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Research Article

Formulation And In-Vitro Release Kinetic Of Aceclofenac Through Polymeric Film System Using Modified Polymers

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ABSTRACT

Transdermal films of aceclofenac using chitosan, modified chitosan, HPMC, and sodium alginate were developed by solvent casting technique and evaluated with respect to various physical parameters. As a plasticizer, glycerin was utilized in a variety of weight ratios. The article also discusses conjugating chitosan with thioglycolic acid and the modification of chitosan with acetaldehyde and propionaldehyde, respectively for creating Schiff's bases (polymers-I and II). Modification and compatibility were confirmed by differential scanning calorimetry (DSC) and FTIR analysis respectively. The produced films were assessed for a number of characteristics, including thickness, folding resistance, swelling index, bursting strength, tensile strength, moisture content, water vapour transfer (WVT) rate, and in vitro drug permeation studies. All of the formulations for physical and mechanical characterization were observed, and it was found that the formulations produced the best results and the membranes were stable

INTRODUCTION

The lack of new FDA-approved medications, the high costs associated with creating new medications, and the expiration of patents for current medications were the three most significant issues facing the pharmaceutical industry in the latter half of the 20th century. As a result, many pharmaceutical companies faced a lack of pharmaceuticals covered by patents that they may profit from. The creation of unique and patented drug administration systems was acknowledged as the solution to this conundrum by the research and development plan. The goal is to construct drug delivery systems using the principles and methods of controlled drug administration in a way that maximizes the

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effectiveness of clinically tested medications1. One of the most significant innovations was the development of transdermal delivery system, which have a variety of advantages over oral delivery methods2. Since the Food and Medication Administration approved the first transdermal medication delivery device method (Transderm Scop® Patch) in 1979, a successful alternative to systemic drug administration has been developed. Transdermal delivery methods, despite their comparatively greater prices, have proven effective for delivering a few medications, including nicotine, nitroglycerin, scopolamine, nitroglycerin, clonidine, estrogens, and testosterone. These systems offer higher uniformity of drug concentrations in plasma throughout their period of use, as well as improved patient compliance when compared to oral dose forms.

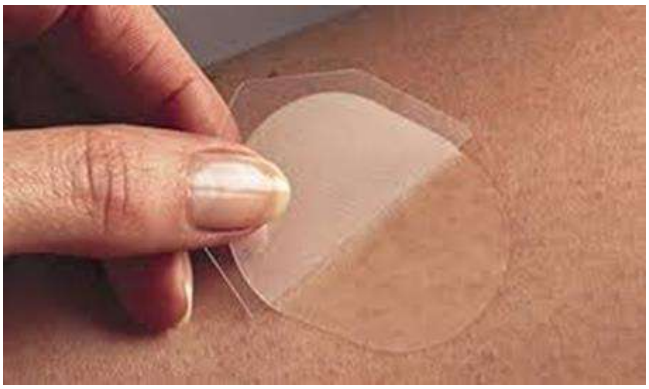


Figure 1. Transdermal patch

For a period of several hours to days after application to the skin, the majority of transdermal patches are made to release the active component at a zero-order rate. This is particularly advantageous for preventive therapy or maintenance therapy in chronic illnesses when the patient would otherwise need to carry about oral pills and remember to take them several times each day. In these situations, the development of oral drugs with long-acting, prolonged, or sustained-release has been helpful. Contrary to transdermal patches, which can prolong medication release for up to seven days (e.g., Catapres-TTS® or Climara®), these dosage forms must be taken at least once per day. For medications that were inactivated by gastrointestinal enzymes or pH and could not be administered orally in the past, parenteral delivery was the sole option (e.g., estrogens, testosterone, nitroglycerin). Now, these medications can be administered via a non-invasive transdermal route—through carefully thought-out patch systems—directly into the systemic circulation. Most significantly, unlike injectables, medication therapy can be stopped at any time if toxicity develops by removing the patch. Iontophoresis has more recently made it possible to distribute hydrophilic medicines more effectively via the skin. The driving factor that allows ions to penetrate the skin is an electric current that is applied to it. Similar to this, phonophoresis uses ultrasound energy to improve drug absorption through the skin. These methods need specialised equipment and training, and their use is currently only permitted in medical offices and hospitals3.

Advantages of transdermal drug delivery over the conventional dosage forms

- Avoid intravenous therapy's hazards and hassles.
- Evade the variations in absorption and metabolism brought on by oral delivery.
- Allow the continuous administration of medications and the use of medicines with a brief biological half-life. By passing hepatic first-pass elimination, drugs are given greater bioavailability and effectiveness.
- Reduce both inter and intra-patient variability, which is especially important when transdermal patch drug release is slower than stratum corneum drug diffusion.
- Drug levels can be kept in the systemic circulation for a long time if they are kept within the therapeutic window (i.e., above the minimum effective concentration but below

the level at which side effects become noticeable).

- Through the prolonged, pre-planned distribution of medication at the necessary therapeutic rate, the likelihood of overdosing or underdosing is reduced.
- Allow the transdermal drug delivery system to be easily removed from the skin's surface to quickly stop the medication, if necessary.4,5,6
- Ensure self- administration appropriateness.
- Patients who are queasy or unconscious benefit greatly from it. Because transdermal distribution avoids direct effects on the stomach and intestine, medications that induce gastrointestinal disturbances may be suitable candidates.
- Medications that are broken down by the digestive system's enzymes and acids are also suitable choices.7,8

Disadvantages

The following is a list of the transdermal medication delivery system's drawbacks:

- Due to the fact that solute diffusivity is inversely proportional to its size, a molecular weight of less than 500 Dalton is required to allow easy diffusion over the stratum corneum
- Drugs must have sufficient aqueous and lipid solubility, with a Log P (octanol/water) between 1-3, in order to successfully penetrate the stratum corneum and the aqueous layers underneath it
- Human skin that is both healthy and diseased has a permeability that is influenced by intra- and inter variability. As a result, different biological reactions are predicted to result from fast, slow, and typical skin absorption profiles. Because unbroken stratum corneum represents a barrier, only extremely potent medications—like nicotine, which has a therapeutic effect at concentrations of just 10 to 30 ng/ml in the blood—can be administered by this route
- Preliminary systemic metabolism enzymes found in the skin, such as peptidases and esterase, may convert a medication into a form that is therapeutically inactive, decreasing its effectiveness.
- Dermal and transdermal delivery's "Achilles heel" is skin sensitivity and irritation. Exposure to particular stimuli has the potential to trigger the skin's immunological barrier. This could apply to medications, excipients, or parts of delivery devices that cause erythema, oedema, etc. Innovative methods including iontophoresis, electroporation, and ultrasound can partially alleviate the drawbacks of transdermal drug delivery systems caused by ionic medicines, large molecular weight pharmaceuticals, and distribution in a pulsatile manner.4,9

MATERIALS AND METHODS

Utilizing a double beam Shimadzu 1601 spectrophotometer, the UV Spectrophotometric method was developed for the drug analysis.

Calculation of λmax

Aceclofenac was dissolved in phosphate buffer, then further diluted with it, and scanned for maximum absorbance in a UV spectrophotometer in the wavelength range of 190 to 380 nm, using phosphate buffer pH 7.4 as a blank. A 273nm maximum was discovered for the drug.

pH 7.4 phosphate buffer preparation13

250 ml of the 0.2 M potassium dihydrogen phosphate solution was combined with 195.5 ml of the 0.2 M sodium hydroxide solution, and the volume was then increased to 1000 ml with distilled water. The buffer's pH level was changed to 7.4.

