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FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY PATCH CONTAINING ATORVASTATIN CALCIUM FOR TREATMENT OF HYPERLIPIDEMIA

Peeyush*[1, 2], Preeti Kush[2], Ajay K. Gupta[3], Preeti Verma[2], Pratiksha Jayaswal[4]

[1]Maharana Pratap College of Pharmacy Kanpur, Kothi, Mandhana Kanpur - 209217, Uttar Pradesh, India.

[2]Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University Gangoh, Saharanpur (U.P.) 247341.

[3]University Institute of Pharmacy , Chhatrapati Shahu Ji Maharaj University, Kanpur - 208024, U.P., India.

[4]Faculty of Pharmaceutical Sciences, Rama university,Mandhana Kanpur-209217, U.P,India

Corresponding author:
Dr.Preeti Kush
Associate Professor
Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University
preetikush85@gmail.com

ABSTRACT
The purpose of this research work was to improve a matrix-typetransdermal drug delivery system (TDDS) those containing atorvastatin calcium act as a hyperlipiemic drug which having different ratios of Ethyl cellulose (EC) and hydrophilic (HPMC).Tween 80 and plasticizer glycerine used by the solvent evaporation technique. The Transdermal patch system has been providing controlled continuous drug delivery via the skin into the systemic transmission. The aim of this study to develop thetransdermal patches of Atorvastatin Calcium for the prevent its first pass metabolism and finally get achieve controlled release. The formulation of AtorvastatinCalciumhaving a property to sustained release transdermal drug delivery system.AtorvastatinCalcium is commercially available as tablets of 10mg, 20mg, and 40mg and 80mg strengths as immediate release dosage form. Matrix films were evaluated for their physicochemical characterization tracked by in-vitro evaluation. The medication indicated faster release because of hydrophilicity. The assessment plans were completed known as rate dampness content, rate dampness take-up, collapsing continuance, thickness, weight variety, physical appearance, UV-Visible spectrophotometer, λ max and IR spectroscopy and quantitative estimation of the medication. It was appeared by all the awareness that the antilipidemic tranquilize atorvastatin calcium could fill in as a fitting possibility for TDDS that can improve the bioavailability and sustain release of action, so that it would be better medication in the form patch for treatment of hyperlipidaemia.

KEYWORDS: Atorvastatin Calcium, Transdermal patch, Transdermal delivery**,** IR spectroscopy, Skin permeation, Dialysis membrane.

INTRODUCTION

Hyperlipidaemia is a condition excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called **hypolipoproteinaemia** because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation**[1]**.Atorvastatin Calcium was chosen as the suitable candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular mass, high lipid solubility, effective in low plasma concentration as well as a high degree of first-pass metabolism. The aim of this study was to develop and evaluate transdermal patches of Atorvastatin Calcium so as to prevent its firstpass metabolism and achieve controlled release. These factors in addition to its low molecular weight low bioavailability (12%), low melting point (159.2-160.7°C), high lipid solubility and effective in low plasma concentration necessitates the formulation of sustained release transdermal drug delivery system for AtorvastatinCalcium**[2]**.

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Since early, dosage of Transdermal therapeutics system has been available commercially. Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin**[3]**. Transdermal drug delivery system allows delivery of contained drug into the systemic circulations via permeation through skin layers at a controlled rate. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. However, the outermost layer of skin, stratum corneum (SC), forms a major's barrier to most

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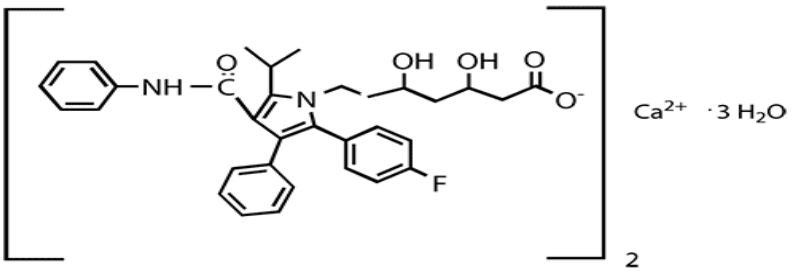
exogenous substances including drugs. The main challenges of many transdermal formulations are to effectively increase the permeability of the active ingredients through the stratum corneum while avoiding skin irritation**.**A chemical skin permeation enhancer increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. Among the alterations are increase in hydration of stratum corneum, a change in the structure of the lipids and lipoproteins in the intracellular channels through the solvent action or denaturation, or both. Example: they include acetone, dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide (DMSO), ethanol, oleic acid, propylene glycol, and polyethylene glycol and sodium lauryl sulphate.The most recent cholesterol management guidelines (the third report of the adult treatment panel ATP III), which are issued by the national cholesterol education program redefine the levels at which blood cholesterol should be treated**[4]**. These new evidence-based recommendations are departures from the NCEP's previous guidelines (ATP II) in several ways.The fat-protein complexes in the blood are called lipoproteins. The best-known lipoproteins are LDL (low-density lipoprotein) and HDL (high-density lipoprotein). Excess LDL cholesterol contributes to the blockage of arteries, which eventually leads to heart attack. Population studies have clearly shown that the higher the level of LDL cholesterol, the greater the risk of heart disease. This is true in men and women, in different racial and ethnic groups, and in all adult age groups. Hence, LDL cholesterol has been labelled the bad cholesterol. Atorvastatin Calcium is a lipid lowering-agent and widely used to treat hypercholesterolemia and it is a potent inhibitor of HMG-CoA reductase. This enzyme catalyses the conversion of HMG CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream**[5]**.
The fastening of all trans-dermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally**[6]**. **Atorvastatin** is a hypolipidemic drug used to maintain the cholesterol level in the body, it is widely used to treat hypercholesterolemia and it is a potent inhibitor of HMG-CoA reductase**[7]**.

