ISSN 2521-0521

JOURNAL OF CONTEMPORARY PHARMACY

Volume 8: Issue 2: 2024

https://doi.org/10.56770/jcp2024821

DEVELOPMENT AND CHARACTERIZATION OF DIACEREIN CREAM WITH CURCUMA LONGA HAVING POTENT ANTI-INFLAMMATORY EFFECT

Muhammad Razi Ullah Khan

Faculty of Pharmacy, The Superior University, Lahore

Submitted: August 11, 2024; Revised: September 30, 2024; Accepted: October 7, 2024; Published: December 31, 2024

ABSTRACT

Objective: Osteoarthritis, the most common type of arthritis, affects an increasing number of people and greatly diminishes their quality of life. Treatments for Osteoarthritis are divided into two categories: NSAIDs, which provide symptomatic relief, and disease-modifying agents. Diacerein, a disease-modifying agent, targets critical disease mechanisms and effectively slows the progression of structural changes in patients with knee Osteoarthritis. This study aims to develop and evaluate a novel cream formulation that combines Diacerein with Curcuma longa, which is renowned for its strong anti-inflammatory properties, to enhance treatment effectiveness in Osteoarthritis. **Materials:** A cream formulation containing Diacerein (3%) and Curcuma longa (1%) was prepared and evaluated for various physicochemical properties, including homogeneity, pH, spread-ability, tube extrudability, viscosity, and in-vitro drug diffusion, to determine its suitability for topical application. Accelerated stability testing was performed at different temperatures, and the remaining drug content was measured using a UV-Visible spectrophotometer assay. The formulated cream was also assessed for skin irritation and anti-inflammatory effects on albino rabbits. Furthermore, the efficacy of the Diacerein cream was evaluated in knee Osteoarthritis patients using the VAS and Lequesne scales. **Results**: The results were promising, with the Diacerein cream formulation combined with Curcuma longa extract stored at room temperature (22±5°C) showing the most favorable outcomes for all physicochemical parameters compared to storage at 40°C and 60°C. **Conclusion**: The formulated cream significantly lowered the scores on the VAS and Lequesne scales, demonstrating its effectiveness in treating knee joint Osteoarthritis. No adverse events were reported, indicating that the formulation is safe for use in Osteoarthritis of the knee joint.

Keywords: Diacerein, Curcuma longa, Cream, Stability study, VAS, Lesquesne scale.

*Corresponding Author. E-mail: rukhanpharmacist@gmail.com

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder that can affect any synovial joint in the body, most frequently impacting the hands, knees, hips, and spine **[1]**. Clinically, OA is characterized by joint pain, brief morning stiffness, limited range of motion, and crepitus, along with associated pathological and radiographic changes **[2]**. To manage OA symptoms, patients and healthcare providers often employ a variety of strategies, including lifestyle changes, medications, exercise, and surgical interventions **[3,4]**. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed medications for OA pain management; however, they carry risks of serious gastrointestinal and vascular side effects and do not improve the underlying joint structure or cartilage damage **[5]**. Consequently, there is a significant need for disease-modifying therapies for OA patients.

Disease-Modifying OA Drugs (DMOADs) are essential to slow disease progression and alleviate symptoms such as pain and limitations in daily activities due to impaired physical function **[6]**. Diacerein, also known as Diacetylrhien (4,5-diacetoxy-9,10-dihydro-9,10-dioxo-2-anthracene carboxylic acid), is a novel anti-inflammatory, analgesic, and antipyretic agent specifically developed for the treatment of OA **[7]**. As an anthraquinone derivative, Diacerein has demonstrated in vitro and in vivo efficacy in inhibiting the production and activity of the cytokine interleukin-1β (IL-1β), which is responsible for reducing cartilage-specific macromolecule production. Diacerein also decreases the IL-1β-stimulated release of metalloproteinases and aggrecans, thereby protecting cartilage from degradation by these enzymes **[8]**.

