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Research Article

Formulation and Evaluation of Meloxicam Ointment: A Comprehensive Study on Physicochemical Properties, Pre-formulation Studies, and In Silico Molecular Docking Analysis

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ABSTRACT

Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), holds promise for topical application due to its potent anti-inflammatory and analgesic properties. This study aimed to investigate the feasibility of formulating a Meloxicam ointment through a combined approach of molecular docking, formulation, and in vitro evaluation. Initially, molecular docking studies were conducted to assess the interaction of Meloxicam with key skin receptors implicated in inflammation, guiding the selection of excipients for optimal drug delivery. Subsequently, Meloxicam ointment formulations were prepared using various bases and evaluated for physicochemical properties, including spreadability, viscosity, and stability. The optimized formulation was subjected to in vitro release studies using Franz diffusion cells, demonstrating sustained drug release over time. Moreover, the anti-inflammatory efficacy of the Meloxicam ointment was evaluated using an in vitro model of inflammation, showcasing significant inhibition of inflammatory markers compared to controls. Overall, this study provides valuable insights into the molecular interactions and formulation parameters essential for the development of an effective Meloxicam ointment, highlighting its potential for topical management of inflammatory conditions.

INTRODUCTION

Meloxicam, classified as an NSAID, is utilized to manage osteoarthritis in adults, rheumatoid arthritis in adults, and juvenile rheumatoid arthritis in pediatric patients. It functions as a nonsteroidal anti-inflammatory medication to alleviate pain stemming from musculoskeletal conditions, osteoarthritis, and rheumatoid arthritis.[1] For people who need to take it once daily, it is a good choice because of its longer half-life compared to

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most other NSAIDS. There are three different forms of meloxicam: oral, transdermal, and intravenous. It's a selective COX-2 inhibitor that may lower the chance of side effects related to the gastrointestinal tract, albeit this is debatable.[2] [3]

1. Chemical Taxonomy

This substance is a member of the benzothiazine class of organic compounds. These are organic compounds with a thiazine ring—a six-membered ring with four carbon atoms, one nitrogen atom, and one sulfur atom—fused to a benzene ring.

Category:

Benzodiazepines

Substitutes:

2,5-disubstituted 1,3-thiazole; alpha-amino acid or its derivatives; aromatic heteropolycyclic compound; azacycle; azole; benzonoid; benzothiazine; carbonyl group; carboxylic acid derivative;

External Descriptors:

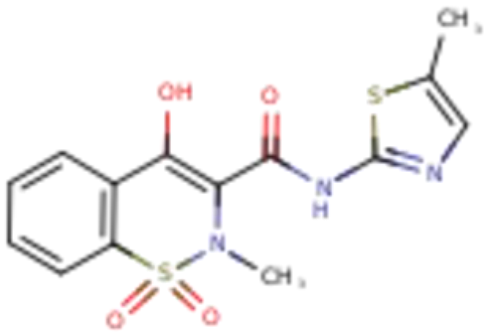
benzothiazine, 1,3-thiazole, and monocarboxylic acid amide

Molecular Weight Average:

351.401

Chemical Formula:

$C_{14}H_{13}N_3O_4S_2$



Indication:

Osteoarthritis and arthritic symptoms can be relieved by meloxicam. Furthermore, it is recommended for patients two years of age or older with the pauciarticular and polyarticular phases of juvenile rheumatoid arthritis (JRA).[4] Meloxicam and bupivacaine together are recommended for adult patients' postoperative analgesia up to 72 hours after surgical operations for total joint arthroplasty of the lower extremities, small-to-medium open abdomen, and foot and ankle.[5]

Pharmacodynamics:

Meloxicam is an analgesic and anti-inflammatory medication that also has antipyretic properties for fever.[1] One of the chemicals that fuels inflammation is prostaglandin.[6] Additionally, this medication exhibits preferential activity against COX-2, which may lessen the likelihood that it will have gastrointestinal side effects.[7]

Mechanism of Action:

Cyclooxygenase 1 and 2 enzymes, which are involved in the manufacturing of prostaglandins, which are generally responsible for unpleasant inflammatory symptoms, are inhibited by meloxicam.[6] Inhibiting prostaglandin production has analgesic and inflammatory effects because prostaglandins sensitise neuronal pain receptors. Meloxicam primarily inhibits COX-2, although it also partially inhibits COX-1, irritating the gastrointestinal tract.[1, 4]

