**ADVANCED TOPICAL DRUG DELIVERY SYSTEM CONTAINING**

**FENOPROFEN OINTMENT FOR RHEUMATOID ARTHRITIS**

**Gineeta devi\*, Shailendra Narwariya, Mineeta Mahra, Priyanka Keshri**

**SOS Pharmaceutical Science ITM University Gwalior (M.P.) Pincode - 470401**

# Email – gineetamahra@gmail.com

**ABSTRACT:**

Rheumatoid Arthritis (RA) is a chronic, Inflammatory autoimmune disease. That initially affect the small joints of patients, and progression occurs in large joints and ultimately to the eye, skin, heart, kidney, lungs. frequently when the bone and cartilage get destroyed then ligaments and tendons got weaken. The risk factors are age, gender, genetic and the environmental exposure (air pollutants, smocking cigarette smoking). In this disease mostly NSAID’s drugs are used for reducing the pain and inflammation.

The fenoprofen is propionic acid derivative NSAID’s class of COX-1 selective and non-selective inhibitor and it come into II class of biopharmaceutical classification (BCS) which are poorly water soluble. The main purpose of this study to prepare a fenoprofen ointment for topical application to treat Rheumatoid Arthritis (RA).

**METHODS:**

Ointment is prepared by the fusion method. The preparation contains different excipients like gelling agents, surfactants, and ointment bases. Ointment base is prepared by melting some ingredients, such as wool fat, cetostearyl alcohol, hard paraffin, white soft paraffin, or yellow soft paraffin sunflower wax. The performance of the formulation is controlled by the nature of the ointment base. The formulation's physicochemical characteristics, stability study, spreadability, drug content, PH studies, and ointment viscosity were all assessed. The ointment base act as a carrier or vehicle for the medication.

**RESULTS:**

The physicochemical parameters of each prepared formulation were assessed, and all of the results were within acceptable bounds. Compared to the IP, USP, formulation's recommended standard preparation.

**KEYWORDS:**

Rheumatoid Arthritis, NSAIDs, sunflower wax,

**INTRODUCTION**

An inflammatory condition known as rheumatoid arthritis affects the joints and the tissues surrounding them (ligaments, muscles, and tendons) [1]. It is a vital syndrome that affect majority of elderly patients [2]. As a result, there may be irreversible long-term disability and joint cartilage destruction [3]. 

This disease mainly affects the knees and shoulders [4]. In the treatment of rheumatoid arthritis NSAIDS class of drugs should be used by systemic or local route [5]. These medications given to relief the pain and inflammation are offered in conventional dosage forms, such as capsules and tablets. Conventional medication has many disadvantages like GI distribution, fluctuation of drug level, this may lead patients to suffer with over dosage. To reduce these problems or increase the bioavailability of drug. There are many advanced dosages form are available. Transdermal drug delivery system (TDDS) is the delivery system which help the permeation of drug molecule from the surface to various layer of the skin into the systemic circulation. In comparison to the conventional dosage form, it has a number of benefits, such as the prevention of gastric irritation and first pass effects, increased patient compliance, improved therapeutic effect, and decreased side effects. [6]. NSAIDs are non-steroidal anti-inflammatory drugs (NSAIDs) that are equally efficient and safe when applied topically to treat rheumatoid arthritis..

The release of proinflammatory cytokines like interleukin-1 (IL-1) and tumor necrosis factor (TNF-) into the synovial cavity controls the inflammatory process in rheumatoid arthritis. [7].

Fenoprofen or other NSAID’s are used to reducing or modulating the inflammatory process by inhibition of production of prostaglandins in the body through the inhibition of the cyclo-oxygenase (COX-2) enzymes [8,9]. Fenoprofen is a non-steroidal medication used as an analgesic, anti-inflammatory, and antipyretic. It is used to treat osteoarthritis and rheumatoid arthritis. Despite being quickly absorbed when taken orally [10]. Fenoprofen is a non-steroidal medication used as an analgesic, anti-inflammatory, and antipyretic. It is used to treat osteoarthritis and rheumatoid arthritis. Despite being quickly absorbed when taken orally It undergoes significant 1st pass effect, very short half-life, gastric irritation etc. To increase drug action or delivery into systemic circulation. The present study was aimed to develop or evaluate fenoprofen ointment then in-vitro drug release was studies, stability studies at various temperature was carried for the best formulation [11].