A notable advantage of Diacerein in OA treatment is that it does not interfere with prostaglandin synthesis, thereby avoiding harmful effects on the upper gastrointestinal mucosa - a significant benefit compared to NSAID therapy **[9]**. Curcuma longa, a

perennial plant from the Zingiberaceae family, has been used for centuries in Ayurvedic medicine to treat inflammatory conditions **[10]**. The primary pigment compound in Curcuma longa, Curcumin, possesses strong anti-inflammatory properties, inhibiting enzymes such as lipoxygenase and COX-2, as well as cytokines like TNF alpha and IL-1 beta **[11]**. Curcuma longa is also utilized in formulations to achieve a synergistic anti-inflammatory effect in mild to moderate OA **[12]**.

MATERIALS & METHODS

Chemicals

Diacerein was received as a gift from Stand Pharm Pakistan (Pvt) Ltd., Cetostearyl Alcohol (BDH Labs, England), White Bees Wax (Kukdong oils and chemicals, Korea), Methyl Paraben and Propyl Paraben (BDH Labs, England), Liquid Paraffin (Kukdong oils and chemicals, Korea), Polyoxyethylene (80) Sorbitan Monooleate (Tween 80) (Merck, Germany), Sodium Metabisulfite (Glenmark Generics, USA), Carbopol 980 NF Polymer (Lubrizol, USA), Glycerin (Merck, Germany), De-ionized Water (Medilines Diagnostic Division)

Plant Material

The plant material used in this study was collected from the area around Kasur city, Pakistan, in January. It was identified by the Department of Botany, Faculty of Biological Sciences at Superior University, Lahore.

Apparatus

UV-Visible Spectrophotometer (Shimadzu, Japan), Weighing balance (Analytical grade), Magnetic stirrer/Hot plate (Made in Germany), pH meter (Model No: 3510, Germany), Homogenizer (Euro-Star, IKA D 230, Germany), Brookfield digital viscometer (Model DV-III+, Brookfield Engineering Laboratory, Inc., USA), Franz diffusion cell apparatus (Perm Gear, USA), Refrigerator (PEL, Pakistan), Soxhlet apparatus, Incubator (Sanyo MIR-162, Japan), Oven (Schutzartdin 40050 IP-20, Germany)

Preparation of Turmeric Extract

The rhizomes of Curcuma longa were cleaned, washed with de-ionized water, sliced, and sun-dried for one week. The dried rhizomes were then cut into small pieces and ground into a fine powder using an electronic mill. A 200-gram sample was placed into a thimble and subjected to extraction in a Soxhlet apparatus. The extraction process involved using various solvents, ranging from non-polar to polar, with one liter of each solvent added and extraction conducted according to their boiling points for seven hours **[13]**. The solvents used were chloroform (B.P. = 61°C), ethyl acetate (B.P. = 77°C), methanol (B.P. = 65°C), and acetone (B.P. = 56.53°C). After extraction, the dark brown extract was cooled and concentrated using a rotary evaporator, resulting in a crude dried extract that was black and orange in color **[14]**.

Development 0f Diacerein Cream Containing Curcuma Longa

3% by weight of Diacerein cream containing 1% curcuma longa was made according to the formulation given in **Table 1**.

PREPARATION OF CREAM

A Diacerein topical cream combined with Curcuma longa extract was prepared in the laboratory. The oil and aqueous phases were heated separately to 75ºC in a water bath. The oil phase contained Diacerein, Curcuma longa extract, Liquid Paraffin, White Bees Wax, Cetostearyl Alcohol, Tween-80, and Carbopol 980, while the aqueous phase comprised Methyl parabens, Propyl parabens, Glycerin, Sodium metabisulfite, and De-ionized water **[15]**. The aqueous phase was gradually added to the oil phase dropwise with constant stirring at 2000 rpm using a homogenizer for 20 minutes. The homogenizer speed was then decreased to 1000 rpm, and mixing continued for an additional 5-10 min. Finally, the speed was further reduced to 500 rpm, with homogenization extended for another five minutes. This process yielded the Diacerein cream combined with Curcuma longa extract.

