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FORMULATION AND EVALUATION OF TDDS OF FLUVASTATIN SODIUM

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ABSTRACT

The aim of the present study was to develop transdermal patch of Fluvastatin sodium with different permeation enhancers and release retarding polymers to achieve extended-release of Fluvastatin sodium . Fluvastatin sodium transdermal patch prepared by solvent casting method. Different formulations were prepared by changing the different release retarding polymers and different permeation enhancers to check the impact of polymer and permeation enhancers on the performance of prepared patches. All the patches were uniform and translucent. These were having good strength and visually smooth surfaced. The patches were evaluated based on their physical characteristics like, film thickness, folding endurance, percentage moisture content ,moisture uptake and their evaluation like, drug content uniformity and *in vitro* drug permeation study. The patches show thickness values in between 0.1 cm to 0.2cm, Folding endurance was found to be in the range of 106 for formulation F6. Similarly, the patches are also subjected to drug content uniformity study which suggest uniform dispersion throughout the transdermal patches. *In vitro* permeation studies using egg membrane shows highest drug release for HPMC100 M patch containing solid dispersion of drug with transcutol i.e., 87.27% in 8 hrs. Among permeation enhancers transcutol has improved permeation to 87.27% in 8 hrs in HPMC100 M. The mechanism of release of drug was diffusion rate limited.

KEYWORDS: Fluvastatin sodium, HPMC 4 M, HPMC15 M, HPMC100 M, DMSO, transcutol.

INTRODUCTION

Oral route is the popular route of drug delivery. Although it has some disadvantages including first pass metabolism, drug degradation in gastrointestinal tract due to enzymes, PH etc. To cross these problems, a novel drug delivery system was developed. In this transdermal drug delivery system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. Medicated adhesive patches or transdermal patches are of different sizes, having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways-through hair follicles, through sebaceous glands, through sweat duct. Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.

Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as parental route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections; and the limited controlled release options of both.

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Today the most common transdermal system present in the market mainly based on semipermeable membranes which were called as patches.

The aim of the current study was to develop transdermal patch of Fluvastatin sodium with different permeation enhancers and release retarding polymers to achieve extended-release of Fluvastatin sodium.

MATERIALS AND METHODS

Fluvastatin sodium (Mylan pharma limited, Hyderabad), HPMCK4M, HPMCK15M, HPMCK100M (MSN formulations divisions, pashamylaram),and Ethyl cellulose (Amul India Ltd, Mumbai), PVP (Essel fine chem, Mumbai), Transcutol, DMSO(s d fine-chem. limited,Mumbai).

Preparation of transdermal drug patches of Fluvastatin sodium

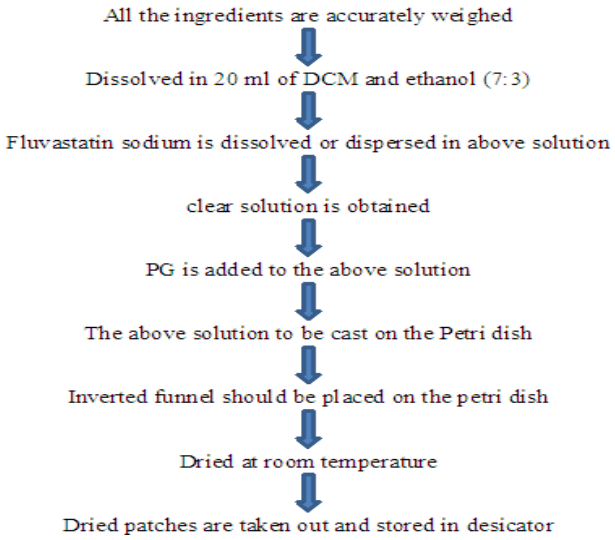

Table 1: Composition of different formulations.