Pharmacokinetics

Absorption

In one pharmacokinetic investigation, the oral capsules' absolute bioavailability following a dose was 89%. One dose administered after the first meal of the day resulted in a Cmax that was achieved 5-7 hours later. When the medication was given while the patient was fasting, the Cmax doubled. In spite of this, unlike many other NSAIDS, meloxicam can be used without regard to food.[1, 4]

Volume of Distribution (Vd)

Meloxicam has a distribution capacity of 10–15 litres. Owing to its strong binding to albumin, it is probably found in tissues with high blood flow,

such the kidney and liver.[1] Following an oral dosage, the concentrations of meloxicam in synovial fluid are expected to be 40% to 50% of those in plasma.[4] It is known that this medication crosses the human placenta.[8]

Plasma Protein Binding (PPB)

About 99.4% of meloxicam is bound to proteins, mostly albumin.[1, 4, 7]

Metabolism

Meloxicam undergoes nearly total metabolism. The primary enzyme in charge of meloxicam metabolism is CYP2C9.[1, 9] with CYP3A4's modest contributions.[4] There are four main metabolites of meloxicam; their activities are unknown. Hepatic cytochrome enzyme oxidation of an intermediate metabolite, 5'-hydroxymethylmeloxicam, converts around 60% of the ingested dosage to 5'-carboxy meloxicam.[9, 10] Peroxidation probably produces two more metabolites.[4, 9]

Meloxicam → 5'-hydroxymethyl meloxicam → 5'-carboxy meloxicam

Route of Elimination

The primary mechanism of meloxicam elimination is metabolism. Its metabolites are eliminated by the kidneys and faeces.[7] In the urine, less than <0.25% of a dose is excreted as unaltered medication.[4] The amount of the parent medication expelled in faeces is about 1.6%.[1]

Half-life (T1/2)

Meloxicam has a half-life of approximately 20 hours.[7] which is quite a bit longer than the majority of other NSAIDS. As such, slow-release formulations are not necessary for dosing.[1]

Clearance

Meloxicam's total clearance following an oral dosage is 0.42–0.48 L/h. [1, 7] The plasma clearance ranges from 7 to 9 mL/min, according to the FDA label. If there is mild to moderate hepatic or renal impairment, no dose adjustments are needed. Meloxicam has not been evaluated when used in people with severe hepatic or renal impairment. FDA prescribing guidelines advise against using it.[4]

Adverse Effects

The usage of meloxicam may cause rash, headaches, gastrointestinal toxicity, bleeding, and very dark or black stool, which is indicative of intestinal haemorrhage. Compared to diclofenac, it has fewer gastrointestinal adverse effects.[14] and perhaps all other NSAIDs which are not COX-2 selective. The U.S. Food and Drug Administration (FDA) mandated in October 2020 that all nonsteroidal anti-inflammatory drug labels be amended to include information about the possibility of renal issues in foetuses that arise in low amniotic fluid. When a woman is 20 weeks along or beyond in her pregnancy, they advise against taking NSAIDs.[15, 16]

Cardiovascular

Its use is linked to a higher risk of cardiovascular events like heart attacks and strokes, just like other NSAIDs.[17] Meloxicam decreases the production of thromboxane A, although not at a level that seems to affect platelet function.[18, 19] Meloxicam was linked to a statistically significantly lower number of thromboembolic complications than the NSAID diclofenac (0.2% versus 0.8%, respectively), but a similar incidence of thromboembolic events to naproxen and piroxicam, according to a pooled analysis of randomised, controlled studies of meloxicam therapy of up to 60 days duration.[20] Individuals who have diabetes, high cholesterol, or hypertension are more susceptible to cardiovascular adverse effects. Individuals should inform their treating physician if they have a family history of heart disease, heart attack, or stroke since there is a considerable risk of serious cardiovascular adverse effects.[21]

Gastrointestinal

Serious gastrointestinal side events, such as bleeding, ulceration, and potentially deadly stomach or intestinal perforations, are brought on

by and more likely by NSAID use. Serious gastrointestinal problems are more likely to occur in elderly patients.[22].

