FORMULATION OF METFORMIN TRANSDERMAL PATCHES (TDDS) EMPLOYING TWO POLYMERS FUSION

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ABSTRACT

The purpose of this research was to determine whether or not the polymeric combinations of HPMC and ethyl cellulose could be used to create an effective matrix-type transdermal drug delivery system (TDDS) of Metformin HCL (EC). In a solvent system of dichloromethane and methanol (1:1), 6 matrix patches were produced employing these polymeric materials with propylene Glycol as a plasticizer and vegetable oils (eucalyptus oil) as permeation enhancers. Weight, medicament content, water content, hydration uptake, flatness, folding durability, and thickness were all measured and analysed to describe the formulations. Scanning electron microscopy (SEM) of the generated TDDS were recorded to see the drug - delivery pattern, and the stability of the preparations and in vitro dissolution of the trial formulations were utilized to calculate the quantity of metformin HCL in the patches. The FTIR spectroscopy technique was used to investigate drug-excipient interactions. Drug distribution homogeneity in the matrix was confirmed by in vitro dissolution tests, and maximal drug release in 24 hours was achieved with formulation F6 (containing Eucalyptus oil).

Keywords: Metformin HCl, SEM, FTIR, Solvent Evaporation Method, Dichloromethane.

INTRODUCTION

Oral medication administration is widespread and simplifies administration. Poor bioavailability owing to hepatic first-pass metabolism and fast blood level fluctuations (both high and low) require high and/or frequent dosing, that is unpleasant. For these problems, a novel medicine delivery mechanism is needed. Transdermal medication delivery uses self-contained, discrete dose forms that, when applied to undamaged skin, transfer the drug to the systemic circulation [1,2,3]. TDDS is a key feature of new drug delivery systems. Transdermal medication administration improves bioavailability and action time, reducing dose frequency. Reduced side effects, and if toxicity occurs, the patch can be removed. Topical patches give drugs painlessly and noninvasively. This route delivers medications more effectively than oral, parenteral, etc., which are broken down by stomach acids, poorly absorbed by the gut, or destroyed by the liver. Long-term stabilisation of blood levels. They are Non-invasive and cause prevention of parenteral therapy. They improve compliance by extending therapy with a single application. More frequent dosing with other dosage types. Short-half-life medicines' action is extended via a drug reservoir and regulated release [4,5]. Eliminating a drug from the skin can end treatment quickly. Its physicality, characteristics, and distinguishing marks make them simple to recognize in crises (e.g., inattentive, unconscious, or coma patient). Improve therapy efficacy by reducing inter- and intrapatient variance.

Disadvantage

Topical site discomfort is possible. Drug, adhesive, or other patch excipients might produce erythema, irritation, and local edoema. Large drug molecules hinder absorption. Ideal medication molecule size is 800-1000 Daltons. Many hydrophilic medicines have slow skin permeability and therapeutic effect. Transdermal delivery works well with lipophilic drugs. The skin's barrier function varies from one individual to the next, and with age. Transdermal medication delivery can't achieve maximum blood/plasma levels. Since patches are small, drug molecules should be powerful. Discomfort and hypersensitivity are possible. No medications which need high blood levels could be given [6,7].

MATERIAL AND METHODS

Materials such as HPMC, dibutyl phthalate, and metformin hydrochloride have been procured from the institute. Analytical grade materials also employed for all other compounds and solutions in the study.

Methods

Metformin HCL Calibration Curve in 7.4 Phosphate Buffer

1) 7.4 phosphate buffer preparation

50mL of 0.2 M Potassium Dihydrogen Phosphate should be combined with 39.1 mL of 0.2 M Sodium Hydroxide and vol. 200mL makeup.

2) Stock Solution preparation

Take 100 milligrams of metformin HCl in a 100 mL volumetric flask and combine it with enough phosphate buffer. then add phosphate buffer upto 100 mL for vol. makeup. Now, take 10 mL out from previously mentioned solution, make it up to 10 g/mL (stock solution), add 0.1 mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, and 0.7 mL to 10 phosphate buffer, and then perform spectrophotometric analysis at 232 nm using 7.4 buffer solution as a blank. and after that, observations were noted.