Aceclofenac standard curve in phosphate buffer, pH 7.4

Stock solution I was made by carefully weighing 100 mg of Aceclofenac and dissolving it in 100 ml of PB pH 7.4. To create stock solution II, 100ml of the aforementioned solution was diluted from

10ml with the same solvent, further 0.3ml, 0.6ml, 0.9ml, 1.2ml, 1.5ml, 1.8ml, 2.1ml, 2.4ml, 2.7ml and 3.0ml of stock II was again diluted to 10ml with the same solvent to get solution containing 3µg/ml, 6µg/ml, 9µg/ml, 12µg/ml, 15g/ml, 18µg/ml, 21µg/ml, 24µg/ml, 27µg/ml and 30µg/ml as the final solutions. The absorbance was then determined using PB pH 7.4 as a blank in a UV Spectrophotometer at 273nm. The resulting absorbances were tabulated as shown in Table 2. Figure 2 displays the plotted calibration curve.

Chemical modification of chitosan10,11

By dissolving the polymer in a 1% W/V acetic acid solution made in distilled water, chitosan (2% W/V) solution was created. Chitosan was thoroughly dissolved before adding 50ml of the solution to 2gm of either acetaldehyde (to prepare polymer I) or propionaldehyde (to prepare polymer-II). At 600C, stirring lasted for another three hours. Later, acetone was added to the polymer solution to precipitate the chitosan that had undergone chemical modification.

Conjugation of polymer chitosan-thioglycolic acid

A 1% W/V solution of chitosan hydrochloride was created by hydrating 500 mg of chitosan in 4 ml of 1M HCL and dissolving it with demineralized water. EDAC was then added, with a 50mM final concentration. 500mg of TGA was added to the chitosan hydrochloride solution after EDAC had dissolved entirely in it. Using 1M NaOH, the pH was brought down to 4.0. The reaction mixture was incubated at room temperature for 3 hours. The chitosan-thioglycolic acid conjugate that resulted from this process was isolated by dialyzing at 100C against 1mM HCl, twice against the same medium but also containing 1% NaCl, and finally exhaustively against 1mM HCl. The sample was then kept in a dessicator under vacuum until it had fully dried. A glass mortar and pestle were used to powder the dried conjugated chitosan, which was then put through sieve number 60 and kept in a dessicator until it was needed.

Confirmation of modified chitosan

The conjugation of chitosan with acetaldehyde or propionaldehyde and thioglygolic acid was verified by FT-IR and DSC.

FT-IR spectrophotometric analysis14

The samples of chitosan and modified chitosan were prepared as KBr pellets and submitted to scanning with an FT-IR spectrophotometer from 4000cm-1 to 600cm-1 (SHIMADZU FT-IR 8400).

Compatibility study using differential scanning calorimetry

To look into any potential interactions between the medicine and the applied polymers, DSC thermograms of pure drug (Aceclofenac) and its physical combination with polymers were conducted. The heating rate was kept at 200C raise per min up to 3000 C to better integrate the information.

Preparation of drug loaded transdermal films

By using the solvent casting technique, films were created. In order to create the films, various concentrations of plasticizers and polymers were used; the corresponding compositions of the films were created by combining polymers with a drug and a solvent. In Table 1, the formulation of the films is described. At first, films were created utilizing Chitosan, HPMC, and sodium alginate. Accurate weights of the polymers were used to measure, soak, and triturate them to create a uniform gel. The entire gel was sonicated to prevent air bubbles from becoming trapped inside the film. These gels were placed into polyethylene-coated glass Petri dishes and dried in a hot air oven at 40 °C until a flexible film developed (24 h). Prior to usage, the dried films were cut into patches, wrapped in aluminum foil, and placed in an airtight desiccator.

Table No 1: MATERIALS USED IN THE FORMULATION

Sr. No.	Materials	Suppliers
1	Aceclofenac	FDC Pvt Ltd., Mumbai
2	Chitosan	Sigma-Aldrich chemicals Pvt Ltd., Mumbai
3	HPMC (K15M)	Colorcon Asia Pvt Ltd., Goa
4	Sodium Alginate	Loba chemie Pvt Ltd., mumbai
5	Glycerine	S.D Fine Chem Pvt Ltd., Mumbai
6	Acetaldehyde	S.D Fine Chem Pvt Ltd., Mumbai
7	Propionaldehyde	Spectrochem Pvt Ltd., Mumbai
8	Dialysis membrane (110)	Himedia Pvt Ltd., Mumbai
9	EDAC	Himedia Pvt Ltd., Mumbai
10	Sodium Hydroxide	S.D Fine Chem Pvt Ltd., Mumbai
11	Sodium Chloride	S.D Fine Chem Pvt Ltd., Mumbai
12	Thioglycolic Acid	Nice chemicals Pvt Ltd, Cochin

EVALUATION OF TRANSDERMAL PATCHES

Thickness10

The drug content can be significantly changed by the divergent thickness of the films. For films containing strong medications, uniform thickness is crucial. With the use of a Dial micrometre (Mitutoyo, Japan), the thickness of the film was measured at various locations using the smallest unit measurement count of 0.1 mm. Three films of each formulation were measured, and the average values were calculated.

Weight variation15

The weight uniformity of the formulated films was assessed. Three films from each formulation were chosen at random, cut into 1 cm2 squares, and then each one was weighed on a digital balance. The film's weight on average was computed.

Folding endurance7

The folding durability of the membrane was evaluated using a modified USP tablet disintegration tester. It was comprised of both fixed and moveable jaws that could be raised and lowered at a speed of 30 strokes per minute. The two jaws were separated by 6 centimeters at their greatest distance and 0.5 centimeters at their closest. The membrane, which was 6 cm long, was held in place between the jaws so that when the jaws were close together, the membrane stretched across its middle, and when they were far apart, the membrane was in a stretched form. The membrane went through one cycle of bending and stretching as a result of each stroke of the movable jaw. The number of strokes needed to break or cause visible membrane cracks to form is how the folding endurance is calculated. 20 minutes, or 600 strokes, were used to complete the test.

Bursting strength

Using a common bursting strength tester, the bursting strength of each patch was assessed. The films are placed over the diaphragm by cutting it in to required dimensions and apply the pressure

by using regulator which is present on the platform until the film bursts. The readings were recorded from the dial meter and reported in terms of kg/cm2.

Swelling studies12,16

The films of 1cm2 were weighed accurately and placed separately in Petri dishes containing 10 ml of phosphate buffer (pH 7.4) solution. The films were carefully removed at intervals of 5, 10, 30 and 60 minutes, blotted with filter paper to remove any water that remained on their surface, and then precisely weighed. Using the following formula, the swelling index was determined:

$$\text{Swelling index} = \frac{\text{Wet weight} - \text{Initial weight}}{\text{Wet Weight}} \times 100$$

Percentage of moisture content

Each 1 cm2 piece of film was weighed separately and kept dry for 24 hours at room temperature in a desiccator made of fused calcium chloride. Multiple measurements of a certain membrane's weight were made until it remained constant. Calculated as the difference between initial and final weight relative to final weight, the percentage of moisture content was determined.

$$\text{\%Moisture Content} = \frac{\text{Initial weight - final weight}}{\text{final weight}} \times 100$$

Percentage of moisture uptake11,17

Sodium chloride (Nacl), sodium bisulphate (NaHSO4.H2O), and potassium dichromate (K2Cr2O7), respectively, were used to expose a weighed membrane of size 1 cm2 that had been kept in a desiccator at room temperature for 24 hours to 74.9%, 52%, and 98% relative humidity (RH). These samples were weighed repeatedly until no further weight gain was noted. The difference between the final and initial weights relative to the initial weight was used to calculate the moisture uptake percentage.

Water vapor transmission study11,18

Glass vials with similar diameters served as the study's transmission cells. These transmissions had a thorough cleaning before being dried in an oven to a fixed weight. The vial was filled with about 1gm of fused calcium chloride to act as a desiccant, and 1cm2 polymeric films were then adhered over the brim with adhesive tape. These pre-weighed vials were put in a sealed desiccator with a saturated potassium chloride solution. Every day for the seven days of storage, the cells were taken out and weighed. The following formula was used to get the water vapour transmission rate:

$$WVT = \frac{WL}{S}$$

Where,

W = Weight of water vapor transmitted in g,

L = Thickness of film in cm2

S = Exposed surface area in cm2

Tensile strength test

The films' tensile strength was assessed using a house field universal testing machine. The machine has a sensitivity range of 1 mg to 500 mg. There are two load cell jaws in it. The lower one is fixed, while the upper one is adjustable. The grips were used to hold films of a certain size (5 cm x 1 cm), and the upper jaw was operated at a pace of 100 mm per minute while progressively applying strain until the films broke. The dialed reading in kilos and the film's extension in millimeters were used to determine the tensile strength of the films.

