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Development and Evaluation of Diclofenac Sodium Cream and Its Released Studies

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Abstract

Objective: This study aimed to develop and evaluate diclofenac sodium cream and it's in vitro rerelease studies with various enhancers.

Methodology: Various formulations of diclofenac cream were developed with good solubility excipients and various enhancers. For in vitro release studies Franz diffusion cell with cellulose membrane and spectrophotmetric method were used for analysis. The study used sophisticated advanced techniques including Diffraction (XRD) Scanning Electron Microscopy (SEM) and Transform Infrared Spectroscopy (FTIR) to examine the physicochemical properties of the cream. The study included physical evaluations of the cream as well as measurements of its pH level and drug content, stability study and skin irritation was performed.

Results: The transdermal delivery of diclofenac sodium showed significant improvement when penetration enhancers were added. Formulation F1 and F2 showed best released (71.993-72.83%).The enhanced permeation in a pattern DMSO>Thymus oil >Clove oil >castor oil> Ethanol, demonstrates that the diclofenac cream formulation successfully by passes the membranes to deliver medication more effectively

Conclusion: Penetration enhancers in diclofenac sodium cream formulation lead to a significant increase in skin absorption. Researchers demonstrated that this method holds potential for creating successful formulations for topical pain treatment options.

Keywords: Diclofenac sodium cream, DMSO, thymus oil, Clove oil, Castor oil, in vitro studies.

Introduction

Diclofenac sodium is a frequently used anti-inflammatory drug for osteoarthritis, musculoskeletal pain, and many other inflammatory conditions. Its limited skin permeability however poses a challenge to the effective use of topical formulations. The limitation can be efficiently overcome with transdermal drug delivery systems TDDS which provide an extended release duration and reduced systemic side effects since they bypass the liver and gastrointestinal tract. (1). But, the key issue that has to be solved is how much better drugs go through the skin. The most used penetrate helpers in local medicines are surfactants, alcohols, and fatty acids. These are commonly added in topical medicines to help drug passage by

changing skin barrier function. To help movement across to the working part, it can disturb the lipid setup of the stratum corneum. (2).

Diclofenac sodium is a nonsteroidal anti-inflammatory drug commonly used to reduce discomfort and inflammation in conditions such as arthritis, menstrual cramps, and various musculoskeletal disorders. Here's a detailed overview of diclofenac sodium (3) . Diclofenac sodium is chemically known as 2-[(2,6dichlorophenyl) aminobenzene acetic acid, monosodium salt, and has the molecular formula C5H8NO4Na. It is derived from phenylacetic acid and contains two chlorine atoms on a phenyl ring, which confer its anti-inflammatory property. (4).

Diclofenac sodium can be administered orally, intramuscularly, or topically. It is absorbed well from the gastrointestinal tract and achieves peak plasma concentrations(ppc) within 2 hours of oral administration. (5). The situation is highly protein-bound(HPB) (99%) and has a relatively large volume of distribution(vd), indicating extensive distribution into body tissues (6). Diclofenac undergoes hepatic metabolism primarily by cytochrome P450 enzymes, forming several metabolites, including 4'-hydroxydiclofenac, which also has pharmacological activity.(7).

The purpose of this study is to formulate a cream containing diclofenac sodium and assess how different chemical enhancers can improve its penetration. Characterization of the formulation utilizing FTIR, SEM, and XRD techniques is another aspect of the investigation.

Materials and Methods

Materials

The provider of diclofenac sodium (DS) and Carbopol 940 was Martindow Mark Quetta. Penetration enhancers DMSO, thymus oil, Clove oil, Castor oil and ethanol were employed obtained from Pharmacy department UOB, Additional components glycerin from nearby vendors, stearic acid, and emulsifying wax from united traders Quetta. Every chemical was used of analytical grade.

