RESEARCH ARTICLE

Transdermal drug delivery system (TDDS) of Metformin HCL using Two Different Polymeric Combinations

Gupta Jyoti, Thakur Anjana*, Thakur Shivani

Abstract

This present study was to develop a suitable matrix-type transdermal drug delivery system (TDDS) of Metformin HCL using two different polymeric combinations, i.e., hydroxyl propyl methyl cellulose and ethyl cellulose (EC). Six matrix patches were prepared by using these polymers using propylene Glycol as plasticizer and vegetable oils (eucalyptus oil) as permeation enhancers in dichloromethane and Methanol(1:1) as a solvent system. The formulations were characterized, including uniformity of weight, drug content, moisture content, moisture uptake, flatness, folding endurance, and thickness to study. The stability of the formulations and in vitro dissolution of the experimental formulations were performed to determine the amount of metformin HCL present in the patches, and scanning electron microscopy (SEM) of the prepared TDDS were taken to see the drug distribution pattern. Drug–excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. In vitro dissolution studies showed that the drug distribution in the matrix was homogeneous and it was found that the maximum drug release in 24 hrs was with formulation F6 (containing Eucalyptus oil).

Keywords: Ethyl Cellulose, HPMC, Metformin HCl, Solvent evaporation method.

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Introduction

Nowadays, the most common route for the delivery of drugs is the oral route. This has the advantage of easy administration. It also has significant drawbacks, namely poor bioavailability due to hepatic first-pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be inconvenient. To overcome these difficulties, there is a need for the development of a new drug delivery system.[1]

- 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 a controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.[2]
- Transdermal drug delivery systems can improve bioavailability and longer duration of action resulting in a reduction in dosing frequency.
- Reduced side effects and, in addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch.
- Topical patches are a painless, noninvasive way to deliver a drug directly into the body.
- This is an effective route to deliver drugs than the other system (oral, parenteral, etc.)are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver.3
- Maintains stable or constant and controlled blood levels for longer, period of time.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provide extended therapy with a single application, improving compliance over
- Other dosage forms requiring more frequent dose administration.
- The activity of drugs having "s" short half-life is extended through the reservoir of a drug in the therapeutic delivery system and its controlled release.

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- Drug therapy may be terminated rapidly by removing it from the surface of the skin.
- They can easily and rapidly be identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
- Avoid inter and intrapatient variation and enhance therapeutic efficacy.[4]

Disadvantage

- The possibility of local irritation may develop at the site of application. Many problems like Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
- Drugs have large molecular size makes absorption difficulty. So drug molecule should ideally be below 800-1000 Daltons.
- Many drugs with a hydrophilic structure having a low penetration through the skin and slowly to be of therapeutic benefit.
- Drugs with a lipophilic character, however, are better suited for transdermal delivery.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
- Transdermal drug delivery system cannot achieve high drug levels in blood/plasma.[5,6]

- Drug molecules must be potent because patch size limits the amount that can be delivered.
- Skin irritation and hypersensitivity reactions may occur.
- Drugs that require high blood levels cannot be administered.[7]

Materials

Metformin hydrochloride was obtained as a gift sample from Theon Pharmaceuticals Ltd.HPMC was obtained from MOLYCHEM. Dibutyl phthalate was obtained from SD Fine Chemicals, Mumbai. All other chemicals and reagents used in the study were of analytical grade.

Methods

Calibration Curve of Metformin Hcl in 7.4 phosphate buffer.

