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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF ANTI HYPERLIPIDEMIC AGENT

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ABSTRACT
This century has witnessed several spectacular developments in the field of pharmaceutical sciences especially in the drug delivery systems. The newer drug delivery technology has received an increasing attention in the face of growing awareness that drugs are excessively toxic and sometimes ineffective, when administered or applied by conventional means. Thus, conventionally administered drug formulations such as tablets, capsules, injections and oral liquids that are administered as multidoses usually produce large fluctuation of drug concentration in the blood stream. Transdermal drug delivery system has been in existence for a long time. The occurrence of systemic side effects with some of these formulations is indicative of absorption through skin. A number of drugs have been applied to the skin for systemic treatment.

KEYWORDS: Pharmaceutical sciences, administered, Transdermal drug delivery system.

INTRODUCTION
The skin was thought to be an impervious barrier. At the turn of the century, during World War II, munitions workers experienced fewer anginas attacks while working with nitroglycerin. This has challenged the traditional belief that the skin is a perfect protective barrier and also triggered intensive research activities to study the feasibility of transdermal drug delivery for systemic medication.[2,3]

Several transdermal drug delivery systems (TDDS) have recently been development with the aimof accomplishing the objective of systemic medication through the trans dermally controlled delivery of pharmaceuticals. The potential of TDDS was first demonstrated by the successful development of a scopolamine releasing TDD system in 1981 (Transderm- Scop system, Ciba) for 72-hour prophylaxis or treatment of motion induced sickness and nausea, then by the marketing success of several nitroglycerin releasing TDD systems of once – a-day medication of angina pectoris[4], Clonidine – releasing TDD systems for weekly therapy of hypertension[5] and Estradiol- releasing TDD systems for twice a day week treatment of post- menopausal syndrome.

Transdermal drug delivery system has been in existence for a long time. The occurrence of systemic side effects with some of these formulations is indicative of absorption through 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. The advantages of transdermal drug delivery include its ease of use, patient compliance, sustained drug delivery, local application and safety. Oral medications must pass through the gastrointestinal tract, into the liver- where drugs are broken down, possibly lowering their effectiveness. With the transdermal patch, drugs enter directly into the bloodstream, reducing the risk of gastrointestinal side effects and bypassing breakdown by the liver.[6]

METHODOLOGY
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.

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.

Melting point of Atorvastatin Calcium
Fine powder of the Atorvastatin Calcium was filled in glass capillary tube (previously sealed at one end) and kept inmelting point apparatus. The temperature at which the drug melts was noted. This was performed thrice and averagevalue was noted.

Solubility analysis of Atorvastatin Calcium
The solubility of the drug was determined by adding small amount of drug in the different solvents.

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**.** Finally, the buffer solution was separated, clarified by filtration and assayed for drug content using UV spectroscopy at its respective λ max.

Determination of λ max of Atorvastatin 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.

Identification of Atorvastatin 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 wereobtained and interpreted.

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)

FT/ IR spectral studies
Compatibility studies of the drug and the polymers were carried out using FT/ IR JASCO- 410 spectrometer. 1 part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into transparent, thin pellets. The pellets are then scanned under IR region and the spectra were recorded and discussed in the later part.

FORMULATION OF TRANSDERMAL PATCHES
In the present study, matrix type transdermal patches of Atorvastatin calcium were prepared by moulding techniques. A flat circular glass moulds having diameter 4.5 cm and height of 1 cm with a total surface area of 15.91cm^2 was fabricated for this purpose.

PREPARATION OF CASTING SOLUTIONS
The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture of chloroform and methanol at 1:1 ratio. The drug, plasticizer and permeation enhancers were then added to the various polymer solutions individually and thoroughly mixed to from a homogenous mixture. It was placed aside without any disturbances to allow the entrapped air to bubble out.

PREPARATION OF TRANSDERMAL PATCHES
About 3 ml of casting solutions were pipetted into circular glass moulds especially designed to hold contents, which is casted on mercury surface. The glass moulds containing the casting solutions were allowed for drying at room temperature for 24 hrs and the patches are dried in over at 40-45 for 30 minutes in order to remove the residual solvents. The patches were removed and cut into circular discs with 4.4cm diameter (15.21cm^2 surface area). These patches were wrapped in aluminum foil and stored in desiccator for further studies.[7]

Table 03: Formulation of Patches.