3) Phosphate buffer preparation with pH 7.4

Properly quantified, in a 200 mL volumetric flask, we mixed 50 mL of 0.2 M potassium dihydrogen orthophosphate with 39.1 mL of 0.2 M sodium hydroxide. Distilled water was added to bring the total volume to 200 mL; the mixture then is stirred and the pH was altered to 7.4 using 0.2 M sodium hydroxide.

4) 0.2 M potassium dihydrogen phosphate solution preparation

Monobasic potassium dihydrogen phosphate, precisely weighed at 27.218 g, then diluted in 1000 ml of purified water and combined.

5) 0.2 M sodium hydroxide solution preparation

8 g of sodium hydroxide pellets that had been precisely measured then diluted in 1000 millilitres of distilled water and blended.

METHODOLOGY

Transdermal Patches of Metformin Hydrochloride preparation

In a solvent system consisting of an equal volume of methanol and dichloromethane (1:1), ethyl cellulose and PVP K-30 were dissolved together with metformin HCL (20% w/w of the dry mass of the polymer), propylene glycol (30% w/w) as a plasticizer, and eucalyptus oil (2%, 5%, and 7%) as a permeation enhancer to produce a polymeric

At first, the solution was prepared by utilising a number of different polymeric mix ratios; however, a permeation enhancer was not included in the process. The ingredients for the transdermal patches were generated by following the technique that had been explained earlier with varying polymer concentrations, and the patches were then stirred on a magnetic stirrer for forty-five minutes to make an even mixture. After combining the drug and the polymer, the resulting solution was mixed into a glass ring that was placed on a Petri plate that contained a mercury pool. The mixture was then let to stand for 15 minutes in order to remove any air bubbles that may have formed. In order to produce the drug-polymer matrix patch, the solvent was allowed to evaporate at a temperature of 40 degrees Celsius for twenty-four hours. After a period of twenty-four hours, the patch was recovered and stored in a desiccator until it was required once more. In the preparations, HPMC E50 was used as a release retardant, and PVP K30 was used as a polymer. Both of them were made with PVP. Methanol and dichloromethane were utilised in this process as the solvents of choice. Dibutyl phthalate was utilised in this process in the capacity of a plasticizer [8,9].

Physical appearance

The colour, clarity, flexibility, and smoothness of each created patch have all been checked thoroughly.

RESULT

The emergence of the films demonstrated their formation. Due to the use of propylene glycol, a plasticizer that assisted in the manufacture of flexible films, patches were discovered to be off white in colour, smooth, clear, and soft.

Patch thickness

A digital micrometre is used to determine the thickness of the drug-loaded patch at various sites, which yields the average thickness.

Flatness

Three longitudinal strips, one from the centre, one from the left, and one from the right, were cut out of each film. Each strip's length is calculated, and the difference in length due to non-uniformity in flattening was assessed using a percent constriction measurement, where 0% constriction is equivalent to 100% flatness.

100% constriction = I1-I2-I2

where I1 is the starting length for each strip

I2 is the total length of each strip.

Folding Endurance

It was assessed by repeatedly folding a single film until it split. The measure of folding endurance is determined by how many times a film can be folded within the same location without breaking or cracking.

Percentage of Moisture Content

Each film was weighed and maintained in an activated silica-filled desiccator over 24 hours at room temperature.

Each film is measured until they emerged as consistent. The difference among first and last weights in relation to total mass was used to compute the % of moisture content.

Percentage of moisture content = (X-Y/Y) 100 X=initial weight, Y=final weight.

Moisture uptake

The patches were assessed, dried in a vacuum desiccator at room temperature for 24 hours, and then subjected to 84% relative humidity (potassium chloride solution).

(Y-X/X) 100 = % moisture absorption

X=initial weight, Y=final weight.

Drug content study

Using pH 7.4 phosphate buffer, drug content was studied. 1cm2 patches were crumbled and placed in a 100ml volumetric flask. 5 hours of stirring with a teflon-coated magnetic bead. The supernatant was UV spectrophotometer tested for drug concentration at 233 nm.

Weight variation

Each formulation had three randomly picked patches. 3 films out of each batch were examined individually to determine weight variation.

