FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF DICLOFENAC SODIUM

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ABSTRACT

Diclofenac Sodium is classified as an anti-inflammatory and is categorized as a non-selective cox inhibitor utilized in the treatment of various, including rheumatoid arthritis, osteoporosis related pain and inflammation. The purpose of the current study was developed and assess transdermal patches that contain diclofenac sodium. With the new transdermal medicine delivery technology, the drug's active ingredients are delivered through the skin. In order to prevent first pass metabolism and improve patient compliance, a transdermal patch containing diclofenac sodium was developed. Polyvinyl pyrrolidone and ethyl cellulose were used as polymer, methanol and chloroform as solvent and oleic acid as penetration enhancer and dibutyl phthalate used as a plasticizer to establish a transdermal system of the matrix type. In term of physiochemical examination, every patch was identical.
Physiochemical evaluations revealed uniformity among the patches, and various assessment parameters including surface pH, patch thickness, folding endurance, weight variation, % moisture content, were measured. F1 formulation show less thickness that was 0.58mm, more folding endurance that was 70 times, and F1 showed the maximum *in-vitro* drug release that is 63.5 on a period of 180 minutes, the most effective result compared to other formulation.

KEYWORDS: Transdermal patch, Diclofenac sodium, PVP, Oleic acid.

INTRODUCTION

Since its release onto the market in 1981, TDDS have been more and more popular, as evidenced by the growing number of drugs available in the formulation. TDDS are among one of the most promising techniques for medication administration. The range of drugs that can be injected subcutaneously and
get into the bloodstream is expending. Significant interest in and study into the transdermal treatment system has come from the pharmaceutical industry. [12]
Transdermal administration employs many dose forms to address a multitude of disorders in individual.
These dosage forms allow the medication to be release suddenly, and several technologically sophisticated drug delivery techniques have recently been created. These methods are useful in regulating the pace of drug release. The following drugs have been reported to be effective when applied transdermally in the last 10 years: scopolamine, diclofenac, testosterone, estrogen, nitroglycerine, nicotine, lignocaine, fentanyl. [14,12]

NSAIDs have been the first choice of treating TDDS because of their better local effects and ability to prevent gastrointestinal side effects. [4]
The goal of developing cyclooxygenase (cox)-2 selective medications NSAIDs; coxib was to lessen
negative effects that were connected to classic nonselective NSAIDs, especially in relation to the upper GI tract. Studies that lasted up to a year demonstrated the efficacy of coxibs for the term management of osteoarthritis patients.
Therefore, employing polyvinyl pyrrolidone, ethyl cellulose as a polymer, and oleic acid as a penetration enhancer, this project aims to produce and assess transdermal patches, contain diclofenac sodium.
The term “transdermal drug delivery system” describes how medicinal dosage are injected into the bloodstream through the various skin layers.
FDA (Food and Drug Administration) in the United States authorized Novartis “Transdermal Scrap,” the first transdermal patch, for use in humans in 1979. The aim of this patch was to prevent nausea and vomiting related to travel. [11,3]

MATERIALS AND METHODS

MATERIALS

Diclofenac sodium (Sigma Aldrich), Chloroform (Singh Scientific Corporation), Ethyl Cellulose (Singh Scientific Corporation), Micrometre Screw Gauge (Harrison’s pharma machinery Pvt.Ltd), Weighing machine (Essae- Teroka Ltd.), Desicator (Borosil@), Spectrophotometer (Systronics), pH meter
(Labtronics).

METHODS

Fourier Transform Infrared Spectroscopy

With FTIR spectroscopy, using the KBr disk approach, the possible interaction between the medication and excipients was examined. The sample's FTIR analysis was used to identify the compound. The
range of the powered drug's scan was 400-4000cm^{-1}.

Method for the construction of diclofenac sodium standard calibration curve [1]

20mg of diclofenac sodium was dissolved in 100 ml of phosphate buffer (pH 7.4) to prepare the stock solution. Appropriate dilutions were made from the stock solution and were analyzed
spectrophotometer at 320 nm and absorbance value were recorded.

Preparation of phosphate buffer (7.4)

S.No.	Components	Quantity (gm)
1.	Na_2HPO_4	20.20
2.	NaH_2PO_4	3.394

Following steps involved in preparation of phosphate buffer-:

1. Take 800 ml of distilled water in a volumetric flask.
2. Add 20.20 gm of Na_2HPO_4 in distilled water.
3. Continuous stirred of this solution.
4. Add 3.394 gm of NaH_2PO_4 to the solution.
5. Stirred the solution.
6. Adjust pH 7.4 of the solution using HCl with the help of pH meter.
7. Add distilled water to make up the volume is 1L. [5]

Preparation of Transdermal Patch of Diclofenac sodium [1]

Diclofenac sodium was the active substance used in the preparation of transdermal patch. As a polymer, PVP and EC is utilized, and as a plasticizer, dibutyl phthalate.

