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FORMULATION OF DICLOFENAC SODIUM TRANSDERMAL PATCH FOR RHEUMATOID ARTHRITIS

Neha Rathore*, Sonam Mahant, Anish Chandy

School of Pharmacy, Chouksay Engineering College Bilaspur (C.G.) , 495550, India

Corresponding Author's E-mail: rathoreneha554@gmail.com

ABSTRACT

The pathogenesis of rheumatoid arthritis focused on auto antibodies and immune complexes. Rheumatoid arthritis is the most common inflammatory arthritis and is a major cause of disability. T-cell-mediated antigen-specific responses, T-cell-independent cytokine networks, and aggressive tumour-like behaviour of rheumatoid synovial have also been implicated. Based on the pathogenic mechanisms, specific therapeutic interventions can be designed to suppress synovial inflammation and joint destruction in rheumatoid arthritis. "Diclofenac sodium" is a non-steroidal anti-inflammatory drug (NSAIDs) advocated for use in painful and inflammatory rheumatic and certain non-rheumatic conditions. It is available in a number of administration forms which can be given orally, rectally, topically or intramuscularly. The main objective of this study was to prepare the optimized formulation of Diclofenac sodium transdermal patch for the treatment of Rheumatoid arthritis. This study is further aimed to analyse, concentration of drug reaching in the body and to study its effect.

KEY WORDS:

Rheumatoid arthritis, Diclofenac sodium, Transdermal patch

1. INTRODUCTION

Transdermal patch is a medicated patch that is placed on the epidermis to deliver a specific dose of medication through the epidermis and into the blood flowing through the circulatory system [1-4]. Frequently, this promotes healing to an injured area of the skeleton [5,6]. Transdermal drug delivery route administered as oral, topical, intravenous, intramuscular etc [7,8]. In numerous clinical trials the efficacy of Diclofenac is equivalent to that of the many newer and established NSAIDs with which it has been compared. As an analgesic it has a fast onset and long duration of action [9-12].

Transdermal patches are disclosed, including a backing layer, a liner layer, and a monolithic adhesive and drug-containing layer between the backing layer and the liner layer [13,14]. Transdermal patches are disclosed, including a backing layer, a liner layer, and a monolithic adhesive and drug-containing layer between the backing layer and the liner layer [15-17].

Indomethacin clearly produces more CNS effects than diclofenac, and gastrointestinal complaints are also somewhat more frequent with indomethacin. The tolerability of diclofenac appears similar to other commonly used NSAIDs such as ibuprofen, ketoprofen and naproxen [18-21]. Diclofenac can be used in rheumatic conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis and bursitis, and in other inflammatory or painful conditions such as strains and sprains, dysmenorrhoea, back pain, sciatica and postoperative pain [22,23]. Transdermal delivery systems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method. A wide variety of pharmaceuticals are now available in transdermal patch form. The drug so utilized is moderately soluble in the plasticizer [24-26].

This is reflected in animals and humans in vivo by reduced concentrations of various prostaglandins in urine, gastric mucosa and synovial fluid during treatment with diclofenac [27,28]. Also, in common with other NSAIDs, diclofenac is a potent reversible inhibitor of the secondary phase of induced platelet aggregation. However, diclofenac at usual therapeutic dosages has little effect on bleeding time in humans. The drug also affects polymorphic nuclear leukocyte function, thereby reducing chemo taxis, superoxide production and protease production[29-32].

Diclofenac is rapidly and efficiently absorbed after conventional oral, rectal or intramuscular administration [33,34]. After intramuscular administration peak plasma concentrations are attained after 10 to 30 minutes. With the enteric-coated formulation peak concentrations are reached after 1.5 to 2.5 hours, and this is delayed by food to 2.5 to 12 hours. After a single 50mg dose of these formulations, mean peak plasma concentrations of unchanged diclofenac are 0.7 to 1.5 mg/L [35-38]. Like other NSAIDs, diclofenac is highly (≥ 99.5%) protein bound. The mean total volume of distribution is 0.12 to 0.17 L/kg and that of the central compartment is 0.04 L/kg. The drug efficiently penetrates inflamed synovial fluid where high concentrations are maintained compared with plasma concentrations. Diclofenac and its metabolites cross the placenta in animals, and small amounts may be found in the breast milk of women [39-43].