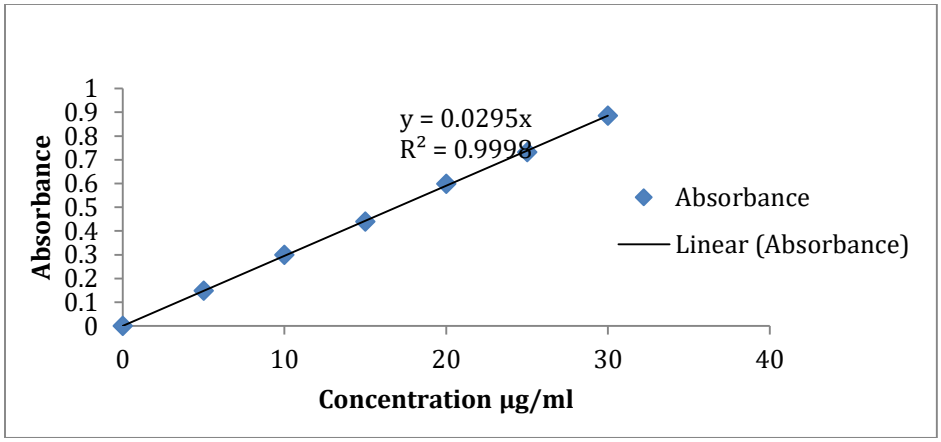
Diclofenac Sodium Cream Preparation

To make creams, we employed the emulsification method. Distilled water of the aqueous phase was maintained at 70°C. The oily phase was a blend of stearic acid, emulsifying wax, and diclofenac sodium. It was also maintained at 70°C and was kept stirring continuously in order to blend with the aqueous phase. The preparation was also supplemented with 1% (w/w) of penetration enhancers (DMSO, thymus oil, Clove oil, Castor oil and ethanol). After the cream was brought to normal temperature, it was stored in an airtight jar to be further tested.(8). As shown in Table 1.

Diclofenac sodium Calibration Curve

To establish Diclofenac sodium standard curve, a solution in stock was come about in 10mg of Diclofenac powder, dissolved in Methanol (50 ml) through stirring of multiple minutes and accomplishing 100ml volume with methanol. From the stock solution, dilutions were made as 5, 10, 15, 20, 25, 30 and µg/ml. At 276nm ultraviolet (UV)-visible spectrophotometer (Shimadzu UV-1601, Japan) was employed and absorbance of entire dilutions was analyzed. The graph for linearity is delineated in Figure 1.

Figure1: Calibration graph of Diclofenac Sodium drug.



Organoleptic Properties

A diclofenac sodium cream was analyzed for its color, shape, and even its finesse. (9).

pH Determination

A compatability pH meter for skin was utilized, which is a digital pH meter (Model: pH 210, Thermo Fisher Scientific). (8).

Spreadability

A combination of techniques for determining spreadability was more successful by placing a defined weight of the cream on two glass plates and measuring the area of spread after a period of time. (8)

Viscosity

The viscosity was also determined by a Brookfield viscometer (Model LVDV-II, Brookfield Engineering) at 25°C. (8).

Drug Content

The drug content quantification was based on the known mass of the cream. The cream was first dissolved in methanol, filtered and the UV spectrophotometer with an measurement at 276 nm was used. (10).

In Vitro release Studies

A Franz diffusion cell with a membrane was used to study the s penetration of diclofenac sodium. Phosphate buffer saline (PBS, pH 7.4) was present at 37°C during the receptor phase. UV spectrophotometry was used to quantify the drug content of time samples that were periodically removed. (11).

In Vitro Release Kinetics

The amount of substance impregnated was determined and identified using the spectroscopic technique. The drug dosage in the receptor sample was collected and measured at specific time intervals between 0 and 12 hours." For each formula, the linearity regression research and the drug impregnation release threshold were assessed. To determine whether the drug release followed zero-order, first-order, Higuchi, Korsmeyer-Peppas, or Hixon-Crowell diffusion models, the correlation coefficient (r) was

calculated(12). It is carried out for every formula. Complete computations were performed using a verified software application, DDSolver for Microsoft Excel 2007. In relation to the following kinetics equations.

$Qt = Qo + K_0 t$ (Zero order)

$\ln Qt = \ln Qo + K_1 t$ (First Order)

$Qt = K^H \sqrt{t}$ (Higuchi Model)

$Mt/M\infty = Kt^n$ (Korsmeyer-Peppas Model)

$Qt / Qo = K_k t^n$ [13].(Hixson–Crowell Model)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was used to determine the interaction between diclofenac sodium and penetration enhancers. A PerkinElmer FTIR spectrometer (Model: Spectrum Two) was used to analyze the materials in the 4000–400 cm-1 range in order to get the spectra. (13).

X-Ray Diffraction (XRD)

X-ray diffraction (XRD) was utilized to assess the crystallinity of diclofenac sodium cream. The XRD patterns were acquired using a Bruker D8 Advance X-ray diffractometer (Bruker AXS, Germany), which scanned an angle range from 5° to 40° using Cu Kα radiation at 40 kV and 40 mA 20. (14).

