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Formulation and *In-Vitro* Characterization of Transdermal Film Using *Hyptis Suaveolens* Seed Mucilage

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ABSTRACT

Transdermal films of Diclofenac Sodium were formulated by using *Hyptis suaveolens* seeds mucilage as film forming agent in various concentration. According to the research articles and mucilage can be used as film forming agent. *Hyptis suaveolens* seeds mucilage is naturally occurring polymer containing polysaccharide which cannot be used as film forming agent before. There are tremendous researches on natural polymers in today's world because of various advantages of natural polymer over synthetic. Therefore we can take it for further examination as film forming agent and its evaluation. Drug polymer interactions determine by using FTIR and DSC. The medicated films were evaluated for physicochemical properties and also medicated films were evaluated for area variation, drug content and percent cumulative drug release. *In vitro* drug release study through cellophane membrane indicates that hydrophilic polymer showed higher release. The release rate found to follow first order rate kinetic. The prepared patches will evaluated for thickness, folding endurance, tensile strength, drug contain uniformity, *in-vitro* permeation study. *In vitro* drug release study was performed by using artificial membrane.

Keywords: *Hyptis suaveolens* seed mucilage, Diclofenac Sodium, *In vitro* drug release.

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INTRODUCTION

Diclofenac Sodium is nonsteroidal anti-inflammatory agent, widely used in musculoskeletal disorders, arthritis, toothache, etc., for symptomatic relief of pain and inflammation. Diclofenac sodium is reportedly used for topical applications. The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation. This originates the need of an alternative choice of route of administration for such drugs. The Diclofenac sodium also possesses the ideal characteristics such as poor bioavailability, short biological half life and smaller dose etc., to be formulated in to a transdermal patch. Transdermal patches offer added advantages such as maintenance of constant and prolonged drug level, reduced frequency of dosing, self administration and easy termination of medication leading to patient compliance. The aim of the present study was to develop transdermal matrix films by using *Hyptis suaveolens* mucilage as film forming agent in various concentration. [1,2,3,6]

MATERIALS AND METHODS

Isolation and characterization of *Hyptis suaveolens* mucilage:

Fresh dried seeds of *Hyptis suaveolens* were collected in month of january and february. The seeds of *Hyptis suaveolens* (10 g) were soaked in water (800 ml) for 1 hr at room temperature and then stirred vigorously for 2 hr. The resulting viscous aq. extract was squeezed through a muceline cloth then add acetone and ethanol 1:1 concentration (3:3ml.) was added. The polysaccharide was collected by centrifugation, washed with ethanol, acetone and dried in hot air oven under 50 ^{o}C. Then powder it by grinding in grinder and use it in powdered form.[5]

Materials:

(*Hyptis suaveolens* mucilage confirmed from department of botany, nagpur and Authentication Number is 9297,Diclofenac sodium (a gift sample of zim laboratory Pvt. Ltd. India Chemicals, polyethylene glycol (PEG), glycerin, methyl paraben,propyl paraben (Loba Chemie), oleic acid (Qualingenes fine chemie), All others ingredients used were of analytical grade

Preparation of transdermal film:

Method used for the preparation of film is solvent casting technique. Table 4 shows composition of transdermal films of Diclofenac sodium and distilled water stir vigorously by using magnetic stirrer up to 30min.then separately add oleic acid as penetration enhancer, methyl paraben, propyl paraben as preservative then add glycerin and polyethylene glycol as plastisizers. all the solution stir vigorously in magnetic stirrer. After 30 min prepared solution was poured into a petridish and was dried at room temperature for 48 hours. The petridish was covered by inverted

funnel, to avoid rapid evaporation of the solvent.

Table 4: Formula for preparation of film

Batch	Drug	Mucilage of Hyptis suaveolens in (%)	Plasticizer (Poluethyline Glycol & Glycerin)	Permeation enhancer
F1	Diclofenac Sodium	0.2%	1.5ml&.5ml respectively	Oleic acid
F2	Diclofenac Sodium	0.4%	1.5ml&.5ml respectively	Oleic acid
F3	Diclofenac Sodium	0.6%	1.5ml&.5ml respectively	Oleic acid

Drug excipient compatibility study using FTIR and DSC:

Drug Mucilage compatibility studies using FTIR Spectroscopy:

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labeling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration might need to be addressed.