In healthy volunteers, mean plasma clearance of diclofenac is 16 L/h, and the mean elimination half-life of the terminal phase is 1.1 to 1.8 hours. The mean elimination half-life after a radio labelled dose is about 30 hours for the tracer [44-49]. The initial dosage of conventional or enteric-coated Tablets of diclofenac is 150mg daily in 2 or 3 divided doses with meals, and in most patients' therapeutic control can be maintained on 100mg daily [50-52]. A sustained release formulation can be administered once daily, and suppositories can be administered once or twice daily. Intramuscular diclofenac 75mg can be given for the urgent relief of acute pain such as renal or biliary colic. A further dose may be administered after 30 minutes if necessary, but as with oral administration the daily dosage should not exceed 150mg [53-59].

Diclofenac is not recommended for children less than 18 months of age, and only when essential in pregnant or lactating women [60]. Dosage reductions are not required in the elderly or in patients with hepatic or renal insufficiency. However, these patients should remain under close supervision as should those with a history of gastrointestinal disease [61,62]. (**Figure 1**) explains the effect of Diclofenac sodium transdermal patch for the treatment for arthritis applicable at joints.

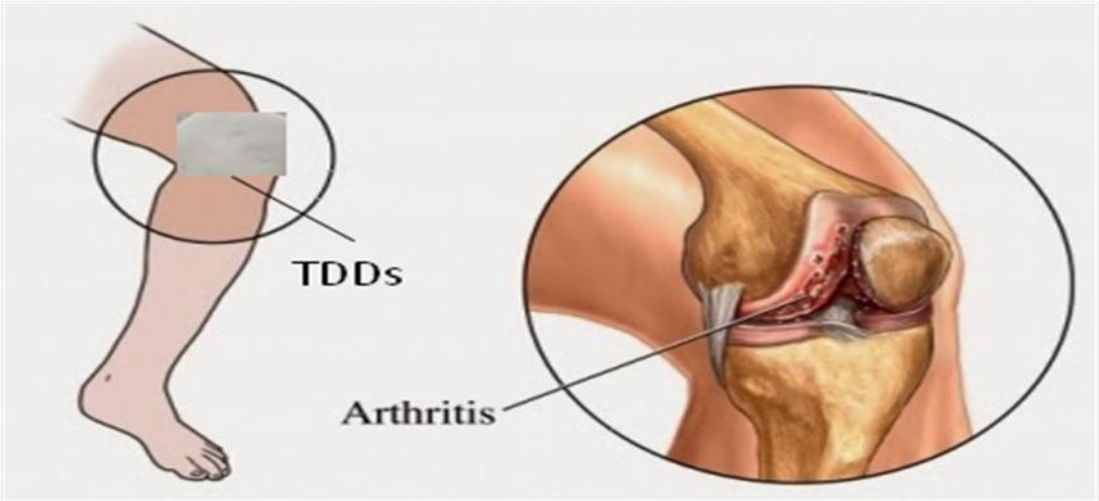

Fig. 1: Diclofenac sodium transdermal patch is applicable at joints for the treatment for arthritis.

2. MATERIALS AND METHODS

2.1 Materials

Diclofenac sodium collects from pharmaceutical industry. All the reagents and materials were of analytical or pharmacopoeia grade. Formulation of Transdermal patch- drug, backing agent, plasticizer, penetration enhancer and solvents are use. Ingredients list mention in **Table 1**.

Table 1: Ingredients Table of Diclofenac sodium patch

S. No	**Ingredient`s**	**Activity**
1.	Diclofenac sodium (mg)	Active ingredient (Drug)
2.	Ethyl Cellulose (mg)	Backing agent
3.	PEG-400 (ml)	Plasticizer
4.	Dibutyl phthalate (ml)	penetration enhancer
5.	Chloroform: Methanol (ml)	Solvents