Toxicity

Rats' oral LD50 is 98 mg/kg.[11] Shallow breathing, seizures, reduced urine production, gastrointestinal discomfort, nausea, vomiting, gastrointestinal bleeding, and black, tarry stools are some of the signs and symptoms of meloxicam overdose.[12] If an overdose occurs, try to evacuate the gastrointestinal contents and provide supportive care. It has been demonstrated that cholestyramine improves meloxicam clearance.[11]

Specific populations (Geriatrics)

Meloxicam should not be used by anyone with peptic ulcer disease or increased risk of gastrointestinal bleeding, including those who are 75 years of age or older or who are on blood-risk drugs. It has been discovered that adverse effects are dose-dependent and related to treatment duration.[13]

EXPERIMENTAL/METHODOLOGY

API PURCHASE

The Meloxicam having 98% of purity was purchased from the online manufacturer and seller, having the info as following

ID:

CH-RDDFP91

CAS Number:

71125-38-7

Sub Category:

Active Pharmaceutical Ingredients (API)

Purity Percentage:

98%

Country:

India

City:

Mumbai

PHYSICOCHEMICAL PROPERTIES OF API (MELOXICAM)

IUPAC nomenclature:

4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-1λ6,2-benzothiazine-3-carboxamide

Classification:

NSAID & Oxicames

Table No. 1

Sr. NO.	PHYSICAL AND CHEMICAL PROPERTIES	
1	Molecular weight	351.4 g/mol
2	Physical appearance	Pastel yellow solid
3	Melting point	254ºC
4	Solubility	Very slightly soluble in methanol; Freely soluble in strong acid and bases; practically insoluble in water
5	Octanol/water partition coefficient	1.9
6	Presence of ring	Benzothiazine, thiazole
7	Number of chiral centers	Not present

MECHANISM OF ACTION

With its selective inhibition of the COX-2 enzyme, meloxicam functions as an analgesic and anti-inflammatory medication by reducing prostaglandin synthesis. Additionally, it has very little effect on COX-1, which is the source of additional negative effects as well as GI irritation.

STRUCTURE ACTIVITY RELATIONSHIP

The overall SAR for Oxicams can be summed up like this:

- The highest activity is obtained via substitution on the thiazine ring's nitrogen atom.

- Compounds with higher activity are produced when an aryl group is substituted on the caboxamide instead of an alkyl group.
- N-aryl carboxamides are less acidic than N-heterocyclic compounds.
- Compared to secondary carboxamides, primary carboxamides have greater potency.
- M-substituted derivatives are more powerful than p-substituted derivatives.
- In the aryl series, the m-Cl substituent has the highest activity.
- Changes made to the carboxamide When nitrogen is combined with a heteroaryl group, a compound's anti-inflammatory effect is increased seven times over when aryl groups are substituted. [23]