Drug content

A content uniformity test was conducted to ensure that Aceclofenac was distributed uniformly throughout the movie. A 100 ml volumetric flask containing 50 ml of phosphate buffer with a pH of 7.4 was added with the 1 cm2 film inside. The flask was placed on a mechanical shaker and continuously shaken for 24 hours before the final volume was adjusted with phosphate buffer pH 7.4. The solution was filtered, and the filtrate was tested for drug content at 273 nm using a UV-Spectrophotometer (UV-1601 Shimadzu, Japan).

In vitro permeation studies

Studies on permeation were conducted using the Franz diffusion cell, which has two compartments with a combined capacity of 10 ml and an effective surface area of 0.785 cm2. To keep the temperature at 37oC, a jacket was placed over the receptor chamber. The formulations that used a dialysis membrane were the subject of the study. Earlier, the phosphate buffer was used to soak the dialysis membrane for 12 hours (pH 7.4). Phosphate buffer pH 7.4 was added to the receptor chamber, where the film formulations of 1 cm2 were mounted between two chamber stands. The receptor chamber was then tightly fastened to the specially made diffusion cell using rubber bands. A Teflon-coated bead was used to stir the solution in the receptor compartment at a constant speed while hot water was circulated inside the water jacket to keep the temperature of the entire assembly at 37°C. The entire assembly was then set up on a magnetic stirrer. 8 hours were spent on the release study. To maintain the sink conditions, the samples (5 ml) were removed and filtered at predetermined intervals up to 8 hours. They were then replaced. The UV-spectrophotometer (UV-1601, SHIMADZU, Japan) was used to measure the drug content at 273 nm. For each formulation, the test was conducted three times.

Stability studies:

Stability of a pharmaceutical product is defined as the capacity of a specific formulation, in a specific container, to retain its physical, chemical, therapeutic, and toxicological requirements during the period of its shelf life.

The length of the study and the storage conditions are outlined by ICH.

Long term testing: 250C ± 20C/75%RH ± 5% for 12 months

Accelerated testing: 400C ± 20C/75%RH ± 5% for 6 months

Method

In accordance with ICH norms, the optimized formulation underwent a two-month stability assessment. Wide mouth bottles with tightly closed lids contained the chosen formulas in aluminium foil bags. After two months of storage at 400C/75%RH, they were examined for their permeation investigation.

RESULTS

Evaluation of developed formulations:

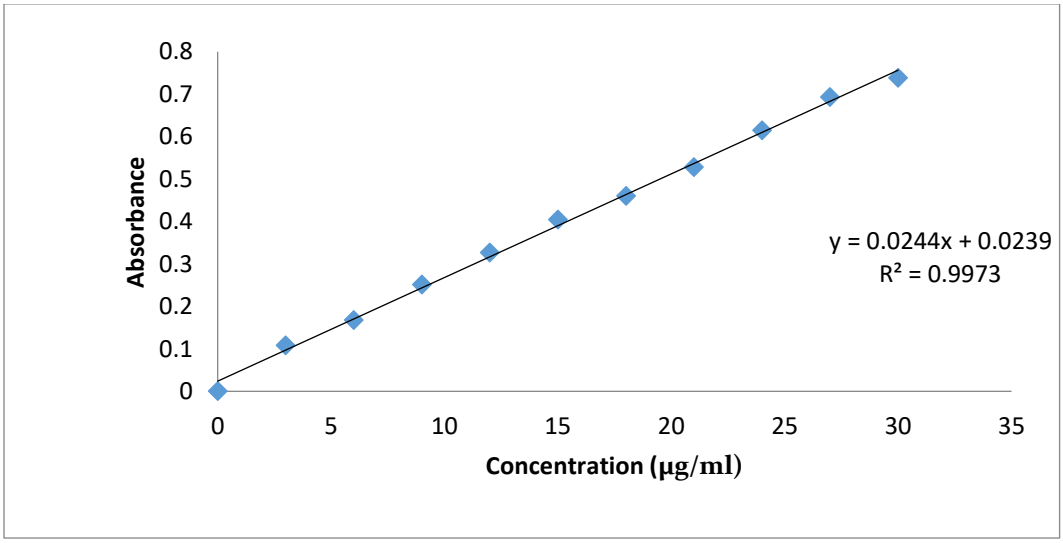


Fig.no. 2 Calibration curve of Aceclofenac:

Table 2. Composition of Aceclofenac transdermal films along with formulation code

Formulation code	Polymer	Polymer concentration(%)	Plasticizer(%) (Glycerin)	Drug (%)
F1	Sodium alginate	1.5	20	20
F2	Sodium alginate	1.5	30	20
F3	Sodium alginate	2	20	20
F4	Sodium alginate	2	30	20
F5	HPMC	1.5	20	20
F6	HPMC	1.5	30	20
F7	HPMC	2	20	20
F8	HPMC	2	30	20
F9	CA	2	20	20
F10	CP	2	20	20
F11	CT	2	20	20
F12	Chitosan	2	20	20

***W/W of the polymer's dry weight**

Table 3: Concentration and absorbance obtained for calibration curve of aceclofenac

Sr. No.	Concentration (µg/ml)	Absorbance (at 273 nm)
1	0	0
2	3	0.108
3	6	0.168
4	9	0.251
5	12	0.327
6	15	0.404
7	18	0.460
8	21	0.528
9	24	0.615
10	27	0.693
11	30	0.738

Table 4: Physicochemical characteristics of aceclofenac transdermal films

Formulation	Thickness (mm)	Weight Uniformity (mg)	Folding Endusing (Strokes)	Moisture Content (%)	Water Vapour Transmission Study
F1	0.11±0.013	24.31±0.12	No visible cracks	16.66±0.54	3.34x10-3
F2	0.18±0.018	26.04±0.15	No visible cracks	11.11±0.44	3.31x10-3

F3	0.15±0.025	29.17±0.15	No visible cracks	18.18±0.89	3.26x10-3
F4	0.18±0.021	32.51±0.11	No visible cracks	9.09±0.54	3.35x10-3
F5	0.10±0.027	21.26±0.20	No visible cracks	12.50±0.44	4.55x10-3
F6	0.14±0.025	23.44±0.15	No visible cracks	9.09±2.38	4.23x10-3
F7	0.13±0.017	24.98±0.20	No visible cracks	20.00±0.54	4.69x10-3
F8	0.10±0.023	26.51±0.12	No visible cracks	20.00±0.44	4.48x10-3
F9	0.14±0.022	31.46±0.11	No visible cracks	12.50±0.89	5.82x10-3
F10	0.14±0.014	33.45±0.11	No visible cracks	14.28±0.44	9.29x10-3
F11	0.14±0.014	34.07±0.18	No visible cracks	20.00±0.44	7.50x10-3
F12	0.14±0.015	36.66±0.20	No visible cracks	16.66±0.44	4.47x10-3

Values are mean ± SD

TABLE 5: Mechanical properties of aceclofenac transdermal films

Formulation	Tensile Strength (Kg/cm^2)	Bursting Strength (Kg/cm^2)
F1	0.7223	2.36±0.20
F2	1.4388	2.50±0.32
F3	0.2651	3.24±0.15
F4	0.1353	3.95±0.25
F5	0.4864	2.54±0.14
F6	0.9041	2.86±0.37
F7	0.3134	4.43±0.26
F8	0.3698	4.52±0.41
F9	0.4987	3.68±0.12
F10	0.5248	3.81±0.44
F11	0.5154	4.14±0.29
F12	0.5326	3.90±0.45

