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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF ATORVASTATIN CALCIUM

***Asija Rajesh[1], Umesh Kumar[2], Asija Sangeeta[2], Patel Chirag J[2], Mangukia Dhruv[2], Patel Pinkesh[2]**

[1]Professor & Principal, Maharishi Arvind Institute of Pharmacy, Mansarover, Jaipur, Rajasthan, India-302020.

[2]Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India-302020.

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ABSTRACT

In present work was designed to develop suitable transdermal matrix type of Atorvastatin calcium, using Hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) with PEG 400, n-DB (as plasticizers) and propylene glycol (as penetration enhancer). The solvent casting technique was employed for the preparation of HPMC, and EC film. The dry films were evaluated for weight variation, thickness uniformity, moisture content, moisture uptake, folding endurance and % drug content. *In-vitro* diffusion studies were performed using cellulose acetate membrane in a Franz's diffusion cell. The concentration of diffused drug was measured using UV- visible spectrophotometer at λ max 246.2 nm. Patches prepared, from each batch, gave release profile for over 24 hours. Cumulative amount of drug release in 24 hours from all the prepared formulations were found to be in following order: F2 > F3 > F7 > F9 > F8 > F5 > F1 > F6> F4 > F10. Prepared patch from HPMC 5 cps and ethyl cellulose (F2) exhibited good characteristics for sustained release action and other parameters evaluated.

KEY WORDS: Atorvastatin Calcium, Transdermal Delivery, Hydroxyl Propyl Methyl Cellulose, Ethyl Cellulose

INTRODUCTION:

Transdermal drug delivery is defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems[1]. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the 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. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Simvastatin is poor aqueous solubility of many drug candidates; it becomes uneasy to drug to reach the market although exhibiting potential pharmacodynamic property. It is very useful to find appropriate formulation approaches to improve aqueous solubility and thus bioavailability of poorly soluble drugs[2].

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 catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin is commercially available as tablets of 10mg, 20mg, and 40mg and 80mg strengths as immediate release dosage form. After oral administration bioavailability is only 5% due to extensive first pass metabolism in the liver. 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 aim of this study was to develop and evaluate transdermal patches of Atorvastatin Calcium so as to prevent its first-pass 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

*Corresponding author: Dr. Asija Rajesh | Email: asijar@gmail.com

release transdermal drug delivery system for Atorvastatin Calcium[1, 3].

MATERIALS AND METHODS:

MATERIALS:

Atorvastatin calcium was received as a gift sample from Ronak Pharmaceuticals Pvt Ltd., Patan. HPMC 5 cps, HPMC 15 cps, HPMC K 100M, Ethyl cellulose, Propylene glycol, PEG 400, n-dibutyl phthalate, Methanol and Chloroform were purchased from Central Drug House (P) Ltd., New Delhi.

METHOD:

Preparation of patches: Matrix type transdermal patches loaded with Atorvastatin calcium were prepared by solvent casting method. Required quantities of polymers were weighed and dissolved in 10 ml mixture of methanol and chloroform in the ratio 1:1. Sonicated for 30 min. Stir for 1 hour on a magnetic stirrer at 400rpm. 78.71 mg of drug was weighed and added to the above solution. Required quantity of PEG 400, n-DB (as plasticizers) and propylene glycol (as penetration enhancer) were measured and added to the above solution. Stir on a magnetic stirrer at 400 rpm for 2 hours. The resulted uniform solution was cast on a Petri dish of area 70.84 cm2, previously containing a layer of mercury. An inverted funnel was placed over the Petri dish to prevent the fast evaporation of the solvent. After 24 hours, the dried patches were taken out, cut into pieces of 3cm * 3cm (area = 9 cm2 and containing 10mg of the Atorvastatin Calcium) and stored in a desiccators[4-7].