Scanning Electron Microscopy (SEM)

The morphology of the surface of the cream was investigated with a scanning electron microscope (Model: JSM-6610LV, JEOL, Japan). A few drops of the cream were placed on an aluminum stub covered with a thin gold layer and viewed under a microscope. (15).

Stability Studies

Stability studies of diclofenac sodium cream containing penetration enhancers were conducted over 90 days at 25 ± 1°C and 40 ± 1°C. (8)

Statistical Analysis

Statistical analysis of diclofenac sodium cream formulations using penetration enhancers was performed to evaluate significance in drug release and stability parameters. Results were expressed as mean ± standard deviation, and ANOVA was used to assess differences among formulations. A p-value < 0.05 was considered statistically significant, confirming the impact of penetration enhancers on drug release and formulation performance.(8)

Table 1: Formulation of diclofenac sodium cream (W/W)

Ingredients	F1	F2	F3	F4	5
Diclofenac sodium	1	1	1	1	1
Cetostearyl alcohol	10	10	10	10	10
White petroleum	5	5	5	5	5
Tween80	10	10	10	10	10
Carbopol	0.8	0.8	0.8	0.8	0.8
Liquid Paraffin	5	5	5	5	5
DMSO	1	-	-	-	-

Thymes oil	-	1	-	-	-
Castor oil	-	-	1	-	-
Clove oil	-	-	-	1	-
Ethanol	-	-	-	-	1
Glycerine	5	5	5	5	5
TEA	1.5	1.5	1.5	1.5	1.5
Deionized Water	60.7	60.7	60.7	60.7	60.7

Results and Discussion

The formulations of diclofenac sodium cream were assessed for consistency, drug content, homogeneity, spreadability, and pH. With pH values within the permissible range, all formulations displayed comparable liquefaction, phase separation, and color behavior. According to earlier research on topical creams containing penetration enhancers, the pH range of the formulations was between 5.51 and 6.46, which is in good agreement with the normal pH range of human skin (4.5 to 6.5) (16).The viscosity was in the range of (2012-2302 cP). When spreadability was evaluated during a ninety-day period, it was found that under shearing pressure, spreadability varied little, ranging from 4.64 to 5.99 g/cm/s. The absence of lumps across the formulations served as confirmation of homogeneity. The results of the drug content study showed that the distribution of diclofenac sodium was highly consistent, with concentrations shown in table 2. The formulations appear to be well-suited for transdermal application based on their general physical attributes. During 90 days of stability testing at 25 ± 1°C and 40 ± 1°C, the cream maintained its stability at 25 ± 1°C with less than 7% drug degradation, showing appropriate long-term stability. A little rise in standard deviation was noted at 40°C, indicating a reduction in stability at higher temperatures. Nonetheless, the findings validate that the ideal storage temperature for preserving the constancy of medication content and formulation integrity is 25 ± 1°C.ranging from 90.21% to 91.35%.

Drug penetration was measured in the in vitro release investigation using cellulose membranes that were 180 µm thick and 0.025 µm in thickness. Effective drug release through the membrane was validated by statistical analysis; formulation F1 showed the maximum release (72.30%). These results are consistent with previous research by (Clement et al), who found that formulations containing penetration enhancers improved drug release. A first-order permeation model described the diclofenac sodium release profiles from the cream formulations.AS shown in Table 3. The cumulative percentage of medication released after 12 hours, varied between 67.133% and 72.833%, demonstrating effective cellulose membrane penetration and corroborating the effectiveness of penetration enhancers in topical diclofenac sodium administration.Indicated in Fig.2

The addition of penetration enhancers significantly increased the permeability of diclofenac sodium, according to the in vitro permeation experiments. The greatest enhancement was seen by DMSO and Thymus oil, which was almost 10% greater than the castor oil and ethanol enhancers.

