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Formulation and Evaluation of Polymer Based Ezetimibe Patches: In Vitro Characterization

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ABSTRACT
In this study an attempt was made to develop and evaluate controlled release transdermal patch formulation with varying ratio of hydrophilic polymer (hydroxypropyl methyl cellulose) and a fixed amount of lipophilic polymer (Ethyl cellulose). The patch formulation was prepared by solvent casting method using blends of the both polymers. Polyethylene glycol was used as the plasticizer while propylene glycol was added as the permeation enhancer in the formulations. The patches were evaluated for surface pH, moisture content, tensile strength, and in vitro release among other factors. The surface pH was between 5.35 to 5.62, and moisture content ranging from 8.13 ± 0.589% to 11.03 ± 0.115%. The tensile strength values ranged from 9.58 ± 0.030 kg/cm^2 and 10.61 ± 0.050 kg/cm^2 and the highest amount of drug released in the in vitro diffusion studies using Franz diffusion cell was found to be 88.63% at the end of 24 hours in formulation EP4. The formulation EP4 released the highest amount of drug and presented highest drug loading. Thus is could be concluded that EP4 was the best formulation with sufficient strength and drug release that would be able to effectively release drug throughout the day.

Keywords: Patch, Ezetimibe, tensile strength, Franz diffusion cell, antihyperlipidemic, solvent casting.

I. INTRODUCTION

Transdermal drug delivery system (TDDS) also known as "patches" (non-invasive delivery) is dosage form designed to deliver a medication across a patient skin [1,2]. Skin is the largest and most accessible organ of human body with the help of skin layers drug reaches into the blood stream given as sustained release, controlled release, or extended-release formulation. It provides systemic delivery of drug through increased bioavailability with reduced dosing frequency [3,4].

Using skin as the site of drug delivery presents an improved patient compliance along with avoidance of gastric irritation and first pass metabolism of the drug. It also aids in rapid termination of therapy just by removal of the patch [5].

Low density lipoprotein cholesterol (LDL-C) reduction is a key factor in preventing coronary heart diseases (CHD). Ezetimibe (EM) (Figure 1) is an azetidinone derivative that acts by inhibiting the protein transporters that are involved in the active transport of cholesterol leading to a decreased absorption of cholesterol in the systemic circulation [6]. It is a classified as a class II drugs by the Biopharmaceutical Classification System, drugs with poor aqueous solubility and high permeability [7].

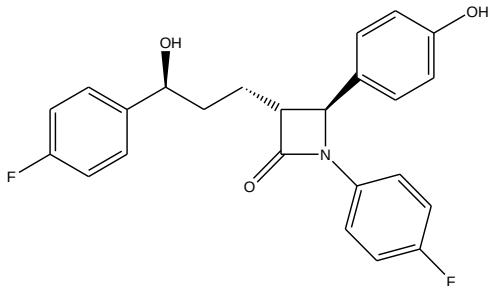

Figure 1 Structure of Ezetimibe

The log P of EM is 4.51 and it has a half life of 22 hours. The typical dose of EM is 10 mg per day. The low dose, long half life and the log P value make EM a potential candidate for transdermal delivery.

The aim of this study was to formulate controlled-released transdermal patches of EM using a blend of hydrophilic polymer (Hydroxypropyl methyl cellulose, HPMC) and lipophilic polymer (Ethyl cellulose, EC) along with

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a plasticizer (Polyethylene glycol, PEG-400) and permeation enhancer (propylene glycol, PG). The formulated transdermal patches were evaluated for physicochemical features.

II. MATERIAL AND METHODS

Materials

Ezetimibe was obtained from Yarrow Pharmaceuticals, India. HPMC and EC were obtained from CDH, India; PEG-400 and PG were procured from Oxford Fine Chemicals, India. Any other chemical used was of general grade and used without purification.