Table 1: Development of diacerein cream with Curcuma longa.

Serial No	Ingredients	Composition (%)
1	Diacerein	3.0
2	Curcuma longa	1.0
3	Cetostearyl Alcohol	10.0
4	White Bees Wax	5.0
5	Methyl paraben	0.12
6	Propyl paraben	0.02
7	Liquid paraffin	5.0
8	Tween- 80	8.0
9	Sodium meta bi sulphate	1.50
10	Carbopol 980	0.60
11	Glycerin	6.0
12	De-ionized water	59.76

Evaluation of Diacerein Cream

Homogeneity

The homogeneity of the Diacerein cream was evaluated through visual inspection. The cream was filled into narrow transparent glass tubes and examined under light to check for the presence of any particulates or lumps.

pH

The pH of the cream formulation was measured using a digital pH meter. The pH meter was calibrated with buffer solutions at pH 3.99, 7.0, and 9.2, and the electrode was rinsed with demineralized water **[16]**. Measurements were performed in triplicate, and the average of the three readings was recorded.

Spreadability

Spreadability was assessed using an apparatus featuring a wooden block with a pulley at one end. This method evaluates the 'slip' and 'drag' characteristics of the creams. A ground glass slide was fixed on the block, and approximately 2 grams of the cream were applied to this slide. Another glass slide of the same dimensions was placed on top, and a 1 kg weight was applied for 5 minutes to remove air and create a uniform cream film. Excess cream was then scraped off from the edges. The top slide was subjected to a pull of 80 grams using a string attached to a hook, and the time (in seconds) required for the top slide to move 7.5 cm was recorded. A shorter time indicates better spread ability **[17]**.

Spreadability was calculated using the formula:
$S=M\times L/T$

where S is spread ability, M is the weight in the pan (tied to the upper slide), L is the length moved by the glass slide, and T is the time taken to separate the slides completely.

Tube Extrudability

Tube extrudability measures the force needed to expel the material from a tube. This method involves assessing the shear force in the rheogram region where the shear rate surpasses the yield value, demonstrating plug flow. The extrudability of the cream formulation was evaluated based on the percentage of cream expelled from a lacquered aluminum collapsible tube when a specific weight was applied, required to extrude at least a 0.5 cm ribbon of cream within 10 seconds. A higher amount of cream extruded indicates better extrudability **[18]**. Measurements were conducted in triplicate, and average values were reported.

Extrudability was calculated using the formula:
Extrudability=Applied weight to extrude gel from t ube (in gm)/Area (in cm^2)

Viscosity

The viscosity of the cream formulation was measured using a Brookfield digital viscometer. The sample was placed in a clean, dry 250 ml beaker, and viscosity was assessed following the viscometer's standard operating procedure, with spindle T-D (Spindle code S 94). The spindle was rotated at speeds of 2.5, 4, 5, and 10 rpm, and readings close to 100% torque were recorded. Measurements were performed in triplicate, and the average values were noted **[19].**

In Vitro Drug Diffusion Protocol

In vitro diffusion studies of Diacerein were performed using a Franz cell apparatus with a synthetic membrane. The synthetic membrane was positioned between the donor and receptor compartments of the Franz cell apparatus, which featured a 25 ml receptor compartment. The dialysis membrane was mounted between the compartments, and the cream formulations were uniformly applied to it. The compartments were clamped together, and the receptor compartment was filled with phosphate buffer (pH 7.4). Hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. The study was conducted over 24 hours, with samples collected at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours **[20]**. At each time point, 2 ml of the sample was withdrawn from the receptor compartment and replaced with an equal volume of buffer. The absorbance of the withdrawn sample was measured spectrophotometrically at 497.5 nm against a suitable blank.