Table 2: Physical Parameters Values for Diclofenac Sodium Formulations

Coded formulations	pH	**Viscosity** (cP)	Spreadability (g.cm/s)	Homogeneity	Drug content (%)
F1	5.51	2203	4.64	Good	98.10
F2	5.94	2113	4.86	Good	97.44
F3	6.42	2302	4.98	Good	98.35
F4	5.88	2112	5.77	Good	97.45

F5	6.46	2012	5.99	Good	97.27

Figure 2: Release of Diclofenac sodium via Cellulose membrane

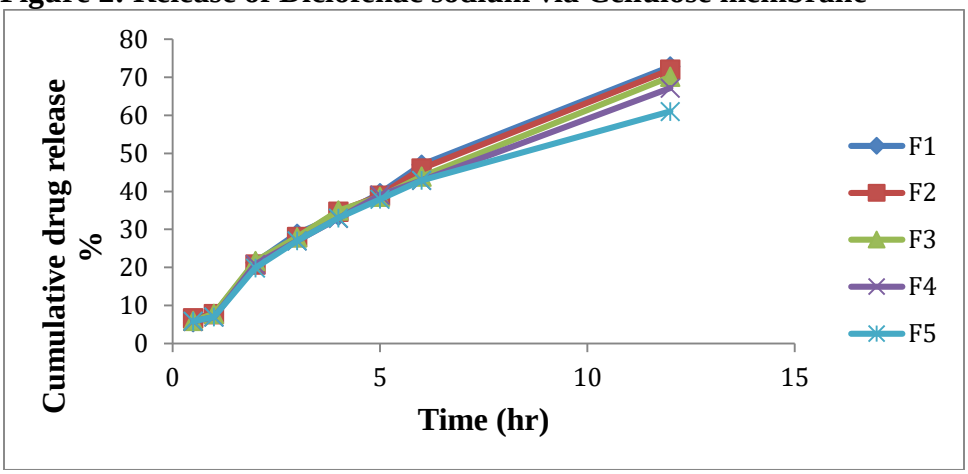


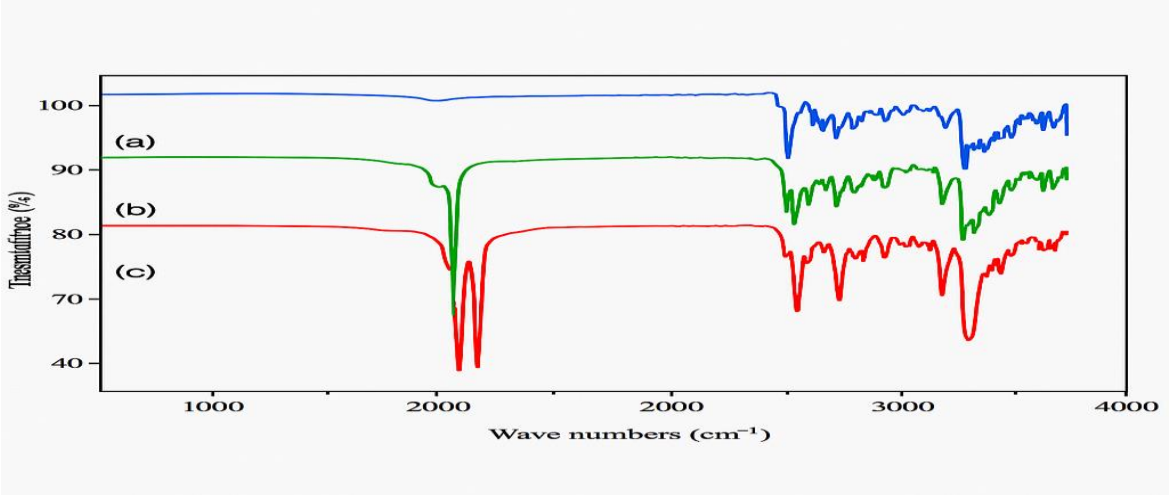
Table 3: Kinetics Models of Diclofenac sodium released (R^2)

Formulation type	Zero (0) Order	First(1st) Order	Higuchi	KorsmeyerPeppass	Hixon-Crowell
F1	0.9802	0.9974	0.9969	0.9954	0.9964
F2	0.9815	0.9976	0.9964	0.9959	0.9968
F3	0.9782	0.9963	0.9969	0.9950	0.9946
F4	0.9749	0.9974	0.9968	0.9939	0.9935
F5	0.9588	0.9917	0.9949	0.9891	0.9850

FTIR Analysis

Diclofenac sodium and its derivatives' FTIR spectra revealed no discernible chemical interactions between the drug and penetration enhancers. Diclofenac sodium's distinctive peaks were present in every formulation, indicating that the drug molecules did not interact or break down while being formulated. As shown in Fig.3.

