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Formulation, Development and Optimization of Transdermal Patch of Domperidone

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***Abstract*— Objective: The main objective of the research paper is to study and prepare *Albizia zygia* based on transdermal adhesive matrix patch of domperidone to improve its compliance for patient,reducing side effects and frequency dosing also for better therapeutic efficacy.**

Methods: Solvent/evaporation casting technique were used for preparation of different patches by using *Albizia zygia* and polymers (sodium alginate) with suitable plasticizer. The prepared polymers were evaluated by physicochemical parameters like drug content, thickness, and weight variation as well as *in vitro* drug release with the help of Franz diffusion cell. For the optimization of transdermal patches, stability studies were done for it.

Result: The pH of all the batches was found to be in range from 6.7 to 7.1. It suggested that the pH was compatible with skin pH and hence no irritation is observed. All the batches of patches were in range from 0.028±0.01mm to 0.036±0.05 mm in terms of thickness. Weight of the batches was observed from 0.036±0.00 gm to 0.053±0.00 gm showing weight uniformity in the batches. Determination of folding endurance of the batches suggested that all the patches possessed optimum folding capacity. Batches F1 to F5 show % Moisture uptake and % moisture content in range from 9.09±0.03 to 42.85±0.04. It suggested that batches other then F4 is very less affected by the moisture thus they are less deteriorated by it. % swellability of all the batches was found to be good in range from 63.15 to 78.26%. Batch F5 possessed the highest tensile strength of 0.042 Kg/mm^2. % drug release of all the batches was in range from 97.04 to 99.12. Batch F3 showed maximum release of 98.82 % while F5 batch shows minimum release of 97.33 % after 480 mins. More than 60 % of the drug is released after a period of 240 mins in all the 5 batches. Batch F1, F2 and F4 shows % drug release of 97.64, 98.00 and 97.34% respectively after 480 mins.

Conclusion: The conclusion of research paper is that domperidone can be formulated as adhesive transdermal patches to extend the release of drug for several hours.

***Keywords*— Domperidone, transdermal delivery system, transdermal patches, in vitro release and Sodium alginate**

I. INTRODUCTION

Transdermal drug delivery systems (TDDS), is defined as dosage forms which are designed for delivering a drug which is therapeutically effective across patient's skin. The comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered for delivering therapeutic and systemic effects for drug. Transdermal drug delivery show less side effects by providing controlled, constant administration for allowing short biological half-lives by elimination of pulsed entry into systemic circulation. The advantages of transdermal drug delivery are as follows:-a)Hepatic first pass metabolism is limited b) Enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine are the evidence of percutaneous drug absorption and through the clinical response of the patient to the administered drug therapy [1, 2, 3].

II. MATERIALS AND METHODS

Materials: Domperidone was given as gift from Arion Health Care Baddi (Himachal Pradesh, India), sodium alginate from LOBA chemicals Ltd Mumbai (India). Glycerine was bought from S.D Fine chemical Ltd. (Mumbai, India). Other analytical reagents grade were used in the study by other laboratory chemicals..

Collection and purification of gum: Crude plant material (*Albizia zygia* gum*)* was bought from general store of Chandani Chowk, New Delhi, Crude plant material (*Albizia zygia* gum*)* was brought from general store of

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Chandani Chawk, New Delhi, India. The purification of plant material involves the various steps such as:i)Take the crude material in a beaker and put the warm water for better soaking of crude material into it for 4 hrs.ii)Boiled the soaked crude material for 2 hrs and kept aside for 2hrs for the better release of gum into water.iii)Take the muslin bag for squeezing of the material and for filteration also.iv)In the viscous gum solution, equal volume of ethyl alcohol was added for better isolation of gum.v)The purified and separated gum was put in oven at 45°C for better drying vi)The powdered gum was passed through sieve no. 80 and then stored in dessicators until further us.

III. FORMULATION OF TRANSDERMAL PATCHES OF DOMPERIDONE

Solvent casting method was prepared for the preparation of different transdermal patches of domperidone. As Firstly Polymer (100 mg) was dissolved completely in 10 ml of warm distilled water. Further Sodium alginsqcxate (400 mg) and drug (100 mg) was added to the solution and thorough mixing was done. Glycerine (2 ml) was added to the prepared solution and volume was made upto 20 ml with distilled water. This solution was casted in a prefabricated mould lubricated with glycerine and kept in oven maintained at 40-50°C to prepare the patch (Batch F1). Increasing the concentaration of polymer and keeping the concentaration of Sodium alginate and Glycerine constant Batch F2-F5 were prepared with Polymer.