Values are mean ± SD

Table 6: % Moisture uptake of formulation F1 to F12

Formulation	52%RH	74.9%RH	98%RH
F1	9.44	14.52	17.82
F2	10.07	12.98	15.77
F3	8.11	11.25	15.18
F4	13.69	16.54	19.30
F5	10.46	13.57	16.69
F6	11.54	15.38	17.22
F7	11.07	14.99	17.18
F8	12.61	15.23	18.04
F9	12.65	19.09	21.69
F10	11.73	15.61	18.55

F11	12.38	17.16	22.81
F12	8.86	13.98	17.20

Table 7: % Swelling Index of formulation F1 to F12

Formulation	5min	10min	30min	60min
F1	39.33	40.97	43.54	45.81
F2	41.94	42.63	44.21	47.05
F3	49.36	51.09	52.93	55.73
F4	66.47	70.09	72.2	74.54
F5	33.19	35.16	38.99	40.72
F6	35.74	36.98	39.45	43.08
F7	41.52	43.66	47.17	48.93
F8	44.21	45.58	49.73	52.09
F9	49.07	50.85	52.64	55.15
F10	26.96	30.5	33.81	37.41
F11	44.16	46.37	48.01	49.17
F12	18.73	20.65	23.61	24.44

Table 8: Drug release kinetics from different formulation of aceclofenac transdermal films

Formulation	Zero order ($r^{2)}$)	First Order (r^2)	Higuchi (r2)	Release Exponent (n)
F1	0.895	0.898	0.972	0.669
F2	0.928	0.962	0.951	0.604
F3	0.971	0.973	0.932	0.571
F4	0.931	0.938	0.974	0.485
F5	0.854	0.873	0.976	0.457
F6	0.794	0.805	0.950	0.431
F7	0.863	0.886	0.959	0.370
F8	0.901	0.915	0.979	0.405
F9	0.980	0.980	0.948	0.729
F10	0.958	0.966	0.980	0.784
F11	0.838	0.862	0.962	0.502
F12	0.896	0.915	0.971	0.520

DISCUSSION

Calibration curve of aceclofenac

The pure drug aceclofenac's calibration curve was created in the concentration range of 3-30 g/ml at 273 nm. Regression coefficient R2 of 0.997, which indicates good linearity, was found. The concentration range tested adhered to Beer Lambert's law. Characterization of aceclofenac and polymers by FT-IR Figure 3 depicts the FT-IR spectra of aceclofenac. The functional groups of a pure drug are thought to be responsible for its distinctive peaks. The peak at 2935 cm-1 in the aceclofenac spectrum was brought on by the C-H stretching of the butanol alkane, while the absorption band at 1711 cm-1 is related to the ketone group C=O stretching of the acyclic saturated pentamido group. The absorption band at 3313 cm-1 corresponds to its O-H hydroxyl

stretching (Hydrogen bonding), 3266 cm-1 for N-H stretching, 3028 cm-1 for C-H stretching, 1579 cm-1 and 1501 cm-1 for C-C stretching (Resonance), 1441 cm-1 for O-H deformation, 1287 cm-1 for C-N stretching, 1247cm-1 for C-O stretching, 962 cm-1 for O-H deformation (Out of plane) and 744 cm-1 for 1,2,3 trisubstituted benzene. The FT-IR spectrum of chitosan conjugation with acetaldehyde is shown in figure 4. The characteristic bands of aceclofenac appeared indicating not much interaction between drug and polymer but exhibited a magnitude shifts in peaks. The intensity of band C-H alkane is reduced to 2910 cm-1. The band C-N stretching of aromatic tertiary amine shifts to 1150 cm-1, 3296 cm-1 for O-H stretching (Hydrogen bonding), 3186 cm-1 for N-H stretching, 1410 cm-1 corresponds to O-H deformation (Overlaps C-H bending of CH3), 1018 cm-1 for C-O stretching.

The FT-IR Spectrum of chitosan conjugation with propionaldehyde are shown in figure 5. There was no interaction between drug and polymer. Spectra shows characteristic peaks with slight shifts.3360 cm-1 corresponds to O-H stretching (Hydrogen bonding), 3243 cm-1 for N-H stretching, 2918 cm-1 and 2872 cm-1 for C-H stretching, 1540 cm-1 for N-H deformation, 1404 cm-1 for O-H deformation, 1151cm-1 for C-N stretching and 1016 cm-1 for C-O stretching. The FT-IR spectrum of chitosan conjugation with thioglycolic acid shown in figure 6. The intensity of C-H alkane band is reduced to 2909 cm-1 and 2872 cm-1 and N-H deformation (secondary CO-NH) to 1591 cm-1due to the presence of polymer. 3356 cm-1 corresponds to O-H stretching (Hydrogen bonding), 3296 cm-1 N-H stretching, 1424 cm-1 for CH2-S deformation, 1370 cm-1 for O-H deformation, 1148cm-1 for C-N stretching and 1021 cm-1 for C-O stretching.