Preparation of 7.4 phosphate Buffer

Take 50mL of 0.2 M Potassium Dihydrogen phosphate and mix 39.1 mL of 0.2 M of Sod. Hydroxide and makeup vol. 200mL.[8]

Preparation of Stock Solution

Take 100mg of metformin HCl in 100 mL volumetric flask, a sufficient quantity of phosphate buffer added to dissolve it. And then makeup to volume 100mL with phosphate buffer. i,e mg/mL solution. Then take 10 mL from above solution and then make it 10µg/ml solution, i,e stock solution and then take 0.1ml, 0.3……0.7 makeup to 10 phosphate buffer and then analyzed spectrophotometrically at 232nm against 7.4 buffer solution as blank.and then observation were recorded.[9]

Preparation of pH 7.4 phosphate buffer

Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 39.1 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 7.4 with 0.2 M sodium hydroxide or 0.2 M orthophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution

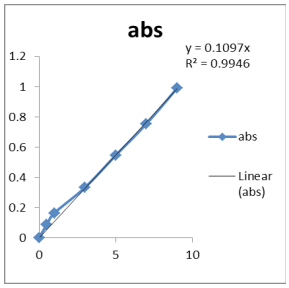
Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution

Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.[10]

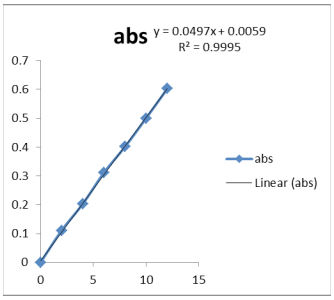
Absorbance data for calibration curve of Metformin HCl in 7.4 Phosphate buffer metformin HCl in phosphate buffer 7.4:

Conc (µg/ml)	*Abs*
0	0
0.5	0.088
1	0.165
3	0.334
5	0.546
7	0.754
	0.989



Absorbance data for calibration curve calibration curve of Metformin HCl in water of XXXetformin HCl in water

Conc (µg/ml)	*Abs*
0	0
2	0.111
4	0.203
6	0.401
8	0.500
10	0.602
12	0.781



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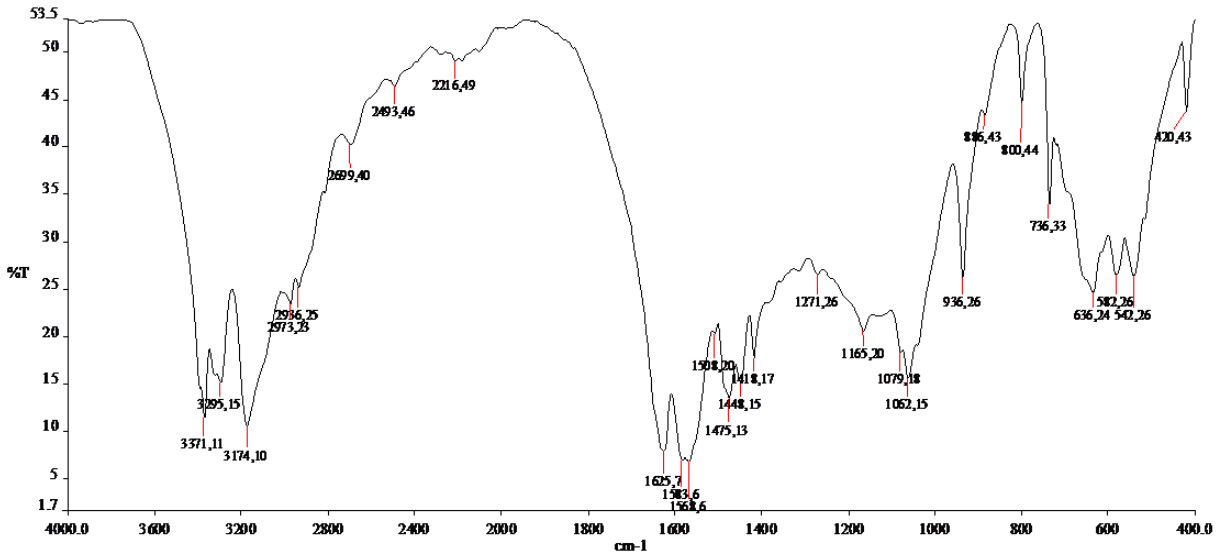


IR spectra of ethylcellulose and HPMC E5 with Drug

Preparation of Metformin Hydrochloride Transdermal Patches

A polymeric solution (5%w/v) was prepared by dissolving ethyl-cellulose and PVP K-30 with metformin HCL (20% w/w of the dry weight of polymer), Propylene Glycol (30%w/w) as a plasticizer and eucalyptus oil (2%, 5%, 7%) as a permeation enhancer in Methanol: dichloromethane (1:1) as solvent system.

