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Development and characterization of transdermal patches loaded with Licorice extract

G Divya [1*], S Jeshwanth [2], Roshini [3], P Naveen [4], G Harshitha [5], Gulafsha [6]
[1] Assistant Professor, Department of Pharmaceutics, Siddhartha Institute of Pharmacy, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana, India
[2-6] Department of Pharmaceutics, Siddhartha Institute of Pharmacy, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana, India

* Corresponding Author: **G Divya**

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Abstract
The objective of present study was to develop matrix type transdermal therapeutic systems of Licorice using various polymers such as sodium alginate and HPMC as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The *in vitro* release study revealed that F3 formulation showed maximum release in 8 hrs. Formulation F3 was subjected for accelerated stability studies. The F3 formulation was found to be stable as there was no drastic change in the Physicochemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Licorice has been developed. F3 formulation showed highest cumulative percentage drug release of 94.70 % were obtained during *in vitro* drug release studies after 8 hrs. The release of Licorice appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data the F3 formulation was concluded as optimized formulation.

Keywords: Licorice, natural and synthetic polymers, FTIR studies, solvent casting technique, in-vitro drug release studies

Introduction

Glycyrrhiza glabra L. (*G. glabra* L., Family Leguminosae) is a traditional medicinal herb that grows in various parts of the world. The plant is widely distributed in the subtropical and warm temperate regions of the world, mainly in the Mediterranean countries and China. Transdermal drug delivery systems, not been widely used until 1970s with the discovery of transdermal patches, is gaining ground on account of its advantages to minimize gastrointestinal side effects and first-pass metabolism when compared to other administration routes. [1] Moreover, transdermal delivery systems could provide a stable blood plasma drug concentration different from oral administration, solving the low therapeutic index of drugs. However, in order to reach therapeutic concentrations in the epidermis and/or in the dermis or even in the systemic circulation, the skin barrier has to be overcome. Polymer is the main backbone for the transdermal drug delivery system which controls the release of the drug from device. [2] Whichever polymer is in formulation it should have biocompatibility and chemical compatibility with drug and other excipients. There are some criteria while choosing the polymer for TDDS formulation. The polymer should be stable and non-reactive with drug, its molecular weight and other chemical functionality of the polymer should be such that drug diffuses in proper manner and releases through it. Its degradation product must be non-toxic. [3] There are many polymers used like natural polymers and synthetic polymers. Transdermal drug delivery systems (TDDS) are the devices which contains the active ingredients of defined surface area that delivers the predetermined amount of active ingredient to the surface of intact skin at predefined rate [4, 5].

TDDS has many advantages over oral dosage forms like, it is a painless method to deliver the drug only by applying the drug on healthy skin, so the needle phobia can be avoided, it avoids gastric irritation, it avoids hepatic first pass metabolism and also increases bioavailability of drug, it improves the patient compliance by reducing the dosing frequency and also suitable the patients who are unconscious [6, 7]. Thus, objective of this study is prevention of first pass metabolism of licorice extract and thereby increasing bioavailability by developing the transdermal patches of licorice extract and also to control release of drug and to deliver the drug directly to systemic circulation in the treatment of bacterial and viral infections.

Materials

Licorice was obtained from Synpharma research Labs, HYD. Natural and synthetic polymers were procured from Synpharma research Labs, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

Methodology

Compatibility studies of drug and polymers [8]

In the formulation of Licorice extract patch formation, API and excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Licorice and the selected polymers. The pure drug and drug with excipients were scanned separately.

Preparation of leaf extract [9]

For extraction, fresh leaf of Licorice was collected from Synpharma labs, HYD, India. Collected leaves were cleaned well with normal water and again cleaned with double distilled water. The leaf is dried under sun with closed pack to free from dust. The dried leaf is ground it to fine powders and 5g of powder is mixed with 100 ml of distilled water then it is boiled to 60ºC for 15 min. After cooling down to normal room temperature, the extract was filtered through normal filter paper to get free from powder and again filtered using what man filter paper to get clear leaf extract. The filtered extract is stored in refrigerator at 4 ºC and used for further synthesis process.