DRUG PROFILE

Generic Name: Atorvastatin calcium

Molecular Structure:



Molicular Formula: $[C_{33}H_{35}FN_2O_5]_2$ Ca .$3H_2O$

Chemical name: Calcium (βR,δR)-2-(p-fluorophenyl)-β,δ-dihydroxy-5- isopropyl-3- phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate**[8]**

Appearance: White to off white amorphous powder

Category: Cardiovascular Agent

Sub-category: HMG-CoA Reductase Inhibitor

Solubility: Freely soluble in methanol and soluble in dimethylsulphoxide (DMSO) and dimethyl formamide (DMF); insoluble in aqueous solution with pH less than 4.0. It is very slightly soluble in distilled water,Phosphate buffer (7.4) and acetonitrile slightly soluble in ethanol. 20.4 ug/mL (pH 2.1), 1.23 mg/mL (pH 6.0)**[9].**

Mechanism of Action: Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles**[11,12]**.

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MATERIAL AND METHODS

PREFORMULATION STUDIES

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailability dosage forms which can be mass produced **[13].**

The Pre-formulation studies have included:

IDENTIFICATION OF DRUG:

The drug sample (Atorvastatin calcium) was utilized during the whole work was firstly identified via different parameters.

Description of Atorvastatin Calcium:

Atorvastatin was physically examined for color. (Table 1)

Melting point of Atorvastatin Calcium:

Fine powder of the Atorvastatin Calcium was filled in glass capillary tube (previously sealed at one end) and kept in melting point apparatus. The temperature at which the drug melts was noted. This was performed thrice and average value was noted**[14]**. (Table 1)

Solubility analysis of Atorvastatin Calcium:

The solubility of the drug was determined by adding small amount of drug in the different solvents (Table 2)

Partition coefficient of Atorvastatin Calcium:

The partition coefficient of the Atorvastatin Calcium was determined by taking equal volume of 1-octanol and aqueous solution in a separating funnel. In case of water- soluble drugs, a drug solution was prepared in distilled water, and in case of water-insoluble drugs, a drug solution was prepared in 1- octanol. Standard solution of the Atorvastatin Calcium was prepared in the 1-octanol. Then; phosphate buffer pH 7.4 solution was added to equal volume of this octanol drug solution in a separating funnel was kept for 24 h at 37 ±°C with intermittent shaking**[15]**. Finally, the buffer solution was separated, clarified by filtration and assayed for drug content using UV spectroscopy at its respective λ max. (Table 1)**[16].**

Partition coefficient = Concentration of drug in organic phase / concentration of aqueous phase

Determination of λ max ofAtorvastatin Calcium by UV spectra:

The λ max of the given sample was determined by obtaining UV spectra which was also done by preparing the methanol solution of Atorvastatin of concentration 10µg/ml after that the sample was scanned at the range of 400-200nm**[17]**.(Figure 1)

Identification ofAtorvastatin by IR spectra:

Infrared (IR) spectroscopy was conducted by using FTIR (Shimadzu) the spectrum was recorded in the wavelength region of 4000 to 600 cm−1. The procedure consisted of dispersing the sample in KBr and compressed into discs by with pressure of 7-8 tons for 5 min in a hydraulic press. The pellet was then placed in the light path and the spectra were obtained and interpreted**[18]**. (Table 3) (Figure 2)

PREPARATION OF STANDARD CURVES OF ATORVASTATIN CALCIUM:

After the identification of the drug and the data obtained above confirmed that the given drug sample was Atorvastatin calcium. The standard curve of drug was prepared in methanol with the use of 10mg drug dissolved in 10 ml solvent to form stock solution. Using the stock solution different dilutions was prepared and absorbance was taken at the λ max of the drug separately. (λ max of Atorvastatin calcium: 245.8nm) **Figure 3**

COMPATIBILITY STUDIES:

Compatibility Studies between the drug and the polymer:

The compatibility between the drug and polymers utilized during the research work was studied by obtaining IR spectra of the mixture of drug and polymers.

Compatibility Studies of Atorvastatin calcium and Hydroxy propyl methyl Cellulose by performing IR Spectroscopy:

The compatibility between Atorvastatin calcium and Hydroxy propyl methyl cellulose polymer was done by obtaining IR spectra of the mixture of drug and polymer and compared with the standard drug and polymer spectra (Table 4).

Compatibility Studies of Atorvastatin calcium and Ethyl Cellulose by performing IR Spectroscopy:

The compatibility between Atorvastatin calcium and Ethyl cellulose polymer was done by obtaining IR spectra of the mixture of drug and polymer and compared with the standard drug and polymer spectra (Figure 5) (Figure 4) **[19]**.

Table 1. Basic descriptions of Atorvastatin calcium.

DRUG	**ATORVASTATIN CALCIUM**
Melting Point	159.2 – 160.7^{0}C
Partition-coefficient	Lypophillic
Color	White

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Table 2. Solubility analysis of Atorvastatin calcium.