Accelerated Stability Studies of Diacerein Cream

Accelerated stability studies for the Diacerein cream were carried out over three months under three different conditions: (a) at 22 ± 1 ºC, (b) at 40 ± 1 ºC, and (c) at 60 ± 1 ºC. The formulation was analyzed using a UV-Visible Spectrophotometer immediately after preparation (at zero time) and then monthly throughout the three-month period. The active content in the cream was determined by measuring the absorbance of the sample solution at 497.5 nm with the UV Spectrophotometer **[21]**. The percentage of remaining active content was calculated using the following formula:

Remaining % Active Content
= (Absorbance of Sample/Absorbance of Standard) × (Conc. of Standard/Conc. of Sample) × % Purity of Standard

Determination of Drug Content by Spectrophotometric Method

Preparation of Standard Solution

50 mg of Diacerein were weighed and dissolved in methanol in a 100 ml volumetric flask. Twenty-five milliliters of methanol were added, and the mixture was subjected to ultrasonication for 25 minutes. The volume was then adjusted to 100 ml with methanol, and the solution was mixed thoroughly. After filtering through Whatman filter paper no. 41, the residue was washed three times with 10 ml of solvent each. The final volume was adjusted to 100 ml with methanol.

Preparation of Sample Solution

5 g of Diacerein cream was weighed and dissolved in methanol in a 100 ml volumetric flask. Twenty-

five milliliters of methanol were added, and the mixture was ultrasonicated for 25 minutes. The volume was then adjusted to 100 ml with methanol, and the solution was mixed thoroughly. After filtering through Whatman filter paper no. 41, the residue was washed three times with 10 ml of solvent each. The final volume was brought to 100 ml with methanol.

Anti-Inflammatory Activity of Diacerein Cream

The anti-inflammatory study was carried out on three albino rabbits (approved by the Institutional Animal Ethical Committee, University of Sargodha, Pakistan), which were divided into two groups. Acute inflammation was induced by injecting 0.1 ml of freshly prepared 1% carrageenan suspension in normal saline into the left hind paw of each rabbit. The medicated formulation (0.25 g) was applied topically with gentle rubbing to each rabbit's paw one hour before and one hour after the carrageenan injection. Paw edema volume was measured using a plethysmometer at 1,2, 3-, and 4-hours post-injection. The average paw edema volume was then calculated **[22]**.

Skin Irritation Study

For the skin irritation study, three albino rabbits were chosen. Twenty-four hours before testing, the test sites on both sides of the spine were shaved and marked for cream application. A measured amount of cream was applied to these sites, and the areas were monitored for erythema and edema at 24, 48, and 72 hours after application.

Efficacy and Safety Evaluation of Diacerein Cream in Osteoarthritis of Knee Joints

A prospective observational study was conducted over 15 days in April 2024 with 30 patients diagnosed with knee Osteoarthritis. The patients were selected from Chaudhary Muhammad Akram Teaching & Research Hospital, Lahore, Pakistan.

Inclusion Criteria for the Study

1. Newly diagnosed with knee Osteoarthritis, 2. Mild to moderate Osteoarthritis (based on Lequesne scale) **[23],** 3**.** Both male and female volunteers, 4. Age between 40-60 years

Exclusion Criteria for the Study

1. History of allergy to Diacerein or Diacerein-containing products, 2 Active skin lesions at the intended application site (e.g., open wounds, rash, papules, vesicles, erythema), 3. Participation in an investigational drug study or receipt of an investigational drug within 30 days prior to the study, 4 non-pharmacological treatment for the injury

Methodology of the Study

The study included 30 human volunteers aged 40-60 years with knee Osteoarthritis, comprising 18 males and 12 females. These volunteers showed signs of inflammation, such as pain, redness, and swelling in the knee joint. Prior to enrollment, informed consent was obtained from each participant in their preferred language. Demographic information (age, sex, weight, and personal history, including smoking and alcohol use) as well as VAS and Lequesne Scale scores were recorded on structured Case Record Forms (CRFs). Treatment allocation was done through simple randomization, and participants were instructed to apply the cream (4 inches) three times daily for 15 days. Patient responses to pain (at rest, while walking, and standing), redness, and swelling were documented before and after treatment (on the 1st and 15th days) using study proforma. Measurements were taken with the VAS (Visual Analog Scale) and Lequesne Scale.