Table 1: Formulation of Atorvastatin calcium transdermal patch

Batch Code	INGREDIENTS							
	Different Polymers Ratio	Drug (mg)	HPMC 5 cps (mg)	HPMC 15 Cps (mg)	EC (mg)	PG (ml)	PEG 400 (ml)	n-DB (ml)
F1	1:2	78.71	460	-	920	0.208	0.3	0.3
F2	2:1	78.71	920	-	460	0.208	0.3	0.3
F3	1:2	78.71	-	460	920	0.208	0.2	0.4
F4	2:1	78.71	-	920	460	0.208	0.4	0.2
F5	1:2	78.71	460	-	920	0.416	0.4	0.2
F6	2:1	78.71	920	-	460	0.208	0.2	0.4
F7	1:2	78.71	460	-	920	0.208	-	0.6
F8	2:1	78.71	920	-	460	0.208	0.6	-
F9	1:2	78.71	460	-	920	-	0.3	0.3
F10	1:4	78.71	270	-	1080	0.208	0.3	0.3

EVALUATION:

1. WEIGHT UNIFORMITY:

The prepared patches are to be dried at 60ºC for 4 hours before testing. Weight uniformity was done by weighing 5 different patches of each batch. All the patches, selected at random, should be uniform in size (3cm * 3cm). Calculate the average weight of three[8].

2. THICKNESS OF THE PATCH:

The thickness of the patch is measured by digital micrometer at different points. For each formulation, three patches were used. The average value for the thickness of single patch was determined[9].

3. FOLDING ENDURANCE:

A strip of specific area (3cm * 3cm) is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance[6, 10].

4. MOISTURE CONTENT:

The prepared films weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The films are weighed again after a specified interval until they show a constant weight[7, 8]. The percent moisture content was calculated by following formula:

% Moisture content = [Initial weight – Final weight / Final weight] x 100

5. MOISTURE UPTAKE:

Weighed films were kept in desiccators at room temperature for 24 hrs. These were then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccators until a constant weight is achieved % moisture uptake is calculated as given below[11]:

% Moisture uptake = [Final weight –Initial weight/ Initial weight] x 100

6. PERCENTAGE ELONGATION BREAK TEST:

Percentage elongation is determined by measuring the length just before the breaking point. The percentage elongation can be determined from the below mentioned formula[10, 11]:

$$\% \text{ elongation} = x100 \frac{L_1 - L_2}{L_2}$$

Where;

L1 = final length of each strip.

L2 = initial length of each strip.

7. % DRUG CONTENT:

A film was cut into small pieces, put into a 100ml of methanol and shaken continuously for 24 hrs. Than the whole solution was ultra-sonicated for 15 min. After filtration, the drug was estimated by UV spectrophotometer at wavelength for 246.2nm and the drug content was determined[12-14].

8. IN-VITRO DRUG RELEASE STUDIES:

The in-vitro drug release studies were carried out in a Franz diffusion cell. The cellulose acetate membrane (pore size = 0.45µm) was mounted between donor and the receptor compartment of the diffusion cell. Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 10 ml and stirred with bent stainless steel pin. The temperature was maintained at 37 ± 1°C with the help of hot plate. The diffusion was carried out for 24 hours and 3ml sample was withdrawn at an interval of 1 hour. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analysed at 246.2nm[4, 8].

RESULTS AND DISCUSSION:

Transdermal patches of Atorvastatin calcium were prepared by solvent evaporation method in a Petri-dish on a mercury platform with an inverted funnel to control the rate of evaporation of the solvent. Different formulation (as shown in table 1) containing Atorvastatin calcium were prepared to achieve the sustain release pattern within the therapeutic range.

INVESTIGATION OF DRUG-POLYMER COMPATIBILITY:

Drug - polymer compatibility was checked by comparing the IR spectra of formulations with that of the pure drug. No significant changes in the functional groups between the two spectra were observed. This ensured the compatibility of polymer with that of the drug.