Scanning electron microscope

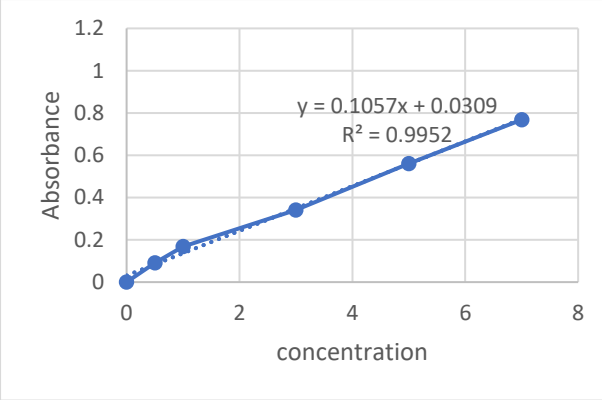
SEM studies drug and polymer distribution in the film. Every sample was sliced and fixed on stubs with double-sided tape for this experiment. Employing fine coat ion sputter, the sections are plated with gold-palladium alloy to make them conductive. The portions are then SEM-examined.

Patches with varying polymer concentrations (no permeation enhancer). Patch release profiles with 2%, 5%, and 7% Eucalyptus oil polymers.

Table 1: Calibration Curve of metformin

Absorbance data for calibration curve of Metformin HCl in 7.4Phosphate buffer metformin HCl in phosphate buffer 7.4:

Conc. (µg/ml)	Abs
0	0
0.5	0.091
1	0.169
3	0.341
5	0.561
7	0.768
8	0.996



Absorbance data for calibration curve of Metformin HCL in water

Conc. (µg/ml)	Abs
0	0
2	0.115
4	0.241
6	0.377
8	0.506
10	0.631
11	0.785

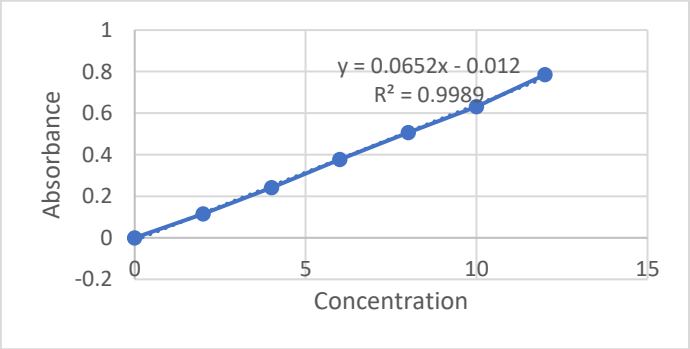


Table 2: Formulation table of transdermal patches

Formulation	Polymer: Ethylcellulose: HPMC:	Drug	Plasticizer	Permeation Enhancer	Solvent System
F1	1:2	20%	30%		Methanol: Dichloromethane1:1
F2	1:2	20%	30%		Methanol: Dichloromethane1:1
F3	1:2	20%	30%		Methanol: Dichloromethane1:1
F4	1:2	20%	30%	Eucalyptus oil 2%	Methanol: Dichloromethane1:1
F5	1:2	20%	30%	Eucalyptus oil 5%	Methanol: Dichloromethane1:1
F6	1:2	20%	30%	Eucalyptus oil 7%	Methanol: Dichloromethane1:1

Different formulation developed for efficiency testing.

Table 3: Evaluation of transdermal patches

S. No.	Formulation Code	Uniformity of weight	Drug Content (%)	Flatness	Folding Endurance	Thickness
1.	FC1	219	93.58	100%	11	.208
2.	FC2	222	94.69	100%	10	.210
3.	FC3	223	94.98	100%	10	.215
4.	FC4	235	92.35	100%	9	.219
5.	FC5	228	93.54	100%	10	.212
6.	FC6	236	95.99	100%	10	.220

FC1 had 219 weight uniformity, 93.58 % drug content and 11 folding endurance and .208 thickness. Less folding endurance seen in FC4 (9). And FC2,3,5,6 showed 10 folding endurances.

DISCUSSION

A hydrophilic polymer such as HPMC and a hydrophobic polymer such as EC were employed in the preparation of the transdermal patches for MFH by a technique known as solvent evaporation. The purpose of the study was to develop once-daily delivery systems for MFH. To do this, a variety of various combinations of the aforementioned polymers were used, with the drug concentration remaining the same across all formulations. Evaluation of six different transdermal patches, including folding endurance, uniformity of thickness, moisture content and moisture uptake, percent flatness study, weight variation study, drug content study, and folding endurance of all the different formulations is shown in the table. Folding endurance of transdermal patches [10,11]. It was discovered that the thicknesses of the films that were created could be characterised. There was a continuous decrease in thickness despite there being an increase in the amount of HPMC. Therefore, it is clear from the results that EC contributes to increasing the thickness of the layer.