RESULTS AND DISCUSSION

The goal of this study was to develop a Diacerein cream formulation combined with Curcuma longa, a highly effective natural anti-inflammatory agent. The cream is designed to target localized areas of the skin for managing Osteoarthritis while minimizing undesirable side effects. The formulation was tested using varying concentrations of excipients and active ingredients and evaluated for several physicochemical parameters.

The cream's homogeneity was deemed satisfactory, with no visible particles or lumps. The pH of the Diacerein cream was measured three times during preparation, averaging 6.73, which is within the normal skin pH range of 6.6 ± 0.6 to 6.8 ± 0.35, suggesting it is unlikely to cause skin irritation (**Table 2**). The spread ability of the cream ranged from 4.75 to 6.25 g/sec, while the extrudability from the collapsible tube varied from 185 to 195 g. The viscosity of the cream ranged from 65,219 cps at 2.5 rpm to 14,673 cps at 10 rpm (**Table 3**).

Table 2: Evaluation data of diacerein cream formulation with herbal extract.

Parameters evaluated	**Study Period**			
	1st Reading	**2nd Reading**	**3rd Reading**	**Average**
pH ± SD	6.65± 0.6	6.74± 0.46	6.81± 0.351	6.73± 0.44
Spread ability (g/sec)	4.75	5.53	6.25	5.51
Tube Extrude ability (g)	185	190	195	190

Our data indicates that the topical cream formulation of Diacerein with Curcuma longa extract releases 91.51% of the drug over a 24-hour period. The in-vitro drug diffusion study shows that this cream effectively controls drug release for an extended duration. This controlled release helps minimize fluctuations in drug levels and can also reduce the overall cost of therapy (**Table 4**). The results from the Accelerated Stability studies indicate that the formulated cream performs optimally at 22 ± 1°C, with the percentage of the drug remaining unchanged by no more than 10% . the percentage remaining of drug content at zero time, 1 month, 2 months and 3 months are given in **Tables 5, 6, 7 and 8** respectively. At this temperature, the standard deviation after three months was minimal and within the acceptable range. Conversely, at 40°C and 60°C, the standard deviation was higher and deviated from the normal range. Therefore, it can be concluded that the cream formulation meets the stability criteria for pharmaceutical creams when stored at 22 ± 1°C (**Figure 1**).

Table 3: Viscosity of diacerein cream formulation (cPs) at different rpm.

Speed in rpm	1st Reading	2nd Reading	3rd Reading	Average
2.5	65187	65235	65235	65219
4.0	34470	34697	34846	34671
5.0	25953	26123	26547	26208
10	14110	14735	15174	14673

Table 4: *In Vitro* drug diffusion study over period of 24 hours.

Time (Hours)	Percentage of drug release
0.0	0.0
0.5	10.73
1.0	18.77
2.0	30.85
4.0	41.12
6.0	51.33
8.0	72.41
10.0	85.62
12.0	89.22
24.0	91.51

Table 5: Percentage remaining of drug content at zero time.

Absorption of Standard	Absorption of Sample	% age of active drug in the sample	Mean	Standard Deviation
0.625	0.623	99.28%	0.624	0.001

Table 6: Percentage remaining of drug content after 1 month.

Temperature	Absorption of Sample	Percentage of active drug in the sample	Mean	Standard Deviation
At 22 ± 1°C	0.617	98.32%	0.621	0.005
At 40± 1°C	0.612	97.52%	0.618	0.009
At 60 ± 1°C	0.610	97.20%	0.617	0.010

Table 7: Percentage remaining of drug content after 2 months

Temperature	Absorption of Sample	Percentage of active drug in the sample	Mean	Standard Deviation
At 22 ± 1°C	0.597	95.04%	0.611	0.019
At 40± 1°C	0.585	93.22%	0.61	0.028
At 60 ± 1°C	0.581	92.58%	0.603	0.031

Table 8: Percentage remaining of drug content after 3 months.