2.2 Methods: - Method of preparation of Diclofenac sodium TDDs is explain in (**Figure 2**)

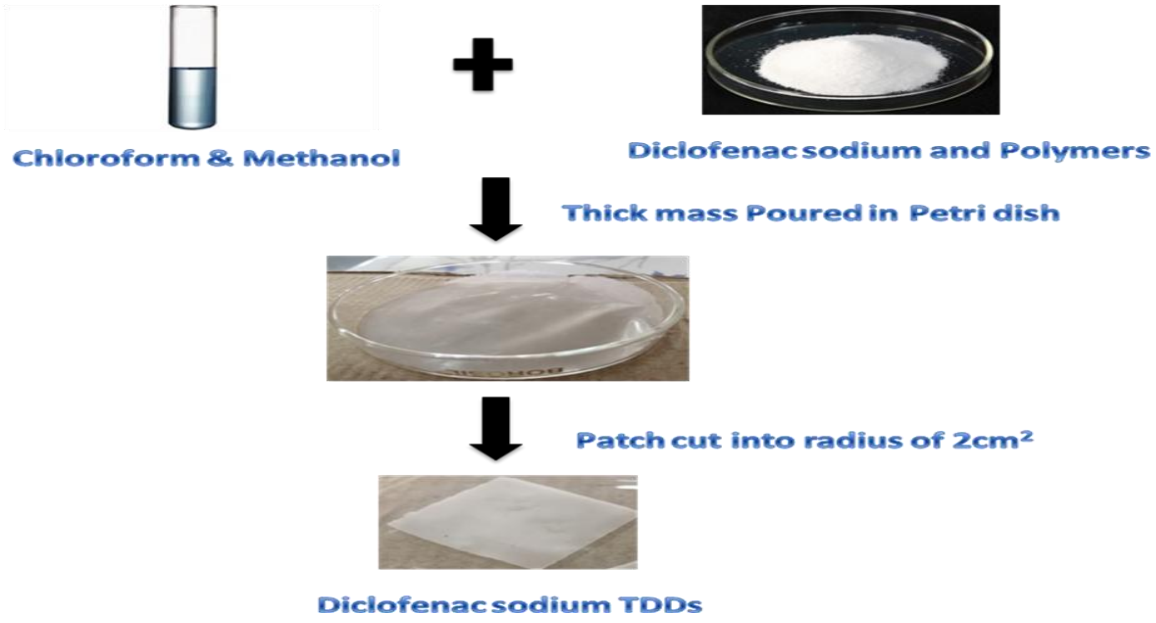

Fig. 2: Method of preparation of Diclofenac sodium TDDs.

The polymer was dissolved in chloroform: methanol (1:1) solvent. The drug was dispersed uniformly in the viscous solution with continuous stirring. The resulting mass was poured into levelled mercury surface in a Petri dish covered with inverted funnel. The Petri dish was left undisturbed at room temperature for one day. The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of $2cm^2$.

Three Formulations were prepared in different ratios of chemicals for the preliminary studies. **Table 2** contain the ratio of ingredients use for the preparation of Diclofenac sodium TDDs.

Table 2: Formulation Table of Diclofenac sodium TDDs in different ratio.

S. No	Intranets Name	F1	F2	F3
1	Diclofenac sodium	10	10	10
2	Ethyl Cellulose	200	300	400
3	PEG-400	1.2	1.2	1.2
4	Dibutyl phthalate	1.2	1.2	1.2
5	Chloroform: Methanol	1:4	1:4	1:4

3. CHARACTERIZATION OF MEDICATED PATCH

After getting the best formula based on accurate Diclofenac sodium, it was further studied for its characterization such as physical appearance, thickness of the patch, weight uniformity, folding endurance, percentage moisture content, content uniformity test, moisture uptake, drug content, shear adhesion test, peel adhesion test, water vapour transmission studies, stability studies [63 – 68].

3.1 Physical appearance

The general appearance of TDDs its visual identity and all over elegance - shape, colour, surface textures. These all parameters are essential for consumer acceptance.

3.2 Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by travelling microscope dial gauge, screw gauge or micrometer at different points of the film.

3.3 Weight uniformity

The prepared patches are dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

3.4 Folding endurance

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

3.5 Percentage moisture content

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\% \text{ Moisture Uptake} = \frac{\text{Initial Weight - Final Weight}}{\text{Final Weight}} * 100$$

3.6 Content uniformity test

Patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

3.7 Moisture uptake

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight – Initial Weight}}{\text{Initial Weight}} * 100$$

3.8 Drug content

A specified area of patch is to be dissolved in a sui Table solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug contain with the sui Table method (UV or HPLC technique). Each value represents average of three different samples.

3.9 Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples are withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

4. RESULT AND DISCUSSION

4.1 Standard graph of Diclofenac sodium

The lambda max of the Diclofenac sodium was found to be 320nm. After the determination of lambda max the calibration curve and absorption are to be evaluated by the UV spectroscopy. The result of the absorption and concentration was given below in the **Table 3**. (**Figure 3**) are help to explain the standard graph of diclofenac sodium.

Table 3: Concentration and Absorption of Diclofenac sodium.