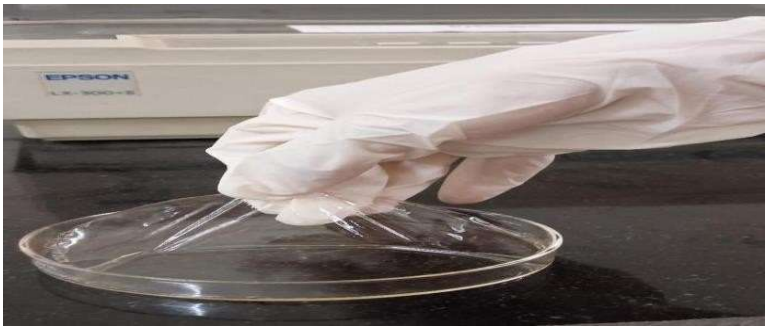
Diclofenac sodium was dissolved in methanol and chloroform, with PVA serving as the backing membrane.

Solvent evaporation method employed for the design of transdermal patch containing diclofenac sodium commenced with the creation of a backing membrane.

For this, 100 ml of distilled water were mixed with 4 gm of PVA dissolved in it, and the mixture was heated to 80℃ until 25% of the liquid was evaporated. A magnetic stirrer used to keep the solution

continuously mixed. After that, 15ml of the solution were transferred into a petri disc, which was then left to dry for 24 hours.

In the 2nd step, weighed amount of EC and PVP was dissolved in 9ml of chloroform and 1ml methanol. After that plasticizer that was DBP was added in above solution. The drug 50 mg of the medication was added to the homogeneous dispersion while being slowly stirred with a magnetic stirrer. This resultant solution was poured into the petri dish which containing PVA backing membrane, a funnel of suitable size was inverted over the petri disc to minimize solvent evaporation. After 48 hours, it covered with aluminum foil, dried at room temperature & stored in desiccator for further studies.



Composition of transdermal patch

S.No.	Diclofenac sodium (mg)	EC (mg)	PVP (mg)	Dibutyl Phthalate DBP (ml)	Oleic acid (ml)	thanol (ml)	roform (ml)
1.	50	200	50	1.5	1	1	9
2.	50	200	100	1.5	1	1	9
3.	50	200	200	1.5	1	1	9
4.	50	200	250	1.5	1	1	9
5.	50	200	300	1.5	1	1	9

EVALUATION OF DEVELOPED TRANSDERMAL PATCH

The physical and mechanical characteristics of the developed transdermal patch, as well as their

permeability, are significantly impacted by the composition and concentration of the transdermal film. The study examined the mechanical and physical characteristics of the medicated transdermal patch, including its –

1) **Physical Appearance**

   The physical appearance of drug such as color, taste, odor and state were determined. [3]

2) **Uniformity of Weight**

   To assess matrix weight of each formulation, the weight of the matrix from each formula is, followed by calculating the weight. [2]

3) **Thickness of Patch**

   The thickness of each patch was measured at five different locations using a screw gauge and an average value was recorded. [6]

4) **Folding Endurance**

   This was assessed by folding a single film at the same point until it fractured. The folding endurance value was calculated based on the number of folds possible at the same location without any breaks or cracks. [8]

5) **Moisture Content**

   After precise measurement, the patch was placed in a desiccator containing $CaCl_2$ for 24 hours. The final weight was then noted. The moisture content was calculated using the following formula. [7]

   % Moisture content = (Initial weight- Final weight) × 100 / Initial weight

6) **Moisture Uptake**

   The prepared patches were transferred to additional desiccators containing a saturated NaCl solution at 25℃ after being kept in desiccators with a silica gel at room temp. for 24 hrs. After that, the patches were weighed. We applied the provided formula to determine the moisture uptake. [3]

   % Moisture uptake = (Final weight – Initial weight) × 100 / Initial weight

7) **Surface pH**

By applying 0.5 ml of distilled water to the surface of each film, it was allowed to swell for 1 hr. at room temperature. After that, the electrode was brought in contact with the film's surface and let to equilibrate for 1 min.to determine the pH. [9]

8) **Stability Study**

The transdermal patches that were produced had been wrapped in aluminum foil covered with polyethylene stored for a month at room temperature and between 7-5℃. After a month, the sample is removed, and any physical changes brought on by storage are appropriately examined. [13]