Formulation of Transdermal Patches of EM [8]

EM loaded transdermal patches were formulated utilizing the solvent casting method. HPMC and EC were accurately weighed and dispersed in 10 mL of water-ethanol (1:1) mixture, stirred for 30 min and allowed to stand in order to obtain a clear solution (Table 1). EM was accurately weighed and added to the above solution and mixed until clear solution was obtained. PEG-400 (30% of polymer weight) and PG (15% polymer weight) were added to the above solution. The mixture was stirred at 500 rpm for 30 min to remove dissolved and entrapped gases. The resulting uniform solution was cast on glass petridish (38.46 cm^2 in area), lubricated using glycerin and dried at room temperature for 24, covered with an inverted funnel. After 24 h, the casting solution was dried in oven at 40°C, peeled carefully and stored in a desiccator for further studies.

Table 5.1 Formula for Ezetimibe loaded transdermal patches

Ingredients	EP1	EP2	EP3	EP4
Ezetimibe (mg)*	45	45	45	45
HPMC (mg)	50	100	150	200
EC (mg)	50	50	50	50
PEG-400 (%w/w)	30	30	30	30
Propylene Glycol (%w/w)	15	15	15	15

*Dose of EM calculated as 5 mg per patch of area 4cm^2

Compatibility Study

Drug and polymer compatibility studies were carried out to evaluate any incompatibilities. An FTIR spectrum of drug and a mixture of drug an polymers was obtained and observed for characteristic peaks of EM.

Physicochemical Evaluation of EM Loaded Patches[9]

The following parameters were evaluated for the EM loaded transdermal patches formulated using the above method.

Physical appearance

The formulated patches were evaluated for homogeneity, transparency, clarity, color, and smoothness.

Thickness

The thickness of each patch was measured by the use of vernier caliper at six different positions of the patch and the average was calculated.

Uniformity of weight test

The patches were subjected to mass variation by individually weighing each formulated patch and checking the weight of patch against the average weight of the formulated patches. Measurement of patch weight was carried out using a calibrated analytical balance. The determination was carried out for each formulation in triplicate.

Surface pH

The surface pH of the transdermal patches was measured using a calibrated pH meter. In a test tube, 1 mL of distilled water and a 1 cm^2 portion of transdermal patch was kept at room temperature (25 ± 2°C) for 2 h. The water from the test tube was decanted and the wet patch was used for surface pH analysis. The pH electrode was placed at three different places at the swollen part of the patch for calculating the average pH.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it cracked or broke. The number of times the film could be folded from the same place without breaking/ cracking represented the value of folding endurance.

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Tensile Strength

The determination of tensile strength of the prepared patches was conducted using pulley apparatus fabricated in the laboratory. The initial patch length was identified using a scale. One side of the transdermal patch was attached to a weighing balance hook, and the other side was attached toa rope that crossed over the pulley and attached to a weighing pan. In the pan, weight gradually increased until a crack or break appeared in the patch. Tensile strength was calculated by the total weight present in the pan.

Drug content test

Three pieces of 4 cm^2 were collected by cutting off zones from different parts of patch from each patch. These pieces were dissolved in 10 ml ethanol and were placed on vortex shaker for 1 hr to dissolve completely the patches. The resultant solutions were filtered through the whatman paper and then 0.1 mL solution was withdrawn into another volumetric flask (10 mL) and dilution was made up to 10 mL. The absorbance of this solution was observed at 240 nm using UV-Visible spectrophotometer and the drug content was calculated.

Percent moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In-vitro permeation study

In-vitro permeation studies of the transdermal patches were carried out by using Franz diffusion cell with a receptor compartment capacity of 30 ml. The formulated patch of surface area of 4 cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (0, 2, 4, 6, 8, 12 and 24 h) and analyzed the drug content by UV at 240 nm by appropriated dilution with ethanol.

III. RESULTS

Compatibility Study

The compatibility of EM with HPMC and EC was studied using FT-IR spectrum of the pure drug as well as the physical mixture. The FTIR spectrum of EM exhibited the stretching and bending vibrations due to OH (3340.56 cm^{-1}), C=O (1699.89 cm^{-1}), C=C (1603.53 cm^{-1}) and C-O (1003.43 cm^{-1}). All these characteristic peaks were present in the FTIR spectrum of the mixture (Figure 2).