Many dermatological products are available for the treatment of skin conditions [12]. Most ointments are made up of an ointment base, which acts as a container or carrier for the medication. [13]



# ADVANTAGES

* Ointment is easier to handle than a large liquid dosage form.
* They are suitable for patient who find it difficult to take the drug by parenteral and oral route.
* They have greater chemical stability than liquid dosage form.
* They make it easier to apply the medication directly to the affected body part and prevent the drug from getting on other body parts.
* They increase the amount of time the drug is in contact with the effect area.
* Since liver passage is prevented by applying an ointment, the bioavailability of the medication is increased.

# DISADVANTAGE

* These dosage forms aren't exactly solid.
* They take up more space than solid dosage forms.
* It can be challenging to determine the exact quality of ointment that needs to be applied to the affected area.

# MATERIAL AND METHODS

**Materials:**

Sunflower wax was purchased from M/s Mahesh Ltd., Mumbai, India, and Fenoprofen was received as a gift sample from Sigma Aldrich India. All other chemicals were in analytical grades.

**METHODS:**

## study of Compatibility

The differential scanning calorimetry (DSC) thermograms of fenoprofen, sunflower wax, white petroleum, white soft paraffin, and optimized preparation were recorded on DSC lab. All sample were weighed (2-3mg) accurately into a tared weighing machine for analysis and sealed with an aluminum lid. The analysis was performed in a N2 gas environment with a heating rate of 10°C/minute over a temperature range of 1-240°C. [14].

**Preparation of ointment formulation** There are two types of topical ointment bases, each with a different grade of aqueous or anhydrous properties: simple ointment IP (T1) and simple ointment USP (T2) and sunflower wax containing formulation prepared by fusion method [15]. The base components were put together in the melting pan and allowed to melt together at 70 degrees C in this method. for 5-6 minutes and cooled them by continues stirring until a smooth consistency was obtained. Stored the preparation at room temperature (25 degree C) and further used for the preparation or analysis [16]. In order to create an ointment with a 1% Fenoprofen content, the optimized formulation F2 was triturated on an ointment slab with a spatula to yield 50g of ointment. Table 1 displays the composition of all formulations.

# EVALUATION OF OINTMENT

The physical and chemical properties of each prepared ointment, including color, consistency, odor, spreadability, and homogeneity, were assessed. pH, permeability, skin irritation (IVIVC), stability, viscosity, strength measurement.

## Organoleptic characteristic

Drug loaded formulation and all blank formulations (formulation without drug) were examined in terms of their physical characteristics, color, texture, homogeneity, and phase separation. These properties were described through visual observation. The texture and homogeneity of the ointment or formulation were assessed by pressing a small amount of it between the thumb and index finger. The consistency of the solution and the presence of large particles were used to evaluate the homogeneity and texture of the formulation.. Also assessed were the stiffness, greasiness, and grittiness of the immediate skin feel. [17] [18].

## pH study

Take about 3g of all formulations into a cleaned or dry beaker and 50mL of water were added. Ointment-filled beaker heated to 60–70 °C in water bath. A pH meter was used to determine the ointment's pH. The averages of the three readings were recorded after this was done in triplicate..

## Spreadability study

The ideal quality of an ointment should have good spreadability, which was used to gauge the formulation's spreadability. Take about 1gm of the gel formulation and place it in the middle of two glass plates with the standard (10x10cm) dimensions. place over it carefully, and put 2kg weight at center of glass plate (avoid sliding of plate).

Diameter is measured after 30 minutes in cm [19]. The formula was used to calculate the spreadability of ointment is:

1. = M×L/T

Where, S = Spreadability

1. = Time (seconds) M = Weight in the pan

L = Length of glass slide moved.