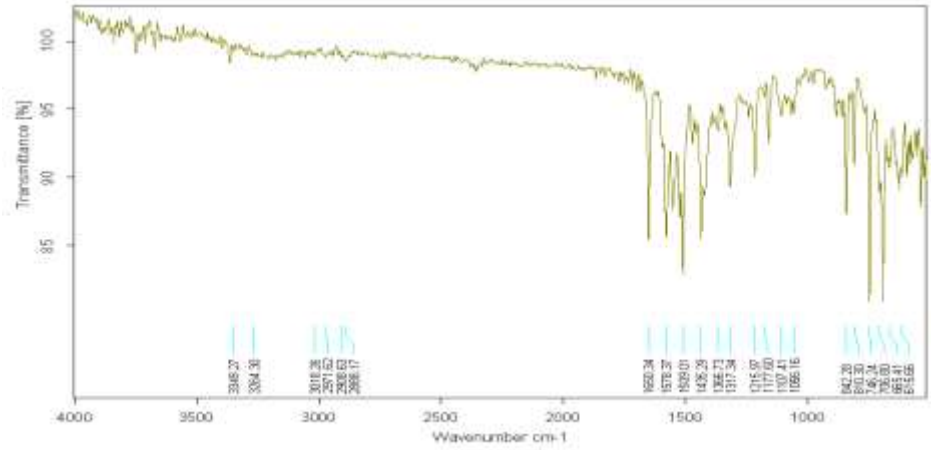

Figure 1: IR Spectra of atorvastatin calcium

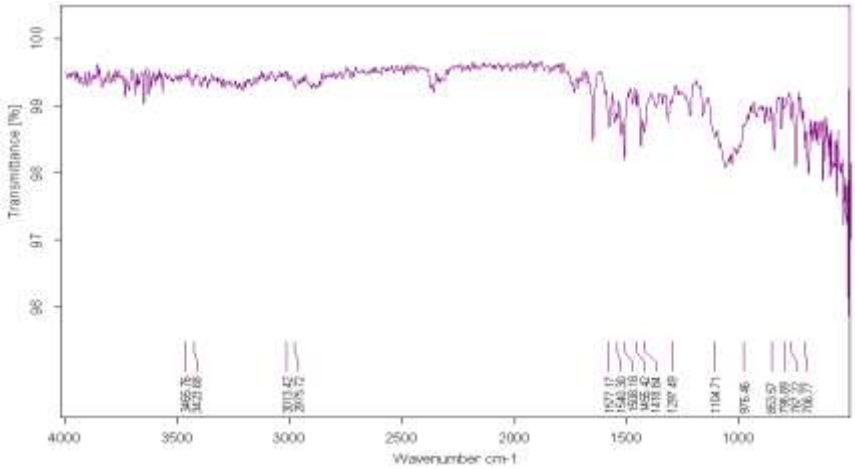

Figure 2: IR Spectra of EC, HPMC 5 cps and Atorvastatin calcium

PHYSICOCHEMICAL EVALUATION OF TRANSDERMAL PATCHES:

Table 2: Physicochemical evaluation parameters

Batch Code	PARAMETERS			
	Weight Variation (Mean (mg) ± SD)	Thickness (Mean (mm)± SD)	%Moisture uptake	%Moisture content
F1	354±4.03	0.14±0.028	5.6	1.1
F2	395±2.42	0.15±0.019	2.8	1.5
F3	321±5.32	0.12±0.018	6.6	1.7
F4	344±4.25	0.15±0.021	6.9	1.4
F5	329±3.10	0.14±0.023	7.3	2.04
F6	319±2.98	0.12±0.016	6.5	1.4
F7	326±4.37	0.11±0.026	5.3	2.3
F8	360.30±3.37	0.16±0.031	6.3	1.9
F9	327.3±5.02	0.14±0.018	5.1	1.4
F10	351±6.43	0.15±0.021	5.09	1.6