SOLVENTS	SOLUBILITY
Water	Slightly soluble
Ethenol	Slightly Soluble
Methenol	Freely Soluble
DMSO	Soluble
n-Octanol	Slightly Soluble
Phosphate buffer (7.4pH)	Slightly soluble

Table 3. Interpretation of IR Spectra of Atorvastatin calcium.

FUNCTIONAL GROUPS	RANGE ($cm^{-1)}$	PEAK VALUE ($cm^{-1)}$	VIBRATIONS
Ether group	1100-1000	1037	C-O stretching vibration
Alkanes	3000-2750	2924.04	C-H stretch
Amino group	3600-3300	3530	N-H stretching vibration
Carboxylic group	1800-1500 3800-3725	1740 3720	C=O stretching vibration O-H stretching vibration

Table 4 Interpretation of Spectra of Atorvastatin and HPMC.

FUNCTIONAL GROUP	RANGE (cm^{-1})	PEAK VALUE (cm^{-1})	VIBRATIONS
Ether group	1100-1000	1037	C-O stretching vibration
Alkanes	3000-2700	2924.04	C-H stretch
Aromatic group	1400-1200	1280.73	Ar-O stretching vibration
Cyclic anhydride	1400-1350	1373.37	ν C-O-C and symmetric bending of methoxy group
Pyranose ring	1000-950	948.98	ν_{as} of pyranose ring
Benzene ring	1600-1400	1545	Stretching vibration
Ethereal group	1100-1000	1026.13	Stretching vibration of C-O-C groups.

Table 5. Interpretation of Spectra of Atorvastatin and Ethyl cellulose.

FUNCTIONAL GROUPS	RANGE (cm^{-1})	PEAK VALUE (cm^{-1})	VIBRATIONS
Ether group	1100-1000	1037	C-O stretching vibration
Alkanes	3000-2700	2924.04	C-H stretch
Amino group	3600-3300	3530	N-H stretching vibration
Benzene ring	1600-1400	1597.06	Stretching vibration
Alkyl and aldehyde	1600-1500	1512.19	C=O and C=C vibration
Ether	1200-1000	1064.71	-C-O-C- stretching vibration
Pyranose ring	1000-800	964.41	Pyranose ring stretching

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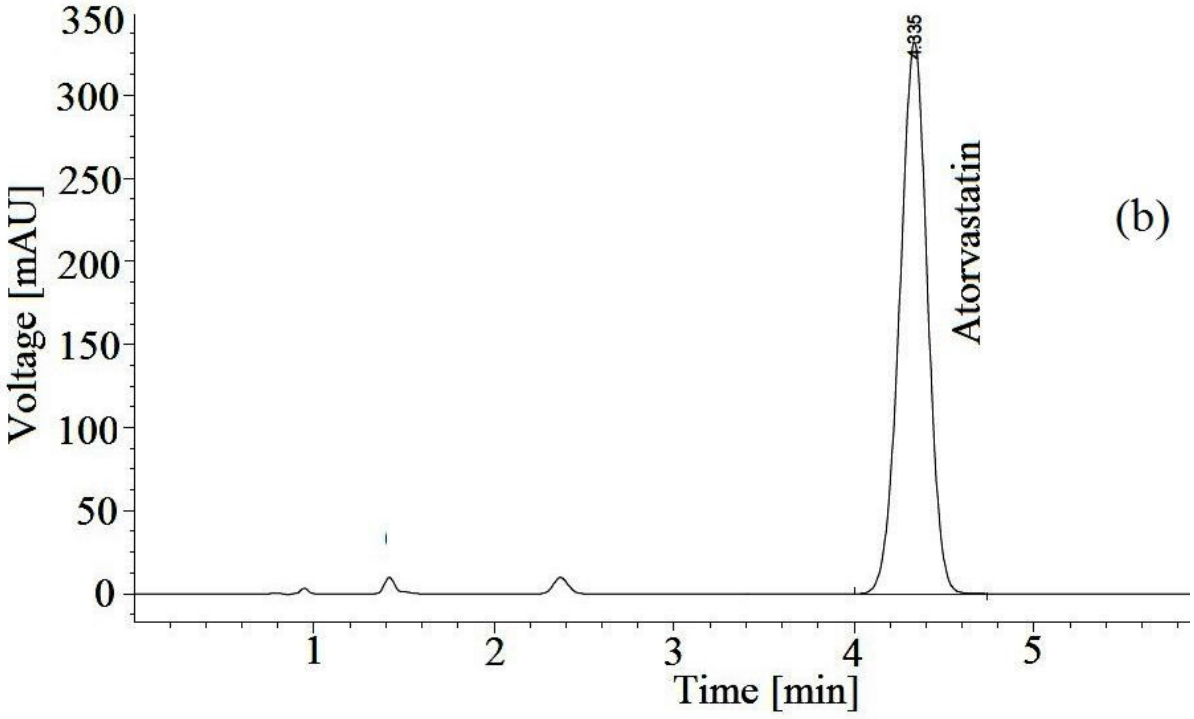