FT- IR Study: Figure 3: FT-IR Spectrum of pure aceclofenac

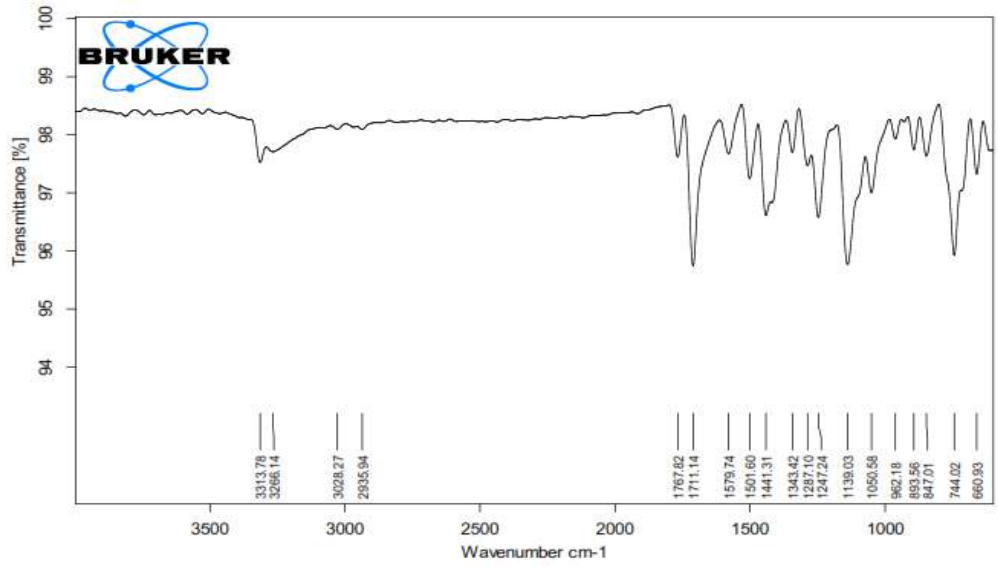


Fig. 4: FT-IR Spectrum of chitosan conjugation with acetaldehyde

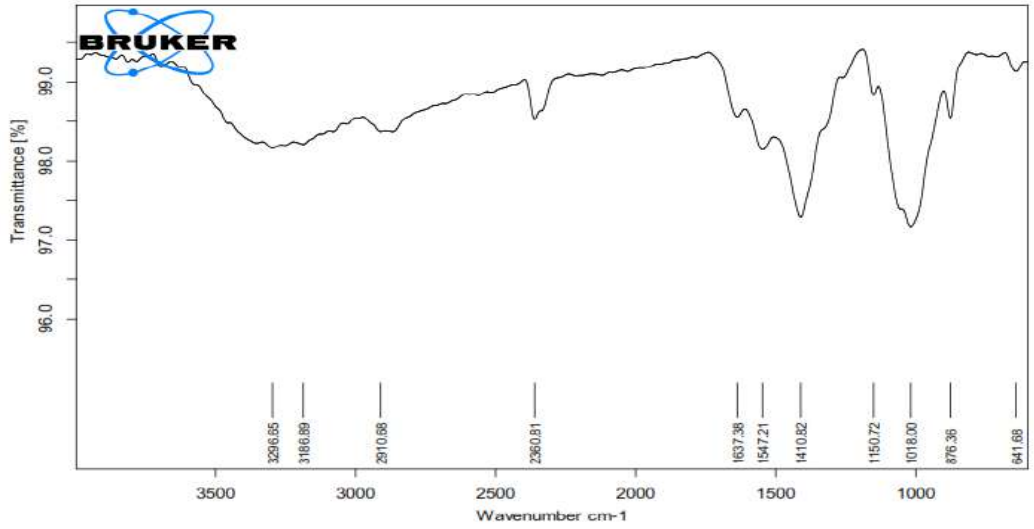


Fig. 5: FT-IR Spectrum of chitosan conjugation With Propionaldehyde

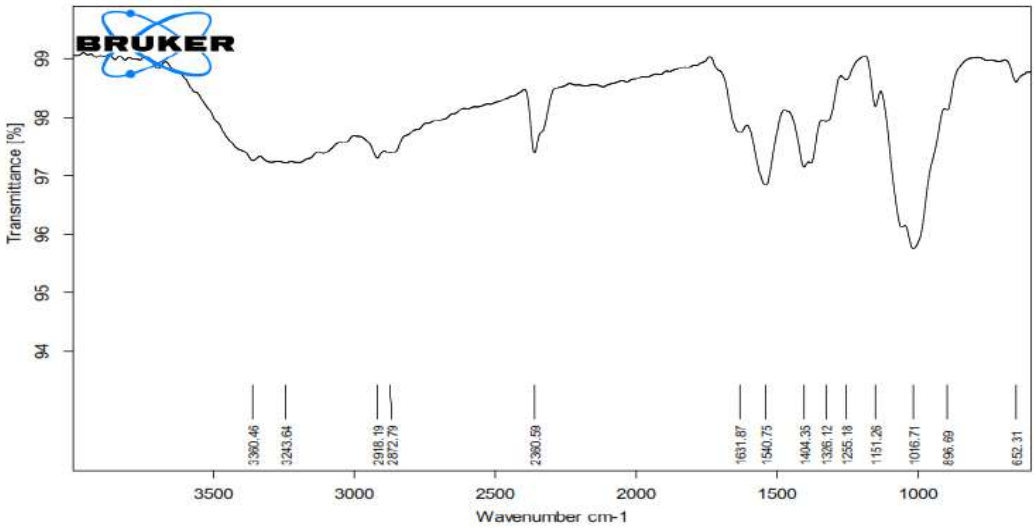
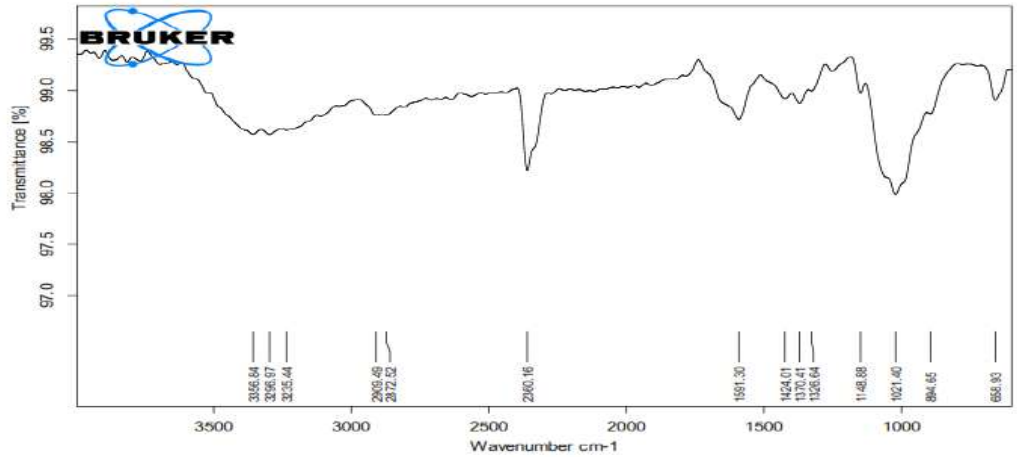


Fig. 6: FT-IR Spectrum of chitosan conjugation with thioglycolic acid



Confirmation of modification of chitosan by DSC

The DSC thermogram of the chitosan conjugation with acetaldehyde, propionaldehyde and thioglycolic acid was taken to confirm the modification of chitosan. The modified chitosan, have shown one extra endothermic peak at 94.490C in chitosan conjugation with acetaldehyde, at 86.380C for chitosan conjugation with propionaldehyde and 70.840C for chitosan conjugation with thioglycolic acid. This has further confirmed the conjugation of chitosan with aldehydes and thioglycolic acid.

DSC Study:

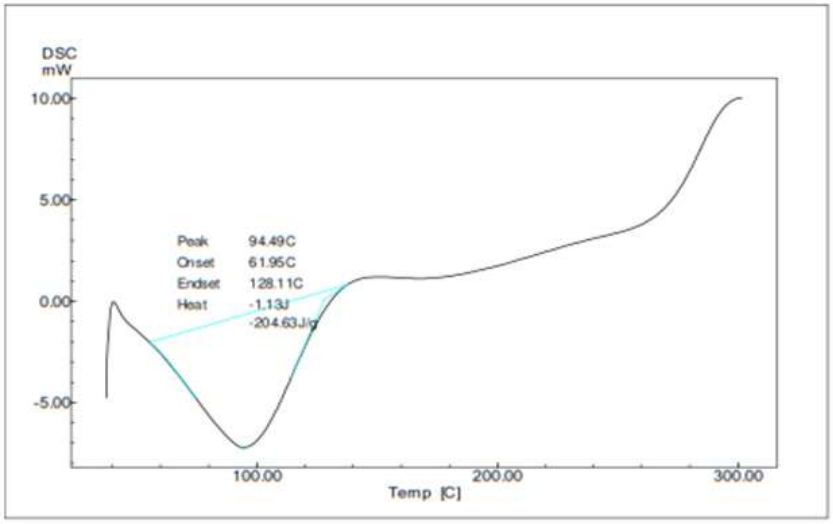


Figure 8: DSC spectroscopy of chitosan conjugation with acetaldehyde

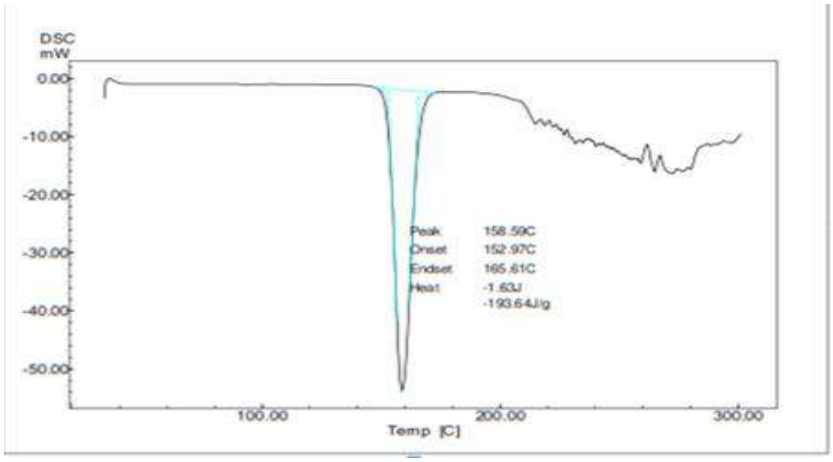


Figure 9: DSC spectroscopy of pure aceclofenac

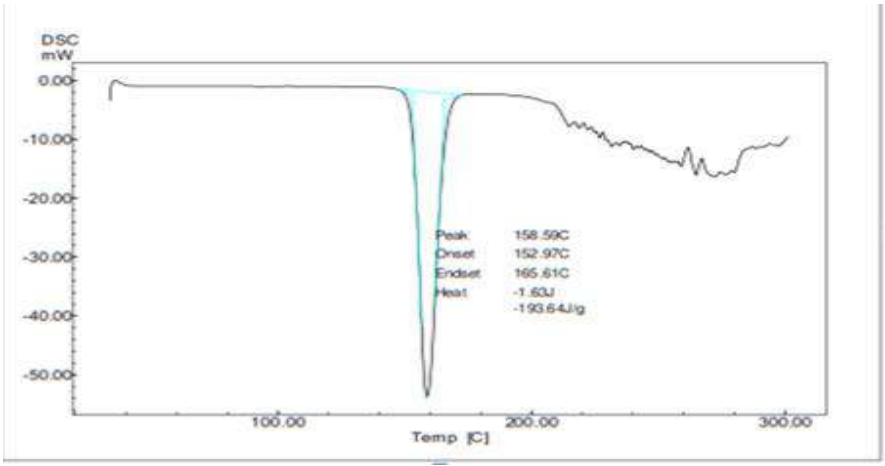


Figure 10: DSC spectroscopy of chitosan conjugation with acetaldehyde

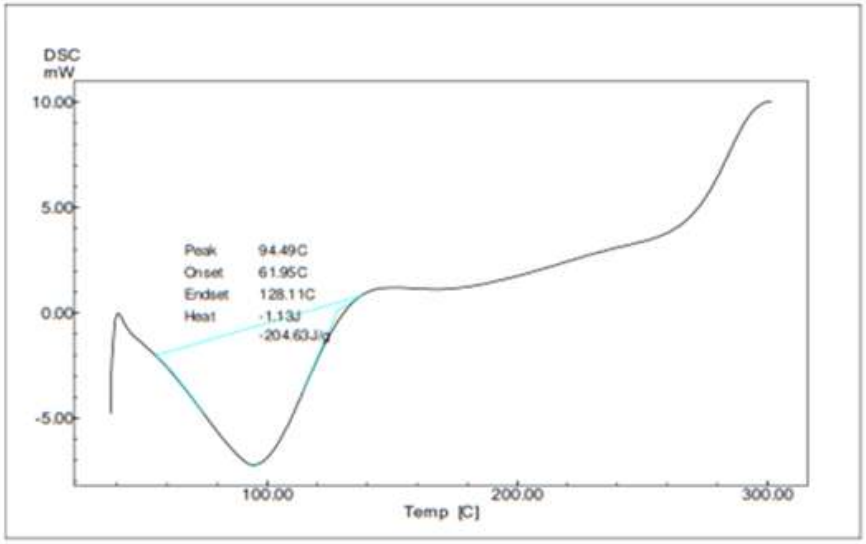


Figure 11: DSC spectroscopy of chitosan conjugation with propionaldehyde

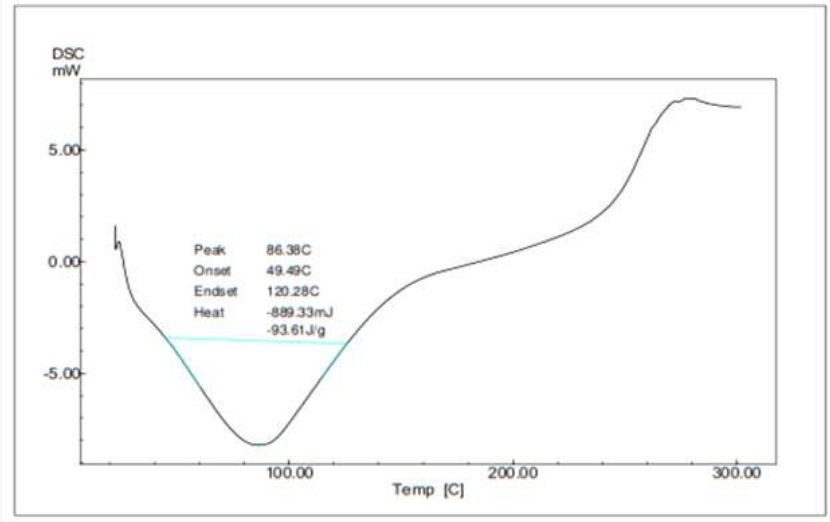


Figure 12: DSC spectroscopy of chitosan conjugation with thioglycolic acid

EVALUATION OF MATRIX TYPE TRANSDERMAL SYSTEMS

Thickness and weight uniformity:

All films were found to be uniform in thickness and weight. The results were shown in table 4.

Folding endurance:

Results indicated that the membrane will keep its integrity with little skin folding when applied.

Swelling index:

The weight of each and every film shown rises over time. When compared to other modified polymers, F12 has the lowest swelling index. Chitosan has a rigid structure and can only allow a small number of water molecules to permeate the matrix. However, when chitosan is conjugated with thioglycolic acid, the polymer chain opens up due to the presence of a thiol group in place of the chitosan's amino group, creating a loose matrix that allows a greater number of water molecules to permeate. So, it was discovered that the swelling index of membranes had increased.

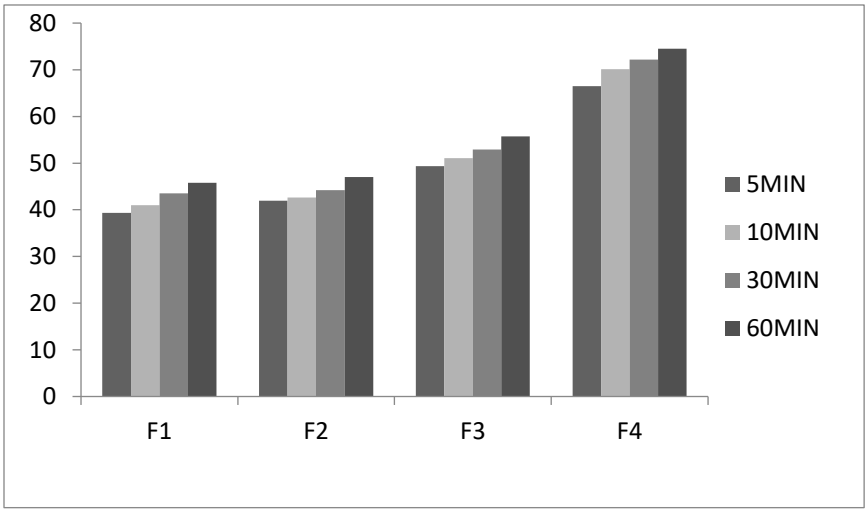


Figure 13: Swelling profile of formulation F1 to F4.

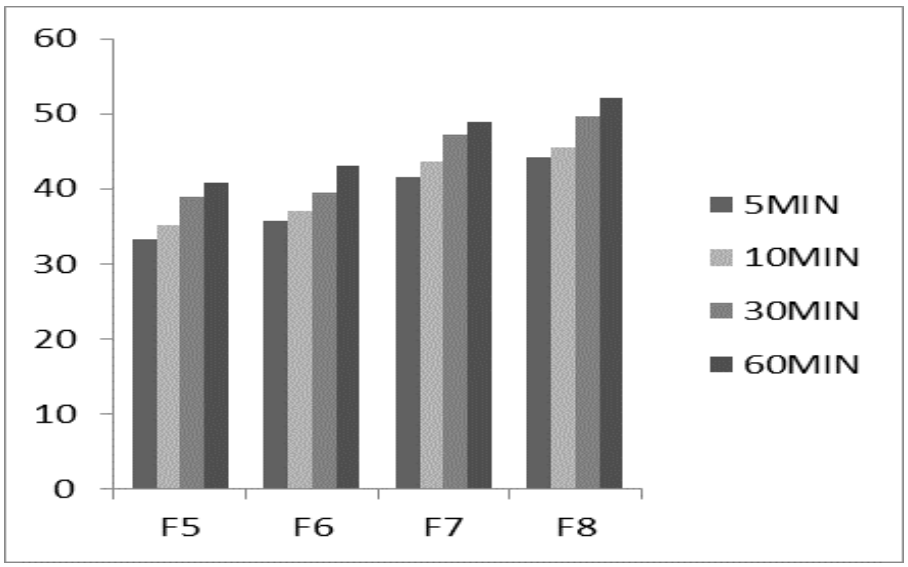


Figure 14: Swelling profile of formulation F5 to F8.