Firstly, the solution was prepared with different ratios of polymeric blend without adding a permeation enhancer. The composition of prepared transdermal patches is given in Table 1. Then again, the patches were developed using the procedure mentioned earlier with different concentrations polymer and stirred for 45 min on magnetic stirrer to mix Homogeneous mixture. After mixing the drug and polymer, a solution was allowed to stand for 15 minutes to remove air bubbles, and the resulting solution was poured in a glass ring placed on a Petri dish containing mercury pool. The solvent was allowed to evaporate at 40°C for 24hr to achieve the drug-polymer matrix patch. After 24 h the patch was collected and stored in desiccators until further use.

In the formulations prepared, the release retardants included was hydroxypropylmethylcellulose E50 (HPMCE50), and Polyvinylpyrrolidone K30 (PVP K30) was used as a polymer. Dichloromethane and methanol were used as solvents. Dibutyl phthalate was used as a plasticizer

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothens.

Result: Film appearance showed that the uniform films were formed. It was observed that patches were found to be off white in the color, smooth, clarity and soft because of the addition of Propylene Glycol, as a plasticizer which helped in the preparation of flexible films.

Thickness of the patch

The thickness of the drug-loaded patch is measured in different points by using a digital Micrometer and determines the average thickness [11]

Flatness

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation inlength because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness [13]

$$\% \text{ constriction} = l1\text{-}l2/\ l2 \times 100$$

Where l1 = initial length of each strip

l2 = final length of each strip

Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking give the value of folding endurance[14]

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hours.

Table 1: Composition of transdermal patches

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

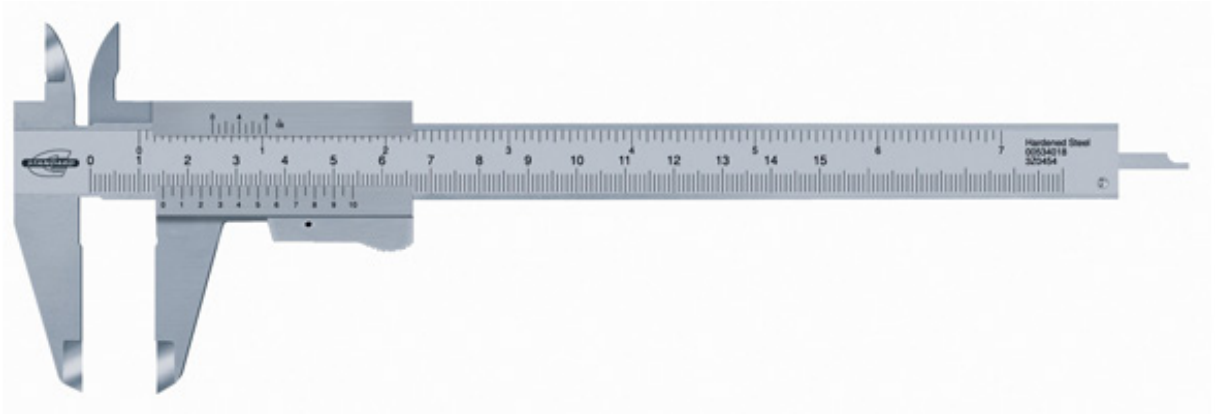


Fig 7.2 Vernier Caliper[12]

Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight

% of moisture content = (X-Y/Y) × 100 Where, X = initial weight, Y = final weight.[15]

Moisture uptake

The weighed patches were kept for drying in a vacuum desiccator at normal room temperature for 24 hours up to a constant weight and then exposed to 84% relative humidity (saturated solution of potassium chloride).[16]

% of moisture uptake = (Y-X/X) × 100

Where, X = initial weight, Y = final weight.