Drug Mucilage compatibility studies using DSC:

The thermogram of the pure drug exhibited a sharp endothermic peak at 289^{o}C -292 ^{o}C corresponding to its melting point. The thermogram of the pure drug exhibited a sharp endothermic peak at 289-292˚Ccorresponding to its melting point, The DSC thermograms of drug mixture showed peaks at 281.18^{o}C to 293.37^{o}C corresponding to pure drug indicated the absence of well defined chemical interaction between the drug and the mucilage.

Physicochemical evaluation:

The prepared films were evaluated for their physical appearance, uniformity of thickness, weight variation, tensile strength, folding endurance, drug content, water vapour transmission rate (WVTR) and in vitro release studies across the artificial membrane.

Weight variation:

2 cm^2 film was cut uniformly and weighed in digital balance and results are reported in table-

Thickness of the film:

Screw gauge was used to determine thickness of the films. It was placed at three different positions by keeping the film in between two glass slides of known thickness and average thickness was calculated and the values are given in table 6.

Folding endurance:

The folding endurance was measured manually. A strip of film having an area of 2cm2 was cut evenly and repeatedly folded at the same place till it broken/cracked. The number of times the film could be folded at the same place without breaking/cracking gives the exact value of folding

endurance and the results are reported in table 6.

Tensile strength:

Tensile strength was measured using analytical two-pan balance. A patch of 20 mm width and 50 mm length was cut and clamped between two clamps on one side. Weights were added to the pan on the other side until the patch is broken. The weight required for breaking the patch was taken as a measure of tensile strength of the patch and the results are reported in tables-

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula. Percentage elongation = (LF- LO) X 100 / LO. Where LF = final length, LO= initial length.[2]

Water vapour transmission studies:

Previously washed and dried vials of equal diameter were used as transmission cells. About one gram of fused calcium chloride was taken in the cell and the polymeric patches were fixed over the brim with the help of an adhesive. Then the cells were weighed accurately and kept in a closed dessicator containing saturated solution of potassium chloride (200ml). The humidity inside the dessicator was measured by a hygrometer and it was found to be 80-90% relative humidity. The cells were taken out and weighed after 2, 8, 12, 24, 48 and 72 h. From the increase in weights, the amount of water vapor transmitted and the rate of water vapor transmitted was calculated using the formula, Water Vapor Transmission Rate = W L /S. where W = Gm of water transmitted, L = Thickness of the patch and S = Exposed surface area of the patch.

Drug content:

A $2cm^2$ film was cut into small pieces and put in a 100ml buffer (pH 7.4). This was then shaken in a mechanical shaker for 2 hrs to get a homogenous solution and filtered. Then sample solutions from this was prepared by diluting to different concentrations and determined spectroscopically at 276nm. [3]The determinations were carried out in triplicates and the average of three readings were recorded and reported in table 5

In vitro release studies across artificial membrane:

The Franz diffusion cell assembly having 100 ml capacity in receptor chamber was used. Artificial membrane trimmed in to circular section of about 3 cm diameter. The patch was then placed over the artificial membrane and mounted with cap of the diffusion cell and clamped securely. The receptor solution containing 100 ml pH 7.4 phosphate buffer solution. The receptor solution was constantly stirred at 37 ± 10C over magnetic stirrer. At hourly intervals, 1ml of the sample was withdrawn and replaced immediately with fresh media. Amount of drug in the withdrawn samples was determined spectrophotometrically at 276nm and reported in table 5.

RESULT AND DISCUSSION:

Drug excipient compatibility study using FTIR and DSC:

Drug Mucilage compatibility studies using FTIR Spectroscopy:

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration might need to be addressed.