Temperature	Absorption of Sample	Percentage of active drug in the sample	Mean	Standard Deviation
At 22 ± 1°C	0.581	92.58%	0.603	0.031
At 40± 1°C	0.547	87.16%	0.586	0.055
At 60 ± 1°C	0.543	86.53%	0.584	0.057

Table 9: Mean paw oedema volume and %age inhibition of oedema in albino rabbits.

Parameters		Mean	Standard Deviation	Standard Error Mean	P value	Inference
VAS scale	Before	7.321	0.9449	0.1786	$2.48\ e^{-14}$	Extremely Significance
	After	4.75	1.1746	0.2220		
Lequesne scale	Before	6.00	1.0540	0.1992	$5.9\ e^{-12}$	Extremely Significance
	After	4.214	1.0923	0.2064		

Table 10: Paired T-test table for diacerein cream.

Time (Hours)	Mean paw edema volume	%age inhibition of edema
0	0.204	24.36
1	0.163	37.59
2	0.103	63.08
3	0.097	70.72
4	0.096	73.41
5	0.099	74.54
6	0.105	75.56

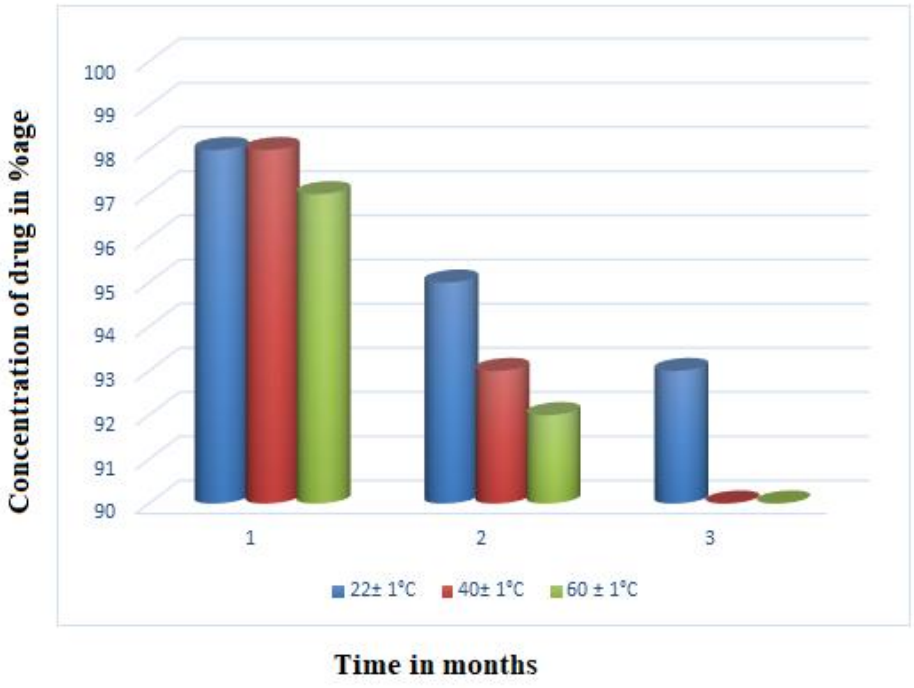

Figure 1: A graphical representation between percentage of drug concentration and time in months.

Figure 2: Rabbit skin - on application of diacerein cream.

The anti-inflammatory study results demonstrated a notable reduction in mean paw oedema volume following the application of the topical formulation. All rabbits treated with the test product showed a decrease in paw volume (inflammation) and an increase in the percentage of inflammation inhibition. Furthermore, the skin irritation test indicated no signs of erythema or oedema in albino rabbits at 24, 48, and 72 hours after cream application (**Figure 2**).

Efficacy of Diacerein Cream in Osteoarthritis

The study initially enrolled thirty human volunteers. However, four patients were withdrawn, resulting in data from twenty-six participants being included in the final analysis.

