

Formulation and Evaluation of Naproxen Sodium Transdermal Patches Using Natural Polymer

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Abstract

Natural polymer from flaxseed *Linum usitatissimum* was used in this study to develop a matrix-dispersion type transdermal Naproxen sodium medication delivery system. Flaxseed mucilage and hydroxyl propyl methyl cellulose were used to make transdermal patches of naproxen sodium. Transdermal patches were made using flaxseed mucilage, which was adopted and tested for its impact on patch quality. The solubility, melting point, and partition coefficient of the medication have been determined as preliminary evaluation metrics. Using Franz diffusion cells, the produced patches were assessed in vitro for in vitro drug release, folding durability, thickness, and weight fluctuation of the patches. For FTIR and DSC, and a stability analysis, the improved formulation was used. Data from FTIR and DSC demonstrated that the medication and excipient had no significant interaction.

Keywords: naproxen sodium, flaxseed mucilage, solvent casting method, folding endurance, Franz diffusion cell.

Introduction

Different pharmacological dose forms have been used to successfully treat both acute and chronic disorders in individuals. These formulations are renowned for their rapid absorption of the active ingredient. New methods of medication delivery, however, have emerged thanks to recent technological developments.

This methodology can regulate the timing of medication delivery. The phrase "controlled release" refers to methods that allow for some kind of regulation over the rate and/or pattern of medication distribution inside the body. That is, the system makes an effort to regulate local medication levels inside the intended tissue or cell

type. This means that continuous-release methods only provide a temporary boost to therapeutic blood or tissue levels. Here we see the distinction between continuous release and controlled release.

The primary goal of researching and developing new methods of administering medication is to improve drug delivery's efficacy and safety while also making the process more convenient for the patient. Extensive studies over the last several years have led to the creation of technologies that satisfy the requirements for non-invasive medication delivery. Technologies like transdermal medicine administration are examples.

Materials & Methods:**Preparation of phosphate buffer pH 7.4:**

The pH was corrected to 7.4 with orthophosphoric acid by using 17.90gms of disodium hydrogen orthophosphate and 1000 ml of water. 0.5% SLS was added to this mixture.

Determination of λ max using UV- Visible spectrophotometer:

By dissolving 100 milligrams of the substance in 100 milliliters of alcohol, a standard stock solution (NS) with a 1 mg/ml concentration was created. Phosphate buffer 7.4 was used to dilute the standard solution, and an absorbance spectrum was used to scan from 200-400nm to determine an analytical wavelength. In order to do additional research, the wavelength with the most absorption was selected.

Standard curves of NS:**Standard graph of Naproxen sodium in phosphate buffer 7.4:**

One milligramme per millilitre (mg/ml) of NS was prepared by dissolving 100 milligrammes of NS in 100 millilitres of methanol and then diluting the solution to the desired strength. The standard stock solution was diluted to 100 micrograms per millilitre with phosphate buffer pH 7.4. To get concentrations of 2, 4, 6, 8, 10, 12, 14, and 16 g/ml, serial dilutions of this solution were made in phosphate buffer 7.4. The absorbance of these solutions was measured using a UVVisible spectrophotometer at 273 nm, with phosphate buffer 7.4 serving as a blank, and a standard graph was drawn with concentration along the X-axis and absorbance along the Y-axis.

Pre-formulation studies:**Solubility measurement: Equilibrium method**

Dissolved in several solvents, the medication was added until it had completely dissolved in each one. Solubility is a measure of the amount of solvent that is absorbed by the sample. Table No. 8 displayed the results.

Partition coefficient:

In a separating funnel, equal volumes of organic phase (n-octanol) and aqueous phase were shaken to calculate the drug's partition coefficient. SLS (0.5%) was added to pH 7.4 buffer and 50ml of this mixture was agitated for 10 minutes with an equivalent volume of N-octanol for 24 hours with occasional shaking. The mixture was then centrifuged. To calculate the partition coefficient, the concentration of NS in the aqueous phase was measured with a UV-Visible spectrophotometer at 273 nm. An equation was used to calculate Log P, or the partition coefficient (log p).