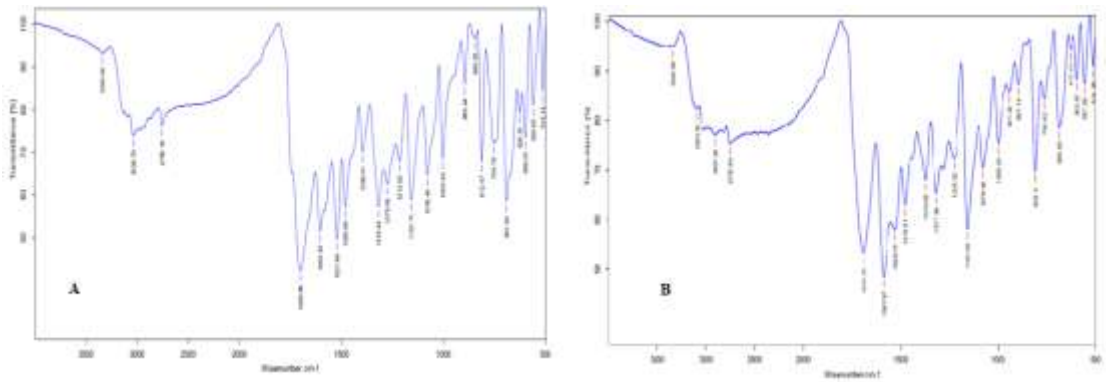

Figure 2 FTIR spectrum (A) Ezetimibe (B) Physical mixture of EM, HPMC, EC

Physicochemical evaluation of EM loaded patches

All the prepared patches were subjected to visual inspection for examining the physical appearance. The physical appearance of the patches gave satisfactory results. All the prepared patches were found to be smooth, non-sticky, opaque, homogeneous, and flexible in nature.

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The evaluation of the patches was done for various physical parameters as per procedure and the results are reported (Table 2).

Formulation	Thickness (mm)	Average weight (mg)	Moisture loss (%)	Drug content (%)	Folding Endurance	Surface pH	Tensile Strength (kg/cm^2)
EP1	0.539 ± 0.005	188.6 ± 2.88	8.13 ± 0.589	91.7 ± 0.6	66 ± 5.03	5.35 ± 0.055	9.58 ± 0.030
EP2	0.571 ± 0.004	204.3 ± 1.15	8.46 ± 0.115	94.7 ± 0.26	72 ± 2.64	5.38 ± 0.023	9.52 ± 0.040
EP3	0.618 ± 0.009	236.0 ± 3.00	9.63 ± 0.230	97.5 ± 0.34	76.5 ± 4.04	5.56 ± 0.025	10.24 ± 0.070
EP4	0.662 ± 0.006	243.6 ± 3.21	11.33 ± 0.115	97.5 ± 0.05	77.5 ± 3.60	5.62 ± 0.015	10.61 ± 0.050

As shown in the table the pH levels of the patches ranged between 5.35 to 5.62 suggesting their suitability of human use and possibly suggesting that no skin irritation would be produced on application of the patches.

The thickness of the transdermal patches ranged from 0.539 ± 0.0050 mm to 0.662 ± 0.0066 mm. This difference in the thickness could be attributed to the nature and concentrations of polymers, i.e., an increase in the concentration of the hydrophilic polymer HPMC led to an increased thickness of the transdermal patch. The weight variation data revealed that the increase in the concentration of HPMC resulted in an increased weight of patches. Folding endurance is of utmost importance for patches because greater folding endurance prevents patches from being easily broken or damaged, and patches are considered to meet good quality. All the formulated transdermal patches exhbited high folding endurance (>60 times).

In vitro permeation study

The in vitro drug release study depicted that the highest amount of drug was released from EP4 (88.63 ± 1.292) while the lowest was released from EP1 (62.92 ± 1.038%) at the end of 24 hours of release study. Faster drug release was observed from formulated patches containing greater amounts of the hydrophilic polymer, HPMC. The study also depicted an increase in hydrophilic polymer that resulted in an increase in burst effect, as well as drug release in the formulation (Figure 3).

