine-chemical Limited. All other reagents and solvents were of analytical grade**.**

METHODS

Preformulation Studies

Fourier Transform Infrared Radiation (FTIR)

Prior to the development of dosage forms the compatibility study was carried out for pure drug alone and along with polymers to check the compatibility between drug (atorvastatin) and HPMC, EC, Eudragit RS 100 which are used to formulate transdermal patches by KBr pellets method. The spectrum was presented in Fig. 1 and 2.

Method of Preparation of Transdermal Patches

Transdermal films of atorvastatin were prepared by solvent casting technique. Solution of PVP with EC, HPMC, and Eudragit RS 100 were dissolved in 10 ml mixture of methanol and chloroform in the ratio 1:1 as per the formulation Table 1 PEG 400 and propylene glycol added in required amounts as per formulation chart to the prepared solution and stirred well. The accurately weighed drug was mixed with the above mixture and mixed well to obtain homogenous mixture. After proper mixing, the solution was kept for stabilization and complete removal of air bubbles. Then the above mixture was casted in a glass mould of 9 cm^2 previously coated with thin layer of glycerine to prevent the adhesion of formed patch to the mould. The rate of evaporation was controlled by inverting a glass funnel over the glass mould. The mould was kept aside for drying at room temperature for 24 hrs. After 24 hrs the dried films was carefully removed from the mould and stored in a dessicator.

Table 1: Composition of Atorvastatin Transdermal Patches.

Formulation code	Drug (mg)	HPMC K100M	EC	Eudragit RS 100	PVP	PG (ml)	PEG 400 (ml)
F1	100	460	-	-	460	0.208	0.3
F2	100	660	-	-	260	0.208	0.3
F3	100	860	-	-	60	0.208	0.3
F4	100	-	460	-	460	0.208	0.3
F5	100	-	660	-	260	0.208	0.3
F6	100	-	860	-	60	0.208	0.3
F7	100	-	-	460	460	0.208	0.3
F8	100	-	-	660	260	0.208	0.3
F9	100	-	-	860	60	0.208	0.3

Evaluation of Patches

Thickness

Thickness of the transdermal patch is measured by travelling microscope, dial gauge, screw guaze or micrometer at three different points of the patch and average of the three is taken as thickness of the patch a uniformly thick patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated [2], results shown in Table 2.

Folding Endurance

Folding endurance is calculated by continuously folding the strip of the patch /film of a specific area at the same place until it breaks or folded up to 300 times. The number of times of folding the patch without breaking gives the folding

endurance of the patch. The folding endurance determines the flexibility of the patch [3], results shown in Table 2.

Drug Content

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of phosphate buffer of pH 7.4 and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution [4] results shown in Table 2.

Weight Variation

This was done by weighing three different patches of individual batch taking the uniform size (3cm x 3cm) at random and calculating the average weight of 3. The tests were performed on films which were dried at 60°C for 4 hrs prior to testing [5], results shown in Table 2.

Moisture Content [6]

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100

Moisture Uptake [7]

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

% moisture uptake = Final weight – Initial weight X 100

Percentage Elongation Break Test [8]

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

Elongation percentage = L1-L2 ×100 L2

Where, L1is the final length of each strip and L2 is the initial length of each strip.

Stability Studies [9]

Stability study is conducted to determine the time period for which the patch remains viable and usable. In unstable patch formulations drug starts degrading gradually so stability is tested according to ICH guidelines Q1C at 40ºC/75% RH for 6 months. Samples are taken at 0, 30, 60, 90 and 180 days and tested for its stability.

***In Vitro* Drug Release Studies [10]**

The *in vitro* release study was carried out using modified diffusion assembly. The transdermal patch (3x3cm^2) was adhered to the cellulose acetate membrane and tied firmly to the diffusion tube. This assembly was lowered in a beaker containing 100 ml of phosphate buffer pH 7.4 solution (PBS), so that the membrane assembly just touches the solution in the beaker The whole assembly was kept on a magnetic stirrer and study was conducted at a temperature of 37 ± 2°C.The contents in the beaker were stirred using a Teflon bead at a constant speed. Samples of 5 ml were collected at predetermined time and replenished with fresh pre-warmed medium. Drug content in the samples was estimated using UV/visible spectrophotometer at 246.2nm. Cumulative percentage of the released drug was calculated and plotted against time.