Table 3: Physicochemical evaluation parameters

Batch Code	PARAMETERS		
	Folding endurance	% Elongation Break Test	% Drug Content
F1	176±5.2	41.1±0.012	93.4±4.02
F2	168±3.2	40.2±0.014	95.9±3.32
F3	184±7.3	38.66±0.012	94.1±5.22
F4	192±3.9	42.1±0.016	93.4±4.13
F5	171±5.5	28.8±0.011	92.12±5.91
F6	89±4.1	25.55±0.017	95.1±3.51
F7	62±7.6	17.7±0.13	93.2±2.99
F8	44.6±7.1	23.3±0.15	92.41±3.12
F9	54.3±4.2	24.4±0.11	94.1±4.72
F10	130±5.3	41.06±0.14	93.7±6.01

The results of the physicochemical evaluation of the transdermal patches are described in table 2 and table 3. The weight variation of all the formulations varied in between 395 ± 2.98 and 319 ± 2.06. The variation in the thickness of all the formulation was in the range 0.11 ± 0.029 to 0.16 ± 0.031. Moisture content of these patches was found to vary from 1.1 to 2.3. % moisture uptake was observed from 2.8 to 7.3 respectively. This difference in the moisture content and water absorption was may be due to the difference in hydrophilicity of the polymers and extent of solvent evaporation during formulation. Folding endurance was found to be in between 44.6±7.1and 192±3.9. The % elongation break test was found to be from 17.7±0.13 to 42.1±0.016. Folding endurance and % elongation break test was found maximum in formulation containing HPMC 5cps and EC as polymers. The % drug content and % cumulative drug release was found maximum in formulation F2 (batch code).

***IN-VITRO* RELEASE STUDIES:**

In-vitro release studies for all the prepared patches were carried out for 24 hours. % cumulative drug release after 24 hours was taken and compared for all the patches. F2 exhibited maximum drug release at the end of 24th hour. Results are as shown in the table 4 and 5.

Table 4: *In-vitro* release profile of atorvastatin calcium transdermal patch of F1-F5

Time (hr.)	Percentage Drug Release (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	8.02	9.92	8.74	8.82	6.87
2	12.31	15.03	12.11	13.32	10.91
3	15.36	19.91	15.07	17.85	14.59
4	18.68	22.79	19.88	20.27	17.55
5	21.41	24.91	23.96	22.91	20.93
6	24.51	27.41	27.24	24.81	23.6
7	26.91	29.92	32.74	27.36	25.98
8	29.5	33.41	36.90	30.13	28.5
9	32.4	36.91	40.57	33.41	31.98
10	35.4	38.97	45.40	36.46	34.5
11	37.98	42.13	49.51	38.91	36.12
12	40.42	44.41	54.31	41.46	38.98
24	51.73	69.22	61.81	48.19	55.61

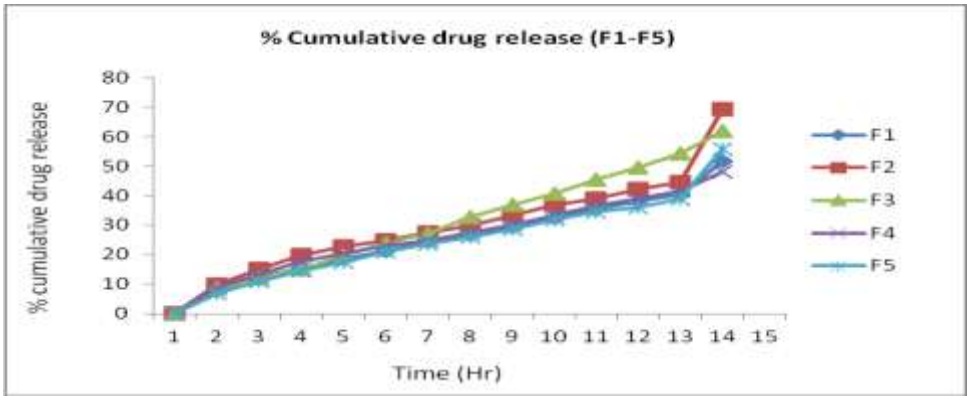

Figure 3: *In-vitro* release profiles of F1-F5

Table 5: *In-vitro* release profile of atorvastatin calcium transdermal patch of F6-F10