9) **IN-VITRO dissolution studies**

The evaluation of the drug release from the produced patches can be done using the paddle method (USP equipment I). Dry films of a certain thickness must be weighed, cut into precise forms, and

adhered to a glass plate using an adhesive. After that, the apparatus was calibrated to 32.50±20c and the glass plate was submerged in 500 ml of phosphate buffer (pH 7.4) or dissolving media. Next, the

paddle was moved at a pace of 50 resolution/ min and positioned 2.5 cm apart from the glass plate. Up to 3 hrs. can pass between the required time intervals for sample withdrawal (5ml aliquots), at which

point they can be subjected to UV spectrophotometer analysis. The experiment must be run and the value was recorded. [10]

RESULT AND DISCUSSION

STANDARD DICLOFENAC SODIUM CURVE

A diclofenac sodium standard curve was developed in phosphate buffer with a pH of 7.4. The absorbance was measured at 320nm, and a curve was formed in the concentration range. The absorbance of the standard solution is shown as follows-

Standard diclofenac sodium curve-

S.No.	Concentration (mg/ml)	Absorbance (nm)
1.	2	0.165
2.	4	0.354
3.	6	0.525
4.	8	0.727
5.	10	0.954

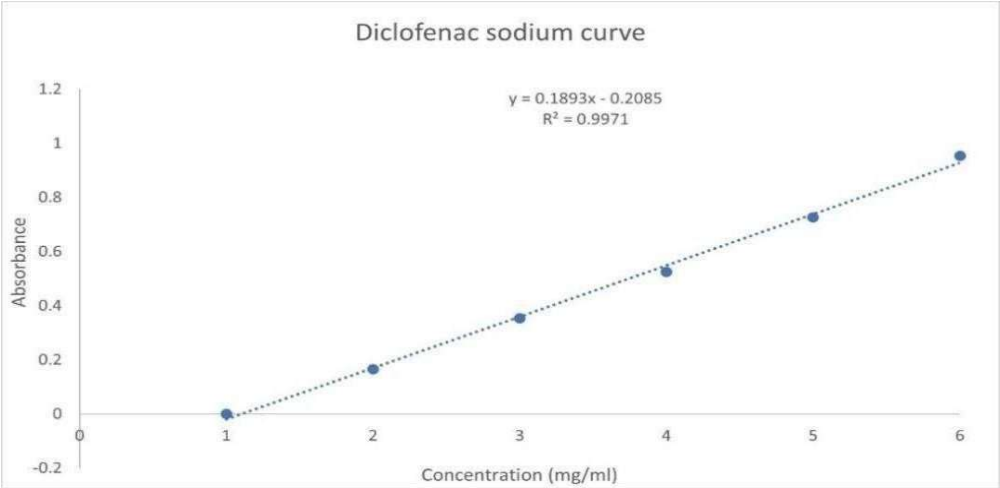
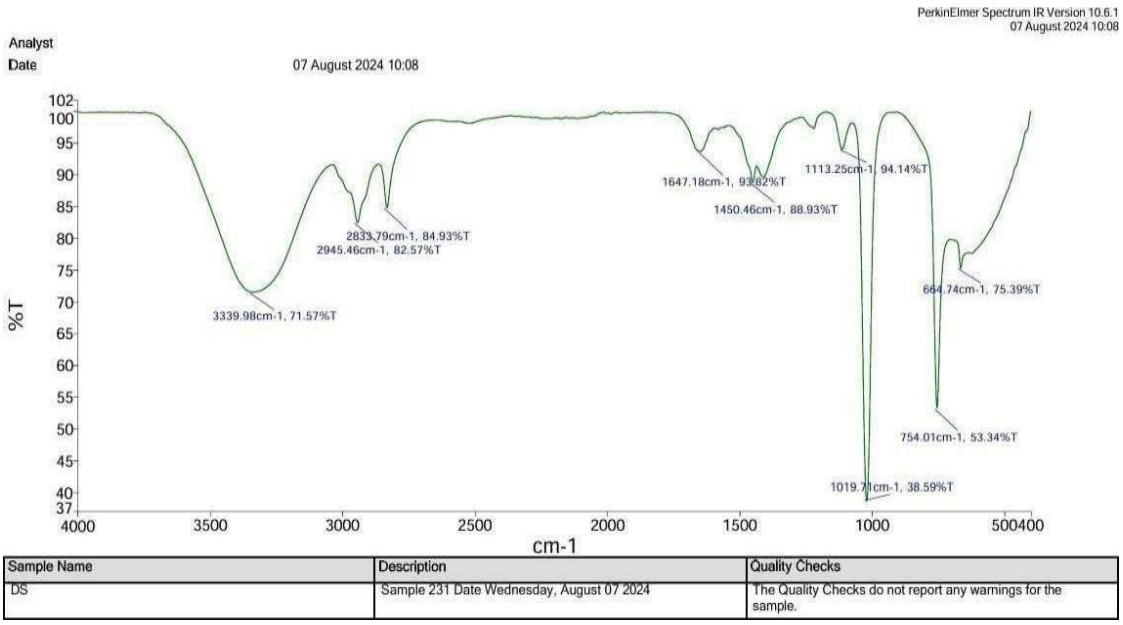