Figure 1: Spectra showing λ max of Atorvastatin calcium at 245.8nm

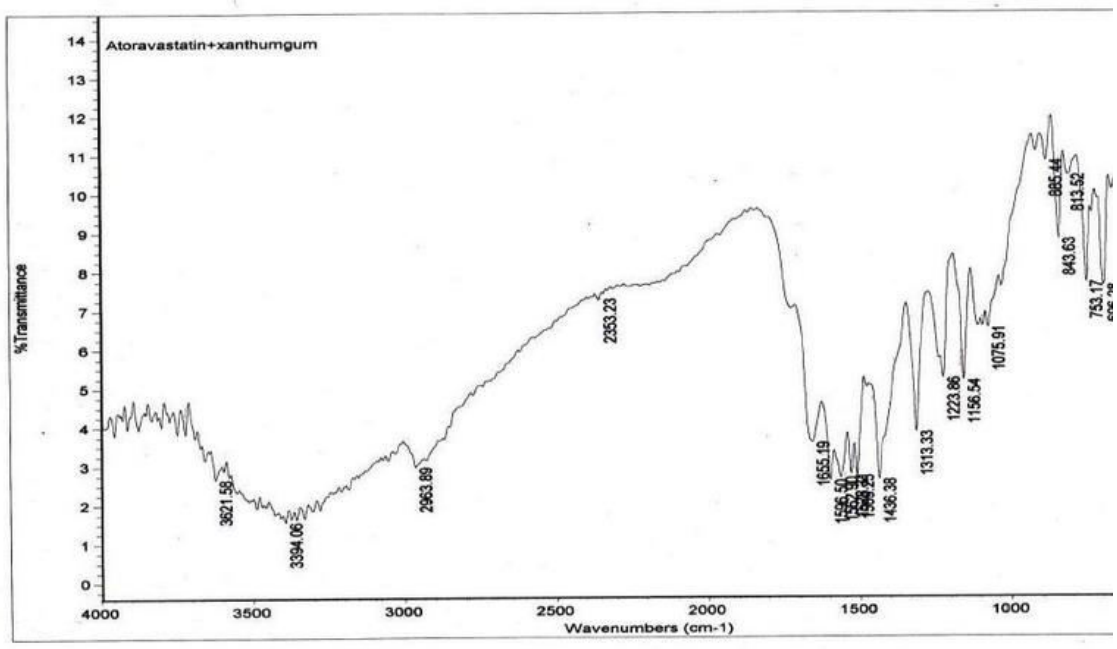

Figure 2:IR Spectra of Atorvastatin calcium

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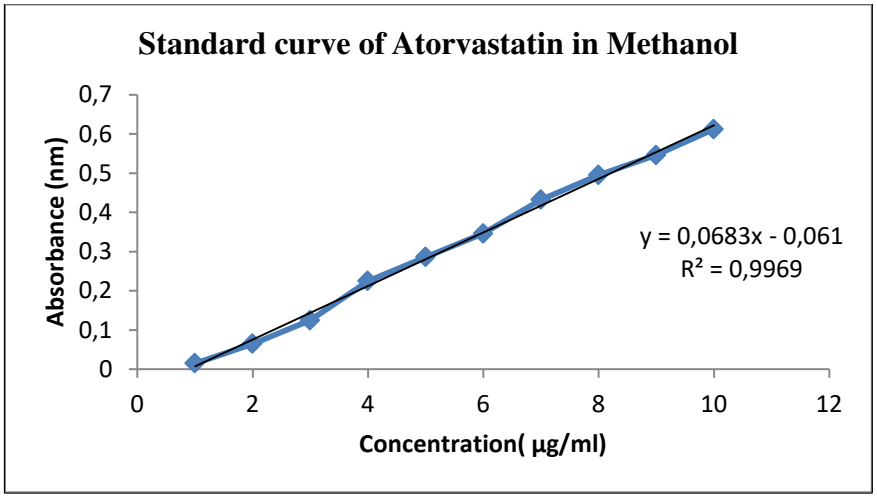

Figure 3: Standard curve of Atorvastain in Methanol

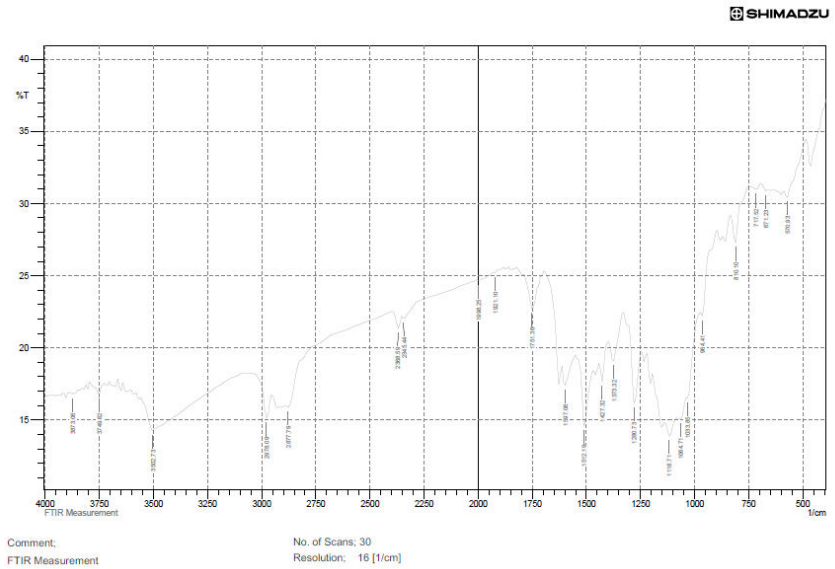

Figure 4: IR spectra of Atorvastatin calcium and Ethyl Cellulose

Preparation of solutions

a. Phosphate buffer (pH7.4) solutions: 250 ml of 0.2M potassium di-hydrogen phosphate was taken in 1000 ml volumetric flask, to which 195.5 ml of 0.2M sodium hydroxide solution was added and the volume was made up to 1000 with distilled water.

b. **Potassium di-hydrogen phosphate (0.2M) solutions:** Potassium di-hydrogen phosphate (27.28) g was added to 1000 ml volumetric containing distilled water and the volume was made up to the mark with distilled water.

c.Sodium hydroxide (0.2M) solution: 8g of sodium hydroxide was taken in 1000 ml volumetric flask containing distilled water and volume was made up to the mark with distilled water.