Drug content study

A drug content study was carried out using pH 7.4 phosphate buffer. Patches of 1cm^2 were taken and crushed using motor and pestle and taken in 100ml volumetric flask. With the help of a teflon coated magnetic bead, the medium was stirred for 5 hours. The contents were filtered using whatmann filter paper, and the filtrate was examined for the drug content at 233 nm spectrophotometrically .[17]

Weight Variation Study

Three randomly selected patches from each formulation were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.[16]

Scanning electron microscopy

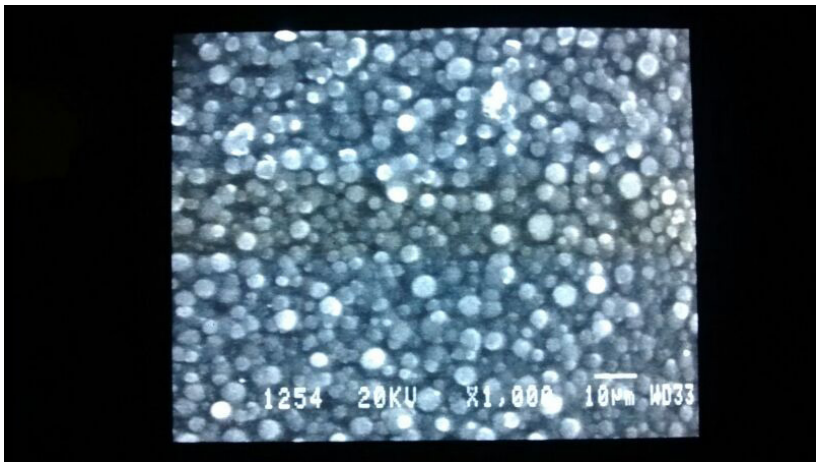
Distribution of drug and polymer in the film can be studied using a scanning electron microscope. For this study, the sections of each sample a cut and then mounted onto stubs using double-sided adhesive tape. The section are then coated with gold-palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope.[18,19]

The release profile of patches (without permeation enhancer) containing different concentration of polymers

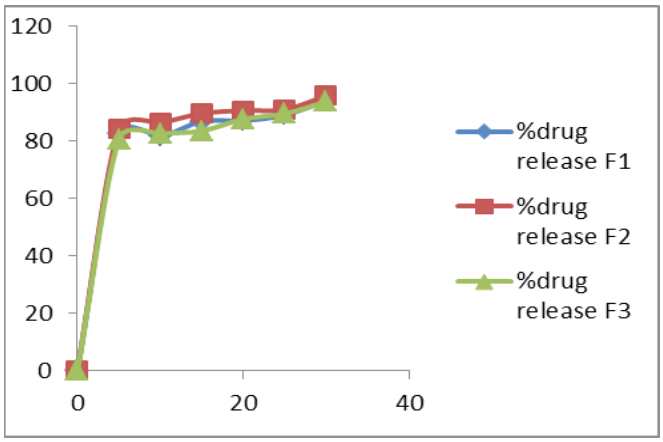
The release profile of patches containing different concentration of permeation enhancer Eucalyptus oil (2%,5%,&7%) polymers

Result and Discussion

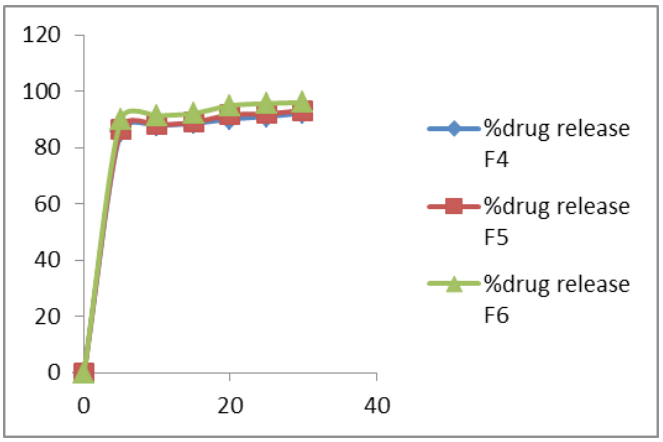
Solvent evaporation technique was used to prepare the transdermal patches of MFH using hydrophilic polymer like HPMC and hydrophobic polymer like EC. The study was targeted to prepare once a day delivery systems of MFH by using a different combination of the above-mentioned polymers (Table 1) and the concentration of drug kept constant for every formulation. Evaluation of six transdermal patches viz. folding endurance, uniformity of thickness, moisture content and moisture uptake, percent flatness study, weight variation study, drug content study, Folding endurance of all the formulations were shown in Table. The thicknesses of the prepared films were found to be described in Table 1. As there was increasing in HPMC, there is a consistent decrease in thickness. So