Figure: Diclofenac sodium Curve FT-IR SPECTROSCOPY STUDY

FT-IR spectroscopy was used to investigate potential drug-excipients interaction. Figure (A) and (B) shown the IR spectra pattern of the identical sample and there is no any interaction between drug and excipients.



Sample Name	Description	Quality Checks
DS	Sample 231 Date Wednesday, August 07 2024	The Quality Checks do not report any warnings for the sample.

Figure (A): Diclofenac sodium FT-IR Analysis

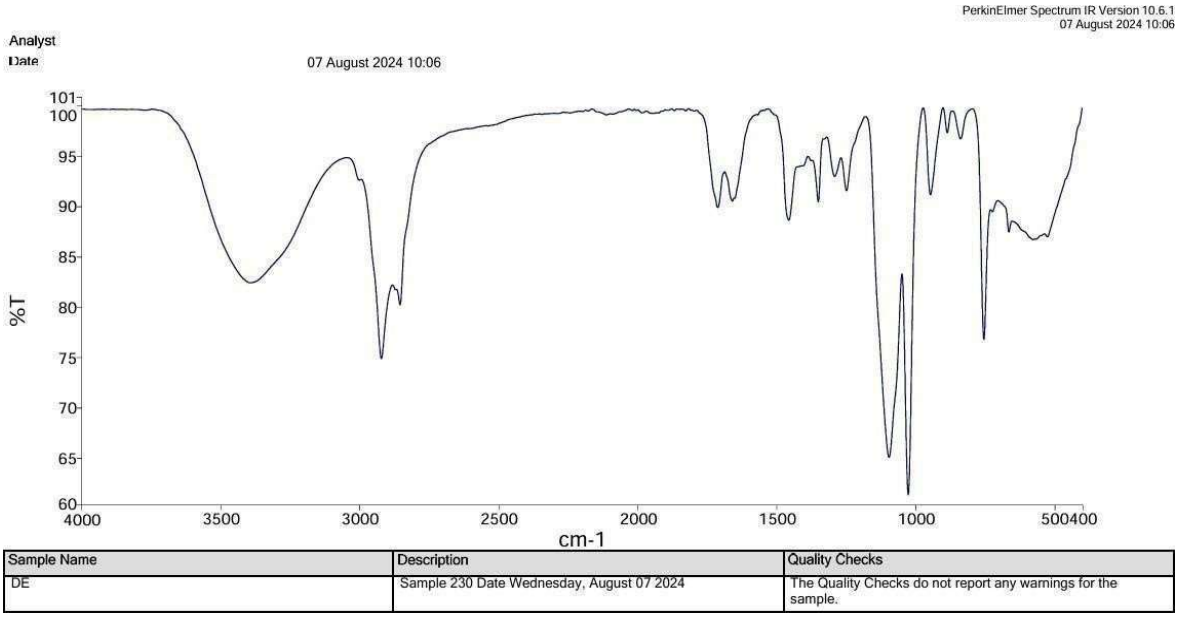


Figure (B): FT-IR Analysis of Drug and Excipients

EVALUATION STUDIES OF DEVELOPED TRANSDERMAL PATCHE PHYSICAL PROPERTIES

The patch's color, flexibility, smoothness, and odor were all examined visually.

S. No	Formulation Code	Colour	Flexibility	Smoothness	Odor
1.	F1	White	Flexible	Smooth	Odorless
2.	F2	White	Flexible	Smooth	Odourless
3.	F3	White	Flexible	Smooth	Odorless
4.	F4	White	Flexible	Smooth	Odorless
5.	F5	White	Flexible	Smooth	Odorless

Thickness of Patch, Folding Endurance, Moisture Content, Moisture Uptake, Surface pH of patches-

Formulation Code	Thickness (nm)	Uniformity of weight (gm)	Folding Endurance	Moisture content	Moisture uptake	Surface pH
F1	**0.58**	**0.725**	**70**	**2.01**	**4.21**	**6.3**
F2	0.78	0.620	65	3.11	5.32	6.0
F3	0.65	0.598	60	3.84	4.80	5.8
F4	0.7	0.65	68	2.08	4.54	6.1
F5	0.64	0.610	63	2.13	4.62	6.5

F1 show surface pH 6.3 which is similar to pH of human skin (6.4) so, there will be less chances to skin irritation which improve patient compliance.