Ingredients	F1	F2	F3	F4	F5	F6
Fluvastatin Sodium	50	50	50	50	50	50
Hpmck4m	900	-	-	900	-	-
Hpmck15m	-	900	-	-	900	-
Hpmck100m	-	-	900	-	-	900
Ethyl cellulose	600	600	600	600	600	600
PVP	300	300	300	300	300	300
Transcutol	600	600	600	-	-	-
DMSO	-	-	-	600	600	600
Propylene Glycol	450	450	450	450	450	450
DCM: Ethanol	20	20	20	20	20	20
PVA	10	10	10	10	10	10

Fourier Transform Infra-Red (FTIR) Spectroscopy

The FTIR analysis of drug loaded beads prepared by ionotropic gelation technique were performed using Shimadzu FTIR-8400, Japan. All the samples were crushed with potassium bromide to get pellets at 600kg cm^{-2}. Spectrial scanning was done in the range of 400-4000 cm^{-1}.

Evaluation Tests

Thickness of the patch: The thickness of the drug loaded patch is measured in different points by using a digital micrometer or vernier calipers and determines the average thickness of the prepared patch.

Folding endurance: A strip of specific film is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Percentage Moisture content: The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content = [Initial weight-Final weight/ Final weight] ×100

Percentage moisture uptake: Patch is weighed individually then it is kept in desicator containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor (RF) then film is reweighed & percentage moisture uptake is calculated by using following formula-

Percentage moisture uptake (%) = (Final weight-Initial weight/initial weight) ×100

Drug content: A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV). Each value represents average of three different samples.

***In vitro* skin permeation studies:** An in vitro permeation study can be carried out by using diffusion cell. Phosphate buffer pH 6.8 placed in diffusion cell along with egg membrane before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant . The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated egg membrane is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analysed spectrophotometrically. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

RESULTS AND DISCUSSION

Table 2: Thickness of formulation F1 to F6.

	F1(cm)	F2(cm)	F3(cm)	F4(cm)	F5(cm)	F6(cm)
Side 1	0.1	0.2	0.1	0.2	0.1	0.2
Side 2	0.1	0.2	0.1	0.1	0.1	0.2
Side 3	0.1	0.2	0.1	0.1	0.1	0.2
Side 4	0.1	0.2	0.1	0.2	0.1	0.2
Avg.	0.1	0.2	0.1	0.15Tble	0.1	0.2

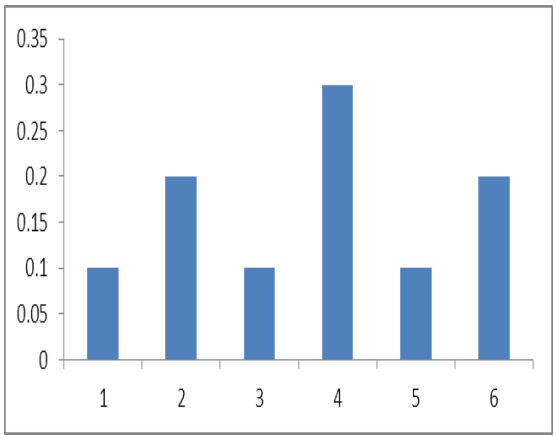

Fig. 1: Thickness of formulation F1 to F6.

Thickness of all transdermal patches at different edges were studied using vernier caliper. Thickness in the different formulations was in the range of 0.1 cm to 0.2cm**.** Maximum thickness was found in formulation F2, while minimum found in formulation F1.

Folding Endurance

Table 3 Folding endurance of formulation F1 to F6.

Formulation	Folding Endurance (no. of times)
F1	141
F2	176
F3	162
F4	121
F5	115
F6	106

Folding endurance was found to be in the range of 106 for formulation F6. The highest folding endurance shows maximum strength for the formulation F2. F2 patch prepared by using polymer HPMCK15M and in case of F6 polymer HPMCK100M is used.

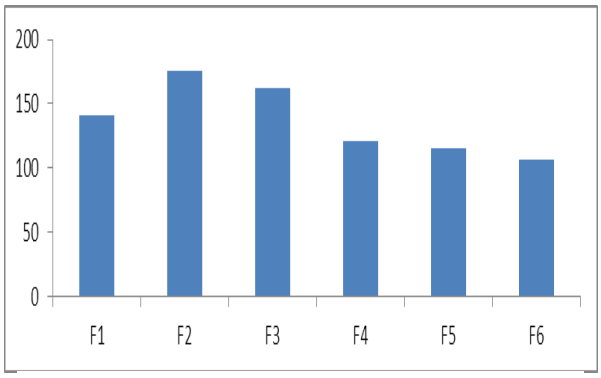

Fig 2: Folding endurance of formulation F1 to F6.