The VAS scale decreased from 7.321 ± 0.9449 to 4.75 ± 1.146 (Mean ± SD), and the Lequesne scale dropped from 6.0 ± 1.054 to 4.21 ± 1.0923, with both changes being statistically significant. The Diacerein cream resulted in a reduction of 2.57 on the VAS scale, which is greater than the 1.5 level reduction reported by Dr. B Mehdi. The Lequesne scale decreased by 2.17, slightly less than the 2.50 level reduction observed by Ashish Prasad. Overall, the Diacerein cream showed a significant reduction in both the VAS and Lequesne scales, demonstrating its effectiveness in treating knee osteoarthritis. Additionally, no adverse events were reported, indicating that the cream is safe for use in this condition.

CONCLUSION

The cream formulation was designed to minimize direct contact of the active drug with the stomach wall, thereby potentially reducing the risk of gastric mucosal damage associated with solid NSAID dosage forms. This formulation combines Diacerein, a potent disease-modifying agent, with Curcuma longa, which is renowned for its strong anti-inflammatory properties. Diacerein is effective in managing pain and inflammation in conditions such as rheumatoid arthritis and osteoarthritis, while Curcuma longa enhances these anti-inflammatory effects **[24]**. The results indicate that the 3% Diacerein and 1% Curcuma longa cream is a viable option for topical application, demonstrating performance comparable to existing marketed products.

Acknowledgments

The authors acknowledge the Department of Pharmaceutics, Faculty of Pharmacy for provision of facilities to carry out present research work., Lipoid, Switzerland for phospholipids as a gift material for my research work.

Author(s) Contribution*:* Methodology, analysis, review and submission, M. Raziullah.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

***Ethical* Approval:** Approval for the animal study was taken from IRB committee, Faculty of Pharmacy, The Superior University dated April 10, 2024.

Conflict of Interest: The authors declare no potential conflict of interest.

Consent for Publication: All authors approved the manuscript for publication.

REFERENCES

1. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. The Lancet. 2005 Mar 12;365(9463):965-73. doi:0140-6736(05)71086-2/abstract
2. Altman RD. Criteria for classification of clinical osteoarthritis. The Journal of rheumatology. Supplement. 1991 Feb 1;27:10-2. https://doi.org/10.1016/0049-0172(91)90026-v
3. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis and cartilage. 2007 Sep 1;15(9):981-1000. https://doi.org/10.1016/j.joca.2007.06.014
4. Blandizzi, C., et al. "Role of coxibs in the strategies for gastrointestinal protection in patients requiring chronic non-steroidal anti-inflammatory therapy." Pharmacological research. 2008. 59(2): 90-100. https://doi.org/10.1016/j.phrs.2008.11.004
5. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. ACC Current Journal Review. 2002;1(11):15. doi:10.1001/jama.286.8.954
6. Bellamy NI, Kirwan J, Boers M, Brooks P, Strand VI, Tugwell P, Altman R, Brandt K, Dougados MA, Lequesne

MI. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol. 1997 Apr 1;24(4):799-802. https://doi.org/07.1014/j.jra.2007.04.014