Ingredients	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T^9
AtorvastatinCalcium(mg)	10	10	10	10	10	10	10	10	10
HPMC (mg)	5.5	4.5	4.5	4.5	4	3.5	4.5	6.5	3.5
Ethyl Cellulose(mg)	3.5	2.5	2.5	4	3	3.5	4.5	2.5	3.5
Eudragit(mg)	1	3	3	1.5	3	3	1	1	3
Glycerol (ml)	30	30	30	30	30	30	30	30	30
DMSO in w/w	20	20	20	20	20	20	20	20	20

EVALUATION OF TRANSDERMAL PATCHES

The prepared patches were evaluated for their physico-chemical parameters, in vitro diffusion studies, skin irritation and stability studies.[8]

PHYSICO- CHEMICAL PARAMETERS

The matrices were evaluated for the following parameters.[9,10,11]

FILM THICKNESS

The thickness was measured at six different places using an Electronic Digital Micrometer (AEROSPACE- CHINA) and the mean Value was calculated.

DETERMINATION OF AVERAGE WEIGHT AND WEIGHT VARIATION

As weight variation between the formulated patches can lead to difference in drug content and in-vitro behaviour, a study was carried out by weighing 6 patches in an electronic balance (table: 6-8). The average weight of a patch and its standard deviation was calculated by using the following formulas.

DETERMINATION OF TENSILE STRENGTH:

The instrument, which was designed in our laboratory, was used for the measurement of tensile strength. The strip was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the film was cut.

DETERMINATION OF HARDNESS

The apparatus designed in our laboratory to study the hardness of the strips consists of a wooden stand of 11cms height and top area of 16 X 16 cm. A small pan was fixed horizontally on one end of the 2 mm thick iron rod whose other end is reduced to sharp point. A hole of 0.2 cm diameter was made at the center of the top area of wooden stand for supporting the pan rod. An electric circuit was made through a 3-volt battery in such a way that the bulb lights up only when circuit is completed through the contact of the metal plate and the sharp end of the rod.

DETERMINATION OF PERCENTAGE MOISTURE CONTENT

Moisture content can influence the mechanical strength and drug release behaviour of the transdermal therapeutic systems and therefore, in the present study determination of the moistureof the formulated patch was estimated by keeping the patch under vacuum desiccation until constant weights were obtained The percentage moisture content of the patch was calculated by the following formula.

DETERMINATION OF PERCENTAGE MOISTURE UPTAKE

The weighed films kept in a desiccator at room temperature for 24hrs was taken out and exposed to 75% relative humidity (a saturated solution of sodium chloride) in a desiccator until a constant weight for the film was calculated as the difference between final and initial weight with respect to initial weight.

PROCEDURE FOR IN-VITRO DRUG RELEASE STUDIES

In vitro permeation studies were performed by using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane[84] was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated patches were placed over the membrane. 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 bead at 50 rpm; the temperature was maintained at 37 ± 1^0C. The samples were withdrawn at different time intervals and analyzed for drug content. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative percentage release of drug permeated per cm^2 of patches were plotted against time.

PRIMARY SKIN IRRITATION STUDIES

Patches were applied to the shaved skin on the backs of albino rats and secured using adhesive tape. On one side of the back, control patch and on other side an experimental patches were secured. The animals were observed for any sign of erythema or oedema for a period of 24 hours.[65,84]

STABILITY STUDIES

To any rational design and evaluation of dosage forms of drugs the stability of the active component must be a major criteria in determining their acceptance or rejection. Drugs instability by a change in the physical appearance color, odor, taste or texture of the formulation whereas in other instances chemical changes may occur which are not self-evident and may be ascertained through chemical analysis. Hence to assess the stability the selected films were kept at room temperature and at 40ºC over a period of 45 days. Patches were evaluated at 15^{th}, 30^{th}, 45^{th} day for their physico-chemical properties and in vitro diffusion studies.

RESULTS AND DISCUSSION

Transdermal drug delivery system of Atorvastatin calcium was developed using polymers like HPMC, EC, and ERS100; employing glycerine as plasticizer and DMSO as the permeation enhancer. Formulated patches were subjected to physico- chemical evaluation such as physical appearance, weight variation, thickness, % moisture content, % moisture uptake, tensile strength, hardness and drug content. The in vitro drug release studies across cellulose membrane were conducted and the best formulations where subjected to stability studies.

Table 4: Basic descriptions of Atorvastatin calcium.