Preparation of standard stock solution:

Accurately weighed 100 mg of Atorvastatin in a 100 ml volumetric flask, dissolved in methanol and made up to the volume to get a concentration of 1000 µg/ml. The 10 ml of the above solution is diluted upto100 ml using the same methanol to get a concentration of 10 µg/ml (standard stock solution).

Preparation of calibration curve:

From the above standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and made up to 10 ml with methanol, so as to get a separate drug concentrations of 2.0 to 10 µg/ml. The absorbencies of all these drug solutions were recorded at λmax 428nm.

Preparation of Atorvastatin Transdermal patch:

The matrix-type transdermal patches were prepared by solvent evaporation method and containing **Atorvastatin calcium** and using different ratios of ethyl cellulose and hydroxy propyl methyl cellulose polymers. The polymers in different ratios were dissolved in the respective solvents (Dichloromethane: methanol). Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Polyethylene glycol 400 was used as plasticizer. Tween 80 was used as the penetration enhancer. Then the solution was poured on the Petri dish

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having surface area of 63.5 cm^2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch is approximately 40 mg. and stored in desiccators **[20,21]**.(**Table 6)**

Table 6 Formulation Chart of Atorvastatin Transdermal patch:

S.No	Ingredients	B1	B2	B3	B4	B5
1.	HMPC (mg)	100	50	75	65	95
2.	EC (mg)	50	100	75	95	65
3.	Polyethylene glycol 400 (ml)	0.6	0.6	0.6	0.6	0.6
4.	Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2
5.	Dichloromethane : Methanol (4:1) (ml)	7	7	7	7	7

CHARACTERIZATION OF ATORVASTATIN TRANSDERMAL PATCH

Table 7 Physical appearance of Transdemal patches.

S.No	Formulation code	Colour	Clarity	Flexibility	Smoothness
1.	**B1**	Yellow orange	Clear	Medium Flexible	Smooth
2.	**B2**	Yellow orange	Clear	Medium Flexible	Smooth
3.	**B3**	Yellow orange	Clear	Medium Flexible	Smooth
4.	**B4**	Yellow orange	Clear	Medium Flexible	Smooth
5.	**B5**	Yellow orange	Clear	Medium Flexible	Smooth

Table 8 Post Characterizations values of Transdemalpatchs.

S.No	Formulation Codes	Thickness (mm)±S.D*	Weight (gms) ±S.D*	%Moisture absorption± SD*	%Moisture Loss ±SD*	Folding Endurance ± S.D*
1.	**B1**	0.21±0.00	0.29±0.03	4.5±0.78	5.9±1.26	47±2.24
2.	**B2**	0.23±0.00	0.29±0.00	3.41±1.81	3.9±1.52	43±8.77
3.	**B3**	0.20±0.00	0.33±0.03	2.69±0.00	2.8±0.25	54±3.16
4.	**B4**	0.20±0.00	0.34±0.03	3.31±1.38	4.2±1.34	43±1.07
5.	**B5**	0.19±0.00	0.35±0.03	3.49±1.51	4.2±1.00	41±7.07

SD*=Standard deviation, n=3

Table 9 Post Characterizations values of Transdemalpatchs.

S.No	Formulation Codes	Tensile strength ± S.D	%Elongation ± S.D	%Drug Content ± S.D	Water Vapour transmission rate ± S.D
1.	**B1**	3.3±0.31	7.62±2.01	89±0.80	0.071±0.00
2.	**B2**	3.1±0.54	4.61±3.64	92±0.67	0.057±0.01
3.	**B3**	3.3±0.60	4.76±0.00	95±0.56	0.047±0.02
4.	**B4**	2.5±0.77	7.62±2.05	94±0.43	0.059±0.04
5.	**B5**	2.4±0.88	9.04±0.01	93±0.90	0.063±0.01

SD*=Standard deviation, n=3

Table 10 Data obtained from Adhesive property of (B3) patch by Thumb tack test.

Formulation code	B3
Adhesive property	**+**

(+) = Slight adhesive property.

(+ +) = Moderate adhesive property

Table 11 Data obtained from Skin-irritation test of optimized formulation (B3).

Formulation code	B3
Skin irritation	**-**

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(-)= No irritation **, (+) =** Well defined irritation

In-vitro **drug release study of Atorvastatin calcium Transdermal patch by USP paddle method.**

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The dissolution studies of patches are crucial because one needs to maintain the drug concentration on the surface of the SC consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation.

The dissolution study using USP paddle Type Dissolution Apparatus was carried out at 37 ±1°C at 50 rpm frequency of the paddle. 500 ml of Phosphate buffer of pH 7.4 was used as the dissolution media. The patches were tied over thin glass plate with a thin copper wire and then placed in a jar. Samples were withdrawn at different time intervals and then analyzed using a UV spectrophotometer at 245.8nm. **(Table-12, 13 and Table-14)**

Percentage of drug released was determined using the formula:

$$\% \text{ of drug released} = D_a / D_t \times 100$$

Where, Dt- indicates the total amount of drug in the patch

Da – the amount of drug released.