7. Hunter DJ, Le Graverand-Gastineau MP. How close are we to having structure-modifying drugs available?. Rheumatic Disease Clinics of North America. 2008 Aug 1;34(3):789-802. https://doi.org/10.1016/j.rdc.2008.05.003
8. Boittin M, Redini F, Loyau G, Pujol JP. Effect of diacerhein (ART 50) on the matrix synthesis and collagenase secretion by cultured joint chondrocytes in rabbits. Revue du Rhumatisme (Ed. Francaise: 1993). 1993 Jul 1;60(6 Pt 2):68S-76S. https://doi.org/10.1034/j.1600-0773.2003.910104
9. Bartels EM, Bliddal H, Schøndorff PK, Altman RD, Zhang W, Christensen R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis and cartilage. 2010 Mar 1;18(3):289-96. https://doi.org/10.1016/j.joca.2009.10.006
10. Pujol JP, Chadjichristos C, Legendre F, Baugé C, Beauchef G, Andriamanalijaona R, Galéra P, Boumediene K. Interleukin-1 and transforming growth factor-ß 1 as crucial factors in osteoarthritic cartilage metabolism. Connective tissue research. 2008 Jan 1;49(3-4):293-7. https://doi.org/10.1080/03008200802148355
11. Franchi-Micheli S, Lavacchi L, Friedmann CA, Zilletti L. The influence of rhein on the biosynthesis of prostaglandin-like substances in-vitro. Journal of Pharmacy and Pharmacology. 1983 Apr;35(4):262-4. https://doi.org/10.1111/j.2042-7158.2003.tb02929
12. Petrillo M, Montrone F, Ardizzone S, Caruso I, Porro GB. Endoscopic evaluation of diacetylrhein-induced gastric mucosal lesions. Current therapeutic research. 1991;49(1):10-5. https://doi.org/10.1016/j.joca.2001.10.006
13. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta medica. 1991 Feb;57(01):1-7. DOI: 10.1055/s-2006-960004
14. Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. International journal of clinical pharmacology, therapy, and toxicology. 1986 Dec 1;24(12):651-4. https://doi.org/10.3390/molecules16064567
15. Prasad V, Dorle AK. Evaluation of ghee based formulation for wound healing activity. Journal of ethnopharmacology. 2006 Aug 11;107(1):38-47. https://doi.org/10.1016/j.jep.2006.02.006
16. Wood JH, Catacalos G, Lieberman SV. Adaptation of commercial viscometers for special applications in pharmaceutical rheology II: severs extrusion rheometer. Journal of Pharmaceutical Sciences. 1963 Apr 1;52(4):375-8. https://doi.org/10.1080/03639045.2003.1993889
17. Gupta GD, Gaud RS. Release rate of tenoxicam from acrypol gels. The Indian Pharmacist. 2005;4(35):69-76. https://doi.org/10.1016/j.jep.2005.04.006
18. Chakole CM, Shende MA, Khadatkar SN. Formulation and evaluation of novel combined halobetasol propionate and fusidic acid ointment. Int. J. Chem. Tech. Res. 2009 Jan;1(1):103-16. https://doi.org/10.3109/08982104.2009.843192
19. Umadevi SK, Ravi P, Kusumanchi RR, Muthuprasanna P, Lakshmi PK. The effects of polymers and permeation enhancers on in vitro release of aceclofenac from topical gel formulations. Biosciences Biotechnology Research Asia. 2016 Feb 10;5(1):237-44. https://doi.org/10.1081/DDC-100108371
20. Alexander KS, Thyagarajapuram N. Formulation and accelerated stability studies for an extemporaneous suspension of amiodarone hydrochloride. International journal of pharmaceutical compounding. 2003 Sep 1;7(5):389. https://doi.org/10.1016/j.pharma.2003.02.001
21. Shinde Anilkumar J, Bhise Satish B, Jarag Ravindra J, Jadhav Namdeo R. Preparation of cream containing Tridax paocumbens, Curcuma lomga and Azadirachta indica and its evaluation for wound healing property. The Indian Pharmacist. 2005;4(41):107-10. https://doi.org/10.1002/ptr.931
22. Nakhat PD, Rathi LG, Yeole PG. Development and evaluation of sorbitan monostearate organogels of ibuprofen. Indian Drugs-Bombay. 2006;43(5):421. 10.1007/s100670050025
23. Dalal B, Kubavat A, Kshatriya RR. A randomized, active controlled, clinical trial to assess the efficacy and safety of celecoxib+ diacerein fixed dose combination in adult Indian patients suffering from osteoarthritis. IJMHS. 2012;2(2):31-4. https://doi.org/10.1093/rheumatology/keh121
24. Prasad A, Mahajan M, Chaturvedi A. Oxaceprol in the Management of Osteoarthritis. The Indian Practitioner. 2012;65(10):631-4. https://doi.org/10.1006/phrs.2012.0051