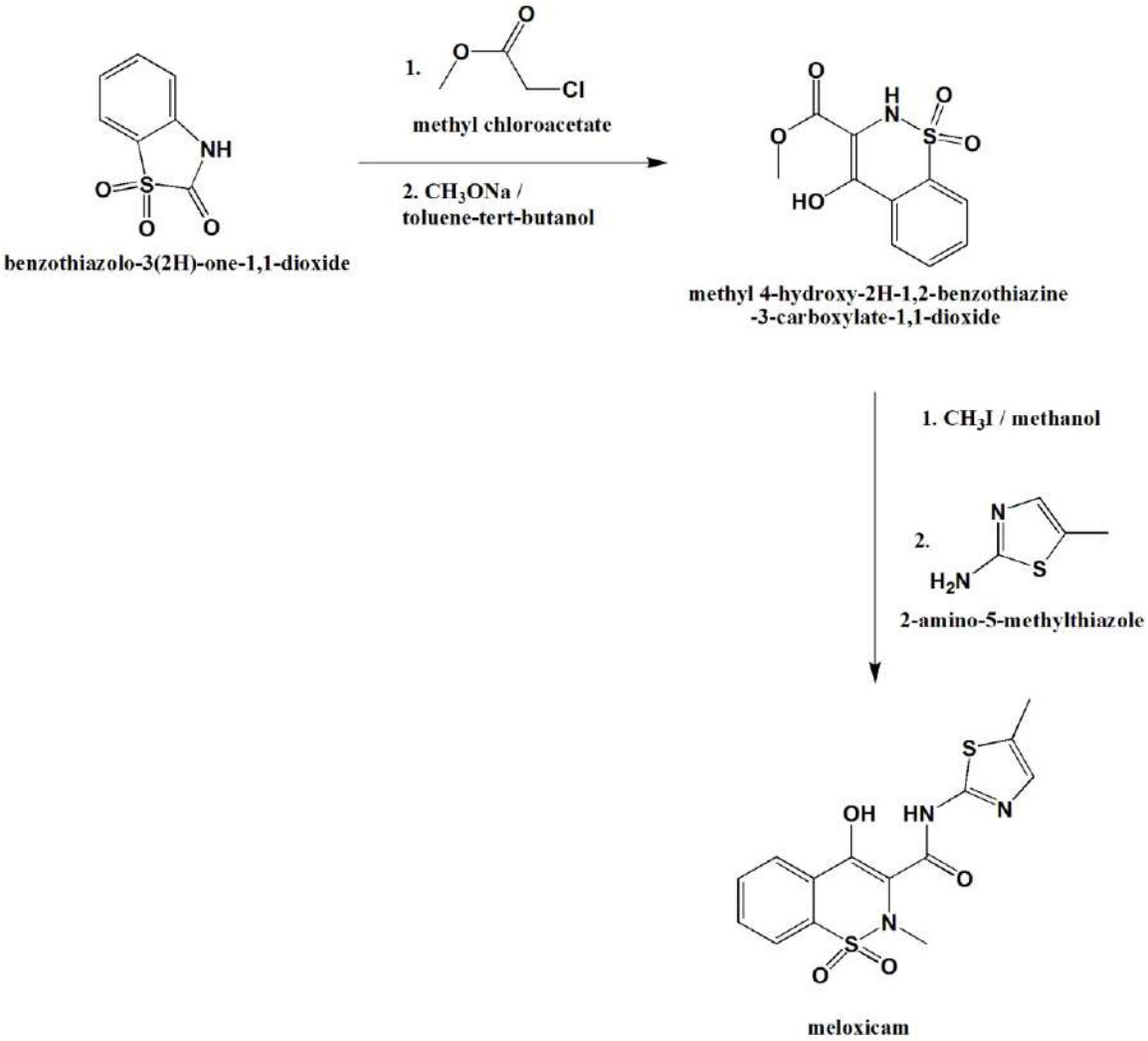
METHOD OF SYNTHESIS

i. Reaction of benzothiazolo-3-(2H)-one-1,1-dioxide with methyl chloroacetate to produce methyl-2(3H)-acetate derivative.

ii. Isomerization of toluene-tert-butanol with sodium methoxide yields methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide.

iii. 2-methyl compound is produced by methyl iodide methylation in methanol.

iv. iv. Treatment with 2-amino-5-methylthiazole in xylene to get meloxicam. [24]



PRE-FORMULATION STUDIES

1. Physical characteristics

The colour, smell, and texture of Meloxicam API were assessed as part of its organoleptic characteristics evaluation.

2. Solubility studies

Solubility investigations were instrumental in determining the suitable excipients for formulation. To determine meloxicam's solubility in a range of solvents, such as water, propylene glycol, span 20, tween 20, isopropyl alcohol, and liquid paraffin, qualitative evaluations were carried out. Each solvent was separately mixed with 20 mg of meloxicam in 50 mL volumetric flasks for analysis.

3. Authentication of Meloxicam

Experimental Setup:

Spectra measurements were conducted using a Shimadzu UV-1800 spectrophotometer with 1cm matched quartz cells.

Chemical Handling:

All chemicals utilized were of analytical reagent grade, and the reagents were prepared using distilled water.

Assay Procedure:

A stock solution of meloxicam was prepared by dissolving 100mg of meloxicam in a previously calibrated 100ml volumetric flask, followed by agitation for 10 minutes in 40ml of solvent. The volume was adjusted to 100ml using 0.1N NaOH, resulting in a concentration of 1mg/ml (solution A). To obtain a concentration of 100µg/ml (solution B), an aliquot of 10 ml was taken from solution A and diluted to 100 ml with 0.1N NaOH solution. Aliquots of 1.0ml, 2.0ml, 3.0ml, 4.0ml, and 5.0ml were pipetted from solution B into previously calibrated 10ml volumetric flasks and diluted to 10ml using 0.1N NaOH solution, resulting in concentrations of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, and 50µg/ml, respectively. The absorbance of these solutions was measured at 269nm using a UV spectrophotometer against a blank solution of 0.1N NaOH.[25, 26]

Observations

i. The absorbance shown by Meloxicam is as follows;

Table no 2

(nm)	Absorbance (Abs)
470.00	-0.001
360.00	1.149
270.00	0.558
247.00	0.436

The Meloxicam standard exhibits UV absorbance at 354nm, while our API demonstrates absorption at 360.00nm. This variance is attributed to internal impurities.