***Ex Vivo* Skin Permeation Studies [11]**

Modified Franz diffusion cell with an inner diameter of 5cm^2 was used for *Ex Vivo* permeation studies. A full thickness of Albino rat skin was excised from dorsal site and washed with water. The fatty tissue layer was removed by using surgical scissors. The outer portion with hairs was applied with depilatory and allowed to dry. With the help of wet cotton the hairs were scrubbed and washed with normal saline solution. The skin was kept in normal saline solution and allowed to equilibrate at room temperature prior to diffusion study. The skin was mounted between donor and receptor compartment of cell and clamped in such a way that the dermal side (inner side) will be in contact with receptor medium.

The stratum corneum side of the skin was kept in intimate contact with the transdermal patch under the test. The receptor compartment was with 100 ml of PBS of pH 7.4.The whole assembly was kept on a magnetic stirrer and study was conducted at 37 ± 2°C.The amount of the permeated drug was determined by removing 5 ml at pre determined time and replenishing with an equal volume of fresh medium. The samples were analysed for drug content using UV spectrophotometer at 246.2 nm.

RESULTS AND DISCUSSION

FT-IR spectras of pure drug and physical mixture of drug and polymer were obtained and compared for confirming compatibility of the drug with the polymers used for formulation. The absorption spectra and their principle peaks at or around the corresponding range of the pure drug. It is inferred that there was no interaction between drug and polymer and other additives. The integrity of the drug was maintained in all physical mixtures. Spectra showed no incompatibility between the polymer and atorvastatin drug shown in Fig. 1 & 2

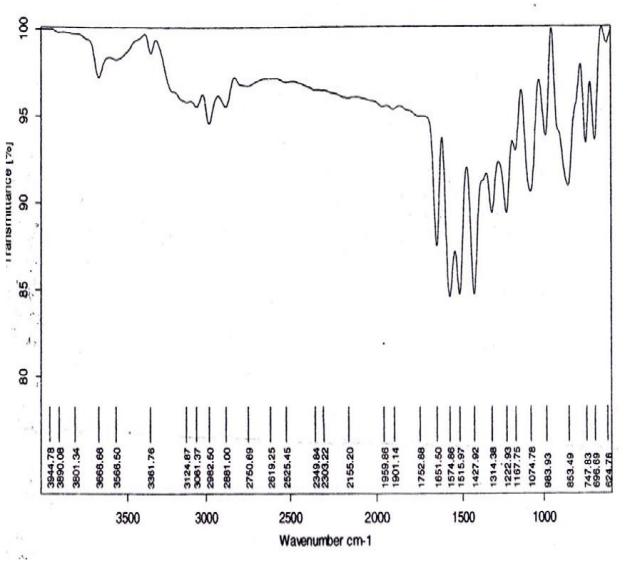

Figure 1: FTIR Spectra of Atrovastatin calcium

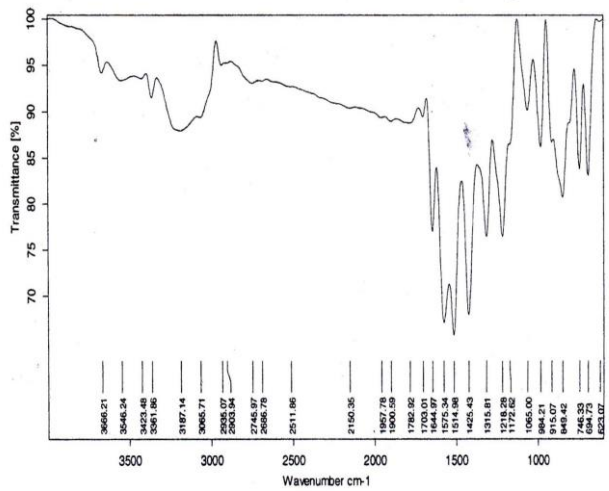

Figure 2: FTIR Spectra of Atrovastati + Ethylcellulose + HPMC Eudragit RS 100

Thickness and Weight Variation

All the films exhibited uniform weight and thickness and there was no much deviation in the weight of any formulation. Among various batches the uniformity of weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches. The results of thickness, was in the range of 0.11±0.026 – 0.16±0.031 and weight variation was 0.009±0.003 – 0.015±0.004 was shown in Table 2.

Drug Content Uniformity

All the prepared formulations found to have uniform drug content which is in the acceptable range of IP. The drug content analysis of the formulation have showed that the process employed for the mixing and preparation of the films were capable of giving films with uniform drug content with minimum batch variability. Drug content of the formulations was found to vary between 91.1±5.22 to 95.9±3.32.

The folding endurance was found to be in the range of 179±4.1 to 197±7.6. This data revealed that the patches had good mechanical strength along with flexibility.