Time (hr.)	Percentage Drug Release (%)				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	9.1	10.28	1.05	2.94	8.40
2	14.91	15.92	2.84	8.257	11.43
3	19.77	19.95	15.68	14.95	14.55
4	22.98	22.85	19.48	25.35	18.92
5	23.5	25.63	27.27	29.48	23.17
6	25.91	28.91	29.38	37.46	26.78
7	28.42	31.68	34.76	43.31	30.95
8	32.49	35.51	37.43	47.27	36.13
9	35.32	38.03	40.28	52.25	40.65
10	37.32	41.18	46.19	53.84	40.71
11	40.19	43.46	50.47	53.84	-
12	43.13	45.91	54.24	54.32	-
24	49.62	59.47	56.52	58.21	-

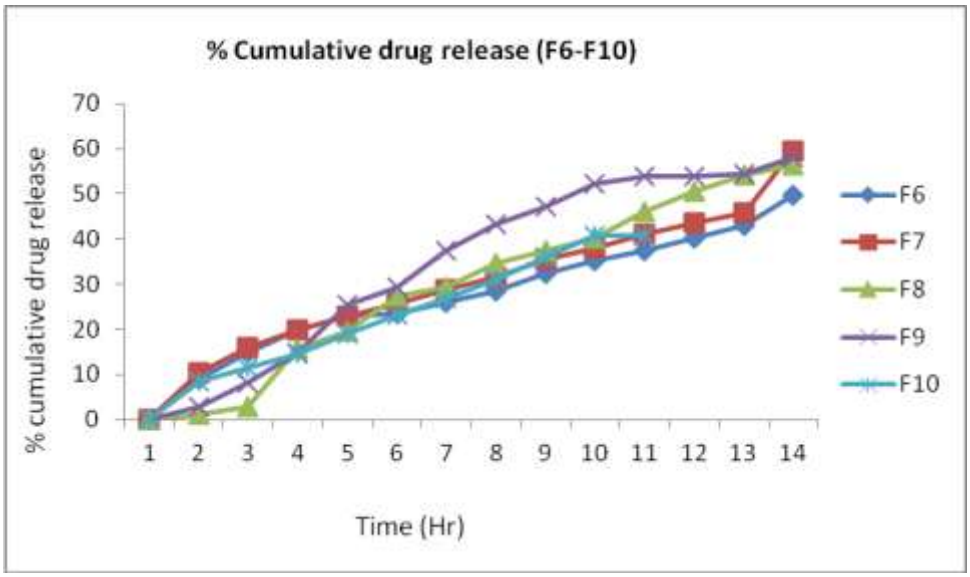

Figure 4: *In-vitro* release profiles of F6-F10

CONCLUSION:

All ten formulations were evaluated for thickness, folding endurance, moisture uptake, physical appearance and results found for all satisfactory. IR studies revealed that the drug and polymer were compatible with each other and all the batches prepared and evaluated, F2 showed promising results. It was concluded that HPMC 5 cps and ethyl cellulose are useful in formulating sustained release patches. Moreover, patches prepared from HPMC 5cps and EC (batch code = F2) exhibited better in-vitro drug release-time profile. Also, amongst the two plasticizers used alone and in various combinations, batch F1, F3 and F4 produced patches that exhibited high folding endurance and good manageable characteristics. Based on the In-vitro drug release and drug content Result, formulation F2 was concluded as an optimized formulation, which shows its higher percentage of drug release.

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