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Formulation and Evaluation of Pravastatin Sodium Transdermal Patch

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Original Research Article

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Abstract: The aim of the present study was to formulate and evaluate Pravastatin Sodium transdermal patch. Pravastatin is a lipid lowering agent, because of its short biological half life (t1/2, 1-3 hours) only 18% of its dose reaches to the systemic circulation of the blood on oral administration. Hence it is a suitable drug to formulate into transdermal form. Transdermal patchs of Pravastatin Sodium was prepared by using different polymers like HPMC 3000, HPMC K15M,HPMC E5 by solvent casting method. FTIR study reports have shown that there was no interaction between drug and excipients. The prepared patches were evaluated for Folding Endurance, Uniformity of weight, Drug content, Moisture content, In-vitro diffusion study, a series of 12 formulations were prepared by using different polymers composition in different concentrations among them F11 formulation prepared by using HPMC K15M was showed satisfactory results with 88.6% of drug release in diffusion studies was found to be suitable for formulating as transdermal patch in order to increase the bioavailability and to decrease the dosing frequency of Pravastatin Sodium.
Keywords: Transdermal patch, Pravastatin Sodium , HPMC.

INTRODUCTION

TDDS (transdermal drug delivery system) can be one of the potential routes for systemic delivery of drugs. Transdermal patches are innovative drug delivery systems intended for skin application to achieve a systemic effect [1]. A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981 by FDA. The main components to a transdermal patch are: Backing layer , Drug containing reservoir (Polymer matrix , Drug, Permeation enhancers , Plasticizers), The release control layer , The adhesive , The peel strip , The packet[2,3].

Ideal properties of drug for Tdds

- Dose of a drug should be low.
- Half life of a drug in hrs should be 10 or less.
- Molecular weight of a drug should be less than 500.
- Partition coefficient of a drug Log P (octanol-water) should be between –1 and 3.
- Skin permeability coefficient of a drug should be less than 0.5 x10-3cm/hr.
- Drug should be non-irritating to the skin[4].
- Oral bioavailability of a drug should be low.
- Therapeutic index of a drug should be low.
- The concentration of a drug used should be low.
- The pH of drugs saturated aqueous solubility should be between 5-9.
- Dose deliverable should be <10mg/day[5].

Methods for Enhancing Transdermal Drug Delivery

Drug/prodrug, Eutectic system, Liposomes and vehicles, Solid lipid Nanoparticles, Iontophoresis, Electroporation, Laser radiation and photomechanical waves.

Types of Transdermal Patches

Single-layer Drug-in-Adhesive, Multi-layer Drug-in-Adhesive, Reservoir, Matrix, Vapour Patch[6-8].

Advantages of Transdermal patches

- Provide relatively steady and sustained drug concentration in plasma in contrast to conventional systems where peaks and troughs are a common feature.
- Variability due to factors such as pH intestinal motility, food intake, etc, which make vast difference in the bioavailability of the drugs given through oral route, are not existent.
- The hepatic first pass metabolism is avoided.
- A constant rate of absorption is possible in a vast variety of adverse patient population.

- Ease of administration and patient convenience[9-11].
- Drug input terminable by mere removal of the Transdermal patches.
  - Drugs that cause gastro intestinal upset can be good candidates for Transdermal delivery
  - Increased therapeutic value due to avoidance of hepatic first pass effect, gastro intestinal irritation and low absorption problem.
  - Drugs that are having short biological half-life can be given by this therapeutic systems and it also reduces dosing frequency.
  - Transdermal patches are used for cessation of tobacco smoking.
  - Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.

Disadvantages of Transdermal patches

- Can be used only for drugs, which require very small plasma concentrations for action.
- Local irritation and arythmea are possible. Enzymes in epidermis or derived from micro organisms present on the skin may denature the drugs[12].

Events to take place during drug transport

Drug release from device, Partitioning of the drug on skin surface. Drug partitioning between stratum corneum/viable epidermis boundaries, Diffusion of drug and bio-conversion in viable epidermis, Drug absorption into blood [13-15].