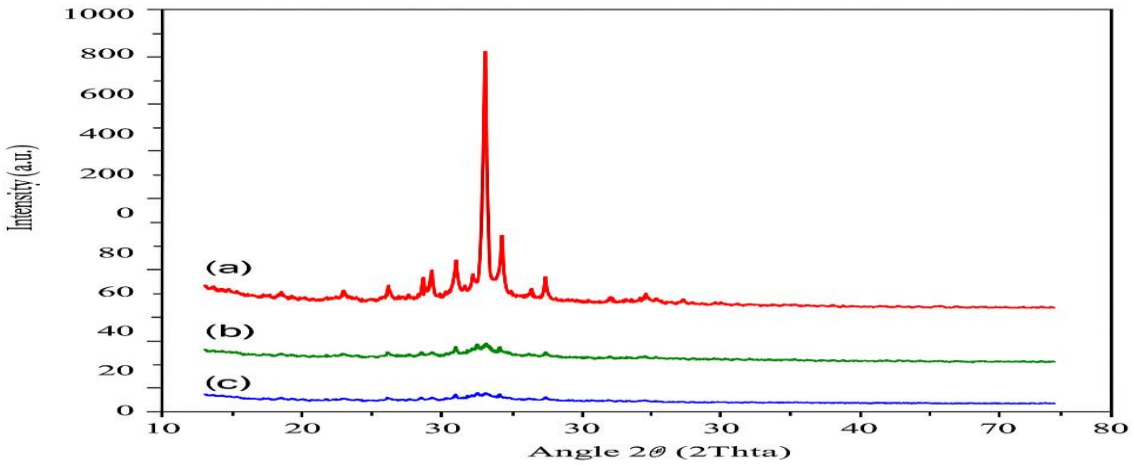
Figure 3: FTIR spectra of diclofenac sodium drug A, Blank B, Formulation F1 is C



XRD Analysis

According to XRD analysis, the cream formulation's crystallinity decreased, suggesting that diclofenac sodium had transitioned from a crystalline to an amorphous state. This might have enhanced skin penetration and solubility.As shown in Fig.4

Figure 4: X-ray diffractogram ofdiclofenac drug A, Blank B, Formulation F1 is C

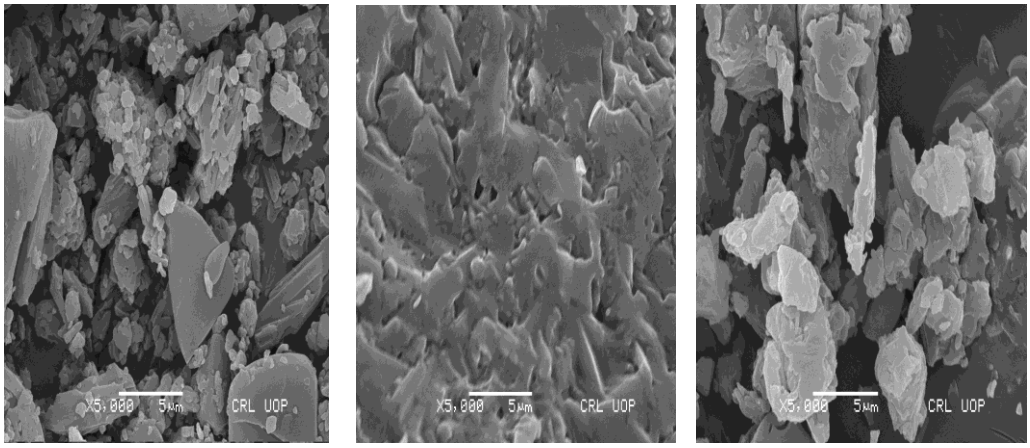


SEM Analysis

The cream had a uniform texture and a smooth surface, according to the SEM pictures. The use of penetration enhancers was shown by the increased permeability of the cream-treated skin's surface, which was made up of smaller and better-organized lipid bilayer structures.As shown in Fig.5

Figure 5: Scanning electron microscopy of diclofenac drug A, Blank B, Formulation F1 is C

A B C



Conclusion

The transdermal administration of diclofenac sodium cream was greatly enhanced by the use of penetration enhancers in its formulation. The greatest improvement in penetration was achieved by using DMSO and thymus oil as an enhancer. The formulation's stable drug content and favorable physicochemical characteristics were demonstrated. Studies using FTIR, SEM, and XRD demonstrated the function of penetration enhancers in improving drug delivery and validated the integrity of diclofenac sodium in the cream. According to this investigation, the formulation shows promise as a transdermal medication delivery system for diclofenac sodium.

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Conflict of interest

The writers declare that there is no conflict of interest

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