In-vitro **cellophane membrane study by Franz Diffusion cell.**

In-vitro permeation studies were carried out optimized Formulation using dialysis membrane as barrier.

The dialysis membrane soaked in phosphate buffer pH 7.4 for overnight was fixed carefully to the receptor compartment of the diffusion cell so that it just it touches the receptor fluid surface. The Transdermal system of $4cm^2$ area was placed above the dialysis membrane fixed to the donar compartment. The receptor compartment was filled with 10 ml of phosphate buffer of pH 7.4 as diffusion medium. The receptor medium was magnetically stirred using a magnetic bead for uniform drug distribution and was maintained at 37±1°C. The samples (1ml) were withdrawn every hour up to 24 hrs and estimated spectrophotometrically (UV) at 245.8 nm to determine the amount of drug release. The volumes withdrawn at each interval were replaced with an equal volume of fresh, pre warmed buffer solution **[23,24]**. **(Table 15)**

IN-VITRO DRUG RELEASE

In-vitro **skin permeation study by franz diffusion cell:**

In- vitro skin permeation studies were carried out optimized Formulation through Rat skin.

Preparation of skin

A full thickness of skin was excised from dorsal site of dead rat and skin was washed with water. The fatty tissue layer was removed by using nails of fingers. 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 in refrigerator until skin was used for diffusion study. Prior to use, the skin was allowed to equilibrate with room temperature. Then skin was mounted between donor and receptor compartment of cell. The skin was clamped in such a way that the dermal side will be in contact with receptor medium.
In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor capacity of 10ml. The skin membrane was mounted between the donor and receptor compartment of the diffusion cell**[25] (Table 16)**

The formulated patch was cut into $2cm^2$ and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37±0.5 °C. The samples of 1ml were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hr analyzed for drug content spectrophotometrically at 245.8nm. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amount of drug permeated per square centimeter of patch was potted against time.

The diffusion kinetics of the drug Atorvastatin calcium was analyzed by graphical method:

- Zero order graphs were made by plotting cumulative % drug release against time in hours.

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- First order graph were made by using Log cumulative % drug remaining against Time in hours.
- The diffusion pattern release of the formulation was studied by plotting Higuchi's graph using Cumulative % drug released against square root of time

Table 12 *In-vitro* release profile of B1 formulation

Time (h)	SQRT	Log T	% Cumulative drug release	Log % Cumulative drug release	%Cumulative drug retained	Log % Cumulative drug retained
0	0	0	0	0	100	2
0.5	0.708	-0.302	7.726	0.887	92.276	1.965
1	1	0	12.680	1.102	87.319	1.940
2	1.415	0.302	22.038	1.343	77.964	1.892
3	1.733	0.478	26.236	1.434	72.674	1.862
4	2	0.602	27.177	1.535	65.867	1.818
5	2.236	0.698	34.348	1.589	61.127	1.785
6	2.449	0.778	38.873	1.651	55.186	1.741
7	2.645	0.845	44.813	1.686	51.371	1.710
8	2.829	0.904	48.629	1.727	46.692	1.669
9	3	0.945	53.308	1.755	43.029	1.633
10	3.162	1	56.971	1.767	41.700	1.619
11	3.316	1.041	61.310	1.786	38.689	1.587
12	3.465	1.079	64.143	1.807	35.858	1.555
24	4.898	1.38	71.221	1.852	28.778	1.458

Table 13 *In-vitro* release profile of B2 formulation.

Time (h)	SQRT	Log T	% Cumulative drug release	Log % Cumulative drug release	%Cumulative drug retained	Log % Cumulative drug retained
0	0	0	0	0	100	2
0.5	0.708	-0.302	13.944	1.145	86.058	1.935
1	1	0	19.299	1.285	80.701	1.906
2	1.415	0.301	25.164	1.400	74.835	1.873
3	1.733	0.477	34.051	1.531	65.949	1.818
4	2	0.603	44.554	1.649	55.447	1.744
5	2.237	0.698	50.179	1.700	49.821	1.697
6	2.449	0.779	55.655	1.744	44.345	1.643
7	2.646	0.847	59.037	1.771	40.965	1.613
8	2.829	0.905	62.388	1.795	37.614	1.576
9	3	0.946	66.516	1.822	33.484	1.524
10	3.163	1	69.030	1.838	30.970	.490
11	3.317	1.041	71.569	1.859	28.430	1.453
12	3.465	1.079	73.787	1.867	26.212	1.418
24	4.899	1.38	82.495	1.916	17.505	1.243

Table 14 *In-vitro* release profile of B3 formulation.