Moisture Content

Moisture content can cause significant changes in properties such as reduced crushing strength, increased pore diameter in the patches containing hydrophilic polymer. But the moisture in the prepared patches was found to be low, and it varied very little in the formulation. The little moisture content helps the formulation to be stable and prevents them from becoming completely dried, brittle product

Moisture Uptake

The difference in the moisture uptake may be due to the increase in concentration of hydrophilic polymers and difference in resistance of matrix network structure to the movement of water molecule through the formulation. The moisture uptake was found to be decreased in formulations with the decrease in content of PVP.

Percentage of Elongation

Percentage elongation of films gives information of how much a specimen can elongate before it breaks. The percentage elongation at break point is measured on scale and the data of the percentage elongation found to be in the range between 23.7±0.13 -35.33±0.017.

In Vitro Drug Release Profile

The results of *in vitro* drug release studies from Transdermal patches are depicted in Fig. 3. The cumulative percentage of drug release from the various formulations was found to be very

between 90.75 and 98.68. Formulation F4, F5, exhibited greatest 98.68 and 98.61 percentage of drug release compared to other formulations and drug release was found to be less in formulations F3, F8, and F9.

The drug release from all the films was rapid in the initial hours (up to 6h), which could be due to the presence of drug on the surface of the films. Later the drug was released slowly from the patches.

In Vitro Skin Permeation Studies

The *in vitro* skin permeation studies were done through rat skin membrane, which showed that the formulations have good permeation properties. The formulations were showing good permeation because of Propylene glycol which is used as permeation enhancer. Formulation F4 showed good permeation properties compared to other formulations. The values obtained for all the formulations were given in Fig. 4.

Kinetics of Drug Release

The results of dissolution data were fitted to various kinetic equations to analyze the release mechanism. All the selected formulations were found to follow Korsmeyer peppas model. The kinetic values obtained for selected formulations are tabulated in Table 4 and the kinetic plots are shown in Fig. 6(a), 6(b) and 6(c).

Stability Studies

The stability studies were carried out on the most satisfactory formulations F1, F4, F7 at 40±2°C /70±5 % RH for two months to assess their stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties and *in vitro* drug release. There was no significant difference in the physicochemical parameters and *in vitro* drug release profiles and was found to be super imposable with the initial observations (Fig. 5).

Table 2: Physicochemical evaluation parameters

Batch Code	PARAMETERS						
	Weight Variation (Mean (mg) ± SD)	Thickness (Mean (mm)± SD)	%Moisture uptake	%Moisture content	Folding endurance	% Elongation Break Test	% Drug Content
F1	0.009±0.003	0.14±0.028	4.12	2.41	195±5.2	31.1±0.012	94.4±4.02
F2	0.013±0.002	0.15±0.019	4.19	3.12	186±3.2	32.2±0.014	95.9±3.32
F3	0.014±0.016	0.12±0.018	5.29	3.29	179±7.3	33.66±0.012	91.1±5.22
F4	0.012±0.003	0.15±0.021	5.14	3.08	189±3.9	28.1±0.016	95.4±4.13
F5	0.015±0.004	0.14±0.023	4.18	2.78	181±5.5	32.8±0.011	93.12±5.91
F6	0.014±0.010	0.12±0.016	3.18	2.74	179±4.1	35.55±0.017	94.1±3.51
F7	0.013±0.005	0.11±0.026	4.12	3.45	197±7.6	23.7±0.13	93.2±2.99
F8	0.012±0.008	0.16±0.031	3.14	2.17	184±7.2	25.3±0.15	92.41±3.12
F9	0.013±0.006	0.14±0.018	4.81	2.04	185.3±4.2	24.4±0.11	92.1±4.72