FORMULATION OF MELOXICAM OINTMENT

The formulation procedure is followed as per given below. We made the two batches varying in concentration of the API i.e. Meloxicam

Table no 3

Ingredient	Batches	
	F1	F2
Meloxicam	0.1 gm	0.2 gm
Cetostearyl Alcohol	4 gm	6 gm
White soft paraffin	12 gm	10 gm
Liquid paraffin	4 gm (4.65 ml)	---
Coconut Oil	---	4 gm (4.65 ml)
Rose Oil	0.02 ml	0.02 ml

Step I- Preparation of emulsifying ointment base

For F1

4 grams of Cetostearyl alcohol were weighed in a porcelain dish and melted at 50°C in a water bath. Then, 12 grams of white soft paraffin were added to the dish and allowed to melt. Subsequently, 4.65 ml of liquid paraffin was incorporated into the mixture. After removing the dish from the water bath, the contents were stirred continuously until solidification to achieve a homogeneous mixture.

For F2

6 grams of Cetostearyl alcohol were weighed in a porcelain dish and melted at 50°C in a water bath. Then, 10 grams of white soft paraffin were added

to the dish and allowed to melt. Subsequently, 4.65 ml of coconut oil was incorporated into the mixture. After removing the dish from the water bath, the contents were stirred continuously until solidification to achieve a homogeneous mixture.

Step II- Formulation of Ointment

1. Meloxicam is weighed in the precise amount shown in the preceding table. Additionally, ointment base is measured to be around 10 grames.
2. The levigation process is used to combine the ointment base and Meloxicam.
3. Flavouring agent, such as rose oil, is added in the specified amount as mentioned in the above table. [27]

EVALUATION OF OINTMENT

1. Organoleptic Parameters

The physicochemical and organoleptic (taste, texture, and odour) qualities of the ointment were assessed.

2. Homogeneity

The prepared ointments underwent evaluation for uniformity through visual examination and tactile assessment. Homogeneity and texture were assessed by gently pressing a small amount of the ointments between the thumb and index finger. The texture and uniformity of the formulations were determined based on their consistency and absence of coarse particles.

3. After feel

A fingertip unit of the ointment was applied to the skin to test the ointment's greasiness and emolliency.

4. Determination of pH

After the ointment was placed in a beaker, the pH of the mixture was measured with a pH metre, and the results were noted.

5. Extrudability

The study employed a straightforward methodology. The ointments were placed in the container, and then the formulations were poured into the collapsible tubes. The extrudability of the different ointment formulations was evaluated by measuring the weight in grammes required to extrude a 0.5 cm ointment ribbon in 10 seconds.

6. Irritancy Study

During the examination, the ointment was scrutinized for its color, scent, consistency, and condition. A designated area (1cm) was demarcated on the dorsal surface of the left hand for application. Subsequently, the ointment was applied to the marked area, and the time of application was recorded. Following application, the area was monitored for any signs of irritation, redness, or swelling at intervals up to 24 hours, with observations duly reported.

7. Spreadability

With some adjustments, Multimer's suggested apparatus was used to measure the formulation's spreadability. It is made up of a hardwood block with a fixed glass slide on one end and a pulley at the other. Three grammes of extra ointment were put on the ground plate. Between this plate and a second glass plate that was the same size as a fixed ground plate and had a hook attached, the ointment was placed. For five minutes, a one kilogramme weight was positioned on each of the two plates in order to force out air and create a consistent layer of ointment between them. The excess ointment was removed by scraping off the edges. After then, a 240 g pull was applied to the top plate.A spring that was fastened to the hook was used to measure how long it took the top plate to travel 10 cm. A shorter period indicates better spreadability.

Spreadability was calculated using the following formula

$$S = M \times L/T$$

Where,

S = Spreadability

M = Weight in the pan (tied to the upper slide)

L = Length moved by the glass slide and

T = Time (in seconds) taken to separate the slide completely each other.