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| **Ingredients%**  | **Formulation code**  |  |  |  |  |  |  |
| **IP (T1)**  | **USP** **(T2)**  | **F1**  | **F2**  | **F3**  | **F4**  | **F5**  | **F2 – SA\***  |
| White petrolatum  | 85%  | 95%  | 95  | 96  | 97  | 98  | 99  | 96  |
| White beeswax  | -  | 5  | -  | -  | -  | -  | -  | -  |
| Sunflower wax  | -  | -  | 5  | 4  | 3  | 2  | 1  | 4  |
| Wool fat  | 5  | -  | -  | -  | -  | -  | -  | -  |
| Hard paraffin  | 5  | -  | -  | -  | -  | -  | -  | -  |
| Cetostearyl alcohol  | 5  | -  | -  | -  | -  | -  | -  | -  |

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 The sample (10g) was placed in a beaker and was allowed to equilibrate for 5 min.

**Viscosity:**

The viscosity of ointment was determined by Brookfield Synchro-lectric Viscometer (Model RVT) was used for rheological studies.

The sample (10g) was put in a beaker and given five minutes to equilibrate.Dial readings are measured using a T-D spindle at 10, 20, 30, 50, 60, and 100 rpm. At each speed, the viscometer's corresponding dial reading was recorded. The spindle speed was then gradually decreased, and the corresponding dial reading was recorded. The measurements were made in triplicate at room temperature. Multiplication of the dial readings directly using the Brookfield Viscometer's factors produced

\*Optimized ointment formulation F2 with 8% Fenoprofen drug

## Drug Content

By combining a volume of more than 100 ml with a pH 7.4 phosphate buffer and 2g of ointment equivalent to 2g of drug, the content of the drug Fenoprofen was ascertained. At 275 nm, the UV visible spectrometer's absorbance was measured. Calculating the drug content, the average of three determinations was recorded. [20].

## Strength or Hardness

The strength of formulation was determined by using texture analyser. It is based on how quickly the probe moves into the cream (the sample) at a specific distance.

## Diffusion study by in-vitro method

The release of drug was studies by using Franz diffusion cell. The cellulose membrane's surface had the ointment evenly applied. Two chambers are the receptor and the donor chamber the cellulose membrane was clamped between the chambers of diffusion cell. Fill the phosphate buffer pH 7.4 in a receptor chamber (compartment) and the assembly was kept at 37°C with 0.5°C magnetic stirring continuously. Regarding Scale-up and Postapproval Changes, the FDA recommendations were followed. To prevent drying out, 4g of ointment was put to the donor compartment membrane and then covered with aluminum foil. Over the course of an hour, the aliquot component was removed at regular intervals, and the amount of fenoprofen released was measured at 275 nm using a UV spectrophotometer. [20,21,22].

## Permeability study

A light skin cleaner was used to clean the rat's skin, any hair was removed, and subdermal fat and fascia were employed to test the permeability of the ointment. The stratum corneum of the prepared rat skin was oriented upward and put on the Franz diffusion cell, which has a 3.14 cm effective diffusion area and a 2-7 ml cell volume. The permeability of drug was determined by follow the same procedure as per the diffusion study methods [21,23].

### Skin irritation study

Healthy albino rats weighing 150–200 g were utilized as the model animals for cutaneous irritancy and sensitization. Standard care for the animals included 12 h light/dark cycles, 22 2 °C, and 35–60% humidity. The study was registered and given approval by the Institutional Animal Ethical Committee of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. [24,25].

Albino rats (weighing between 150 and 200 g) was used to perform the test. Four batches of six creatures each make up the groupings of the animals. One day before the commencement of the experimental trial, the rats' dorsal hairs were shaved, and to prevent interaction with the other rats kept separately in case. Improved formulation to compare the results of the rat skin irritation investigation, F2-SA containing sunflower wax, USP (T2), and IP (T1) simple ointments were utilized. Each was divided into two groups, with the other two groups serving as the test groups. 1 square cetimeter area of different animal abraded skin were used to apply 50mg of each formulation. The standard irritant was a 0.8% formalin aqueous solution. On the basis of animal skin, the irritancy and sensitization effects were assessed. For seven days, the animals were observed for any signs of edema and erythema. The photos were taken, and the degree of skin irritation was determined.. [26,27,28,29]

### Stability study

According to the recommendations set forth by the International Conference on Harmonization (ICH), a stability study of prepared ointment is conducted. For a period of three months, the produced ointment was placed in collapsible tubes and stored at various humidity levels and temperatures, including 60% RH/5% RH/25°C/2°C, 65% RH/5% RH/30°C/2°C, and 75% RH/5% RH/40°C/2°C. The pH, viscosity, and spreadability appearance were then examined. [30,31].