Table: Composition of Transdermal patch of Domperidone:

S. No	Ingredients	Formulations				
		F1	F2	F3	F4	F5
01.	Domperidone (mg)	100	100	100	100	100
02.	Albizia zygia (mg)	100	200	300	400	500
04.	Sodium alginate(mg)	400	400	400	400	400
05.	Glycerine (ml)	2	2	2	2	2
06.	Purified water q.s. (ml)	20	20	20	20	20

Evaluation of Transdermal patches:

Evaluation of prepared transdermal patches and their characterization for the following parameters as given below:-

Physical Appearance: Visually observation for all the prepared transdermal patches for colour, homogeneity, uniformity and smoothness [4].

Surface pH Measurement: By using calibrated digital pH meter, we can measure surface pH for prepared transdermal patches. The readings were taken in triplets for each patch [4, 5].

Thickness: By using Vernier Calliper ,there is a measurement of thickness for prepared transdermal patches. The readings were taken thrice and average value was calculated [4, 5].

Weight Variation: Each prepared patches were weighed individually thrice and weight variation amongst them was calculated by determining the average values and standard deviation [5, 6].

Folding endurance: Three patches from each batch of size 1cm^2 were cut. To determine the folding endurance the patches were folded repeatedly at the same place till it breaks. The final value of folding endurance of prepared patches were measured by counting the number of times of patches were folded without breaking. [7].

Moisture uptake: 1 cm^2 patches were cut from each batch and weighed using electronic weighing balance and kept in desiccators containing calcium chloride at room temperature. After 24 hrs these films were reweighed and the % moisture uptake was calculated using the formula given in equation 1 [8].

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

--- equation 1

Moisture content: Three patches were cut from each batch of size 1cm^2 and weighed individually using electronic weighing balance. At room temperature, patches were kept in a desiccators containing calcium chloride. These films were reweighed after 3 hrs and then calculate the % moisture content using the formula given in equation 2 [9].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

--- equation 2

Swelling index: By calculating the weighing known area of the films from all the batches (W_O),swelling index of the prepared patches were determined. In a petri dish which contains 10 ml of double distilled water,there patches were put and reweighed after a fixed time interval (W_t). The degree of swelling was calculated using the formula given in equation 8.3 [10, 11].

$$\text{Swelling index (\%)} = \frac{Wt - Wo}{Wo} \times 100$$ ---equation 3

Where, Wt = weight of film at time t , Wo = weight of film at time 0

Drug content: Patches of equal sizes (1cm^2) were accurately weighed from each batch. There was a stirring for

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24 hrs continuously in Phosphate buffer at pH 6.8 till the film completely dissolves. Then there was a filteration, dilution and analysis using UV spectrophotometer for final solution. The content was determined using the formula given in equation 4 [13, 14].

$$\% \text{ Drug content} = \frac{\text{absorbance} \times \text{dilution factor} \times \text{bath volume}}{1000} \times 100$$

--- equation 4

Tensile Strength: Determination of tensile strength by the flexibility of the prepared patches. With the help of tensile tester (Instron 1121, Japan,) we can measure the tensile strength. Into one end of the patch a hook was inserted using paper holder and fixation of the other end of the film between two iron screens for better support to the patch. A thread was tied to this hook which passed over the pulley to hold small pan carrying weights. A small pointer was affixed on the base plate and it was attached to the thread travelling over the scale. Pulley pulled the films and to increase the pulling force, weights were progressively added to the pan till the patch breaks. By using formula given in equation 5, the tensile strength was calculated in kg/cm^2 [12,13].

$$\text{Tensile Strength} = \frac{\text{Force at break}}{\text{cross sectional area of film}} \times 100$$

--- equation 5

Water vapour permeability (WVP) evaluation: WVP is expressed in kg/cm^2 per 24 hr. It is determined using an air circulation oven by the formula given in equation 6 [15,16]

$$WVP = \frac{W}{A} \text{ ---}$$ equation 6

Where, W = amount of vapour permeated through the patch expressed in kg/24 hrs

A = surface area of the exposed samples expressed in cm^2

***In vitro* Drug Release Studies:** Franz diffusion cell equipment-MCF10 (3D Technologies, India) was used in all release studies. It consists of six Franz diffusion cells arranged in a water jacket with a heater to get a constant experimental temperature 32 ± 1°C, on magnetic stirrers at equal speed of rotation, temperature and rotation were equilibrated electronically. All Franz diffusion cells using in experiment consist of two compartments:

1- Upper donor compartment.