"Partition coefficient" is defined as the ratio of drug concentrations in the organic phase and the aqueous phase (1).

Melting point determination:

Capillary tubes were filled with a little amount of the drug and placed in a melting point apparatus to ascertain its melting point; the temperature at which it melts was recorded.

***In vitro* permeation studies through egg shell membrane:**

The aim of this study was to determine the permeability of drug across egg shell membrane.

Procedure:

With a diameter of 2.4cm (4.52cm² area) and a receptor compartment volume of 50ml, a Franz diffusion cell was used for this experiment. When the barrier was erected, it was placed between the donor and the recipient compartments, with the dermal side facing the recipient compartment. Phosphate buffer pH 7.4 was used to generate a 10mg/ml medication solution. Donors received one millilitre of the aforesaid solution in their donor compartments. Phosphate buffer pH 7.4 is the fluid in the receptor compartment. A magnetic stirrer was used to keep the complete set-up at a constant 37°C (approximately 0.50°F). The samples were taken at intervals of 0.5, 1, 1.5, 2, 3,

4, 5, 6, 8, 10, 12 and 24 hours and kept cool until analyzed.

Compatibility studies of drug and polymers:

Drug and polymer may interact during film formation, resulting in the drug's inability to perform its intended function. A thorough understanding of how drugs and polymers interact is crucial in the selection of the best polymers. NS and the chosen polymers were tested for compatibility using FT-IR spectroscopy. Both the medication in its purest form and its excipients were scanned.

The spectra were taken when potassium bromide was combined with a medication and/or polymer. The NS FT-IR spectrum was compared to the NS polymer FT-IR spectrum. The appearance and area of the peak in the spectra were examined for any changes.

Due to C–O stretching (acid), COO– stretching (COOH), and C–C aromatic stretching (C–H aliphatic), the NS revealed distinct functional group peaks. These vibrations, at 1725 cm⁻¹ and 1684 cm⁻¹, are attributed to non-hydrogen-bound –C=O stretching and hydrogen bonded –C=O stretching of the catemer.

FTIR Spectra of drug along with various grades of HPMC and mucilage

Formulation design:

Flaxseed mucilage (FSM) preparation: Bring 2 cups of water to a boil, then add 1-2 teaspoons of entire flax seeds. Slowly reduce the heat to medium-low and cook for 8 minutes until the water has thickened and appears glossy, with white streaks resembling egg whites, with the lid off. The mucilage was stored in a jar in the refrigerator until it had cooled and was ready to use again.

Preparation of transdermal patches (Solvent casting method)

Methods for making transdermal NS patches via solvent evaporation were used. In 0.5ml of oleic acid, the medication NS was completely dissolved. NS, FSM, and EE100 were introduced to HPMC E15cps in a boiling tube. The risk of lumps forming was minimized to the greatest extent possible. The plasticizer PEG 400 (15 percent dry polymer weight) was added to the mixture and stirred thoroughly. To ensure that no air was retained, the Petri plate was left for two hours before being moved to a previously cleaned Petri plate (40 cm²) and dried in a vacuum oven at room temperature. FSM and EE 100 patches were prepared in the same way. A desiccator was used to keep the dried patches dry while they were evaluated further.

Table 1: Formulation Design of Naproxen sodium Transdermal Patches

Sr. No.	Formulation code	Ingredients (mg)				
		Drug (mg)	FSM	HPMC E15	HPMC EE100	PEG 400
1	F1	250	30.00	-	-	2.5
2	F2	250	25.0	10.5	-	2.5
3	F3	250	15.0	-	20.5	2.5
4	F4	250	10.0	25.5	-	2.5
5	F5	250	25.0	5.0	5.5	2.5
6	F6	250	15.0	20.5	-	2.5
7	F7	250	10.0	-	25.5	2.5
8	F8	250	25.0	-	10.5	2.5
9	F9	250	15.0	10.0	10.5	2.0

Evaluation of transdermal formulation:**Physico- chemical evaluation:****a. Physical appearance:**

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

b. Folding endurance:

Repeated folds at the same spot were used to measure the patch's folding durability. When a patch can be folded over and over without breaking, its folding endurance is measured. The mean and standard deviation were computed after three iterations on each patch.

