Research Article

Formulation and evaluation of novel herbal antidiabetic transdermal patch

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ABSTRACT

Aim: The aim of the present study was to formulate and evaluate the Transdermal Drug Delivery System of an antidiabetic herbal drug. And to increase the efficacy and to improve the patience compliance of the herbal medicine which can be achieved by developing alternative drug delivery system. **Materials and Methods:** The polymers that were used for selected sustained release of drug are HPMC E5 and polyethylene glycol used as a plasticizer. Transdermal patches of herbal extracts were prepared by solvent casting method. The patches were optimized on the basis of physicochemical evaluation such as thickness, folding endurance, physical appearance, uniformity of weight, moisture content and moisture uptake studies. The optimized formulations were further evaluated for the drug content, in vitro drug release, FESEM studies. **Results:** The results of the study revealed that the herbal transdermal patch using the HPMC polymer showed the better physiochemical parameters such as thickness, folding endurance, physical appearance, uniformity of weight, moisture content and moisture uptake studies. The prepared formulations were found to be uniform with respect to thickness and folding endurance and showed the least moisture content and moisture uptake. **Conclusion:** The patches prepared using the 30 % w/v of plasticizer showed the higher drug release from the herbal transdermal patch than the 20 and 25 % w/v during the in vitro studies in 24 hrs.

Keywords: *Azadirachta indica*, herbal extracts, hydroxypropyl methylcellulose, *Momordica charantia*, transdermal drug delivery system

Introduction

The definition of controlled release is a technique in which active chemicals are made available to a specified target at a rate and duration designed to accomplish an intended effect. At present, synthetic drugs form a major line of the treatment in the management of diabetes and few synthetic pharmacologically active substances can currently be administered through transdermal patches and production is technically demanding the development and optimization of dermatological delivery system is a challenging task in respect to herbal drugs and research is ongoing to improve the systems and expand the indications.[1,2] A number of transdermal patches have been developed by various investigators to achieve controlled release for extended duration, for example, antihypertensive patch,[3] contraceptive patch containing estrogen,[4] antirheumatic patch.[5]

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Hence, they would replace the need for multiple and frequent dosing. Local drug release would provide added benefit as a lower dose of the drug at the target site will be needed as opposed to higher doses required by whole body administration. This would provide maximum efficacy with minimum side effects. Hence, turning to safe, effective and time-tested Ayurvedic herbal drug formulation would be a preferable option and prime concerning issue of our study.[6]

Transdermal drug delivery system

The winds of change in the drug scenario are blowing forcefully worldwide. The emergence of new technologies provides unique opportunities to exploit novel approaches in drug delivery. A shift from conventional drug delivery to novel drug delivery is noticed a shift from conventional drug delivery suffers from various drawbacks, for example, pulsating blood levels, frequent dosing, patient noncompliance, more side effects, whereas novel drug delivery system is tailor-made system. The rate controlled drug delivery system results in:

- Constant and continuous output.
- Maintenance of constant plasma drug level.
- Lesser side effects.

Table 1: Composition of formulations containing different concentrations of PEG

Formulation	Polymer (%w/w)	Drug (%w/w)	Plasticizer (%w/v)	Solvent system (1:1)
B1	5	20	20	Ethanol: Water
B2	5	20	25	Ethanol: Water
B3	5	20	30	Ethanol: Water
C1	5	20	20	Ethanol: Water
C2	5	20	25	Ethanol: Water
C3	5	20	30	Ethanol: Water
D1	5	20	20	Ethanol: Water
D2	5	20	25	Ethanol: Water
D3	5	20	30	Ethanol: Water

Table 2: Uniformity of weight, thickness, and flatness of different batches

Formulations	Uniformity of weight (mg)	Thickness (mm)	Flatness (%)
B1	221	0.215	100
B2	172	0.222	100
B3	214	0.234	100
C1	205	0.229	100
C2	201	0.230	100
C3	208	0.231	100

- Predicted and extended duration of action.
- Patient compliance.[7]

Materials and Methods

Materials and equipment

Aqueous extracts of Neem, Karela were obtained as gift samples from Sirmour Herbolife. Hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) were purchased from Molychem Limited, Mumbai, India. In the present study, the laboratory chemicals other than mentioned above used in the study were of analytical reagents grade, and several types of equipments employed in the formulation of herbal patches were magnetic stirrer, Petri dish, ultrasonic cleaner, electronic balance, pH meter, ultraviolet-visible spectrophotometer, tray dryer, and hot air oven.