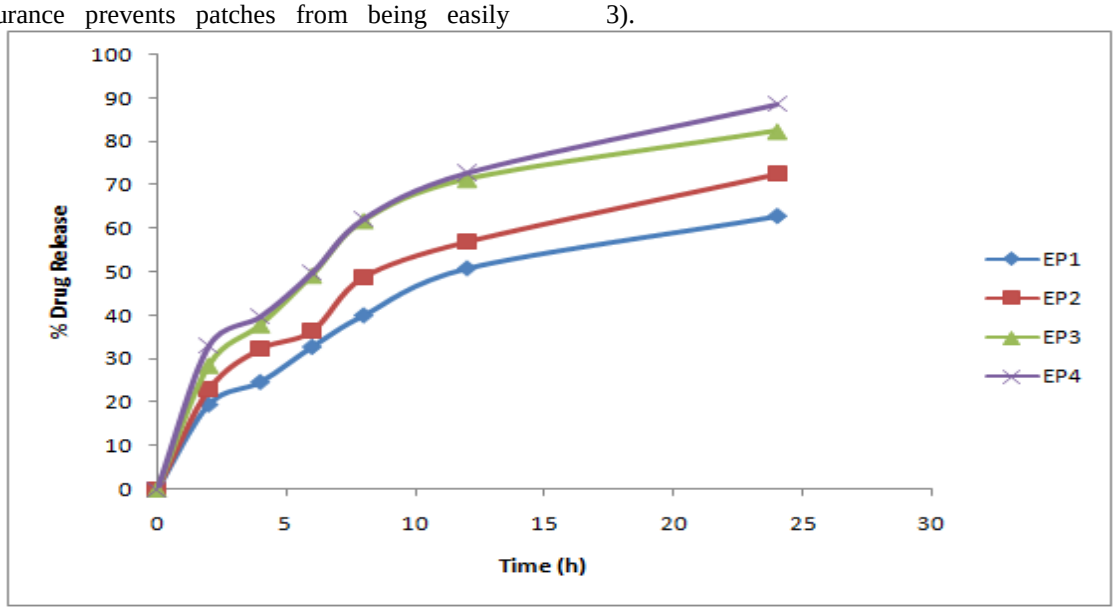

Figure 3 Release (permeation) of EM from patches (in vitro)

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IV. CONCLUSION

present investigation was formulating transdermal patched loaded with Ezetimibe. The formulation was achieved using Hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) as the polymeric release controlling matrix. The ability of the formulated transdermal patches to sustain the release of Ezetimibe for more than 24 hours was conclusive enough that the problems associated with the oral administration were taken care of. The formulation EP4 released the highest amount of drug and presented highest drug loading. Thus is could be concluded that EP4 was the best formulation with sufficient strength and drug release that would be able to effectively managed throughout the day.

REFERENCES

[1]. Dipen P, Sunita A, Bhavesh P, Nikunj B. Transdermal drug delivery system: A review. Pharm Innov 2012; 1: 66-75.

[2]. Ashok JK, Nikhila P, Lakshmanaprabhu S, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res 2010; 3: 49-54.

[3]. Kumar R. Modified Transdermal technology: Breaking Barriers of Drug Permeation via Skin. Trop J Pharm Res 2007; 6: 633–44.

[4]. Rajeswari S, Prasanthi T, Srilaxmi N, Gayathri T. A Review on Transdermal Drug Delivery System: A Novel Tool For The primary objective of the Improving Bioavailability. Innovare J Sci 2021; 9(4): 1-7.

[5]. Garala KC, Shinde AJ, Shah PH. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Int J Pharm Pharm Sci 2009; 1(1): 108–120.

[6]. https://go.drugbank.com/drugs/DB00973; assessed on 08/03/2022

[7]. Stegemanna S, Leveillerb F. When poor solubility becomes an issue: From early stage to proof of concept. Eur J Pharm Sci 2007; 31: 249–261 https://doi.org/10.1016/j.ejps.2007.05.110

[8]. Mo L, Lu G, Ou X, Ouyang D. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure. Saudi J Bio Sci 2022; 29: 266-272.

[9]. Latif MS, Al-Harbi FF, Nawaz A, Rashid SA, Farid A, Al Mohaini M, Alsalman AJ, Al Hawaj MA, Alhashem YN. Formulation and Evaluation of Hydrophilic Polymer Based Methotrexate Patches: In Vitro and In Vivo Characterization. Polymers 2022; 14: 1310. https://doi.org/10.3390/polym14071310