**ADVANCED TOPICAL DRUG DELIVERY SYSTEM CONTAINING**

**FENOPROFEN OINTMENT FOR RHEUMATOID ARTHRITIS**

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**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 fusion method the preparation contains different excipients like gelling agent, surfactants, ointment bases. Ointment base is prepared by the melting of some ingredients are wool fat, cetostearyl alcohol, hard paraffin, white soft paraffin, or yellow soft paraffin sun flower wax. Nature of ointment base selection is very important because it control the performance of formulation. The formulation was prepared and evaluated for its Physicochemical properties, stability study, spreadability, drug content, PH studies, viscosity of the ointment. The ointment base act as carrier or vehicle for the medication.

**RESULTS:**

All the prepared formulation were evaluated for its physicochemical parameter and all the results obtained were within the limits. As compared to the standard preparation as per IP, USP, the formulation.

**KEYWORDS:**

Rheumatoid Arthritis, NSAIDs, sunflower wax, Transdermal drug delivery system , ligaments.

**INTRODUCTION**

Rheumatoid Arthritis is an inflammatory type of disease that affect the joints and their peripheral structures (ligaments, muscles, tendons) [1].

It is a vital syndrome that affect majority of elderly patients [2]. This can destroy the joint cartilage and cause the deformity leads irreversible long-term disability [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 available as conventional dosages form like 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. It has several advantages over the conventional dosage form includes avoidance of first pass effect and gastric irritation, improve patient compliance, improve therapeutic effect, or less side effect [6]. In rheumatoid arthritis topically applied non-steroidal anti-inflammatory drugs are efficacious and safe as oral NSAID’s

The process of inflammation in rheumatism is determined by the secretion of proinflammatory cytokines such as interleukin (IL1) and tumor necrosis factor (TNF-α) into the synovial cavity [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 non-steroidal drug used as antipyretic, analgesic, and antiinflammatory. It is used in the treatment of rheumatoid arthritis, osteoarthritis. Though it is rapidly absorbed by orally [10].

It undergoes significant 1st pass effect, very short half-life, gastric irritation etc. To improve delivery or extent of drug action 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].

There are numbers of dermatological products are available for the treatment of skin diseases [12]. Most of the ointment consist of a ointment base which act as a carrier or vehicle for the drug or medicament [13]



# ADVANTAGES

* Handling of ointment is easier than bulky liquid dosage form.
* They are suitable for patient who find it difficult to take the drug by parenteral and oral route.
* They are chemically more stable than liquid dosage form.
* They facilitate application of the directly to the effected body part and avoid exposure of other parts to the drug.
* They prolong the contact time between the drug and effect area.
* The bioavailability of drug administered as ointment is more since it prevents passage through liver.

# DISADVANTAGE

* They are less than solid dosage forms.
* They are bulkier than solid dosage forms
* When application of an exact quality of ointment to the affected area is required, it is difficult to ascertain the same.

# MATERIAL AND METHODS

**Materials:**

Fenoprofen was obtained as a gift sample form Sigma Aldrich India and Sunflower wax from M/s Mahesh Ltd., Mumbai, India. Analytical grades of all other chemicals were used.

**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 carried out over a temp. range of 1-240°C with heating rate of 10°C/ minute in N2 gas environment (30mL/min) [14].

**Preparation of ointment formulation** Topical ointment base of different grade of aqueous or anhydrous properties are two types namely: simple ointment IP (T1) and simple ointment USP (T2) and sunflower wax containing formulation prepared by fusion method [15]. In this method the base constituents were placed together in the melting pan and allow to melt together at 70C for 5-6 minutes and cooled them by continues stirring until a smooth consistency was obtained. Stored the preparation at room temperature (25C) and further used for the preparation or analysis [16]. The formulation of ointment containing 1% fenoprofenwas done by incorporating 0.5g of drug into the optimized formulation F2 by triturating on an ointment slab with spatula to obtain 50g of ointment. the composition of all formulations is presented in table 1.

# EVALUATION OF OINTMENT

All the prepared ointment were evaluated for the physicochemical parameter such as colour, appearance, odour, spreadability, homogeneity, pH, permeability, skin irritation (IVIVC), stability, viscosity, strength measurement.