Time (h)	SQRT	Log T	% Cumulative drug release	Log % Cumulative drug release	%Cumulative drug retained	Log % Cumulative drug retained
0	0	0	0	0	100	2
0.5	0.708	-0.302	14.556	1.163	85.446	1.932
1	1	0	18.952	1.278	81.049	1.909
2	1.415	0.302	29.287	1.467	70.715	1.849
3	1.733	0.478	34.326	1.535	65.766	1.818

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4	2	0.602	46.840	1.670	53.159	1.725
5	2.237	0.699	55.139	1.742	44.863	1.652
6	2.449	0.778	59.650	1.775	40.349	1.605
7	2.646	0.846	63.581	1.804	36.419	1.561
8	2.828	0.903	67.714	1.830	32.286	1.509
9	3	0.945	70.043	1.844	29.956	1.475
10	3.162	1	72.825	1.858	27.715	1.442
11	3.317	1.042	74.673	1.873	25.239	1.404
12	3.465	1.079	76.652	1.885	23.349	1.368
24	4.898	1.38	86.812	1.938	13.188	1.119

Table 15 *In-vitro* cellophane membrane permeation study of optimized formulation (B3)

Time (h)	SQRT	Log T	% Cumulative drug release	Log % Cumulative drug release	%Cumulative drug retained	Log % Cumulative drug retained
0	0	0	0	0	100	2
0.5	0.708	-0.302	4.07911	0.610	95.920	1.981
1	1	0	12.3215	1.091	87.679	1.943
2	1.416	0.303	21.3779	1.329	78.623	1.896
3	1.734	0.479	29.9165	1.476	70.084	1.846
4	2	0.604	37.1514	1.569	62.849	1.799
5	2.237	0.699	45.4891	1.657	54.511	1.736
6	2.449	0.779	56.3618	1.750	43.638	1.639
7	2.645	0.846	62.120	1.793	37.879	1.578
8	2.829	0.904	68.7847	1.837	31.215	1.494
9	3	0.946	74.4312	1.872	25.568	1.407
10	3.164	1	79.5357	1.901	20.469	1.310
11	3.318	1.043	83.4588	1.921	16.543	1.218
12	3.466	1.079	88.1828	1.945	11.818	1.072
24	4.899	1.38	95.4563	1.979	4.543	0.2966

Table 16 *In-vitro* skin membrane permeation study of optimized formulation (B3).

Time (h)	SQRT	Log T	% Cumulative drug release	Log % Cumulative drug release	%Cumulative drug retained	Log % Cumulative drug retained
0	0	0	0	0	100	2
0.5	0.708	-0.302	5.683	0.751	93.423	1.995
1	1	0	12.232	1.088	88.259	1.974
2	1.766	0.301	22.348	1.349	76.523	1.891
3	1.999	0.477	35.129	1.464	71.252	1.850
4	2.266	0.602	39.472	1.549	63.259	1.805
5	2.563	0.698	42.291	1.626	56.259	1.762
6	2.897	0.778	49.752	1.696	49.259	1.702
7	2.901	0.845	56.843	1.754	42.328	1.636
8	2.998	0.903	63.912	1.805	37.258	1.558
9	3	0.945	72.576	1.860	26.254	1.431
10	3.263	1	79.415	1.899	20.585	1.314
11	3.389	1.041	83.551	1.921	16.449	1.216
12	3.569	1.079	88.642	1.947	11.449	1.059
24	4.012	1.38	93.425	1.970	6.575	0.818

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STABILITY STUDIES

Drug substance and products could degrade by oxidation, hydrolysis, racemization etc. Factors such as temperature, humidity, light, pH, ionic strength, buffer strength, residual metals could enhance the degradation. It is expected that a well designed formulation and packaging protects the product from degradation.

Stability studies of optimized formulation (B3):

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Optimized formulation (B3) was selected for stability studies on the biases of physiochemical characteristics and drug content of formulation. The satisfactory formulation was sealed in an aluminium foil and stored at room temperature, an oven and refrigerator condition for 1 month**[22], [25]**. **(Table 17)**

Table 17 Stability studies of optimized formulation (B3) at different temperature after 30 days.

Sl.no.	Parameters	Room temperature	Oven temperature	Cold temperature
1.	**Appearance**	No change	Slight change	No change
2.	**Weight variation ± SD***	0.40±0.47	0.34±0.83	0.37±0.43
3.	**Folding endurance± SD***	57±2.24	54 ± 1.24	56± 1.89
4.	**Tensile strength± SD***	3.5 ± 0.45	3.4± 0.83	3.4± 0.55
5.	**Drug content ± SD***	94.5 ± 0.37	90± 0.26	95±0.42

SD*=Standard deviation, n=3

RESULT AND DISCUSSION:

TDDS is considered to be the ideal method which can bypass the difficulties of first-pass metabolism, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate. Atorvastatin Calcium was chosen as the suitable candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular mass, high lipid solubility, effective in low plasma concentration as well as a high degree of first-pass metabolism. The drug utilized during the whole research work was subjected to different pre-formulation studies like identification of drugs, preparation of standard curves of both the drugs, determination of λ max and IR spectroscopy. After that, compatibility studies carried between drug and polymers by IR spectroscopy.

CONCLUSION:

This study was 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 is a better formulation among all the prepared formulations. Drug-polymer compatibility studies by FTIR provided the confirmation about their purity and it showed no interaction between the drug and polymers. Various formulations were developed by using hydrophilic polymer like TDDS containing atorvastatin calcium as hyperlipidemic drug with different ratios of Ethyl cellulose (EC) and hydrophilic (HPMC).Tween 80 and plasticizer glycerine by the solvent evaporation technique. Respectively by the solvent evaporation technique with the incorporation of penetration enhancer such as Tween 80 and glycerol as plasticizer.could serve as an appropriate candidate for TDDS that can improve the bioavailability.