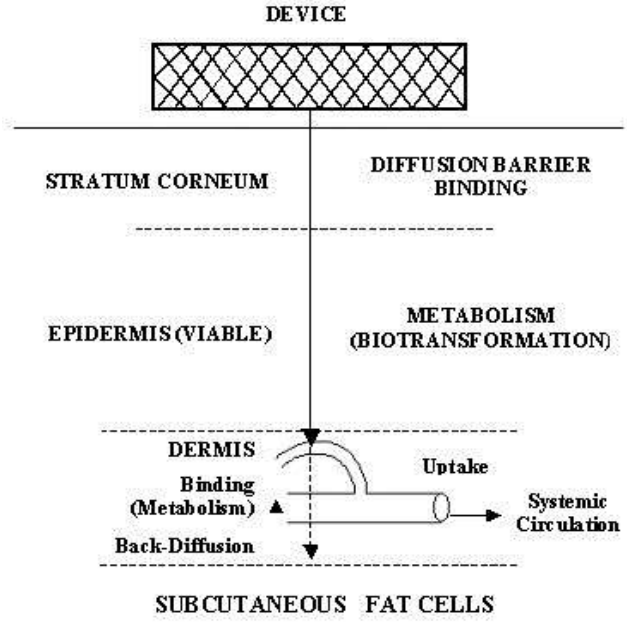

Fig-1: Events of drug transport across skin

Various Methods of Preparation of Transdermal Patches

Solvent casting method**,** Circular teflon mould method, Asymmetric TPX membrane method, Mercury substrate method, IPM (isopropyl myristate) membranes method, EVAC membranes method. [17-20]

MATERIALS AND METHODS

Pravastatin Sodium from (kp labs ,Hyd), HPMC 3000, HPMC K15M, HPMC E5, PEG 400, Methanol, Glycerol are from chaithyanya scientifics vizyawada.

Methodology

Transdermal patches containing Pravastatin Sodium were prepared by solvent casting method using varying ratios of different grades of polymers and plasticizers in different concentrations as shown in the below table.The Matrix type Transdermal patches of Pravastatin Sodium were prepared by the solvent casting method. Solution I was prepared by dissolving polymers HPMC K 3000, HPMCK-15M, HPMCE5 in different ratios in methanol and was allowed to stir for 2 hours and kept for overnight swelling. Solution II was prepared by dissolving the accurately weighed quantity of Pravastatin Sodium in methanol. Then the drug solution added slowly to the polymer solution and stirred on a magnetic stirrer to obtain uniform solution. Propylene glycol, glycerol were used as a plasticizers, PEG 400, Ethanol were used as a penetration enhancers. Then the solution was poured on the petri dish having the area of 18.8cm2 and dried at room temperature. Then the patches were cut into 2X1cm2 patches. Drug incorporated for each patch was 40 mg. The dried patches were wrapped in butter paper and stored in a closed container away from light and in cool place.

Formulation design

Table-1: Composition of formulation

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pravastatin Sodium (mg)	40	40	40	40	40	40	40	40	40	40	40	40
HPMC 3000 (mg)	0.5	1	2	---	---	---	---	---	---	---	---	---
HPMC K15M(mg)	---	---	---	0.5	1	2	---	---	---	2	2	2
HPMC E5(mg)	---	---	---	---	---	---	0.5	1	2	---	---	---
Methanol(ml)	5	5	5	5	5	5	5	5	5	5	5	5
Ethanol(ml)	2	2	2	2	2	2	2	2	2	3	2	1
PEG 400(ml)	1	1	1	1	1	1	1	1	1	1	2	3
Glycerin(ml)	1	1	1	1	1	1	1	1	1	1	1	1
Water(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATION OF TRANSDERMAL PATCHES

Physicochemical evaluation

Physical appearance

All the transdermal systems were visually inspected for colour, clarity, flexibility and smoothness.

Folding Endurance

Folding endurance of the film was determined manually by folding a small strip of the film (4×3 cms) at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the value of folding endurance, where the cracking point of the films were considered as the end point.

Thickness determination

The objective of present study was to check the uniformity of thickness of the formulated films. The thickness was measures at five different points of the film using vernier digital caliper the average of five readings were calculated.

Uniformity of weight

This was done by weighing five different patches of individual batch taking the uniform size at random and calculating the average weight of five. The tests were performed on films which were dried at 60^{o}C for 4h prior to testing.

Drug content

Four piece of 1 cm2 each (1cm × 1cm) were cut from different parts of the film. Each was taken in separate conical flasks containing 100ml of suitable dissolution medium (phosphate buffer) stirred vigorously for 6 h using magnetic stirrer. The above solutions were filtered and suitable dilutions were made. Absorbance was recorded using UV visible recording spectrophotometer at their respective wavelength against a blank solution which was prepared by following the same procedure containing the patch without drug.