Percentage Moisture content

Table 4: Percentage Moisture content of formulation F1 to F6.

Formulation	% moisture content
F1	6.25%
F2	17.39%
F3	20%
F4	9.60%
F5	26.30%
F6	9%

- It was found to be least in case of formulation F1 which contain HPMC K4M (900) and Transcutol (600) were as maximum for formulation F6 which contain HPMC K100M (900) and DMSO (600).
- It shows Formulations with HPMC K4 M absorbed least moisture.
- Formulations with HPMC K 15 M absorbed maximum moisture.

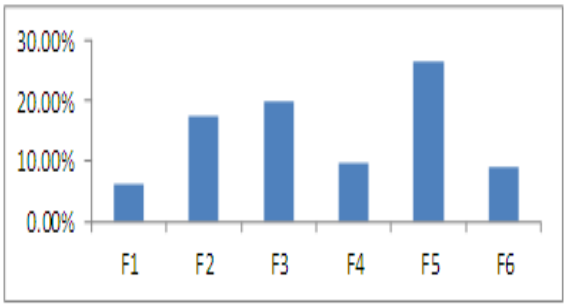

Fig. 3: Percentage Moisture content of formulation F1 to F6.

Percentage Moisture Uptake

Table 5: Percentage moisture uptake of formulation F1 to F6.

Formulation	% moisture uptake
F1	81.80%
F2	66.60%
F3	28.50%
F4	36%
F5	80%
F6	27%

It indicates the hygroscopicity of the used polymers in the formulation as moisture content effects stability of transdermal patches during storage and handling. It can be co- related to the stability indicating parameters to achieve maximum stable transdermal patch of Fluvastatin sodium. Maximum moisture was up taken by

formulations F2 and F5 prepared with HPMCK 15 M after obtaining prepared transdermal patches.

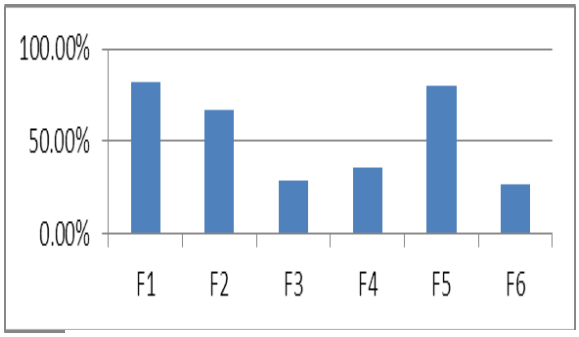

Fig. 4: Percentage moisture uptake of formulation F1 to F6.

Drug content

Drug content of the matrices was carried out to ascertain that the loading of drug is uniform in the formulation. The results obtained are represented in Table 6.The films were found to contain 92.49% - 98.85% of the labelled amount of Fluvastatin sodium indicating uniformity of drug content. The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for content uniformity as per official requirements. All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Fluvastatin sodium in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with acceptable deviation.

Table 6: % Drug content of formulation F1 to F6.

	% drug content
F1	94.36
F2	95.78
F3	92.49
F4	94.24
F5	95.71
F6	98.85

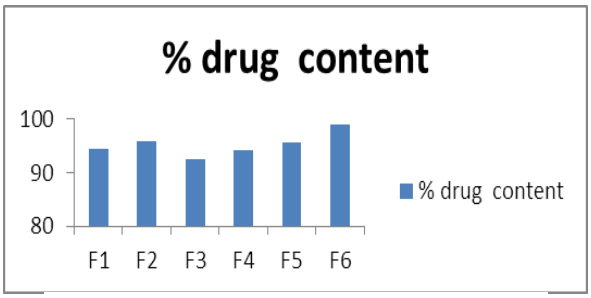

Fig 5: Drug content of formulation F1 to F6.