## Organoleptic characteristic

Drug loaded formulation and all blank formulations (formulation without drug) were tested for physical appearance, texture colour, homogeneity, and phase separation. These properties were characterized by visual observation. Texture and homogeneity were tested by pressing a small quantity of the ointment or formulation between the thumb and index finger. The consistency of the preparation and the presence of coarse particles were used to evaluate the homogeneity and texture of the formulation. Immediate skin feel stiffness, greasiness, and grittiness was also evaluated [17] [18].

## pH study

Take about 3g of all formulations into a cleaned or dry beaker and 50mL of water were added. Beaker containing ointment was heated on water bath at 60-70 degree C. pH of ointment was determined by using pH meter. This was carried out in triplicate the averages of the three readings were noted.

## Spreadability study

Spreadability of the formulation was determined by determining the ideal quality of ointment should possess good spreadability. Take about 1gm of gel formulation and kept it on a center of glass plate [standard dimensions(10x10cm)] and another glass plate 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.

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

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| **Viscosity:** the viscosity in centipoises (CPS). The viscosity of ointment was determined by Brookfield Synchro-lectric Viscometer (Model RVT) was used for rheological studies.

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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  | -  | -  | -  | -  | -  | -  | -  |

\*Optimized ointment formulation F2 with 8% Fenoprofen drug  |

T-D spindle is used to measuring the dial reading at 10, 20, 30, 50, 60, and 100 rpm. The corresponding dial reading on the viscometer was noted at each speed, The spindle speed was successively lowered and the corresponding dial reading was noted. The measurements were carried in triplicate at sorrounding temperature. Direct multiplication of the dial readings with factors given in the Brookfield Viscometer gave

## Drug Content

Content of fenoprofen (Drug) was determined by dissolving 2g of ointment equivalent to 2g of drug in 10ml of ethanol and volume should be up to 100mL with pH 7.4 phosphate buffer. The absorbance of ultra-violet (UV) visible spectrometer was measured at 275nm and drug content was calculated and average of three determinations was noted [20].

## Strength or Hardness

The strength of formulation was determined by using texture analyser. It is based on the speed of displacement of probe into ointment

(sample) at a given distance.

## Diffusion study by in-vitro method

The release of drug was studies by using Franz diffusion cell. In the surface of cellulose membrane, the ointment was 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 maintained at 37°C±0.5 under constant magnetic stirring. The FDA guidelines was followed for reference to Scale-up and Postapproval Changes, 4g of ointment was applied to the membrane of donor compartment and then covered with aluminum foil to prevent drying out. The aliquot part was withdrawn at predetermined time intervals over a period of 1 h and amount of fenoprofen released was analysed at 275 nm using UV spectrophotometer [20,21,22].

## Permeability study

The skin of rat was used for permeability of ointment by cleaning with a mild skin cleanser, removing any hair and subdermal fat and fascia were used. The prepared rat skin was mounted on the Franz diffusion cell (with effective diffusion area 3.14 cm and 2-7-ml cell volume) with stratum corneum facing upward. 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 of 150–200 g body weight was used for skin irritancy and sensitization model. The animals were maintained under standard conditions (12 h light and dark cycles, at 22±2°C and 35–60% humidity).The study was approved by registered Institutional Animal Ethical committee under 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. Animals are divided into four groups, each batch containing six animals. Dorsal hairs were removed from the back of the rats 1 day before start of the experimental study and to avoid contact with the other rats kept individually in case. Optimized formulation F2-SA containing sunflower wax, USP (T2), and IP (T1) simple ointments was used to compare the skin irritation study on rats. Two groups of each were used for standard and control irritant and Other two groups were used as test. 1square cetimeter area of different animal abraded skin were used to apply 50mg of each formulation. Aqueous solution of 0.8% formalin was used as standard irritant. The skin irritancy and sensitization effect were evaluated from the animal skin. For any signs of edema and erythema the animals were observed for 7 days. The pictures were taken and evaluated for the skin irritancy [26,27,28,29]

### Stability study

The stability study of prepared ointment is carried out as per the International Conference on Harmonization (ICH) guidelines. The prepared ointment was filled in the collapsible tubes and stored at different humidity condition and temperatures, namely, 60%±5% RH /25°C±2°C, 65%±5% RH /30°C±2°C, and 75%±5% RH /40°C±2°C for a period of 3 months and studied for pH, viscosity, and spreadabilityappearance [30,31].