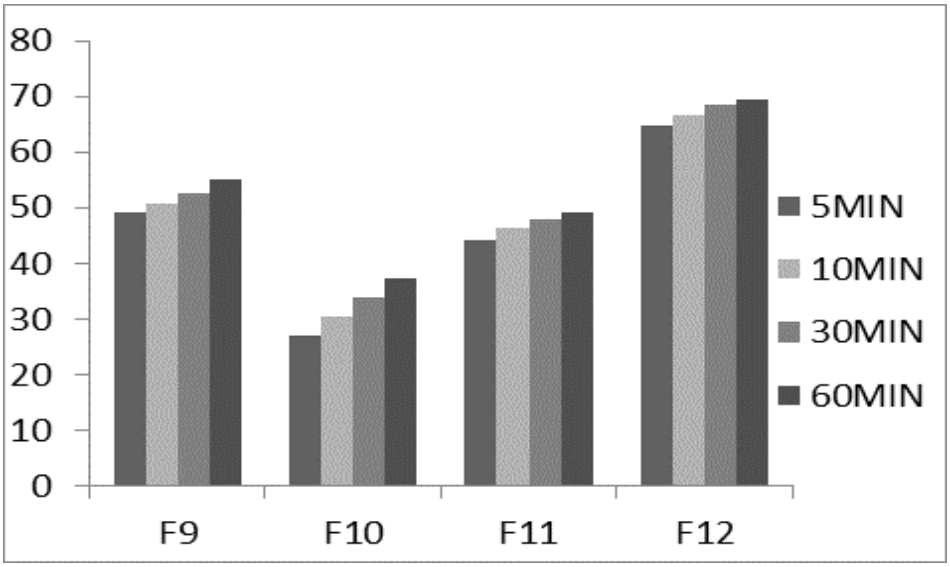


Figure 15: Swelling profile of formulation F9 to F12

Water vapor transmission study:

All of the produced membranes were shown to be water vapor permeable, according to experiments on water vapor transmission. Different formulations show different water vapor transmissions rate. Conjugated polymer showed more water vapor transmission rate then the plain polymer. Formulation F3 shows lowest WVTR 3.26 x10-3 gm/cm2/day whereas formulation F10 shows highest WVTR 9.29 x 10-3 gm/cm2/day. The results are shown in table 4.

Moisture content and moisture uptake:

The greatest moisture content for Formulation F7 is 20.000.54, and the lowest moisture content for Formulation F4 is 9.090.54. Film moisture absorption was tested at various RH levels. The relative humidity increased in every film. Formulation F3 has the lowest moisture update at 15.18% and Formulation F11 has the highest moisture update at 98% RH. Formulation F3 displays a lowest value of 11.25% and a highest value of 19.09% at 74.9% RH. Formulation F9 displayed the maximum 12.65% at 52% RH, while Formulation F3 displayed the lowest 8.11%. Moisture content and membrane absorption increased with an increased conjugated chitosan ratio. This is a result of the primary amino group in conjugated chitosan being replaced by an aldehyde and thiol group, which opens the polymeric network and permits more moisture to be absorbed, increasing swelling. Tables 4 and 6 present the findings.

Bursting strength:

The bursting strength increases linearly as plasticizer content does. Formulation F1 with 20% glycerin was found to be lowest 2.36±0.20 kg/cm2 whereas bursting strength of membrane F8 with 30% glycerin show highest 4.52±0.41 kg/cm2 (Table 5).

Tensile strength:

With increased concentrations of conjugated chitosan, the extension of the films reduced and the tensile strength dropped as a result of the presence of aldehyde and thiol groups in place of the primary amino group. The strongest formulation, Formulation F2, has a tensile strength of 1.4388 kg/cm2, while Formulation F3 has the weakest, 0.2651 kg/cm2. According to the findings, the membranes have a respectable tensile strength (Table 5).

In vitro diffusion studies of prepared aceclofenac transdermal films

An essential technique for anticipating a drug's in-vivo behavior is the in-vitro release profile. With a reduction in conjugated chitosan content, a cumulative amount of medication is less likely to

pass through membranes. Because the primary amino group is swapped out for an aldehyde and resulting in increased drug permeation. When the total amount of drug permeated through the dialysis membrane was plotted versus time, the drug's permeation patterns followed first order kinetics. In order to characterize the controlled release behavior of a drug from polymer matrices, Higuchi and Peppas developed the power law equation Mt/M = Ktn. This is because many release processes can be characterized by a coupling of a Fickian and non-Fickian mechanism. The functioning release mechanism can be determined by calculating the value of n from the slope of ln Mt/M vs ln t. The results of aceclofenac in vitro skin permeation studies from matrix membranes prepared with various polymers, including sodium alginate, HPMC, chitosan, and conjugated chitosan with varying ratios of plasticizers, are shown in figs. 5.13 to 5.15. This causes the polymer chain to open up, increasing swelling index, moisture content, moisture uptake, thiol group, the polymer chain opens, swelling index, moisture content, and uptake all increase, permeation coefficient, and resulting in increased drug permeation. Plotting the total amount of drug that permeated each square centimeter of the dialysis membrane versus time revealed that the drug's penetration profiles followed first order kinetics. The data was also run through Higuchi's equation to see if diffusion played a role in the drug release. The results were comparably linear (R2 = 0.932-0.980), which suggests that diffusion might be a mechanism for drug release. The data was applied to Koresmeyer's Peppas equation in order to corroborate the drug's additional release mechanism. The value of the release exponent "n" was established (Table 8) Based on the "n" value, it can be deduced that the anomalous (non-Fickian) kind of diffusion used in the drug release of formulations F1, F2, F3, F9, F10, and F12 was integrated. Formulations F4, F5, F6, F7, F8, and F11 exhibit diffusion of the fickian typ