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

Solubility analysis of Atorvastatin calcium

Table 5: 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

Determination of λ max of Atorvastatin Calcium by UV spectra

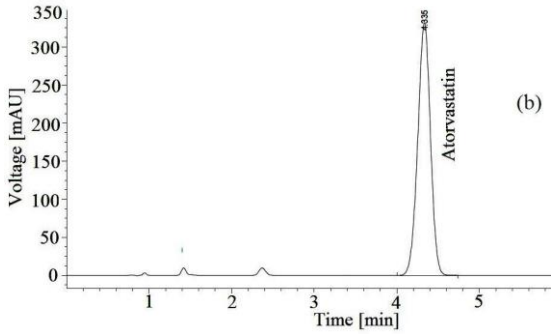


Fig 03: Determination of λ max of Atorvastatin Calcium by UV spectra.

Identification of Atorvastatin by IR spectra

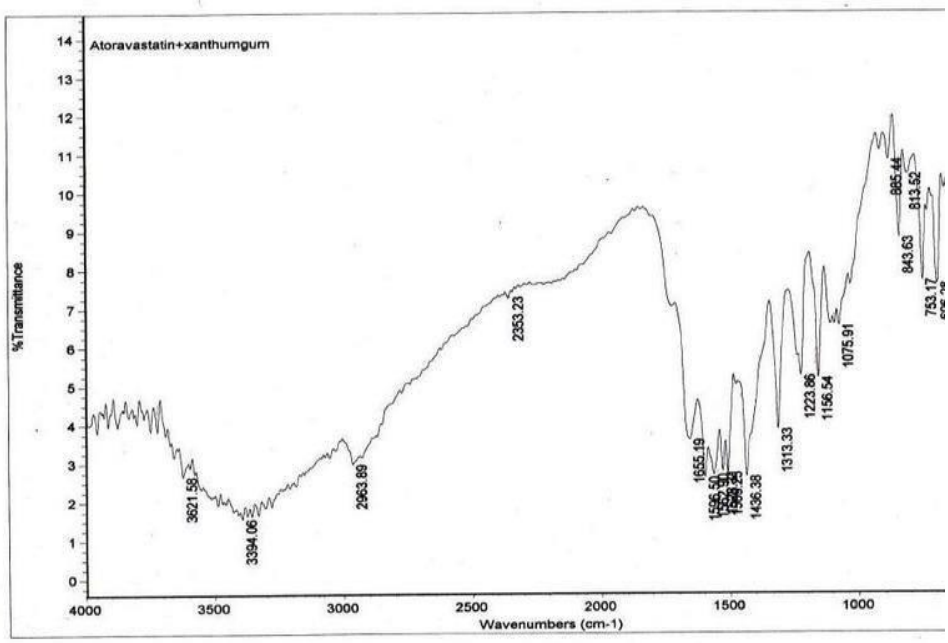


Figure 04: Spectra showing λ max of Atorvastatin calcium at 245.8nm.

Standard curve of Atorvastatin in Methanol

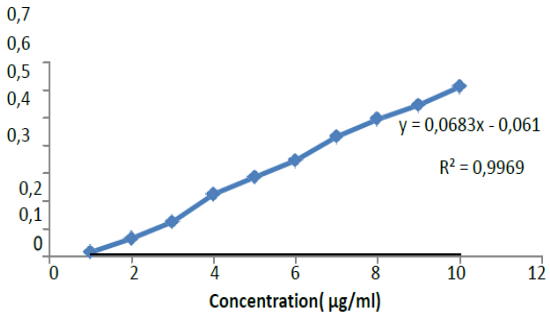


Fig. 05: Standard curve of Atorvastatin in Methanol.