Formulation design

Table 1: Formulation Design of Licorice extract Transdermal Patches

F. Code	Extract	Sodium alginate	HPMC	PEG	DMSO
F1	100	100	-	1ml	0.1ml
F2	100	200	-	1ml	0.1ml
F3	100	-	100	1ml	0.1ml
F4	100	-	200	1ml	0.1ml

Preparation of transdermal patches [10]

Transdermal patches containing Licorice extract were prepared by the solvent evaporation technique. The drug Licorice was dissolved in suitable solvent. Polymers Sodium alginate, and HPMC were taken. These polymeric solution kept under magnetic stirrer after 1 hr get viscous solution solution. After that drug add in to the polymeric solution. Sufficient care was taken to prevent the formulation of lumps. PEG was taken as a plasticizer and permeation enhancer like DMSO, and added to the mixture and mixed well. It was set aside for 2 hrs to exclude any entrapped air and was then transferred into a previously cleaned petri plate drying of patches was carried out in vaccum oven at room temperature. Dried patches were packed in aluminium foil and stored in desiccators for further evaluation.

Evaluation of transdermal formulation [11, 12]

Physicochemical evaluation

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity

The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

Moisture absorption studies [15]

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

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

Moisture loss studies [16]

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs.

Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

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

In-vitro Drug release studies [17]

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

Conditions

Medium: Phosphate buffer pH 7.4
RPM: 200
Temperature: 37 ± 0.5^{0}C
Time intervals: 8 hours

Stability studies [18]

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug release studies of the stored films were investigated after storage at the end of every week.

Results and Discussion

Drug - excipient compatibility studies (FT-IR)