SEM photograph of transdermal patch showing the distribution of the drug in the matrix as particulate distribution



A graph between %drug release and time



A graph between %drug release and time

S. No.	Formulation Code	Uniformity of weight	Drug Content (%)	Flatness	Folding Endurance	Thickness
1.	F1	220	94.08	100%	10	.210
2.	F2	225	95.76	100%	11	.215
3.	F3	221	93.77	100%	10	.208
4.	F4	236	92.22	100%	9	.220
5.	F5	222	93.22	100%	10	.213
6.	F6	230	95.99	100%	10	.221

it is evident from the data that EC help in increasing in the thickness of the film.

The moisture content and moisture uptake of all the formulations was shown in Table 1 and The moisture content is increased as hydrophilic polymer concentration increased and similarly decreased as hydrophobic concentration increased. Among all the patches, FC8 was found to lowest moisture content. The moisture uptake is increased as hydrophilic polymer concentration increased and similarly decreased as hydrophobic concentration increased. FC8 was found to show the lowest moisture uptake among all.

Percent flatness data of the prepared patches were shown in Table 1. It was evident that was no much deviation in the flatness reveals uniform patches. Weight variation data of all the patches shown that there were no significant differences among the patches, and the deviation was within limits. The percentage of drug content was found in the range of 94.23 to 96.48, which is satisfactory, especially in FC4 and FC7. It indicates there was no significant among the patches in an individual set, and the deviation was within limits. The percentage of drug content was found in the range of 94.23 to 95.99. It indicates there was no significant loss of the drug during the formulation and handling of the material and also indicates fit for giving the proper therapeutic effect. With the increase in the hydrophilic polymer in the patches, the tensile strength of the patches decreases significantly, as shown in Table 2. The variation in percentage elongation was found to be significant over the different proportions of the polymers used. Formulation FC8 showed a less percentage elongation and high tensile strength in comparison to other formulation.

From the infrared spectra14, 15 (Figures 2 and 3) it is clearly evident that there were no interactions of the drug with the polymer. The main peak in the spectrum of the drug MFH, both free and with polymer, does not show any substantial difference. The IR spectra has shown a peak at 1688.48, which signifies the presence of C=N (stretch) functional group. Peak at 1254.14 is observed, which signifies the presence of C-N stretching. A peak at 1473.34 signifies the presence of C-H (Bend in the plane). Simultaneously a peak at 732.97 signifies the presence of N-H (rocking) functional group. All the peaks were observed at the fingerprint region of the FT-IR spectra. This proves the fact that there is no potential incompatibility of the drug with the polymers like EC and HPMC used in the formulations. Hence, the formula for preparing MFH transdermal patch with EC and HPMC can be reproducing on an industrial scale without any apprehension of possible drug-polymer interactions. All the formulations showed release up to 24 h and above 80% of drug released with each formulation and follow zero-order rate release. Formulation FC6 showed maximum release in 24 hours during formulation. The formulation FC6 was selected for *evivo*skin permeation study on the basis of its *in vitro* evaluation results. Data obtained after analyzing the samples were plotted against % cumulative drug release vs. square root of time (Figure 5), which was best fitted in Higuchi model. The selective electron microscopic (SEM) photographs of the skin permeation study was presented in this work.

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