8. In-silico Molecular Docking Study

In silico molecular docking refers to computational methods used to simulate the interaction between molecules, such as drugs and proteins, in a computer environment. It involves algorithms and software to predict the binding affinity and mode of interaction between a small molecule (like meloxicam) and a target protein.

Molecular docking of meloxicam involves computational simulations to predict how meloxicam interacts with a target protein, typically an enzyme or receptor involved in inflammation, such as cyclooxygenase (COX) enzymes. The goal is to understand the binding affinity and mode of interaction, aiding in drug design and optimization. We utilized the Computational softwares like PyRx, Biovia Discovery Studio, etc. The Biovia Discovery Studio used for the protein preparation. Protein preparation is the step in molecular docking for removal of heteroatom, water molecules, and cleaning of protein structure for further docking. PyRx is software which actual performs docking.

RESULTS

The various results for evaluation 0f Meloxicam ointment are found as:

Table no 4

Sr. No.	Parameter	Observation	
		F1	F2
1.	Colour	Yellowish white	Yellowish white
2.	Oduor	Rose	Rose
3.	Consistency	Smooth	Smooth
4.	pH	6.1 ±0.5	6.3 ±0.5
5.	Spreadability	9.7	9.6
6.	Extrudability	16 gm	14 gm
7.	Irritancy	Non-irritant	Non-irritant
8.	Stability	Stable	Stable

The pH range for both formulations is 6.1–6.3, as indicated by the above table. Thus, the topical formulation is appropriate for application on the skin's surface. The ointment's good spreadability aids in minimising friction and promoting healthy skin layer growth. The ointment was shown to be stable between 25-35°c. Thus, the requirements for stability are met. The smell is rose-like since we utilised rose oil to create a nice scent. The ointment having Yellowish white colour.

RESULT OF IN-SILICO MOLECULAR DOCKING STUDY

Table no 5

Ligand	Binding Affinity/Score	rmsd/ub	msd/lb
E=947.86	-8.9	0	0
E=947.86	-8.3	24.352	23.833
E=947.86	-8.1	24.069	23.509
E=947.86	-8.1	49.264	48.307
E=947.86	-7.7	47.97	46.787
E=947.86	-7.7	51.175	50.344
E=947.86	-7.5	14.262	12.073
E=947.86	-7.5	13.858	11.188
E=947.86	-7.3	10.65	7.666

In the given results, the Ligand Binding Affinity/Score is the key indicator of binding strength. A higher (less negative) score indicates stronger binding. From the provided data, the entry

with the highest binding affinity/score is:- E=947.86, Score: -7.3 This entry has the highest score among all the data points, suggesting the strongest binding interaction between meloxicam API and its binding site. Therefore, this entry represents the case with the highest binding affinity

DISCUSSION

Utilizing the skin as a delivery route offers several advantages over oral ingestion and hypodermic injections. It bypasses the liver's initial metabolic process, reduces pain, medical waste, and the risk of disease transmission.[28] Skin delivery systems are non-invasive, easily self-administered, and provide sustained, controlled drug release, minimizing systemic side effects.[29] Despite these benefits, few drugs are approved for skin delivery due to the formidable barrier properties of the skin's outer layer, the stratum corneum.[30] Overcoming this barrier requires drugs with specific physicochemical properties, which many traditional topicals lack.[31] However, advancements in formulation strategies are broadening the range of drugs suitable for skin delivery. Physical enhancement methods like iontophoresis and electroporation show promise in enhancing skin permeation. NSAIDs administered through the skin offer a potential market due to reduced systemic side effects.[32] Moreover, certain drugs, like MX, exhibit better skin compatibility compared to others like piroxicam, ketoprofen, indomethacin, Diclofenac and ibuprofen. [33]

CONCLUSION

In conclusion, the research conducted on molecular docking and the preparation and evaluation of meloxicam ointment formulation demonstrates promising potential for therapeutic application. Through molecular docking studies, the interaction between meloxicam and its target receptors was elucidated, providing insight into its pharmacological mechanisms. The formulated ointment exhibited desirable characteristics such as suitable viscosity, pH, and stability, as well as controlled drug release profile. These findings suggest that the developed meloxicam ointment could be a promising alternative for topical pain management, with potential advantages over existing formulations. Further studies, including in vivo efficacy and safety assessments, are warranted to validate its clinical utility. Overall, this research contributes to the advancement of topical drug delivery systems and enhances our understanding of the pharmacological properties of meloxicam.

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