Formulation of a transdermal patch

Preparation of a transdermal patch

The solvent casting method was used to prepare the transdermal patch. The drug matrix was prepared using the polymer HPMC. The polymer was weighed in the requisite ratio and a polymeric solution (5% w/v) was prepared by dissolving HPMC in ethanol:water (1:1) as a solvent system. When the polymer was mixed thoroughly, PEG as a plasticizer was added. After that, the drug solution was added in the polymeric solution and stirred for 45 min on magnetic stirrer to accomplish homogeneous mixture. After mixing, the drug and polymer solution was allowed to stand for 15 min 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 24 h to achieve drug polymer matrix patch. After 24 h, the patch was collected and stored in desiccator until further use.

Preparation of transdermal patch with different plasticizer concentration

The drug matrix was prepared by the above-described method along with different concentrations of PEG (1%, 2%, and 3%) as a plasticizer as shown in Tables 1-5.

Characterization of formulated herbal patches

Field emission scanning electron microscopy (FESEM) study

The surface morphology of samples was examined by FESEM, with operating voltage ranging from 5.00 kV and with 10.0 nm resolution. Electron microscopic studies were conducted to visualize drug distribution in the matrix patches. SEM studies were carried out using the SEM (JSM 6700 JEOL, Tokyo, Japan) for examining the transdermal patch of herbal extract.

Uniformity of weight, patch thickness, and flatness

Uniformity of weight was studied by individually weighing selected patches. After that, each film unit was weighed individually on a digital balance; the average weight was calculated and taken as the weight of the film. The thicknesses of the drug-loaded polymeric films were measured at five different points using vernier caliper. The average of three readings was calculated for each patch of the drug-loaded film. Longitudinal strips were cut-out from each film, one from the center and two from either side. The length of each strip was measured, and then the variation in the length due to the non-uniformity in flatness was measured. Flatness calculated by measuring percentage constriction of strips and a 0% constriction was considered to be equal to a 100% flatness.[8,9]

$$\% \text{ constriction} = (l_1 - l_2)/l_1 \times 100$$

Where, l_1 = Initial length of each strip; l_2 = Final length of each strip.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at

Table 3: Folding endurance, percentage moisture content, and percentage moisture uptake study of different batches

Formulations	Folding endurance	Percentage moisture content	Percentage moisture uptake
B1	11	2.35	4.91
B2	10	2.50	4.93
B3	10	3.10	5.48
C1	11	2.41	5.32
C2	12	2.60	5.96
C3	12	3.10	6.25

Table 4: Drug content study of different batches

Formulations code	Drug content
B1	89.16
B2	92.5
B3	90.4
C1	91.43
C2	94.56
C3	95.23

Table 5: *In vitro* drug release of batches B and C

Formulations	0	0.5	1	2	4	6	8	12	16	24
B1	0	0.13	1.87	4.3	12.5	26.73	34.5	45.6	58.43	67.7
B2	0	1.46	2.53	8.54	18.56	40.56	42.41	57.36	68.55	74.53
B3	0	0.38	2.85	14.36	26.86	38.26	48.8	52.3	72.13	82.4
C1	0	0.51	1.9	5.83	14.56	21.46	28.56	38.53	55.43	64.34
C2	0	0.19	2.35	9.65	17.9	27.46	31.53	54.43	68.83	80.56
C3	0	0.02	3.6	12.93	25.6	30.53	35.53	50.2	75.43	89.5

the same place without breaking/cracking gave the value of folding endurance.[10]

Moisture content

The prepared films were weighed individually and kept in a desiccator containing calcium carbonate at room temperature for 24 h. The films were weighed again and again individually after specified interval until it showed a constant weight. The moisture content was calculated as it was the difference between the constant weight taken and the initial weight and was reported in terms of percentage moisture content using formula:

$$\text{Percent moisture content} = \frac{(\text{Initial weight - final weight})}{\text{Initial weight}} \times 100$$

Moisture uptake

The weighed film was kept in a vacuum desiccator at room temperature for 24 h, was taken out and then exposed to 84% relative humidity using a saturated solution of potassium chloride in a vacuum desiccator until a constant weight for the film was obtained. The moisture uptake was reported in terms of percentage moisture uptake and calculated using formula: [11]

$$\%\ \text{moisture uptake} = \frac{(\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Drug content determination

Drug content was studied by an accurately weighing a portion of the film (about 100 mg) and was dissolved in 100 mL of phosphate buffer pH 7.4, and then the solution was stirred continuously for 24 h on a magnetic stirrer. Then, the whole solution was sonicated. After bath sonication and subsequent filtration, the drug in solution was estimated spectrophotometrically by appropriate dilution.[12]