The amount of moisture contained in each formulation as well as its capacity to absorb moisture When there is a higher concentration of hydrophilic polymer, there is a corresponding increase in the moisture content, and when there is a higher concentration of hydrophobic polymer, there is a corresponding reduction It was discovered that FC8 had the lowest amount of moisture content of all the patches [12,13,14]. When the concentration of hydrophilic polymer increases, the moisture uptake increases as well. On the other hand, the moisture uptake decreases when the concentration of hydrophobic polymer increases. It was discovered that FC8 showed the least amount of moisture uptake among all of them. Data regarding the percent flatness of the patches that were prepared. It was clear that there was not a significant amount of variation in the flatness shows homogenous regions. The data on the weight variation of all of the patches demonstrated that there were no major variations across the patches, and the deviation was acceptable within the parameters set. The proportion of active ingredient found to vary from 94.23 to 96.48, which is acceptable, particularly in FC4 and FC7, was determined to be within this range. It shows that there was no substantial difference between the patches in a single set, and that the deviation was acceptable given the parameters. The amount of substance discovered in the sample ranged from 94.23 percent all the way up to 95.99 percent [15,16,17]. It shows that there was no major loss of the drug throughout the formulation and processing of the material, and it also shows that the product is suitable for providing the appropriate therapeutic effect. The tensile strength of the patches dramatically reduces as the amount of hydrophilic polymer used in the patches increases, yet this is not the case. It was discovered that there was a significantly significant variance in the percentage of elongation across the various proportions of the polymers that were utilised. In comparison to the results of the other formulations, Formulation FC8 demonstrated a high tensile strength and a lower percentage of elongation. It is abundantly clear from the infrared spectra that there were no interactions between the medication and the polymer.

There is not a discernible change in the magnitude of the primary peak in the spectra of the medication MFH when it is either free or combined with polymer. Infrared spectra have revealed that there is a peak at 1688.48, which indicates the presence of a C=N functional group that stretches. The occurrence of a peak at 1254.14, which indicates that C-N stretching is taking place, is seen. The presence of carbon-hydrogen bonds is shown by a peak at 1473.34. (Bend in the plane). Concurrently, a peak at 732.97 indicates the presence of N-H functional group,

also known as the rocking functional group [18,19,20]. Within the fingerprint region of the FT-IR spectra, each of the peaks could be seen individually. This demonstrates that there is no chance for the medicine to be incompatible with the polymers like EC and HPMC that are utilised in the formulations. As a result, the recipe for making an MFH transdermal patch using EC and HPMC can be reproduced on an industrial scale without the need for concern over the possibility of drug-polymer interactions. All of the formulations demonstrated release lasting up to 24 hours, with more than 80 percent of the medication being released with each formulation and following a zero-order rate release pattern. During the formulation process, the FC6 formulation showed maximum release in under 24 hours. Based on the findings of its in vitro evaluation, the formulation FC6 was chosen for the in vivo skin permeation investigation [21, 22, 23]. The results of the sample analysis were plotted against the percent cumulative drug release versus the square root of time. The Higuchi model provided the most accurate results in this comparison. This article provided the selective electron microscopic (SEM) photos that were taken during the skin permeation examination.

CONCLUSION

The objective of this study was to ascertain the feasibility of utilising the polymeric blends of HPMC and ethyl cellulose for the development of a proficient matrix-based transdermal drug delivery system for Metformin HCL. Using a solvent system consisting of dichloromethane and methanol, six matrix patches were created. These patches were made using polymeric materials, with propylene glycol serving as a plasticizer and vegetable oils acting as permeation enhancers. The formulations were evaluated and described based on measurements of weight, medicament content, water content, hydration uptake, flatness, folding durability, and thickness. On the basis of results obtained din this study, it can be concluded that formulation of metformin transdermal patches employing two polymers fusion can be the efficient formulation.

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CONFLICT OF INTEREST: None

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