Moisture content

The film was weighed and kept in dessicator containing calcium chloride at 40^{o}C and dried it for at least 24h. Then the film was weighed again and again until it showed a constant weight.The percentage moisture content was calculated using the following formula:

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

In-vitro diffusion study

To study the in-vitro drug release profile from the prepared Pravastatin Sodium formulations, a modified Franz diffusion cell was used. An elution medium was 20ml of phosphate buffer of pH 7.4 and the goat ear skin was used as the barrier. The film was placed in between the donor and receptor compartment in such a way that the drug releasing surface faced towards the receptor compartment. The receptor compartment was filled with the elution medium, a small bar magnet was used to stir the elution medium at a speed of 60 rpm with the help of magnetic stirrer. The temperature of the elution medium was maintained and controlled at 37±1^{0}c by a thermo static arrangement. An aliquot of 5ml was withdrawn at a predetermined time interval replaced by an equal volume of elution medium, diffusion studies were carried out for a period of 12 hours. The drug concentration in the aliquot was determined by UV spectrophotometrically by using the standard curve. Amount of drug diffused at a various time intervals was calculated and plotted against time.

STABILITY ANALYSIS

The prepared optimized formulation transdermal patches were stored at 40°C ± 2°C/75% ± 5% RH and 30°C ± 2°C/65% ± 5% RH in stability chambers for a period of 3 months. After 3 months patches were evaluated for weight variation, thickness, drug content.

RESULTS AND DISCUSSION

Ftir of Pure Drug of Pravastatin Sodium

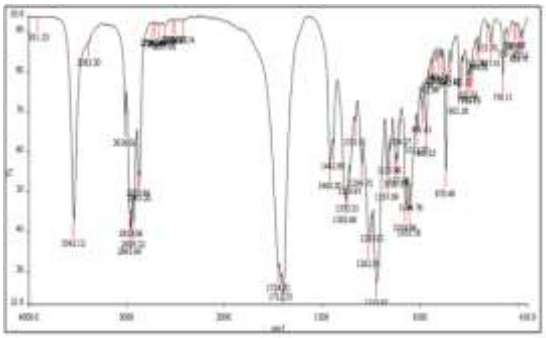

Fig-2: FTIR Spectra of Pravastatin sodium

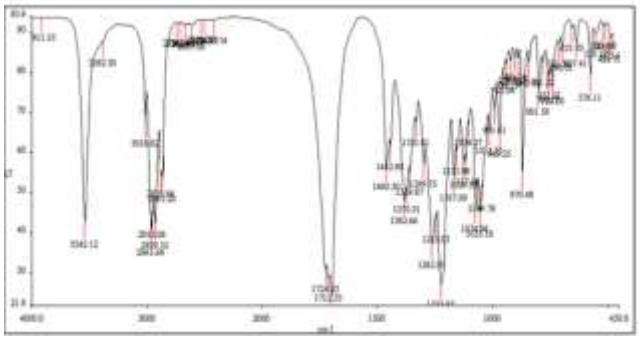

Fig-3: FTIR Spectra of optimised formulation

No significant interactions were observed between the drug and excipients used in the formulation.

Table-2: Result of Evaluation Parameters of Batch F1-F12

Code	Average Weight (mg)	Mean Thickness (mm)	Moisture Content (%)	Drug Content (%)	Folding Endurance
F1	105.3±2.510	0.120±0.013	2 ± 0.957	102.29%±0.5	310 ± 2.33
F2	103.3±3.491	0.150±0.036	4 ± 0.942	95.35%±0.58	315 ± 0.66
F3	107.6±3.055	0.254±0.026	3 ± 0.642	96.37%±0.62	311 ± 1.66
F4	108.6±2.605	0.245±0.032	5 ± 0.744	99.71%±0.07	322± 0.51
F5	110.0±3.605	0.221±0.012	5 ± 0.956	97.95%±0.08	311 ± 2.33
F6	112.3±3.071	0.303±0.032	5 ± 0.342	93% ±0.48	301± 1.05
F7	118.4±2.331	0.284±0.022	6 ± 0.442	98.90%±0.75	303 ± 1.34
F8	120.2±4.461	0.284±0.036	6 ± 0.882	97.13%±0.05	307 ± 2.66
F9	122.3±3.071	0.306±0.042	3 ± 0.342	92% ±0.28	311 ± 1.03
F10	121.3±2.071	0.206±0.032	4 ± 0.842	91% ±0.38	305 ± 1.04
F11	**115.5±4.601**	**0.294±0.021**	**4 ± 0.749**	**98.95% ±0.56**	**308 ± 1.66**
F12	123.3±3.071	0.301±0.022	6 ± 0.542	94% ±0.38	302 ± 1.02