STABILITY STUDY

Stability study were conducted to ascertain the change in physiochemical parameter on storage. The stability tests were carried out in the stability chamber at room temperature and between 2-5℃ for 30 days, and evaluated the sample's nature, color, pH and visual appearance. Even after being exposed to temperature, the patch kept its original characteristics.

Parameters	**Room Temperature**	**2-5℃**
Visual Appearance		
Initial	Transparent	Transparent
Final	Transparent	Transparent
pH		
Initial	6.3	6.3
Final	6.3	6.3
Color	White White	White White
Initial		
Final		
Nature		
Initial	Smooth Smooth	Smooth Smooth
Final		

IN -VITRO DISSOLUTION STUDY

The polymer has an impact on the medication release from transdermal patches. Determining the
medication's therapeutic efficacy is largely dependent on how substance releases from its dosing form.

S. No	Time In Min.	% Cumulative Release				
		F1	F2	F3	F4	F5
1.	15	11.2	9.3	8.6	1.74	11.3
2.	30	21.1	20.33	12.2	1.27	21.8
3.	60	35.7	33.8	17.0	4.20	33.1
4.	120	50.3	45.1	21.3	8.0	45.3
5.	180	63.5	54.0	34.3	13.34	61.7

The drug release *In-vitro* for formulation number 1 (63.5) was determined to be at its highest after 180 minutes of observation, whereas formulation number 4 (13.34) showed the lowest *In-vitro* drug release.

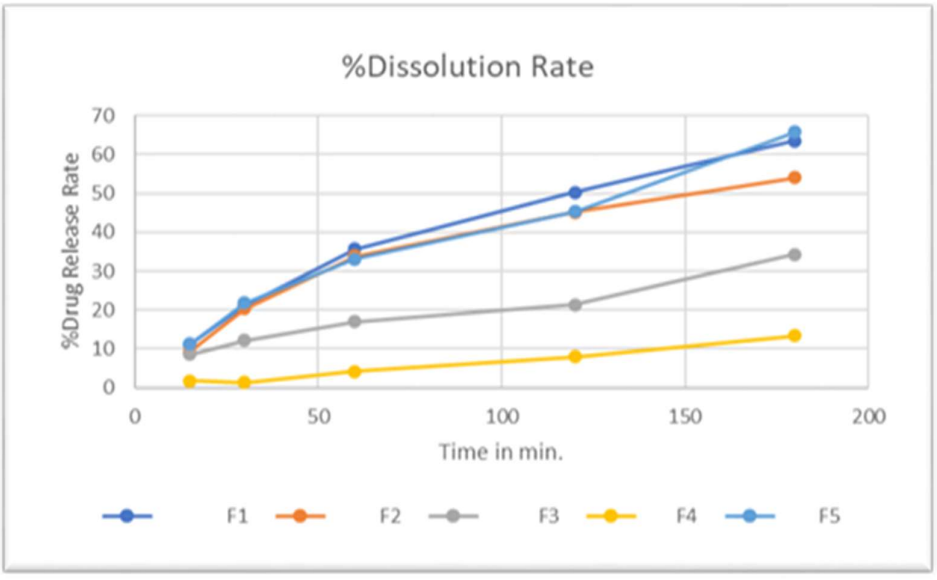


Figure: *In-vitro* % cumulative drug release

CONCLUSION

The current study aimed to create transdermal patches for patients who cannot take oral medication and for unconscious or nauseous patients. Diclofenac sodium is an anti-inflammatory, analgesic properties, used to treat musculoskeletal disorders such as rheumatoid arthritis and osteoporosis related pain and inflammation.

Diclofenac sodium's transdermal patch was formulated by used of PVP, EC as polymers, Methanol and chloroform as solvent and oleic acid as penetration enhancer.

In this studied, transdermal patch showed good physiochemical properties. F1 formulation showed the maximum *In-vitro* drug release which was 63.5 on a period of 180 minutes. F1 formulation having the less thickness of patches 0.58mm, more folding endurances 70 times, less moisture uptake 4.21% and F1 show 6.3 pH which are the closest pH of human skin (6.4) compared to other formulation.

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