**RESULTS AND DISCUSSION**

### Study of Compatibility

DSC analysis was performed and thermograms of the Fenoprofen, sunflower wax, and optimized formulation F2-SA. DSC thermogram showed a distinct melting endotherm of drug and sunflower wax at 170°C and 70°C with an enthalpy value of −356.69 J/g and −1107.56 J/g, respectively. Melting endotherm of drugs was well preserved in most of the cases. For optimized formulation, in all the cases, it preserved with little or no change in enthalpy value of drug, represent the compatibility of drug with selected excipients in the study.

### Physical evaluation of formulation Organoleptic properties

Physical appearance, texture, phase separation, color, homogeneity, and immediate skin feel of the ointment formulations, 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 were all shows no signs of phase separation and with homogenous [32].

### Viscosity

Viscosity of all the formulations was found and noted in the range of 2214±6.23 to 2751±9.83 CPS at 10 rpm as shown in 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 of all formulations lies in the normal pH range of the skin. The pH of all formulations was found to be between 6.82±0.16 and 7.12±0.18 that is within the range, which are presented in Table 3.

### Spreadability

The spreadability of ointment can be categorized into three groups: high moderate, and low. Sunflower wax was inversely proportional to its concentration found After screening, As the amount of sunflower wax increased, the ointment turns out to be thicker, and, consequently, spreadabilitydecreased. The spreadability of all formulations was determined and it was observed that formulation F4 has greater spreadability as compared to other formulations as well as prototype formulations USP (T2) and IP (T1) as shown in Table 3.

### Hardness

Hardness test reveal the strength of ointment formulations and the results are found in the range of 128±5.04–242±4.15 g. It is observed that hardness of the ointment base formulated increases with increase the concentration of sunflower wax. This indicates that the concentration of the sunflower wax must be well controlled in the formulation for optimal hardness because when the product is too hard, its spreadability will be difficult, and thus, the efficacy will be retarded. Optimized formulation F3 showed closed strength such as prototype formulations IP (T1) and USP (T2) represented in Table 3.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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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**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Formulation code**  | **pH**  | **Viscosity at 10 rpm (CPS)**  | **Spreadabilityg.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 Fenoprofen ointment was used in the in vitro release profile as model drug. After 1hr ointment diffusion cell showed that 94.34% of drug was released.

### Permeability study

The drug permeation through rat skin reveal that drug was released continuously through rat skin over a period of 1 h. The optimized formulation with 3% of sunflower wax showed drug permeation of 82.58±1.26 at the end of 1

h.

### 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

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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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.  |

During the stability studies, the appearance of preparations was clear and no significant variation in viscosity, pH, spreadability, and drug content for optimized formulation for the period of 3 months. As per ICH guidelines all the ointment formulations were subjected to stability study.

# DISCUSSION

Optimized formulations were subjected to various evaluation parameters and the result were found within prescribed limits which are shown in Tables 2 and 3. All the formulations was found to be in alkaline pH and it showed pseudoplastic flow based on viscosity. The spreadability of formulation F3 is greater as compared to other formulations. Improve the spreadability by decreasing the concentration of sunflower wax. The Fenoprofen was used as model drug and incorporated in optimized formulation. It showed auspicious results for ex *vivo* permeation and *in vitro* drug diffusion through rat skin and cellulose membrane respectively. Optimized Preparation was subjected to skin irritation study on rats showed no signs of redness when compared with other Preparations. Stability study indicates that optimized formulation is stable for the period of 3 months.

# CONCLUSION

This study exposes that sunflower wax replaced in place of white beeswax did not alter the properties of the simple ointment. Over-all, we can say that sunflower wax is native vegetable wax which is not commonly used until now but can successfully replace to other traditional natural hard waxes in cosmetic and pharmaceutical products. It showed good spreadability, strength, and viscosity, with no signs of skin irritation on rat skin Thus, it could be effective to incorporate sunflower wax in ointment formulations, to avail of its economical and functional benefits. It is anticipated, this work will encourage more research and faith toward utilization of natural active ingredients in pharmaceuticals.

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