In vitro drug release study from the formulation using egg membrane

For the study of drug release profile, various membranes are used which can be natural or synthetic. These natural membranes such as inner layer of egg, peach, tomato, and onion are used for drug permeation studies. Egg membrane is collected by placing an egg in a concentrated 3 M solution of HCL. Wait until the bubbling stops and the foam disappear. The leftover substance is eggshell with yolk and remove the egg-shell membrane from the HCL solution and washed the membrane with PBS (pH 7.4).[13]

In a 100 ml conical flask, 60 ml of phosphate buffer, pH 7.4 was taken. Weight amount of transdermal patch was taken into the egg membrane. The egg membrane sac containing the transdermal patch inside was hanged into the conical flask with the help of glass rod so that the portion of sac with the formulation should dip into the buffer solution. The flask was kept on a magnetic stirrer. The content was stirred continuously at a controlled speed using a magnetic stirrer keeping the temperature 37 ± 5°C. Sampling was done by withdrawing 5 ml from the release medium with the help of pipette and 5 ml of fresh phosphate buffer was added. Samples were analyzed using a spectrophotometer at wavelength 204 nm and 211 nm. With the help of standard curve prepared earlier, drug concentration was determined.[14]

Results and Discussion

FESEM study

The external morphology of the transdermal patches was analyzed using the FESEM. Electron microscopic studies were conducted to visualize drug distribution in the matrix patches. SEM studies were carried out using the SEM (JSM 6700 JEOL, Tokyo, Japan) for examining the transdermal patch of herbal extract. The results obtained are shown in Figure 1.

Uniformity of weight, patch thickness, and flatness

It was found that the weights were uniform with respect to all prepared formulations and showed low standard deviation values. The results of thickness studies for different formulations are shown in Table 2.

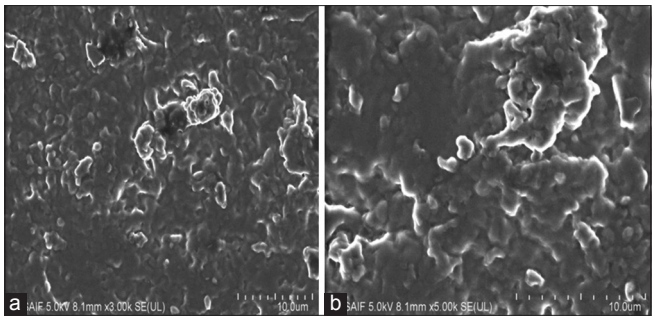

Figure 1: (a) Scanning electron microscopy photograph of the transdermal patch containing the (a) *Momordica charantia* extract and (b) *Azadirachta indica* extract showing the distribution of the drug in the matrix as particulate distribution

The above results obtained show that thickness of all the prepared formulations was found to be uniform (210–238 mm). Flatness studies were carried out to assess the same as shown in Table 2. No amount of constriction was observed in the drug matrix film of any formulation, which is an indicative of smooth flat surface.

Folding endurance

The results of folding endurance studies for different formulations are shown in Table 3. The above data show that the prepared formulations were found to be uniform with respect to folding endurance (8–12).

Moisture content

The moisture content in batches B, C, and D was found to be increased with decreasing concentration of plasticizer PEG. A little moisture content prevents the brittleness of the patches and moisture content in the formulations was found to be low.

Moisture uptake

The percentage moisture uptake was found to be increased with decreasing concentration of plasticizer PEG in all the three batches.

Percentage drug content estimation

The Karela, neem content in the HPMC E-5 matrix patches in various formulations was found in between 85% and 95% in Table 4.

In vitro percentage drug release profile

In vitro studies of batch B (B1, B2, and B3) and C (C1, C2, and C3) were carried out using the Franz diffusion cell. *In vitro* release studies showed that release was 67.7%, 74.5%, and 82.4% from formulations B1, B2, and B3, 70.1%, 80.5%, and 89.5% from formulations C1, C2, and C3. From the results, it is clear that the best release profile was obtained with formulation B3 and C3 (containing 30% plasticizer). This may be due to the presence of 30% plasticizer present in the formulations. Release studies also indicate that by increasing the concentration of the plasticizer up to 30% showed better release than other concentrations (10% and 20%).

Conclusion

It can be concluded that herbal drugs in the form of extracts can also be used in formulating transdermal patches due to the appropriate concentration of release of drug from the formulations by using this novel approach. It can be concluded that herbal drugs in the form of extracts can also be used in formulating transdermal patches due to the appropriate concentration of release of drug from the formulations using this novel approach.

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