2- Lower receptor compartment.

Phosphate buffer solution pH 6.8 was used as a receptor medium with volume of 30 ml for all the release studies of Domperidone to assure sink condition. Firstly all receptor compartments were filled with phosphate buffer solution pH 6.8 and the assembled set up left in instrument to equilibrate to experimental temperature as to get rid of air bubbles for at least half an hour. Then the patches with surface area of 2.25 cm2 were placed on a wire mesh with sieve opening of approximately 800 µm, mounted between the two compartments of the diffusion cells in such a way that the backing layer was facing the donor compartment and the adhesive film facing the receptor compartment, and fastened with an O-ring. The solution in receptor compartment was agitated with a magnetic stirrer at 100 rpm. After assembling the described set up, samples of 1 ml were taken periodically through the sampling port from the receptor compartment at predetermined time intervals (0, 15, 30, 60, 120, , 180, 240, 300, 360, 420, 480 minutes) and replaced with an equal volume of fresh receptor solution at temperature of 32 ± 1 °C to maintain a constant volume of the receptor phase. Samples were analyzed for drug content at 234 nm using UV-Visible spectrophotometer. A cumulative amount of drug released was calculated. All release studies were repeater in triplicates. The results were presented in mean values ± standard deviations [16, 17].

Stability studies: Stability studies of the prepared patch batches were conducted at temperature 40°C and 75% RH for a period of 6 months. The patches were re-evaluated for pH, drug content and drug release [18, 19,20].

IV. RESULTS AND DISCUSSIONS

By using Solvent casting method, there was a preparation of Transdermal patches of Domperidone using the polymer *Albizia zygia* gum using Solvent casting method. Along with this sodium alginate and glycerine were used in a constant concentration (2 %). Five batches of transdermal batches were prepared with constant drug, Sodium alginate and Glycerine concentration and varying the polymer concentration. Sodium alginate was used as film former and Glycerine as plasticizer. All the patches prepared were evaluated for pH, thickness, weight variation, folding endurance, moisture uptake and moisture content, swellability, drug content tensile strength, water vapour permeability (WVP), *in vitro* drug release and stability studies. All the prepared patches were homogenous, uniform and smooth in appearance.

The pH of all the batches was found to be in range from 6.7 to 7.1. It suggested that the pH was compatible with skin pH and hence no irritation is observed.

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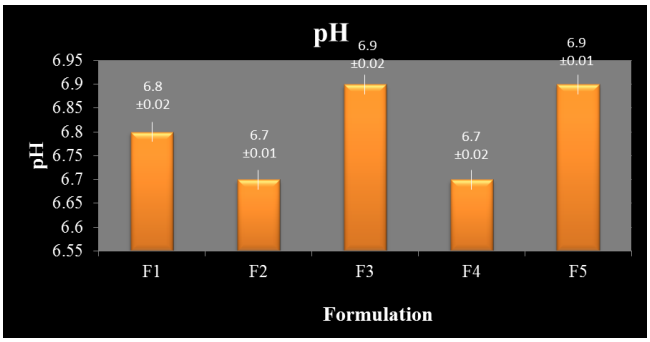
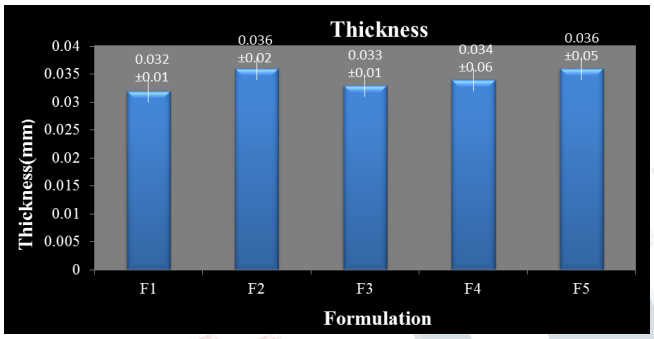


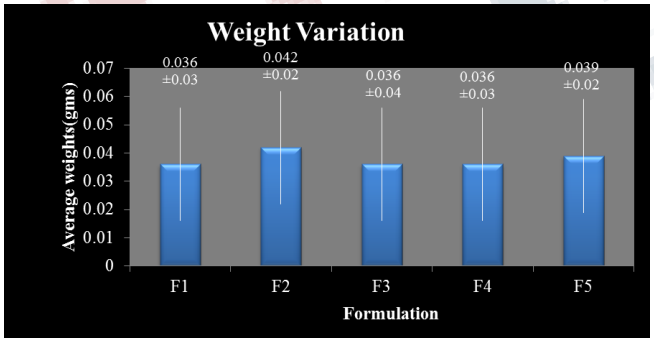
pH study of the prepared formulations

All the batches of patches were in range from 0.028±0.01mm to 0.036±0.05 mm in terms of thickness.