S. No.	Concentration(µg/ml)	Absorption
1	2	0.160
2	4	0.310
3	6	0.463
4	8	0.623
5	10	0.790
6	12	0.925

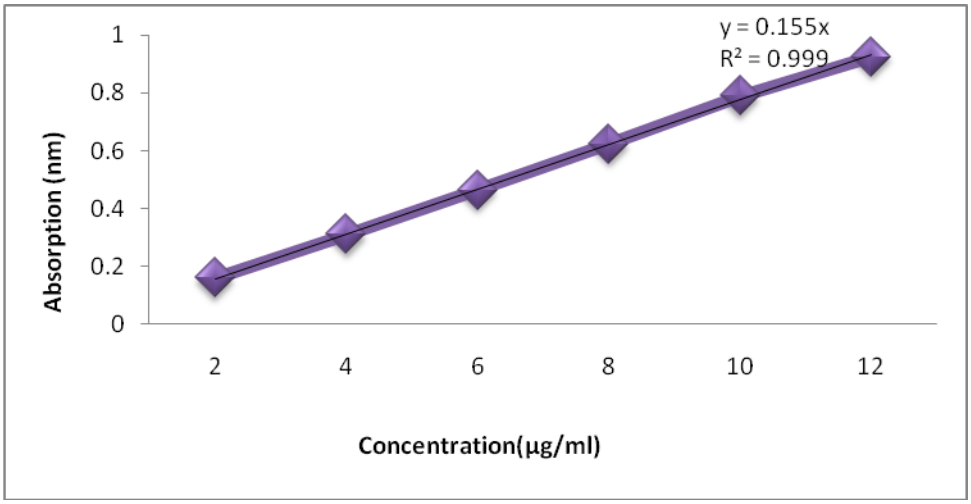

Fig. 3: Standard graph of Diclofenac sodium.

4.2 Physical appearance

The physical appearance test of the transdermal patch is done by observing it through sensory organ and following observation is made. **Table 4** help to explain the physical appearance and (**Figure 4**) show the transdermal patch and (**Figure 5**) Transdermal patch cut in 2cm^2 radius.

Table 4: Physical properties of Diclofenac sodium Patch

S. No	Physical appearance	Result
1	Colour	Off White
2	Surface texture	Smooth
3	Shape	Cube

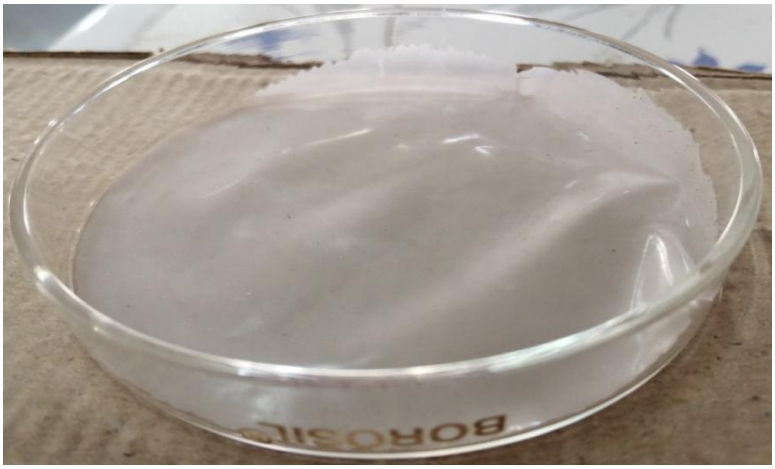

Fig. 4: Transdermal patch.

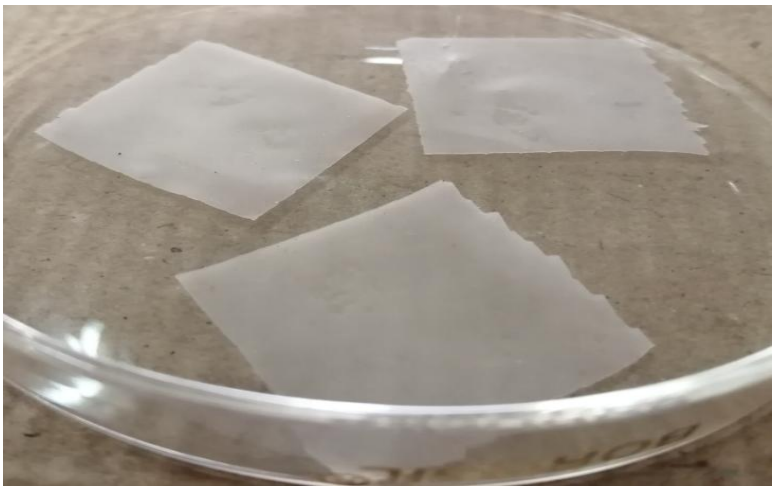

Fig. 5: Transdermal patch cut in 2cm^2 radiuses.