Drug-Excipient Incompatibility Studies

FT-IR spectroscopy was employed to ascertain the compatibility between Fluvastatin sodium and the selected polymers. The individual drug and drug with excipients were scanned separately. Disappearance of Fluvastatin sodium peaks or shifting of peak in any of the spectra was studied.

The FT-IR spectrum of pure Fluvastatin sodium was shown in figure: and the FT-IR spectra of Fluvastatin sodium in formulation are shown in Figure 6. The presence or absence of characteristics peaks associated with specific structural groups of the drug molecule was noted. From the FTIR spectra it was revealed that no interaction occurred between Fluvastatin sodium and different polymers.

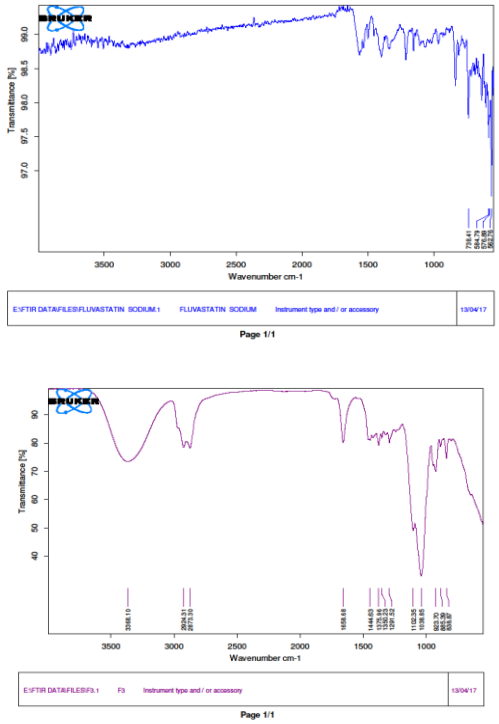

Fig. 6: The FT-IR spectrum of pure Fluvastatin sodium and F3 formulation.

In Vitro Diffusion Study of Matrix Diffusional Transdermal Drug Delivery Device Of Fluvastatin Sodium

The release rate determination is one of the most important study to be conducted for all controlled release delivery systems. The diffusion studies of patches are very crucial, because one needs to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in the body to achieve a constant rate of drug permeation.

Diffusion studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release. In vitro release profile is an important tool that predicts in advance how the drug will behave in vivo. The results of in vitro drug diffusion studies of transdermal patches are depicted in Table 7 and Figure 7:

Table 7: In vitro skin permeation studies.

Time	Cumulative % drug permeated					
(Hrs.)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.25	2.502	0.162	16.743	2.637	15.047	1.654
0.5	6.584	0.349	24.934	8.111	20.217	2.646
0.75	11.707	1.453	34.987	12.584	30.501	7.95
1	14.315	2.377	41.299	15.176	37.451	12.742
2	20.327	2.865	52.01	24.584	48.123	15.864
3	27.221	4.915	57.909	31.501	53.187	25.445
4	35.847	5.959	63.789	39.303	58.564	30.671
5	44.52	8.026	68.976	47.996	65.664	41.012
6	54.936	9.766	74.573	58.43	71.107	49.713
7	67.104	11.514	82.062	70.617	78.273	58.462
8	77.642	15.985	87.276	81.174	83.782	70.649

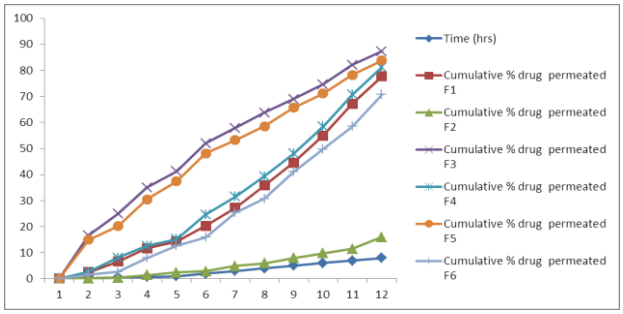

Figure 7: In vitro diffusion profiles of Fluvastatin sodium from F1 to F6 formulation.