Plane Diclofenac Sodium spectra:

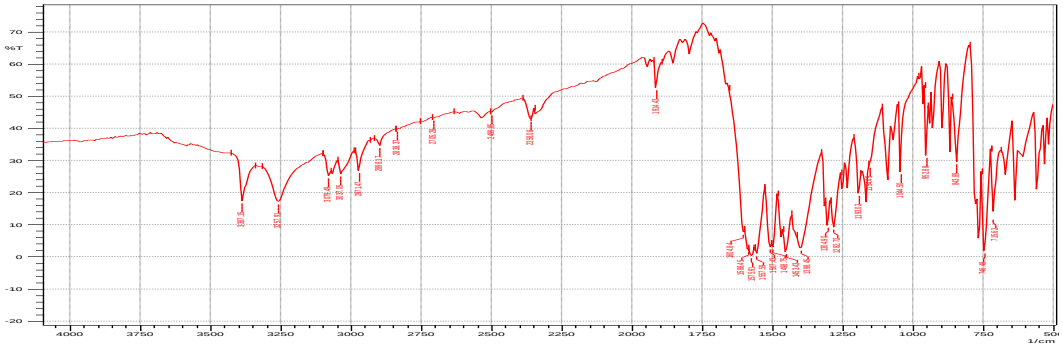

Figure 1: Plane Diclofenac sodium spectra

Interpretation:

Infrared spectra of pure drug Diclofenac Sodium showed sharp peaks at

Table 1: Interpretation of FTIR of Diclofenac Sodium

Standard Absorbance	Functional Group
3387.15	NH
3037.05	CH
2898.7,2971.47	-CH- Streching,CH_2
1604.84	C=O
1588.45	C=C

***Hyptis suaveolens* mucilage spectra** :

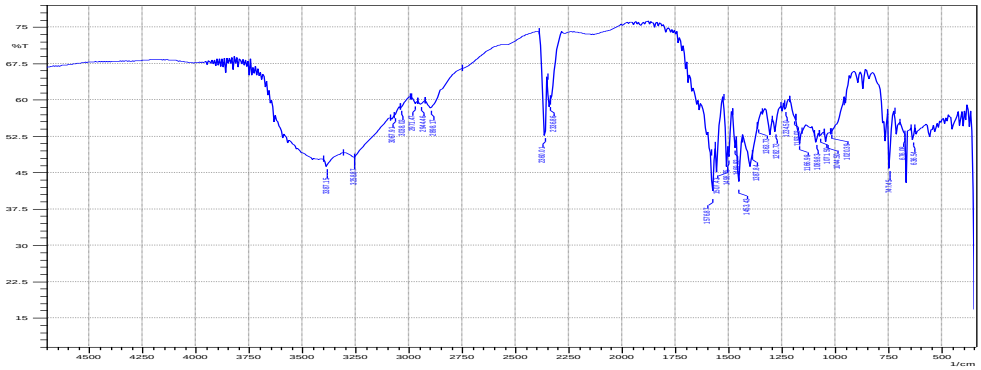

Figure 2: *Hyptis suaveolens* mucilage spectra Interprétation:

Table 2: Interpretation of *Hyptis suaveolens* mucilage spectra

Standard Absorbance	Functional Group
3387.15	OH
3037.05	Aromatic (C=C)
3257.91	-NH-
2898.16	CH_3

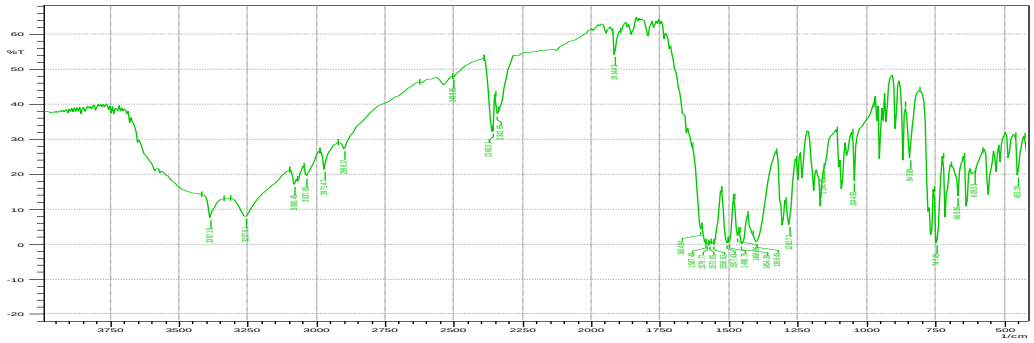

Figure 3: Mixture of Diclofenac Sodium and *Hyptis suaveolens* mucilage spectra

Interpretation:

Infrared spectra of Mixture of Diclofenac Sodium and *Hyptis suaveolens* mucilage:

Table 3: Interpretation of FTIR of Mixture of Diclofenac Sodium and *Hyptis suaveolens* mucilage

Standard Absorbance	Functional Group
3387.15	NH
3037.05	CH
3257.91	-NH-
2705.28	-CH- Stretching
1604.84	C=O
1507.43	Cl-

The I.R. spectra of physical mixture of Diclofenac sodium with *Hyptis suaveolens* mucilage powder showed peaks at same regions according to their functional groups, as compared with pure drug there by proving the absence of incompatibility between the drug and the mucilage powder.

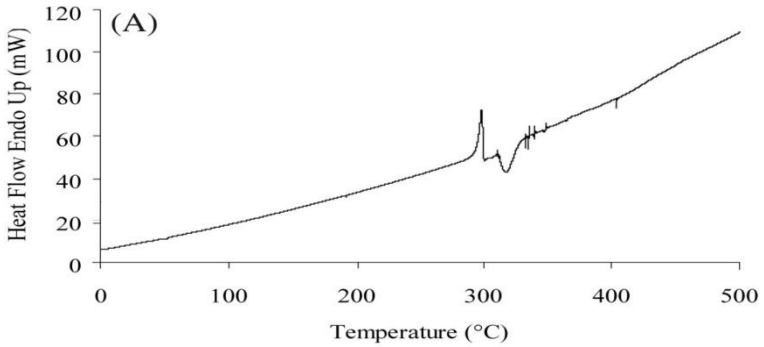

Figure 4: DSC spectra of plane Diclofenac sodium

Drug Mucilage compatibility studies using DSC:

DSC thermograms of Diclofenac Sodium depicted in figure 4. The thermogram of the pure drug exhibited a sharp endothermic peak at 289^{o}C -292 ^{o}C corresponding to its melting point.

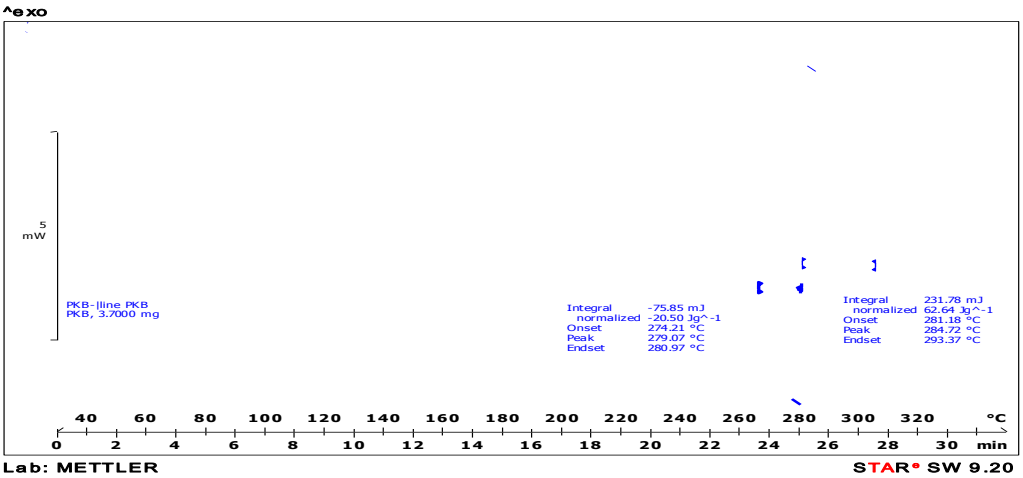

Figure 5: Mixture of Diclofenac and *Hyptis suaveolens* mucilage of DSC spectra

- DSC thermograms of Dicofenac Sodium and mixture are depicted in above figure
- The thermogram of the pure drug exhibited a sharp endothermic peak at 289-292˚Ccorresponding to its melting point, The DSC thermograms of drug mixture showed peaks at 281.18^{o}C to 293.37^{o}C corresponding to pure drug indicated the absence of well defined chemical interaction between the drug and the mucilage.