**RESULTS AND DISCUSSION**

### Study of Compatibility

Fenoprofen, sunflower wax, and the improved formulation F2-SA underwent DSC analysis and thermograms. At 170°C and 70°C, respectively, the DSC thermogram revealed a distinct melting endotherm for the drug and sunflower wax with enthalpy values of 356.69 J/g and 1107.56 J/g. Most of the time, the medicines' melting endotherm was well preserved. The enthalpy value of the medicine was preserved with minimal to no change in all instances for optimum formulation, demonstrating the medication's compatibility with the study's chosen excipients. Physical evaluation of formulation Organoleptic properties

The physical properties of the ointment compositions, such as their texture, phase separation, color, and homogeneity, are included as the organoleptic properties, shown in Table no. 2. Results showed that the ointments had a smooth texture, and good appealing appearance. All formulations were aromatic in odor, and white in color. They are all homogeneous and exhibit no evidence of phase separation. [32].

### Viscosity

All of the formulations' viscosities were discovered and recorded in the 2214.6.23 to 2751.9.83 CPS range at 10 rpm, as shown in the table. Pseudoplastic flow property are showed by all the formulation. Standard deviation was determined by calculating the average of three readings(n=3)

### pH

The pH levels of all formulas are within the typical pH range for skin. The pH values of all formulations were discovered to be between the permissible range of 6.820.16 and 7.120.18, as shown in Table 3.

### Spreadability

There are three categories for ointment spreadability: high, moderate, and low. The ratio of sunflower wax to its concentration was found to be inverse. Screening done, The ointment becomes thicker as the amount of sunflower wax increases, and as a result, spreadability declines. When all formulations were tested for spreadability, it was found that formulation F4 had the greatest spreadability, surpassing prototype formulations USP (T2) and IP (T1), as indicated in Table 3..

### Hardness

The findings of the hardness test, which gauges the potency of ointment formulations, fall between 1285.04 and 242.15 g. It has been noted that as the amount of sunflower wax in the ointment base formulation increases, so does its hardness.. This suggests that for appropriate hardness, the concentration of the sunflower wax in the formulation needs to be carefully managed because too much hardness will make the product difficult to spread, which will slow down its efficacy. Similar to the prototype formulations IP (T1) and USP (T2) shown in Table 3, the optimized formulation F3 demonstrated closed strength.

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| **Table no. 2 Physicochemical evaluation of ointment formulation**

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| --- | --- | --- | --- | --- | --- |
| **Formulation code**  | **Physical appearance**  | **Texture**  | **Phase separation**  | **Homogeneity**  | **Immediate skin feel**  |
| IP (T1) | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |
| USP (T2) | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |
| F1 | Opaque | Rough and hard | No | Homogeneous | No grittiness or greasiness |
| F2 | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |
| F3 | Opaque | Smooth | No | Homogeneous | Little grittiness and no greasiness  |
| F4 | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |
| F5 | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |
| F2 – SA\* | Opaque | Smooth | No | Homogeneous | No grittiness or greasiness |

\*Optimized ointment formulation F3 with 8% **Table 3: Evaluation parameters of ointment formulations**