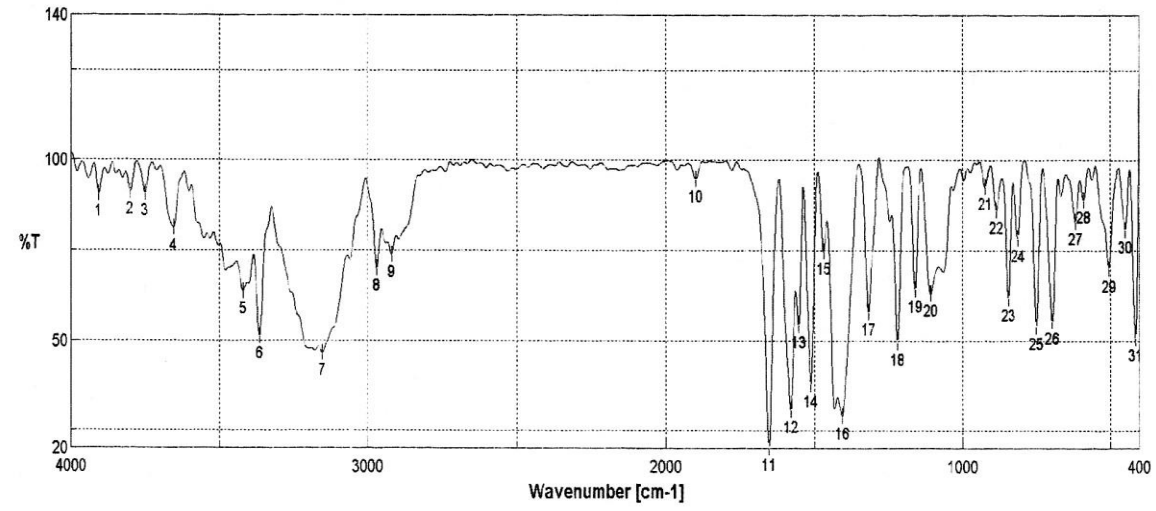
COMPTIBILITY STUDIES

The compatibility studies confirmed that the absence of chemical interaction betweenthe drug and polymers. The physico chemical parameters were evaluated.

FT/ IR spectral studies

Compatibility studies of the drug and the polymers were carried using JASCO FT/ IR spectrometer and the spectras were given in the Fig:7.

The spectra obtained from the mixture of polymers and drug was found to be matching with the spectra of the pure drug. There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of chemical interaction between the drug and polymer.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:07AM	Update	1/4/2008 4:15PM
Operator	C.Geetha		
File Name	Pure drug		
Sample Name	Pure drug		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3904.18	90.5836	2	3800.04	91.2623	3	3751.83	90.7712	4	3657.34	81.1928	5	3419.17	63.6966
6	3386.14	51.2475	7	3155.94	46.5804	8	2969.84	70.0429	9	2921.63	73.9391	10	1901.47	94.8126
11	1650.77	20.399	12	1579.41	30.8466	13	1552.42	54.2983	14	1511.92	38.0736	15	1468.53	74.8431
16	1406.82	29.0883	17	1316.18	57.9198	18	1215.9	49.6048	19	1157.08	64.3819	20	1105.01	63.2327
21	922.771	92.7164	22	883.238	86.051	23	842.74	61.9004	24	809.956	78.414	25	746.317	53.9319
26	693.284	55.3926	27	617.109	82.9562	28	590.111	88.9129	29	504.294	69.892	30	449.333	80.8388
31	413.656	50.7881												

Fig. 07: FT IR of Atorvastatin Calcium.

Physico- Chemical Parameters

Twenty-one patches of Atorvastatin calcium loaded with different ratios of HPMC, EC and ERS100 were prepared by moulding technique. The prepared patches were evaluated for physico chemical parameters and in vitro drug release behavior.

The determination of the average weight of patch, having 15.21cm^2 surface area showed a significant change between the patches prepared with different polymer ratios. The average weight of the patches T1- T9 was given in the table: 6-8. Among the 9 patches, T1- T3 showed a higher average weight compared to other patches and T4-T6 showed less weight. This increase in weight of T1- T3 patches is due to usage of 10%w/w of polymers whereas in other formulationsonly 5%w/w polymers were used.

There was no significant change in the thickness of the patches (T1- T9), which was determined by aerospace digital electronic micrometer This indicates that the patches were uniform and reproducible. The results of moisture content of the coded transdermal patches (T6-T9) showed a marked difference in the moisture content. The patches T6-T9showed higher moisture content and moisture uptake, which was due to the higher content of hydrophilic polymer, HPMC. The patches T1 to T3 showed less moisture content and uptake because of the blend of both hydrophobic polymers.

Tensile strength is found to be higher for the patches T6-T9 when compared to otherpatches and hardness is found to be low for the patches T6- T9 when compared to other patches. All the patches showed uniform drug content, which was determined using SHIMADZU UV- 1700 spectrophotometer.

Table 07: Hardness Profile.