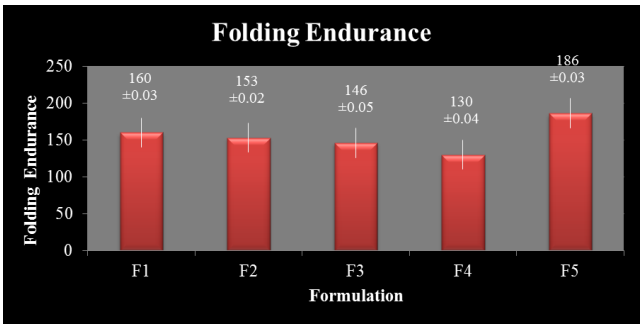
Thickness of the prepared formulations

Weight of the patches were observed from 0.036±0.00 gm to 0.053±0.00 gm showing weight uniformity in the batches.



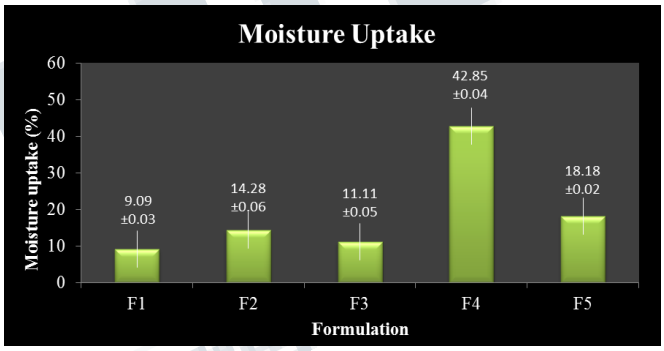
Weight variation of the prepared formulations

Determination of folding endurance of the batches suggested that all the patches possessed optimum folding capacity. F5 batch had maximum folding endurance of 186.

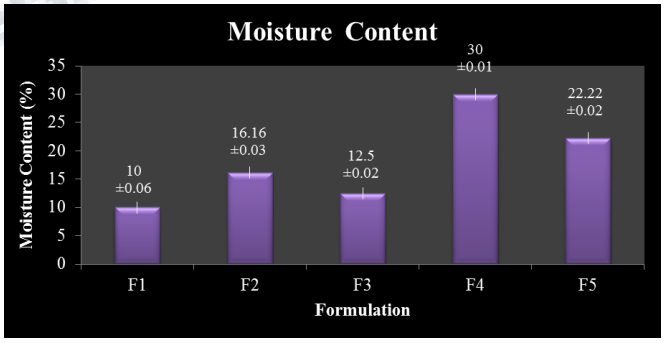


Folding endurance of the prepared patches

% Moisture uptake and % moisture content of batches F1 to F5 was in range from 9.09±0.03 to 42.85±0.04. It suggested that batches other then F4 is very less affected by the moisture thus they are less deteriorated by it.



(%) Moisture uptake of the prepared transdermal patches



Moisture content of the prepared transdermal patches

% Swellability of all the batches was found to be good in range from 63.15 to 78.26%. Batch F5 possessed the highest tensile strength of 0.042 Kg/mm^2.

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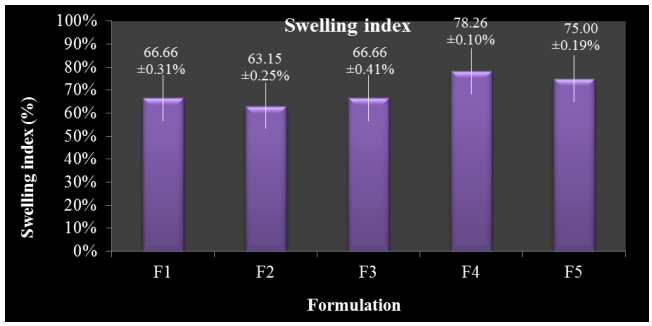
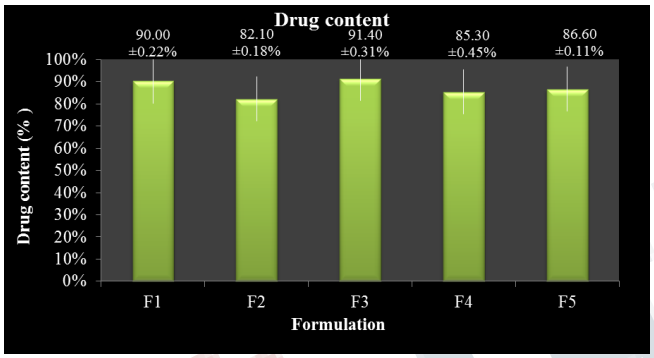