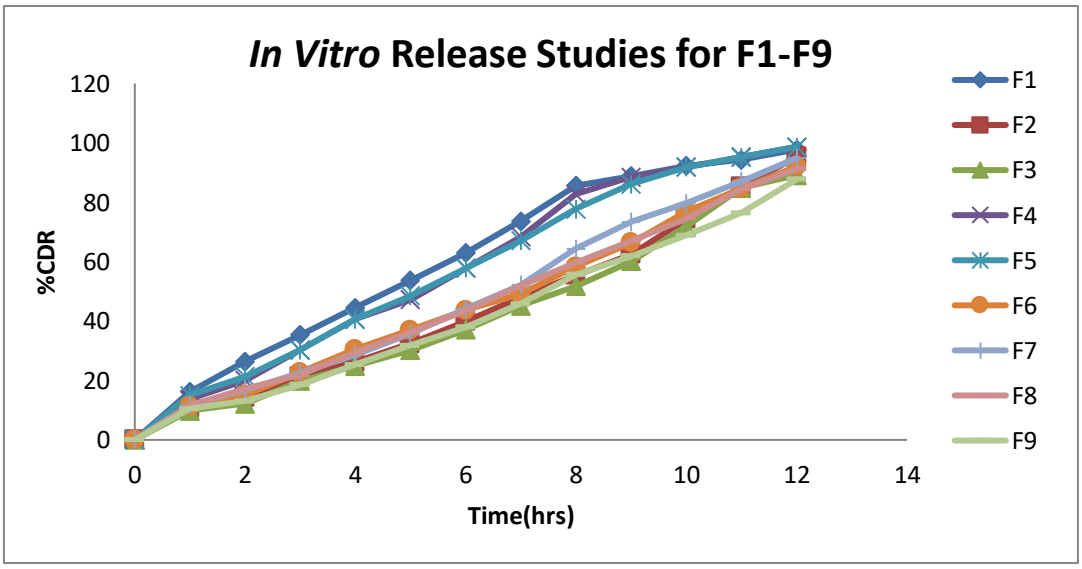

Figure 3: *In vitro* Diffusion study for formulation F1-F9

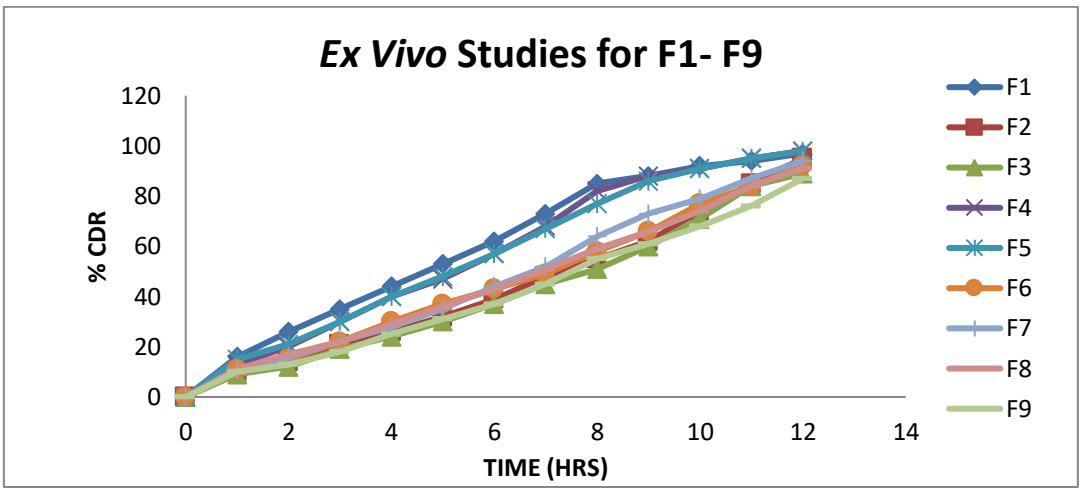

Figure 4: *Ex vivo* skin permeation study for formulation F1-F9

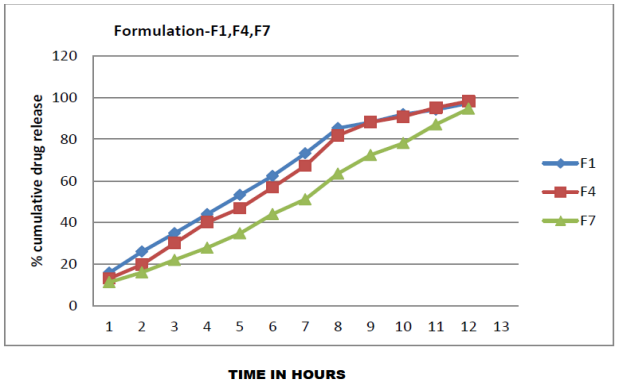

Figure 5: Stability studies of optimized formulations F1, F4, F7

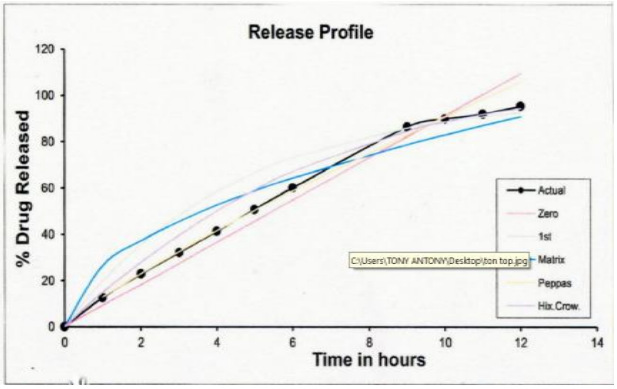

Figure 6(a): Release kinetics of Atorvastatin of formulation F1

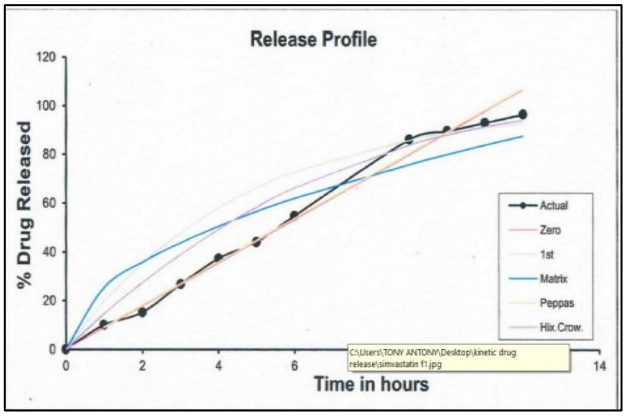

Figure 6(b): Release kinetics of Atorvastatin of formulation F4

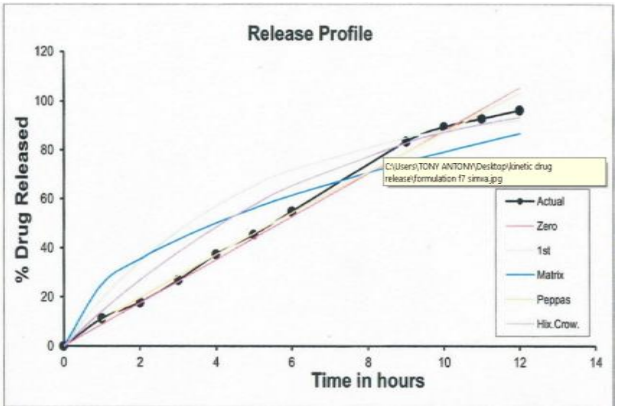

Figure 6(c): Release kinetics of Atorvastatin of formulation F5

Table 3: Drug content for F1, F4 and F7 after stability studies

Parameters	Formulations	0 days	30 days	60 days
Drug Content	F1	97.75	97.42	96.96
	F4	98.68	98.33	98.10
	F7	94.89	94.42	94.14

Table 4: Kinetic data for selected formulations F1, F4 and F7

Formulation	Higuchi matrix	1st order	Zero order	Korsmeyer -Peppas	
	(r^2)	(r^2)	(r^2)	(r^2)	(n)
F1	0.9598	0.9644	0.9774	0.9964	0.8510
F4	0.9345	0.9345	0.9901	0.9940	0. 9908
F5	0.9420	0.9329	0.9935	0.9968	0.9262

CONCLUSION

Hence in this study an attempt was made to deliver Atorvastatin calcium transdermally in order to provide a constant serum level of drug over the prolonged period of time, polymers like HPMC, EC, Eudragit were selected for the study and were used at different concentrations. PEG 400 is incorporated as plasticizers in the formulations.

On evaluation of various parameters it was found that the polymers produced satisfactory results with respect to the physical characteristics of the film and the release characteristics across synthetic membrane. FT-IR for drug and drug with polymer were carried out and there is no interaction between drug and polymer. A total of 9 formulations were made by using 3 different polymers. The formulated patches were subjected to physicochemical evaluatory parameters like folding endurance, thickness, moisture uptake, moisture content, drug content, and % elongation break test to ascertain their integrity and physical stability. The release profile suggested that increase in polymer concentration led to decrease in release rate of the drug. Lower concentration of polymers gave an initial burst release of about 50% within 5 hours and as concentration were increased they were able to sustained the release for prolonged period but could not release the entire content in the prescribed time limit. Hence it was concluded that using HPMC, EC as polymers and PEG 400 as plasticizer will be the most suitable one for the transdermal systems of Atorvastatin calcium as these showed a sustained and a complete release over a period of 12 hours. Stability studies were carried out on the most satisfactory formulations like F1, F4, and F7 for six months as per ICH guidelines QIC. There was no significant difference in the physicochemical parameters and *in vitro* drug and ex-vivo release profiles. All the selected formulations followed Korsmeyer - Peppas matrix i.e., the release follows diffusion mechanism.

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