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| --- | --- | --- | --- | --- | --- | --- |
| **Formulation code**   | **pH**   | **Viscosity at 10 rpm (CPS)**   | **Spreadability g.cm/s**   | **Hardness** **(g)**  | **Water number**   | **Drug content (%)**  |
|  IP (T2)  | 7.12±0.18  | 2487±8.85  | 102.81±5.23  | 147±6.83  | 1.5±0.26  | -  |
| USP (T1)  | 7.08±0.19  | 2458±6.59  | 97.34±4.43  | 126±4.40  | 1.1±0.14  | -  |
| F1  | 6.82±0.16  | 2856±9.83  | 81.00±3.63  | 241±4.15  | 1.2±0.35  | -  |
| F2  | 7.02±0.18  | 2613±8.53  | 109.19±5.03  | 219±3.87  | 1.4±0.09  | -  |
| F3  | 6.92±0.19  | 2477±7.43  | 112.67±4.73  | 158±3.72  | 1.3±0.22  | -  |
| F4  | 6.94±0.25  | 2415±8.02  | 110.26±3.83  | 139±4.23  | 1.3±0.20  | -  |
| F5  | 6.85±0.14  | 2318±6.83  | 115.51±5.11  | 128±5.04  | 1.4±0.09  | -  |
| F3–SA\*  | 6.89±0.19  | 2473±7.43  | 102.81±4.73  | 156±5.82  | 1.4±0.29  | 99.63±5  |
|  |  |  |  |  |  |  |

\*All values are mean± Standard deviation of three determinations. \*Optimized ointment formulation F2 with 8% Fenoprofen   |

**Drug Diffusion** study (in-vitro) The model medication for the in vitro release profile was Fenoprofen ointment. Ointment diffusion cell results after an hour revealed that 94.34% of the medication was discharged.

###  Permeability study

According to the drug's absorption through the skin of the rats, it released constantly over the course of an hour. At the end of an hour, the improved formulation containing 3% sunflower wax demonstrated drug permeation of 82.58±1.26

### Skin irritation

study Optimized Formulation and standard base preparations were found to be safe and do not cause redness of skin. Optimized ointment formulation did not show any sign of edema or erythema when topically applied to the skin of animals throughout the study period**.**

### Stability study

For the duration of the three-month stability experiments, the formulations' viscosity, pH, spreadability, and drug content did not significantly change from their optimal state. All of the ointment formulations underwent a stability assessment in accordance with ICH criteria.

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# Table no.4 Study of Stability for optimized formulation

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| --- | --- | --- | --- | --- |
| **S. No.**  | **Observation**  | **Before stability testing**  | **After stability testing**  |  |
| **1 month**  | **2 months**  | **3 months**  |
| 1. | pH | 6.59±0.96  | 6.49±0.91  | 6.69±0.13 | 6.79±0.12 |
| 2. | Viscosity | 2470±6.96 | 2472±7.45 | 2476±7.96 | 2470±06.23 |
| 3. | Drug content | 98.90±2.32 | 99.19±3.25  | 98.09±2.25 | 99.89±1.24 |
| 4. | Spreadability | 102.91±4.12 | 101.25±3.92  | 102.52±2.56 | 102.25±3.20 |

# \*All values are mean± Standard deviation of three determinations

# DISCUSSION

# A variety of assessment parameters were applied to optimized formulations, and the results were found to be within the boundaries that were set, as shown in Tables 2 and 3. All of the formulations were discovered to have an

alkaline pH and exhibit pseudoplastic flow. In comparison to other formulations, formulation

F3 is more spreadable. Reduce the sunflower wax concentration to increase the spreadability. Fenoprofen was put into an improved formulation and utilized as a model medication. It demonstrated favorable outcomes for ex vivo permeation and in vitro drug diffusion through rat skin and, separately, cellulose membrane. When compared to other preparations, the optimized preparation that was tested for skin irritation on rats exhibited no symptoms of redness. The results of a stability analysis show that the improved formulation is stable for the period of 3 months.

# CONCLUSION

This investigation demonstrates that using sunflower wax instead of white beeswax did not change the characteristics of the straightforward ointment. In conclusion, it can be said that sunflower wax is a native vegetable wax that, although it has not been widely employed up to this point, may successfully take the place of other conventional natural hard waxes in cosmetic and pharmaceutical applications. On rat skin, it displayed good spread ability, strength, and viscosity without causing any skin irritation. In order to take advantage of sunflower wax's practical and cost-efficient advantages, it may be effective to add it into ointment formulations. It is hoped that this work will encourage more research into and acceptance of the use of natural active ingredients in medicines.

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