c. Thickness of the film:

Screw gauze was used to determine the film's thickness. At three distinct points on each film, thickness was measured, and the average thickness of the film was determined.

d. Weight uniformity:

Before testing, the produced patches must be dried at 60°C for four hours. 4.52 cm² of patch must be cut and weighed in a digital balance at various points. Individual weights must be used to compute the average weight and standard deviation data.

e. Flatness:

Using a mediated patch of each formulation, we randomly chose five longitudinal strips for measurement. The length of each strip was measured both before and after 30 minutes of storage at room temperature. By estimating the percentage of constriction, we were able to determine the length variation caused by non-uniformity of flatness.

Constriction percentage = $(\text{Final-Initial length})/(\text{Initial length})/100$

Drug Content:

Each time, the drugs contained in the transdermal formulations were tested. The drug content of three patches from each formulation was tested. Each formulation was cast three times, and the

drug content was measured in one film from each set.

Procedure:

Transdermal films (4.52 cm²) with 0.5% SLS were placed in a conical flask with 100 cc of pH 7.4 phosphate buffer. For two hours, a magnetic bead was used to stir this mixture at 400 rpm. The filtrate was tested spectrophotometrically for drug concentration at 250 nm after it had been filtered. Similarly, transdermal films sans medication was used to create a blank.

Moisture absorption studies:

The films were weighed accurately and placed in a desiccator 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.

Percentage moisture uptake = $(\text{Final weight-Initial weight})/(\text{Initial weight}) \times 100$

Moisture loss studies:

Three films were weighed and dried for 24 hours at 370 degree celsius in a desiccator with calcium chloride. Once there was no additional change in the patch's weight, the final weight was recorded. The moisture loss percentage calculated by subtracting the dry weight from the wet weight, divide the result by the wet weight, then multiply by 100.

Stability studies:

Short-term stability testing was carried out on optimised medicated films. Aluminium foils were wrapped around transdermal films, which were then placed inside an ICH-approved humidity chamber and kept at 40 °C and 75 % RH for three months. After each week of storage, the preserved films' look and drug content were examined.

In-vitro release study:

Cellophane membrane-encased Franz diffusion cells were used to conduct in-vitro permeation investigations on the patch samples. Clips were used to hold the patches in place on the membrane

after they were placed in a donor compartment. Throughout the experiment, the temperature of the receptor compartment was maintained at 37.2°C. In other words, the environment was in contact with the compartment. At predefined intervals, 1 ml of sample was taken from the membrane and replaced with an equivalent volume of buffer to measure drug permeation. Samples were filtered and spectrophotometrically examined after being withdrawn.

Results & Discussion:

Determination of λ max using UV- Visible spectrophotometer:

NS exhibits absorption maxima at 273 nm in phosphate buffer 7.4.

Calibration curves of NS:

Standard graphs of NS in phosphate buffer pH 7.4. The standard graph of NS in phosphate buffer pH 7.4 containing 0.5% SLS showed good correlation between concentration and absorbance with R^2 value of 0.998.

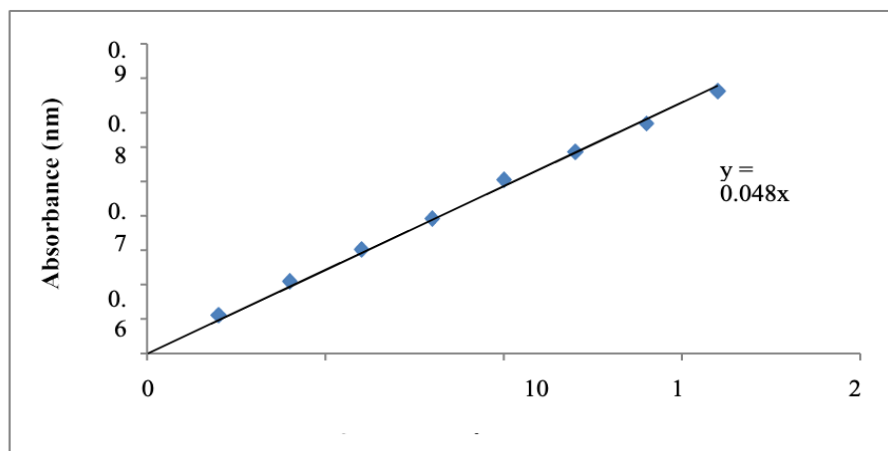


Figure 1: Standard graph of NS in phosphate buffer 7.4

Solubility measurement: By Equilibrium method

Tween 80, PEG 400, Propylene glycol, filtered water, and ethanol were all used to dissolve the medication in the various vehicles used in the