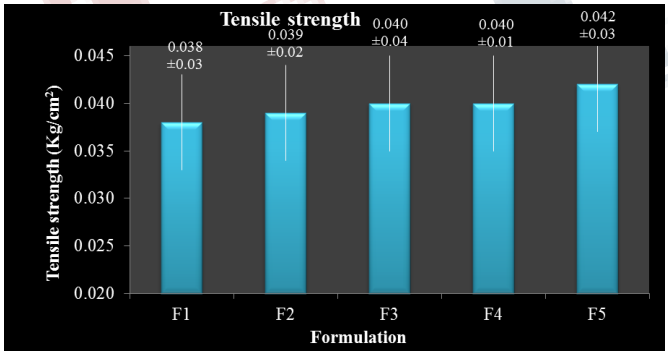
% Swelling index of the prepared transdermal patches

The drug content was found in range of 82.1 to 91.40.



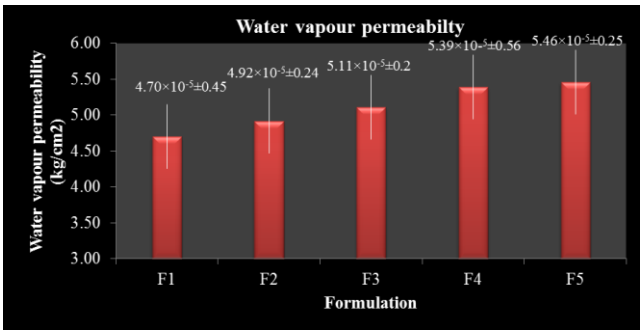
% Drug content of the prepared batches

The tensile strength of the prepared patches were measured and found in range of 0.034 to 0.042 Kg/cm^2.



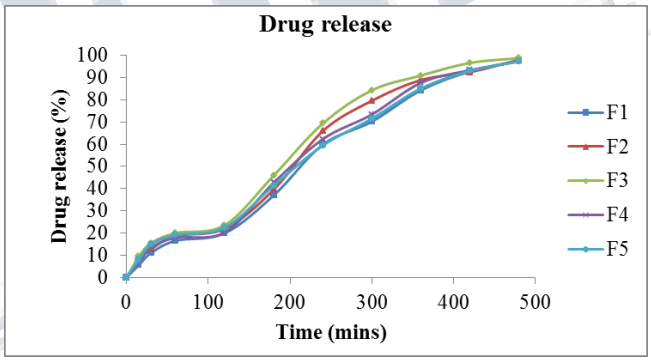
Tensile strength of the prepared transdermal patches

It was found in range of $4.7\times10^{-5}\pm0.55$ to $5.46\times10^{-5}\pm0.25$ kg/cm^2.



Water vapour permeability of the prepared transdermal patches

% Drug release of all the batches was in range from 97.04 to 99.12. Batch F3 showed maximum release of 98.82 % while F5 batch shows minimum release of 97.33 % after 480 mins. More than 60 % of the drug is released after a period of 240 mins in all the 5 batches. Batch F1, F2 and F4 shows % drug release of 97.64, 98.00 and 97.34% respectively after 480 mins.



Stability of the prepared patches was observed for 6 months. No signs of deterioration of patches were observed. Also no difference in pH, drug content and drug release was calculated after 6 months.

V. CONCLUSIONS

In the present study many attempts have been made to prepare the domperidone transdermal adhesive patches by using solvent/evaporation casting technique of different types of polymers with different types of plasticizers. Domperidone was successfully prepared which produced the sustained and controlled release of transdermal patches, which overcome the frequency of administration and provide better compliance for patient. Observations for all the evaluation parameters for domperidone transdermal patches obtained were found to be satisfactory and good. There was a successful release of the drug for a long period of time by the good preparation and evaluation of the

domperidone patches. These outcomes support the continued investigation of domperidone as transdermal paches. Thus, further studies are warranted to clarify its usefulness in a large scale as pharmacokinetic and pharmacodynamic studies on human beings.

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