In vitro permeation studies of formulated aceclofenac transdermal films

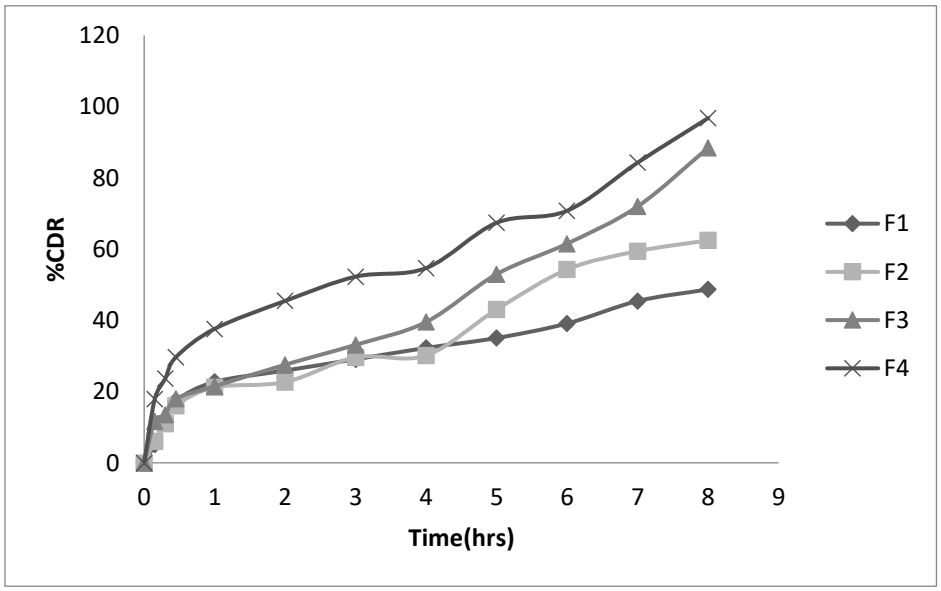


Figure 16: In vitro drug permeation of formulations F1 to F4

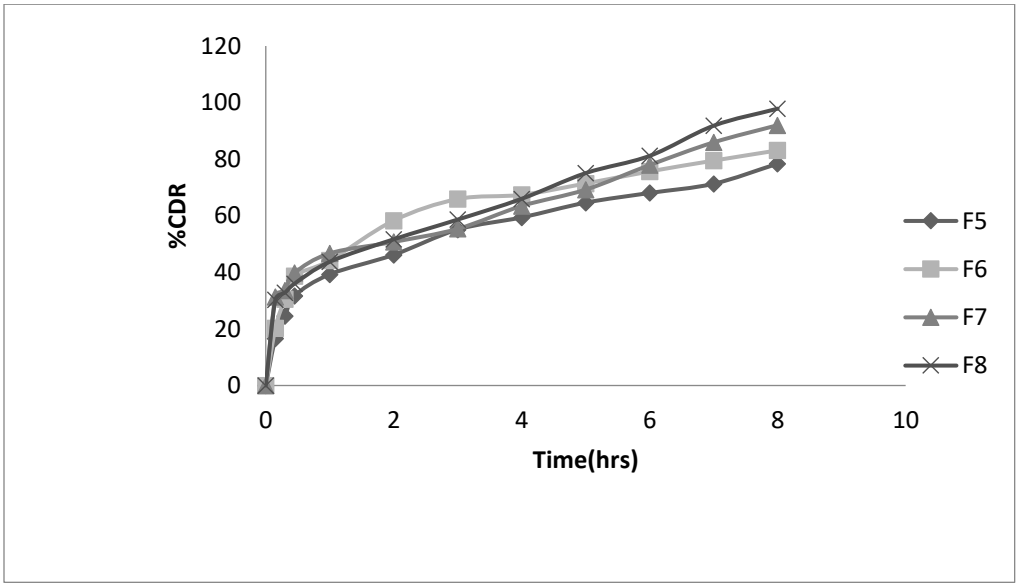
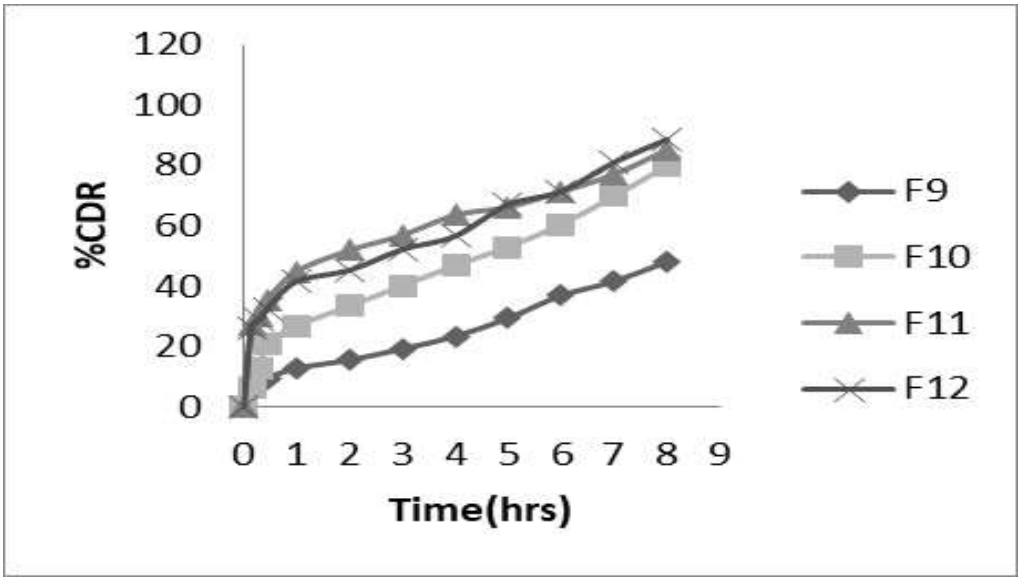


Figure 17: In vitro drug permeation of formulation F5 to F8

In vitro drug permeation of formulation F9 to F12



Release data analysis

The drug permeation data were fitted to various kinetics models to examine the mechanism of drug release from aceclofenac transdermal films (table 8). First order kinetics was used in every formulation from F1 to F12. In Table 8, the outcomes of the drug release mechanism are shown. This assertion was based on the values of "n" obtained by Korsmeyer's plot, which showed that for non-Fickian release, "n" has a value between 0.5 and 1.0, whereas for Fickian diffusion, "n" equals 0.5, and for super case II, "n" exceeds 1, depending on the scenario. The 'n' values for Formulations F4, F5, F6, F7, F8, and F11 ranged from 0.370 to 0.502, respectively. the results showed that Fickian diffusion was the mechanism of drug permeation, whereas formulations F1, F2, F3, F9, F10, and F12 showed 'n' values in the range of 0.520 to 0.784, indicating non-Fickian diffusion as the mechanism of drug permeation.

Stability study:

The formulation F9 was put through 60 days of accelerated stability tests at 400C/75% RH, and a 30-day in-vitro permeation study revealed barely any changes in the permeation profile. The stability studies on the membrane revealed it to be flexible and smooth, and no changes in the membrane's outward appearance were seen.

CONCLUSION

Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with good analgesic, antipyretic, and anti-inflammatory properties. It is used to treat rheumatoid disorders such as osteoarthritis, rheumatoid arthritis, dental pain, and other rheumatologic conditions. However, it has a number of side effects. Its short biological half-life of 4-5 hours and strong protein binding make it an excellent choice for delivery through transdermal method. We created a transdermal patch for the current investigation utilising sodium alginate, HPMC, chitosan, and its conjugates. FT-IR and DSC analysis supported the modification of the chitosan with aldehydes and thioglycolic acid. FT-IR and DSC were used to test the drug and polymer's compatibility, and the results indicated that there was no discernible interaction between the two. The membranes were assessed for a variety of factors, including thickness, weight uniformity, folding endurance, swelling index, moisture content, moisture uptake, tensile strength, water vapour transmission study, and in-vitro permeation studies. The formulations produced the best results, according to observations of every formulation for characterising the physical and mechanical properties. In-vitro diffusion studies across dialysis membrane the cumulative amount of drug permeation is higher for plain chitosan films. The conjugated chitosan showed less drug permeation rate as compared to plain chitosan films. F1 and F9 were found to be superior formulations based on in-vitro permeation studies because they released the drug in a sustained release pattern. After two months, the membrane was examined for in-vitro permeation. Throughout the study period, there was no discernible change in permeation. So, it was obvious that the membranes were stable.

SUMMARY

As evidence of the percutaneous absorption of many drugs has been shown, the transdermal route of drug delivery is growing in popularity. A constant intravenous infusion is provided by the transdermal drug delivery system, which is close to zero order drug input. A suitable matrix system, rate-controlling membrane, and drug reservoir are needed for the fabrication of TDDS in order to achieve this. Aceclofenac, an NSAID that works well as an anti-inflammatory, analgesic, and anti-pyretic, is used to treat rheumatoid disorders such osteoarthritis, rheumatoid arthritis, tooth pain, and other rheumatic disorders. It was chosen as the model candidate for this study because it has many of the characteristics that are ideal for a drug to have when creating a transdermal drug delivery system, including low molecular mass, high lipid solubility, effectiveness at low plasma concentrations, and a high level of first-pass metabolism. In the current study, various polymers like sodium alginate, HPMC, chitosan and modified chitosan were used to prepare matrix type transdermal system of aceclofenac. Modified chitosan was synthesized by modification of chitosan with aldehydes and thio glycolic acid in presence of acid. Differential scanning colorimetry was used to examine the compatibility of drugs and polymers, and the results revealed that there was no interaction between the two. The findings of the permeation testing showed that the medication was absorbed in a controlled manner. The in-vitro permeation data was fitted to the zero order, first order, Higuchi release model, and Korsmeyer and Peppas models in order to examine the mechanism of drug release from the membranes. It was discovered that drug

penetration followed first order, non-Fickian, and Fickian kinetics.

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