experiments. Purified water was shown to be the NS's most effective solvent. Purified water > ethanol > PEG 400 > propylene glycol > tween 80 are the order in which NS is soluble in various vehicles (Table 2).

Table 2: Solubility measurement of NS

Vehicle	Percentage solubility	Amount of drug (mg)
Tween80	84	500
PEG 400	94	500
Propylene glycol	93	500
Purified water	100	500
Ethanol	99	500

Partition coefficient and Melting point determination:

The results of partition coefficient and melting point are tabulated in Table 3.

Table 3: Determination of partition coefficient and melting point

Partition coefficient	Melting point (°C)
1.7	251

Evaluation of transdermal formulation

a. Physical appearance:

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

b. Folding endurance:

All NS patches have a folding endurance of 25 to 41. Folding endurance is a measure of the patches' mechanical strength, and a high value indicates that the patches possess strong mechanical strength. As the FSM content was raised, the folding endurance number improved (Maximum found in F1). When applied to the skin, these results suggested that the patches would not break and would keep their integrity. Table 4 summarizes the findings.

c. Thickness of the film:

Individual strips of a medicated patch were found to vary in thickness from batch to batch, indicating that the entire medicated patch is the same thickness. There is a table 4 that shows the thickness variation results.

d. Weight uniformity:

The mean weights of all the prepared patches are shown in table 4. The weights are in the range of 275 – 290. The F7 formulation patches showed maximum weight.

e. Flatness:

All the patches shown the similar strip length after 24hrs indicating that 100% flatness. Thus no amount of constriction was observed in all patches. The percent constriction of all patches were found to be 0%, so all patches carry 100% flatness, results are showed in table 4.

Drug content:

Patches made using this method had consistently low batch variability in terms of drug content, as evidenced by the analyses performed. The drug content of all patches was determined to be between 97% and 102%. In order to make NS transdermal patches, the solvent evaporation process was used, and it worked well.

In the experimental portion, there were no variations in moisture uptake and moisture loss (data not provided in table)

Table 4: Physico-chemical evaluation of NS patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Drug content (%)
F1	275.5±2.67	0.46±0.75	41±1.25	100	99
F2	280.5±3.58	0.24±0.79	29±2.35	100	98
F3	285.9±2.89	0.36±0.71	27±1.29	100	101
F4	290.5±1.50	0.79±0.81	39±2.81	100	102
F5	276.2±2.63	0.15±0.68	38±1.67	100	98
F6	283.1±1.31	0.82±0.91	33±1.89	100	97
F7	290.6±7.8	0.42±0.56	25±1.13	100	98
F8	289.4±2.19	0.46±0.56	33±4.16	100	99
F9	278.6±1.51	0.26±0.67	28±4.32	100	100

In vitro drug release profiles of NS transdermal patch

This medium, pH 7.4, with 0.5% SLS, was employed for the release investigations, and a correlation coefficient of 0.998 was recorded in the plotted standard graph. Different polymer ratios in NS patches were used to study medication release

characteristics (FSM, HPMC E15, and HPMC EE100). Release profiles revealed that excipient nature and content had an impact on how drugs were released from formulations.

The *in-vitro* drug release study was continued unless until all amount of drug released. Pure drug was also considered in current study. Around 10%

of drug released from all formulations within initial 0.5 h. pure drug exhibited 100 % drug release in 2h. In our study it showed the percentage of drug release from the patch depended on FSM. The formulation "F1" released 101.86 % of drug in 3 h. It also marked the type of HPMC (grades) remarkably affected the drug release. Formulation containing HPMC EE100 extended drug released,

as it can see in "F7"; only 68.13% drug released. Whereas, formulation containing HPMC E15 released quicker drug release as seen in "F8" It found that, "F4" released 101.45% drug from the patch. It can be justified that, the suitable combination of FSM (10 mg) and HPMC E15 (25.5mg) provided significant formulation.