Evaluation of transdermal patch of Diclofenac Sodium:

Physicochemical evaluation:

The formulated transdermal patch of Diclofenac Sodium was evaluated for thickness, tensile strength, folding endurance and content uniformity. Thickness of transdermal patch was measured by micrometer screw gauge. The thickness of the films varies between 0.018 ±0.007 mm to 0.020 ±0.006. The tensile strength of the films was found vary with the nature of the polymer. It was found to vary between 43.52 ±0.44 Gm/102cm to 44.28 ±0.52 Gm/102cm. The transdermal patches containing. Folding endurance of the transdermal patches was measured and it was varied between 92 ±13.8 to 89 ±17.2. The drug content uniformity was determined for all the three formulations by spectrophotometric method. The drug content for prepared batches of transdermal patches of Diclofenac Sodium varies between 98.78 ±0.56 to 97.38 ±0.48. It was considered that the drug is dispersed uniformly throughout the film. The fabricated transdermal patches of Diclofenac Sodium were subjected to in-vitro permeation study across excised artificial membrane using modified franz diffusion cell having a receptor volume of 50 ml and an effective surface area of 3.14 cm^{2}. This study was carried out for 24 hours and cumulative

percent permeated was calculated based on the amount of drug originally present in the patch. In-vitro drug permeation from different batches of transdermal patches of Diclofenac Sodium were depicted in Table.5

Table 6:Physicochemical evaluation

Code	Thickness (mm) n= 5	Weight (mg) n= 5	Drug content (%) n= 3	Tensile Strength Gm/102cm n= 5	Percent elongation n= 5	Folding endurance n= 5	WVTR g/cm2/72hrs
E1	0.018 ±0.007	4.752 ±0.49	97.69 ±0.53	44.64 ±0.44	13 ±0.068	94 ±14.7	0.13588
E2	0.019 ±0.006	4.803 ±0.48	96.86 ±0.87	46.15 ±0.26	11 ±0.087	97 ±16.6	0.14301
E3	0.020 ±0.007	4.971 ±0.91	97.38 ±0.41	45.35 ±0.39	11 ±0.064	92 ±18.5	0.14350

Table 5:In vitro release studies across the artificial membrane:

Time in (Hrs.)	F1	F2	F3
0	0	0	0
1	7	6	2
2	12	8	5
3	23	17	9
4	33	22	12
5	39	24	18
6	42	29	22
7	48	35	27
8	52	42	32
9	56	48	37
10	67	55	38
11	72	57	41
12	83	66	43

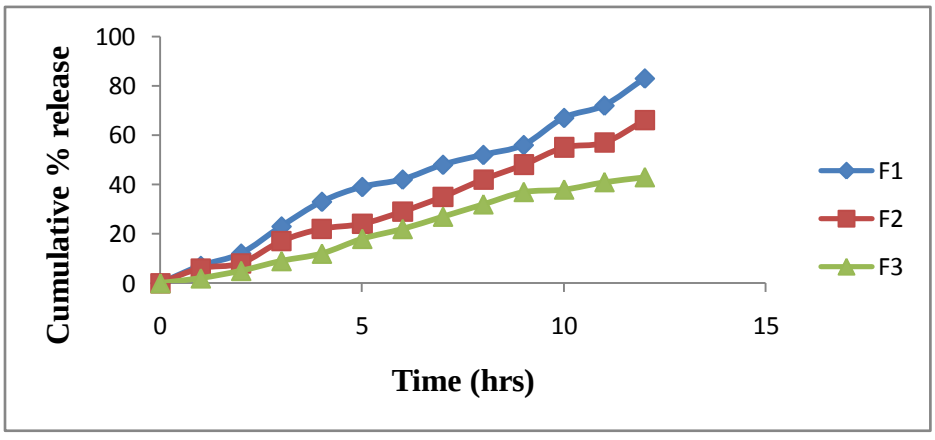

Figure 6: *In-vitro* permeation profile of Diclofenac Sodium from optimum checkpoint batches of Diclofenac Sodium transdermal Film (batch F1-F3)

CONCLUSION:

There is no significant alteration of drug. as per evaluation of formulation of film by using *Hyptis suaveolens* seed mucilage as polymer it is found that formulae F2 is optimum

concentration of polymer give optimum result so for further studies F2 will used.

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