The results of diffusion study of Fluvastatin sodium loaded polymeric matrix formulated using various polymers are presented in Table 1.

Transdermal patches of Fluvastatin sodium were found to be satisfactory. Among the different formulations of matrix type (F1 to F6), the formulation F3 was selected as best formulation, after considering its low percentage moisture content (1.925%), percentage moisture uptake (1.495%),better % drug content (89.010%) and maximum 76.361 % drug permeated through the skin at the end of 24 hrs. The drug permeation profile was found to follow zero order kinetics. The patches were thin, flexible and transparent.

Drug release kinetic studies

Table 8:

	Zero Order		First Order	
Formulation	K	R2	K	R2
F1	9.15	0.9922	0.151	0.8242
F2	1.79	0.9746	0.199	0.759
F3	9.041	0.8772	0.072	0.775
F4	9.569	0.9934	0.146	0.8027
F5	8.911	0.899	0.078	0.789
F6	8.427	0.993	0.174	0.799

- The zero order k value and R2 value was found to be higher than first order.
- Stating that all formulation followed zero order there by, the transdermal patches acted as controlled drug delivery system.

Among all the formulation F1 to F6 the zero order k and R2 value were highest for F4 formulation

SUMMARY AND CONCLUSION

Summary

Fluvastatin sodium is HMG Co - A reductase inhibitors widely used in the treatment of hyperlipidemias and cardiovascular diseases and it is known to have low oral bioavailability (5%) due to an extensive high first-pass effect and its availability in less dose size i.e., in few mg. hence the transdermal patches of Fluvastatin sodium was developed that could be applied to the skin to release the drug directly in systemic circulation to avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.
Methodology in development and evaluation of Fluvastatin sodium transdermal patches using HPMC4, HPMC15 and HPMC100, and permeation enhancers (Transcutol and DMSO) is given. Transdermal patches were characterized for physicochemical properties, *in vitro* permeation.

Fluvastatin sodium transdermal patches prepared by solvent casting method. Patches were found to have good surface texture, folding endurance and drug content within prescribed limits. *In vitro* residence time and permeation of Fluvastatin sodium from the prepared formulations was effected by the permeation enhancer used. Among all the formulations, F4 formulation showed highest permeation when compared to other patches.

The prepared patches gave promising results with respect to release of drug from the developed formulations.

CONCLUSION

In the present study Fluvastatin sodium transdermal patches were prepared using HPMC4, HPMC15,and HPMC100 as film former. Effect of permeation

enhancers were studied. From the present research work following conclusion can be drawn:

- FT-IR studies revealed that there is no chemical interaction between Fluvastatin sodium and the excipients used in the study.
- The prepared film containing Fluvastatin sodium was clear and colour less and smooth surface with some little pores and without any scratches or transverse striations.
- Formulated films gives satisfactorily result for various physico-chemical evaluation of films like physical appearance, and surface texture, thickness uniformity, Folding endurance, Drug content uniformity, and *In vitro* permeation. The drug content of the prepared films indicate weight and drug content uniformity within the batches prepared.
- The patches show folding endurance values in between 211±2.081 to 329 ± 6.557.
- Similarly, the patches are also subjected to drug content uniformity study which suggest uniform dispersion throughout the transdermal patches.
- In vitro permeation studies using egg membrane shows highest drug release for F4 patch containing solid dispersion of drug with transcutol permeation enhancer i.e 87.27% in 8 hrs.
- Among two permeation enhancers transcutol has improved permeation to 87.27% in 8 hrs in HPMC100 patch.
- In all the formulations with respect to elasticity, flexibility, and in vitro permeation of drug formulation containing HMC100 M as film forming polymer has proved to be best formulation.
- The zero order k value and R2 value was found to be higher than first order.
- Stating that all formulation followed zero order there by, the transdermal patches acted as controlled drug delivery system.
  Among all the formulation F1 to F6 the zero order k and R2 value were highest for F4 formulation
- From the above results it can be concluded that Fluvastatin sodium can be delivered in the form of transdermal patches. Release pattern of drug from these patches can be altered by using different formulation variables.

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