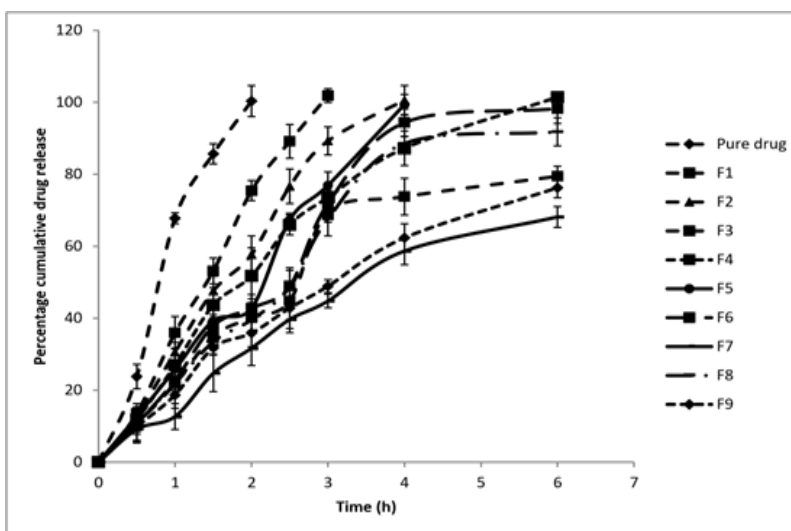


Figure 2: Drug release pattern from pure drug, F1-F9.

Table 5: Regression analysis

Formulation	Zero ord. (r ²)	First ord.(r ²)	Higu.(r ²)	Hixson.- Crowell (r ²)	Korsemyr and Pepas(r ²) and "n" value
F1	0.981	0.997	0.998	0.951	0.916 (0.37)
F2	0.995	0.998	0.997	0.913	0.924 (0.43)
F3	0.974	0.992	0.971	0.894	0.924 (0.39)
F4	0.956	0.998	0.918	0.899	0.956 (0.41)
F5	0.956	0.996	0.938	0.916	0.978 (0.43)
F6	0.945	0.997	0.879	0.673	0.934 (0.47)
F7	0.978	0.993	0.993	0.919	0.916 (0.49)
F8	0.934	0.992	0.983	0.879	0.994 (0.39)
F9	0.956	0.995	0.913	0.911	(0.41)

Maximum first-order correlation was found for formulations F1–F9; this supported the hypothesis that drug release was concentration-dependent (transdermal patch). Q will be close to one on a plot of Q vs t^{1/2} using the basic Higuchi model. Therefore, it is reasonable to conclude that the diffusion regulated release mechanism is the predominant mechanism for drug release.

Korsmeyer and Peppas's well-known empirical equation was used to fit the release data, illuminating the mechanics of transdermal patch breakdown. Fickian diffusion (a solute transport method where the polymer relaxation time (tr) is substantially larger than the typical solvent diffusion time) was seen in all formulations with a "n" value below 0.5.

Selection of optimized formulation:

From the data provided by evaluation parameter (Folding endurance, drug content and percentage drug release), F4 selected as optimized formulation and subjected to further evaluation.

Stability studies:

Formulas that work best In accordance with ICH recommendations, F4 was chosen for fast-track

stability testing. Three months were spent tracking the patches' colour, look, and pliability. It was discovered that the formulation's folding endurance, weight, drug content, and % cumulative drug release were all declining. The severe conditions (400C) under which the trials were conducted may explain this decline. See table 14 for a breakdown of the data.