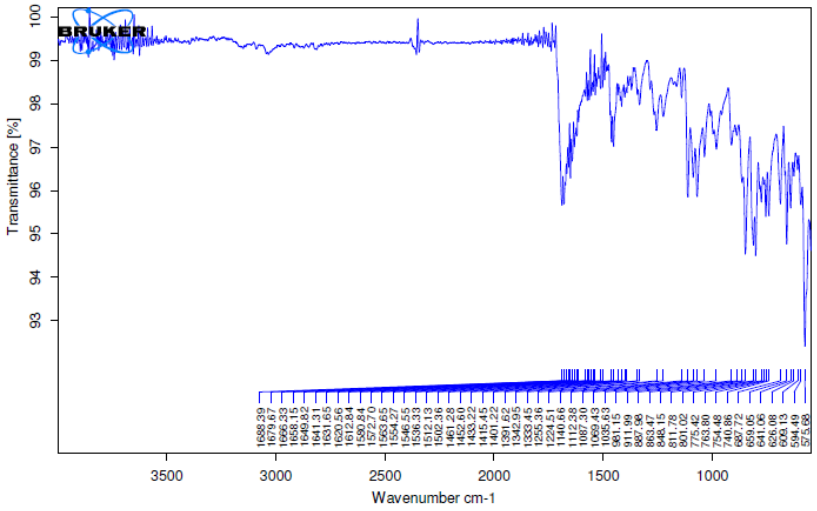

Fig 1: FTIR Studies of Pure Drug

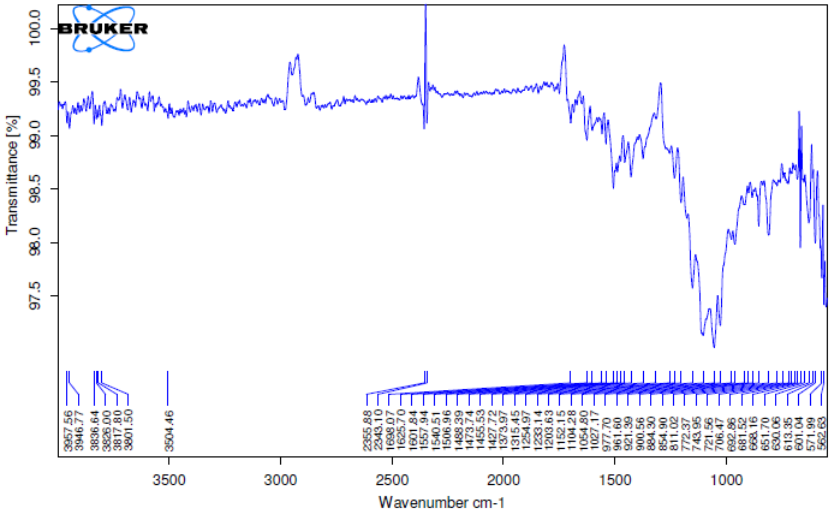

Fig 2: FTIR Studies of physical mixture of drug and excipients

Evaluation of Transdermal formulation

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Licorice patches are 179 – 185. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness..

Weight uniformity

The weights are in the range of 223-254. The F3 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%.So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Licorice transdermal patches.

Table 2: Physicochemical evaluation of Licorice patches

F. no	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% moisture loss	% moisture absorption
F1	235	0.86	185	89.56	6.42	7.25
F2	223	0.74	188	90.25	7.50	8.36
F3	226	0.83	179	93.12	6.99	8.15
F4	254	0.78	185	90.22	7.21	8.56

***In-vitro* release study**

Phosphate buffer pH 7.4was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of patches containing different ratios of natural polymer. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table 3: *In-vitro* drug release profiles of Licorice transdermal patch (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	19.86	20.48	22.25	18.25
2	34.94	37.52	31.71	36.627
3	41.16	49.28	44.36	40.18
4	51.88	53.63	50.25	56.71
5	65.33	67.46	61.07	69.20
6	73.46	78.60	75.53	73.76
7	82.87	83.35	82.15	80.92
8	89.01	92.61	94.70	93.08

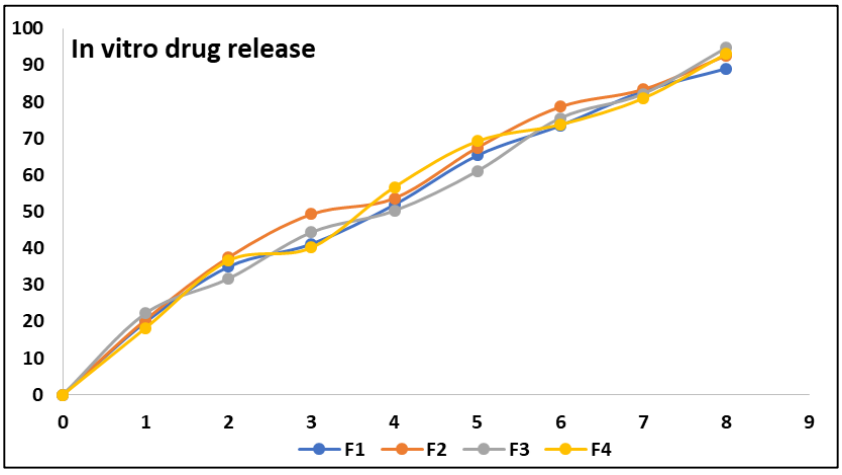

Fig 3: Drug release for (F1-4) formulations

Stability studies

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	93.12	179	No change in color	94.70
90	92.98	178	Slight yellowish color	93.52

Conclusion

Transdermal route is one of the potent alternative routes that can improve undesirable characteristics of oral and topical therapy. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F3 formulation was found to be stable as there was no drastic change in the Physico chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Licorice has been developed. F3 formulations showed highest cumulative percentage drug release of 94.70 %, were obtained during *in vitro* drug release studies after 8 hrs. Based upon the *in vitro* dissolution data the F3 formulation was concluded as optimized formulation.

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