Table-3: In vitro diffusion release data of factorial batch F1 to F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	23.25±0.04	12.65±0.01	22.34±0.05	23.68±0.02	22.91±0.03	24.67±0.03
1	30.24±0.06	16.52± 0.04	24.54± 0.01	26.42± 0.05	26.42± 0.08	31.91± 0.05
2	33.52± 0.04	22.26± 0.05	28.62± 0.02	31.67± 0.06	29.41± 0.05	34.31± 0.09
3	36.47± 0.01	26.19± 0.05	31.22± 0.08	33.91± 0.07	32.35± 0.04	37.85± 0.01
4	39.51± 0.05	28.85± 0.02	36.47± 0.06	35.49±0.08	35.73± 0.09	41.86± 0.07
5	41.38± 0.02	29.74± 0.08	40.45± 0.04	38.18± 0.09	38.94± 0.04	45.83± 0.05
6	43.56±0.08	32.73± 0.07	44.47± 0.07	41.58± 0.04	42.82± 0.01	49.72± 0.02
7	49.48± 0.06	33.46± 0.04	51.48± 0.02	44.82± 0.05	46.57± 0.06	53.64± 0.08
8	56.37± 0.07	41.49± 0.02	54.72± 0.06	49.47± 0.01	52.41± 0.05	57.49± 0.05
9	60.31± 0.05	45.42± 0.08	59.93± 0.05	55.58± 0.02	57.22± 0.02	63.42± 0.04
10	63.65± 0.06	52.19± 0.04	68.43± 0.04	63.35± 0.03	64.86± 0.08	68.31± 0.06
11	68.87± 0.07	55.61± 0.07	71.37± 0.06	68.68± 0.07	68.54± 0.07	73.49± 0.04
12	71.56± 0.08	59.46±0.02	74.91± 0.08	69.97± 0.04	71.62± 0.05	75.49± 0.08

Table-4: In vitro diffusion release data of factorial batch F7 to F12

Time	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
0.5	18.67±0.02	13.85±0.04	14.65±0.01	10.63±0.01	25.64±0.06	11.55±0.01
1	20.22± 0.03	18.45± 0.02	18.52± 0.06	15.42± 0.04	32.47±0.02	17.22± 0.04
2	26.21± 0.08	24.49± 0.04	23.46± 0.05	22.36± 0.05	38.72±0.08	26.66± 0.05
3	29.41± 0.06	27.76± 0.08	26.39± 0.03	24.29± 0.04	43.65±0.04	28.39± 0.03
4	31.81± 0.07	30.46± 0.09	29.85± 0.02	26.85± 0.02	46.12±0.05	30.85± 0.02
5	34.42± 0.04	34.97± 0.07	31.74± 0.08	28.74± 0.08	49.71±0.01	31.64± 0.08
6	38.44± 0.06	38.85± 0.06	35.73± 0.07	30.53± 0.05	53.84±0.08	32.93± 0.06
7	41.48± 0.03	41.67± 0.05	39.46± 0.05	35.46± 0.05	58.86±0.07	33.66± 0.05
8	43.49± 0.08	44.27± 0.01	43.49± 0.06	40.19± 0.05	62.38±0.04	45.49± 0.04
9	46.59± 0.01	49.49± 0.04	47.72± 0.08	43.62± 0.06	68.48±0.06	48.72± 0.08
10	57.6± 0.06	54.72± 0.08	52.49± 0.04	50.49± 0.04	75.56±0.03	52.99± 0.04
11	60.22± 0.05	59.37± 0.07	56.61± 0.08	54.61± 0.08	79.58±0.06	57.61± 0.08
12	63.44± 0.04	67.88± 0.01	62.46±0.04	57.26±0.03	**88.36±0.03**	60.36±0.04

Formulation F11 showed maximum drug release (88.36%), whereas formulation F10 showed lowest release of (57.26%) among the series.

Table-5: Stability Analysis

S.No	Observation	Before Stability testing	After 3 months
1	Average weight	115.5	110.2
2	Mean Thickness (mm)	0.294	0.294
3	Moisture Content (%)	4	4
4	Folding Endurance	308	308
5	Drug release (%)	88	88

CONCLUSION

Good correlation was observed between drug release and drug permeation study *in-vitro*.It can be concluded that such a patches of HPMC 3000, HPMC K15M, HPMC E5 could be a good carrier in transdermal delivery of Pravastatin Sodium. It may also concluded that adhesion of transdermal drug delivery device to skin membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug All the formulated Transdermal patches were visually inspected for color, clarity, flexibility, checked for flatness, physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be within the pharmacoepial limits. The prepared Pravastatin Sodium Transdermal patches were evaluated for *In-vitro* permeation studies using dialysis membrane, among all the 12 formulations F11 formulation was shown 88.36% cumulative drug release within 12 hours. The kinetics of *In-vitro* permeation studies using dialysis membrane for F11 formulation was plotted and the F11 formulation followed the Higuchi mechanism of drug release. Drug release profile of optimized transdermal patch and the marketed tablets (Pravachol 40 mg) was compared and shows advantages over oral marketed formulation.

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