4.3 Thickness of the patch

The thickness of the prepared TDDs are measured by vernier caliper was given in the **Table 5**.

Table 5: Thickness of Samples of Diclofenac sodium Patch

S. No	Sample	Thickness(mm)
1	F1	0.245
2	**F2**	**0.272**
3	F3	0.259

4.4 Weight uniformity

The weight variation of the samples is given below in the **Table 6**.

Table 6: Weight variation of Diclofenac sodium Patch

S. No	Sample	Weight variation (mg)
1	F1	590
2	**F2**	**598**
3	F3	593

4.5 Folding endurance

The folding endurance of the samples are given below in the **Table 7**.

Table 7: Folding endurance of Diclofenac sodium Patch

S. No	Sample	Folding Endurance
1	F1	26
2	**F2**	**30**
3	F3	27

4.6 Percentage moisture content

The Percentage moisture content of the samples are given below in the **Table 8**.

Table 8: Percentage moisture content of Diclofenac sodium Patch

S. No	Sample	% of Moisture content
1	F1	5.2%
2	**F2**	**3.77%**
3	F3	5.12%

4.7 Content uniformity test

The Content uniformity of the samples are given below in the **Table 9**.

Table 9: Content uniformity of Diclofenac sodium Patch

S. No	Sample	Content Uniformity
1	F1	99%
2	**F2**	**100%**
3	F3	97%

4.8 Moisture uptake

The Moisture uptake of the samples is given below in the **Table 10.**

Table 10: Moisture uptake of Diclofenac sodium Patch

S. No	Sample	Moisture uptake
1	F1	7.98%
2	**F2**	**12.6%**
3	F3	13.9%

4.9 Drug content

The Drug content of the samples are given below in the **Table 11**.

Table 11: Drug content of Diclofenac sodium Patch

S. No	Sample	Drug content
1	F1	80%
2	**F2**	**98%**
3	F3	92%

4.10 Stability studies

The Stability of the samples are given below in the **Table 12 - 15** at different temperature.

Table 12: Stability data after 7 days

S. No	Sample	Temperature ·C		
		2-4·C	**20-25·C**	**35-40·C**
1	F1	STable	Stable	Stable
2	**F2**	**STable**	**Stable**	**Stable**
3	F3	STable	Un-sTable	Un-sTable

Table 13: Stability data after 14 days

S. No	Sample	Temperature ·C		
		2-4·C	**20-25·C**	**35-40·C**
1	F1	STable	Stable	Un-sTable
2	**F2**	**STable**	**Stable**	**Stable**
3	F3	STable	Un-sTable	Un-sTable

Table 14: Stability data after 21 days

S. No	**Sample**	**Temperature ·C**		
		2-4·C	**20-25·C**	**35-40·C**
1	F1	STable	Stable	Un-sTable
2	**F2**	**STable**	**Stable**	**Stable**
3	F3	STable	Un-sTable	Un-sTable

Table 15: Stability data after 28 days

S. No	**Sample**	**Temperature ·C**		
		2-4·C	**20-25·C**	**35-40·C**
1	F1	STable	Stable	Un-sTable
2	**F2**	**STable**	**Stable**	**Stable**
3	F3	STable	Un-sTable	Un-sTable

5. DISCUSSION

The important criterion for selection of components for TDDs formulation is their compatibility with other component. It has been demonstrated that only few excipients combinations lead to effective TDDs formulations. Diclofenac sodium was selected as absorbent for the development of the TDDs because it is known to treat the symptoms related with rheumatoid arthritis.

6. CONCLUSION

Transdermal application of Diclofenac sodium for rheumatoid arthritis use was successfully prepared with different polymers by solvent evaporation method. The present work was helped in understanding the effect of formulation process variables especially the concentration of different polymers on the drug release profile. This work is further aimed to perform in Vivo studies for rheumatoid arthritis the concentration of Diclofenac sodium reaching into the skin and to study its effect, which will help to avoid the first pass metabolism and to make novel transdermal dosage form for the treatment of Joint pain.

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