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REFERENCES

1. Elaine M. Urbina MD, Stephen R. Daniels MD, phd, in Adolescent Medicine, 2008, 10: (3), 90-96.
2. Sandhya rani Mandadi, Vishwanadhamyerraguntaformulation and evaluation of atorvastatin calcium sustained release tablets, 2006, 6(3):124-130 ·
3. Mark R. Prausnitzand Robert LangerNatBiotechnol, Transdermal drug delivery, Nat Biotechnol. 2008 26(11): 1261–1268.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 01, 2021

4. Barry, B. W. And Williams, A. C., Permeation Enhancement through skin in Encyclopedia of pharmaceutical Technology,Marcel Dekker Inc., Newyork, 1996,4:(11),51-57.
5. Keerthana Devi R, Radha R, Jayshree N; formulation and evaluation of Solasodine transdermal patches for anti-inflammatory activity; International journal of pharma research & review; 2014, 3:(4). 313-318.
6. Jaydatt k. Jadhav.1, S.A.sreenivas, formulation and invitro evaluation of indomethacinransdermal patches using polymers hpmc e5 and ethyl cellulose, 2011, 4:(1), 550-526.
7. Asija Rajesh, Umesh Kumar, Asija Sangeeta, Patel Chirag J, MangukiaDhruv, Patel Pinkesh, Formulation and evaluation of matrix type transdermal patches of atorvastatin calcium, journal of biomedical and pharmaceutical research(JBPR), 2013, 2:(3),2-3.
8. DarwhekarGajanan,Jain Dinesh kumar, Patidar Vinod kumar; Formulation an evaluation of transdermal drug delivery system of ClopidogralBisulfate; Asian journal of pharmacy andlife science; 2011, 1:(3),4- 9
9. S Mandal, J Thimmasetty, G N Ratan, B H Kilarimath, Mandal S, Thimmasetty J, Ratan GN, Kilarimath BH. Formulation and evaluation of Carvedilol transdermal patches, International Research Journal of Pharmacy, 2011; 2(1): 237-8.
10. Sandhya Mandadi , VishwanadhamYerragunta , UmemaNaaz., formulation and evaluation of atorvastatin calcium sustained release tablets., Int J Pharm 2016; 6(3): 124-130.
11. Barry, B. W. And Williams, A. C., Permeation Enhancement through skin in Encyclopedia of pharmaceutical Technology, Vol-11, Marcel Dekker Inc., Newyork, 1996, 49-58.
12. Allen LV, Popovich NG and Ansel H.C:Ansels Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams and Wilkins, Wolters kluwer, New York, 2005:9, 431-492.
13. Gita Chaurasia, a review on pharmaceutical preformulation studies in formulation and development of new drug molecules, ijpsr, 2015, 7(6).2313-2320.
14. Ruelle P. The n-octanol and n-hexane/water partition coefficient of Environmentally relevant chemicals predicted from the mobile order and disorder (MOD) thermodynamics. Chemosphere. 2000, 40(5):457-512.
15. Ahlam Zaid Alkilani, Maelíosa T.C. mccrudden,and Ryan F. Donnelly'Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum, 2015, 7(4): 438–470.
16. TasnuvaHaque and MdMesbah Uddin Talukder , Chemical Enhancer: A Simplistic Way to Modulate Barrier Function of the Stratum Corneum, 2018, 8(2): 169–179.
17. Duriez P. [Mechanisms of actions of statins and fibrates, Therapie. 2003, 58(1):5-14.
18. Matthew J Baker, JúlioTrevisan, Paul Bassan, Rohit Bhargava,Holly J Butler, Konrad M Dorling,Peter R Fielden, Simon W Fogarty, Nigel J Fullwood, Kelly A Heys Caryn Hughes, Peter Lasch, Pierre L Martin-Hirsch, Blessing Obinaju, Ganesh D Sockalingum, JosepSulé-Suso, Rebecca J Strong, Michael J Walsh, Bayden R Wood, Peter Gardner, and Francis L Martin' Using Fourier transform IR spectroscopy to analyze biological materials, Nat Protoc. 2014, 9(8): 1771–1791.
19. Kalamkarvipul, mashrurajshree, Quantitative Resoution of Atorvastatin Calcium and Fenofibrate in Pharmaceutical Preparation by using Derivative Ratio Spectrophotometry and Chemometric Calibrations". Analytical Sciences, 2007, 23.(4): 445-451.
20. Carda-Broch S, García-Alvarez-Coque MC, Ruiz-Angel MJ. Extent of the influence of phosphate buffer and ionic liquids on the reduction of the silanol effect in a C18 stationary phase. J Chromatogr A. 2018, 20;(15), 112-117.
21. Nidhi Sharma, A Brief Review on Transdermal Patches, Organic & Medicinal Chem IJ,2018, 7:(2), 001-005.
22. Sanjay Bajaj, Dinesh Singla and Neha Sakhuja ,Stability Testing of Pharmaceutical Products, Journal of Applied Pharmaceutical Science, 2012, 2:(03), 129-138.
23. Allison Crouter and Lauren Briens,The Effect of Moisture on the Flowability of Pharmaceutical Excipients, AAPS pharmscitech. 2014 Feb; 15(1): 65–74.
24. Ligang Zhao and Yan Li, 2009. Transdemal delivery of Tolerodine by O-acylmethanol: Invitro/Invivo correlation, Int J Pharm,Vol 374, pp 48-52.
25. Mazzo, D. J., Fong, E. K. F. And Biffar, S. E., A comparison of test methods for determining in-vitro drug relese from transdermal delivery dosage forms., J. Pharmaceutic Biomed. Anal., 1986, 4, pp 40-41.