Formulation code	Hardness(g)
T^1	175
T^2	172
T^3	170
T^4	169
T^5	155
T^6	134
T^7	110
T^8	12.76
T^9	16.59

Formulation Code	Physical Appearance	Weight Variation (grams)	Thickness (mm)	Tensile Strength (kg/cm^2)	Moisture Content (%)	Moisture Uptake(%)
T^1	Translucent, Flexible, Smooth.	0.592±0.028	0.175±0.009	0.946	3.31±0.18	5.43±0.01
T^2	Translucent, Flexible, Smooth.	0.566±0.017	0.184±0.013	0.927	2.77±0.16	4.97±0.004
T^3	Translucent, Flexible, Smooth.	0.474±0.019	0.147±0.003	0.945	2.59±0.43	4.05±0.001
T^4	Translucent, Flexible,Smooth.	0.500±0.009	0.152±0.008	0.943	2.48±0.90	3.77±0.009
T^5	Translucent, Flexible, Smooth.	0.497±0.01	0.167±0.006	0.895	2.43±0.66	3.15±0.01
T^6	Translucent, Flexible,Smooth.	0.502±0.008	0.195±0.018	0.839	2.09±0.49	2.64±0.02
T^7	Translucent, Flexible, Smooth.	0.525±0.001	0.056±0.043	0.890	1.24±0.57	1.99±0.025
T^8	Transparent, Flexible, Smooth	0.322±0.006	0.157±0.015	1.755	8.75±0.015	10.12±0.006
T^9	Transparent, Flexible, Smooth	0.322±0.006	0.120±0.07	1.645	7.55±0.007	9.88±0.009

Fig 08: Physiochemical Properties.

In Vitro Drug Release studies

The in vitro drug release studies carried out indicate the influence of polymers on the release of drug. The cumulative release of drug (mg/cm^2) and cumulative percentage release of T_1- T_9 patches over 24 hrs were determined and are summarized in table 09.

The increase in HPMC concentration resulted in increase in drug released from T_8 patch, whereas T_1 showed lower drug release because both the polymers EC and ERS100 were hydrophilic.

Skin irritation studies

The skin irritation study reveals that the drug loaded and unloaded patches didn't cause any noticeable signs of irritation or oedema on albino rat's skin, indicating the skin compatibility ofdrug as well as polymer matrix ***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.

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.

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.

Stability studies

The stability studies indicate there was no change in physico- chemical and in vitro drug release studies.

Table 09: *In-vitro* skin membrane permeation study of optimized formulation (T8).

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

Stability studies

The stability studies indicate there was no change in physico- chemical and in vitro drug release studies for T1, T4, and T8 patches.

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 (T8)

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 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.

Table 10: Stability studies of optimized Formulation (T8) at different Temperature after 30 days.

S.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

SUMMARY AND 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) 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. An attempt to develop transdermal therapeutic system for Atorvastatin calcium using polymers like HPMC, EC, and ERS100 was carried out for the purpose of attaining maximum bioavailability by tress passing pre-systemic hepatic metabolism. The compatibility studies using TLC and IR spectral studies revealed the absence of interaction between the drug and the polymer. The formulated patches were evaluated for the physico-chemical parameters, in vitro drug release studies, skin irritation studies and stability studies. The patches showed a significant variation in their average weight, which might be due to the variation in the

proportions of polymers used. There was no significant change observed in the thickness of all the twenty- one patches. The percentage moisture content and percentage moisture uptake is found to be high for the patches formulated with HPMC:EC when compared to the patches formulated with HPMC: ERS100 and EC: ERS100. The reason behind the screen might be the higher proportions of hydrophilic polymer, HPMC along with EC; whereas patches with HPMC: ERS100 combination shows lesser moisture content and moisture uptake because of the highly hydrophobic polymer, ERS100.

For the patches with HPMC:EC tensile strength was found to be high and hardness was found to be low when compared to other patches which might be due to the nature of the polymers. All the patches showed uniform drug content.

The formulations showed a better in vitro drug release profile across the cellulose membrane, when compared to the other formulations. This might be attributed to the nature of polymer; plasticizers used and even the permeation enhancer. The skin irritation studies using albino-rats revealed no signs of irritation or oedema, which confirms the skin compatibility of both the drug loaded and plain patches.

As far the above results is concerned formulations T_8 was selected and subjected for stability studies at room temperature and at 40ºC for a period of 45 days. The stability studies results signified that the formulated patches possess adequate shelf life till 45 days. Since the results are encouraging for the formulation T_8, the proper technique should be applied for commercial and mass production of the same formulation. However long term pharmacokinetic and pharmacodynamic studies should be undertaken to establish the usefulness of these patches Since the results are encouraging for the formulation T8, the proper technique should be applied for commercial and mass production of the same formulation.

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