Table 6: Stability studies of optimized formulations

Time in days	Drug cont. (%)	Folding endurance.	Physical appearance.	% Cumulative drug release in 6 h
0	102.16	39	No change in color	101.45±3.7
60	100.24	39	No change in color	100.76±2.8
90	99.67	38	Pale color	99.86±4.1

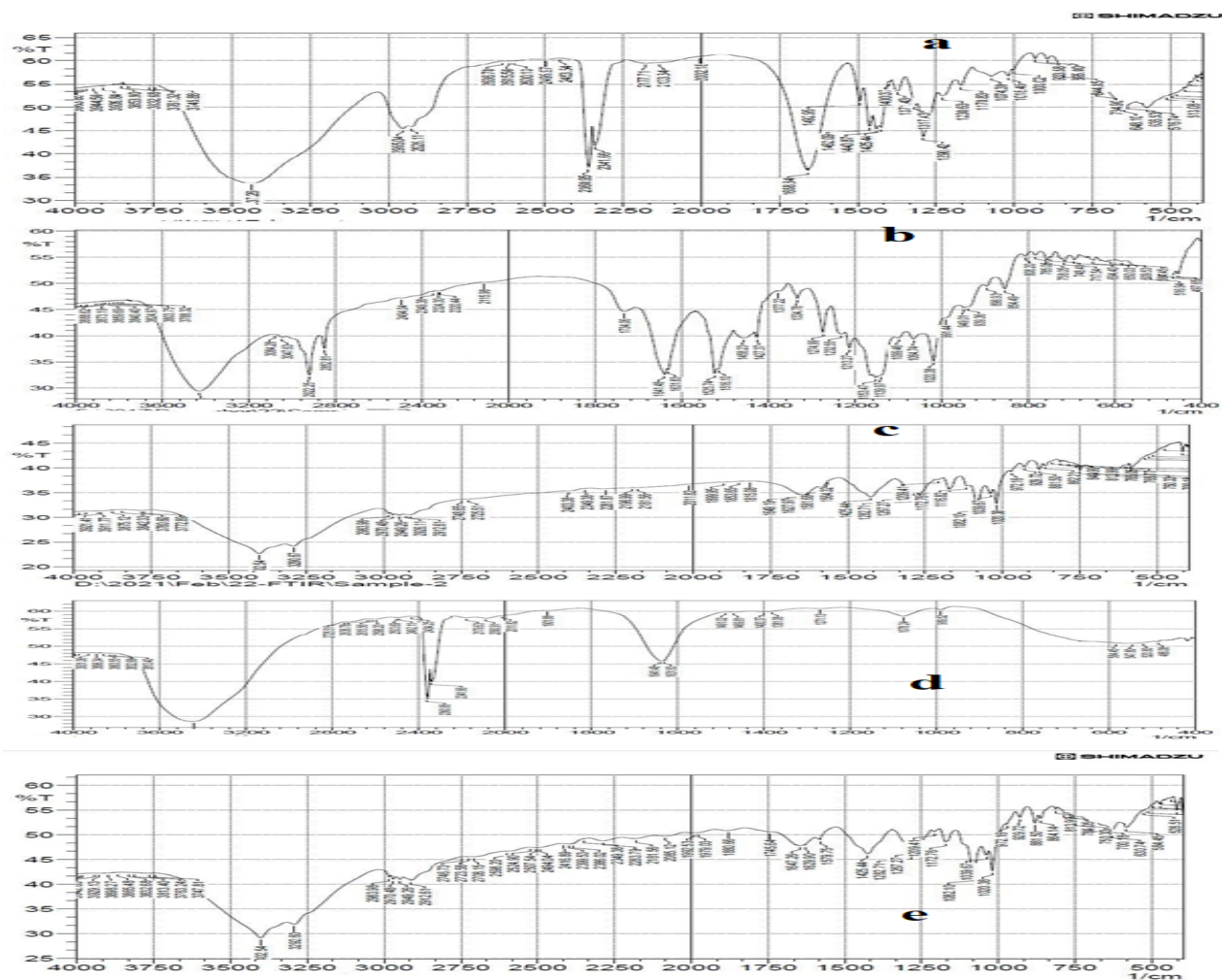


Figure 3: FTIR spectra of a. Naproxen sodium, b. Mucilage, c. HPMC E15, d. HPMC E100 and e. PEG 400

Drug-polymer interaction study of optimized formulation (F4)

FTIR analysis:

Through the use of a Fourier transform infrared spectrophotometer FTIR (FTIR 8400S, Shimadzu) with KBr pellets, the drug-excipient interaction for the drug and powdered formula was investigated and documented. We examined the spectra from 3600 to 450 cm^{-1} . C-O stretching (acid) at 1252 cm^{-1} , COO- stretching at 1583 cm^{-1} , C-C aromatic stretching at 1631 cm^{-1} , and C-H aliphatic stretch at 2840 cm^{-1} were all prominent peaks in the NS, indicating the presence of distinctive functional groups. Non-hydrogen-bonded -C=O stretching at 1725 cm^{-1} and hydrogen-bonded -C=O stretching at 1684 cm^{-1} are the most prominent peaks in the FTIR spectra of naproxen, respectively.

DSC Study:

Differential scanning calorimetry is used to detect the presence, disappearance, and shift of an endothermic or exothermic peak, which may indicate an interaction between the drug and excipients (DSC). Our research on the compatibility of drug excipients utilised DSC 8000 devices manufactured by Perkin Elmer. Researchers found that the melting point of NS, 1620C, corresponded to a strong endothermic peak throughout the experiment. In contrast, the formulation showed a modest shift in peak temperature, peak shape, and the presence of some neighbouring peak, which may have resulted from a decrease in component purity and interaction with excipients.

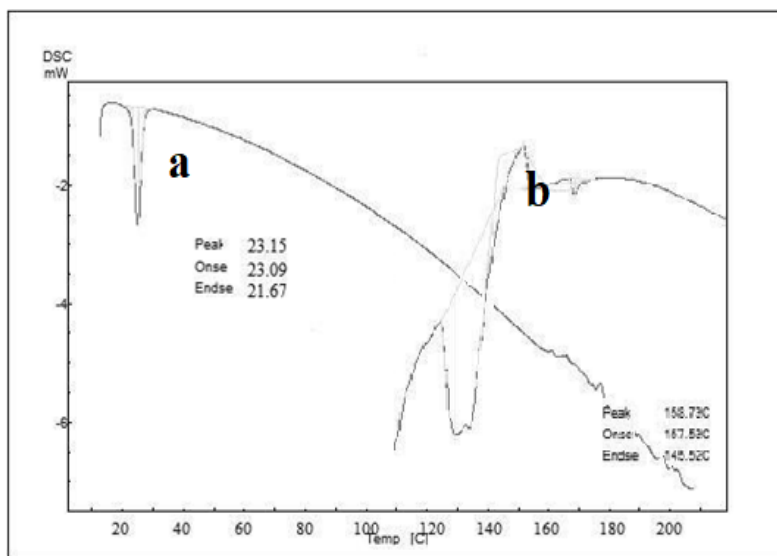


Figure 4: DSC thermogram of a. FSM and b. optimized formulation "F4"

Conclusion:

In this experiment, flaxseed mucilage was evaluated for its potential as a matrix-forming polymer in Naproxen sodium transdermal patches. Sorbitol casting was used to make the patches. In phosphate buffer 7.4, Pure NS showed good linearity. Numerous solvent solutions were tested to determine NS's solubility. The amount of solubility in purified water that can be achieved.

The partition coefficient is 1.7, and the melting point is 2510C. All of the NS patches were determined to have good folding endurance. Increasing the FSM content is expected to boost folding endurance. The weights ranged from 275 to 290 mg, depending on the model. The medication concentration of all the patches was between 97 and 102 percent. So, the solvent evaporation approach adopted for the manufacture of NS transdermal patches is a suitable one.

However, the moisture uptake and moisture loss were found to be identical to what was seen in the experimental part. Since it contained only FSM, Formulation "F1" had a faster release time, but a combination of FSM and HPMC E15 increased the release time to 6 hours. FTIR, DSC, and XRD were performed on the "F4" formulation that was chosen for further investigation. FSM and the medication were found to be compatible. In contrast, the release kinetics of all formulations were studied. Higuchi patterns of the first order and quasi-fiction diffusion were found. In addition, bio pharmacokinetics parameters can be evaluated using an in-vivo pharmacokinetics investigation.

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