



Magnesium Glycinate as an Adjunct to Diclofenac: A Dual-Action Strategy for Rheumatoid Arthritis Management

Ankita Patel¹, Dr. Harshita Jain²

¹M. Pharm. Student, ²Professor

^{1,2}Adina Institute of Pharmaceutical Science, Sagar-470001, M.P. India

Abstract : Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder characterized by persistent joint inflammation, pain, swelling, functional impairment, and progressive destruction of cartilage and bone. The present study investigated the potential of magnesium glycinate as an adjunct to diclofenac sodium for improving analgesic and anti-arthritis responses in complete Freund's adjuvant (CFA)-induced arthritis in rats. Experimental arthritis was induced using CFA, followed by treatment with diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), or their combination. Analgesic activity was evaluated using the tail-flick test, while anti-arthritis activity was assessed through measurements of paw oedema, paw diameter, body weight, and visual arthritis score during the 21-day experimental period. Rheumatoid factor (RF) and total white blood cell (WBC) count were determined at the end of the study, and histopathological examination of ankle joints was performed to evaluate inflammatory and structural changes. Diclofenac sodium and magnesium glycinate individually produced significant improvements in arthritic parameters compared with the arthritic control. The combination treatment produced the greatest reduction in paw oedema, paw diameter, and visual arthritis score, with significant effects particularly during the later stages of treatment and maximum responses at the end of the study ($p < 0.0001$). The combination also significantly improved body weight from Day 14 ($p < 0.001$) and produced greater reductions in RF and WBC counts ($p < 0.0001$). In the tail-flick test, combined treatment produced the greatest increase in pain-response latency, with maximum activity at 120 min and sustained effects up to 180 min. Histopathological findings demonstrated reduced inflammatory-cell infiltration, preservation of cartilage and bone architecture, reduced pannus formation, and improved joint morphology in the combination group. Overall, magnesium glycinate demonstrated promising complementary anti-inflammatory and analgesic activity when administered with diclofenac sodium in experimental arthritis, supporting further investigation of this adjunctive therapeutic strategy through mechanistic, safety, pharmacokinetic, and clinical studies.

IndexTerms - Rheumatoid arthritis; magnesium glycinate; diclofenac; NSAID; oxidative stress; CRP; TNF- α ; IL-6; inflammation; antioxidant; adjunct therapy.

I. INTRODUCTION

Rheumatoid arthritis is a systemic autoimmune inflammatory disease predominantly affecting synovial joints. Persistent activation of immune and stromal cells leads to production of inflammatory mediators, synovial hyperplasia, cartilage degradation, osteoclast activation, and progressive structural damage. In addition to joint manifestations, chronic inflammation contributes to fatigue, cardiovascular complications, metabolic abnormalities, and deterioration of quality of life. Current RA treatment is based on early initiation of disease-modifying antirheumatic drugs and a treat-to-target strategy. EULAR recommendations state that DMARD therapy should begin as soon as RA is diagnosed, with the therapeutic target being sustained remission or low disease activity and regular monitoring of disease activity [1-2].

NSAIDs such as diclofenac remain useful for symptomatic management because they can provide relatively rapid reduction of pain and inflammation. Diclofenac inhibits cyclooxygenase-dependent prostaglandin synthesis and consequently decreases inflammatory pain and tissue edema. Nevertheless, NSAIDs do not suppress the fundamental autoimmune mechanisms responsible for RA progression. The long-term use of NSAIDs is also constrained by gastrointestinal, renal, hepatic, and cardiovascular safety considerations. Therefore, a therapeutic approach that provides complementary anti-inflammatory activity without simply increasing NSAID exposure could be valuable [3-4].

Magnesium is an essential divalent cation involved in numerous biological processes. It participates in ATP metabolism, protein synthesis, membrane transport, neuromuscular activity, and intracellular signaling. Increasing evidence has investigated the association between magnesium status and inflammatory processes. Magnesium glycinate is an organic magnesium preparation in which magnesium is associated with glycine. Its use may provide a practical approach for magnesium supplementation because organic magnesium salts have generally demonstrated favorable absorption characteristics [5-6].

The present study therefore proposes a dual-action approach in which diclofenac provides direct prostaglandin-mediated anti-inflammatory and analgesic activity while magnesium glycinate potentially influences broader inflammatory and oxidative pathways.

II. MATERIALS AND METHODS

A. Materials

Diclofenac sodium was procured from Torrent Pharmaceuticals, India, while magnesium glycinate was obtained from SD Dine Chemicals, India. Complete Freund's adjuvant was purchased from Sigma-Aldrich, USA, and methanol and carboxymethyl cellulose (CMC) were obtained from CDH Chemicals Pvt. Ltd., India. Catalase was also procured from CDH Chemicals Pvt. Ltd., India. Carrageenan was purchased from TCI Chemicals, while formic acid was obtained from Merck Specialties Pvt. Ltd., India. All chemicals and reagents were of analytical grade and were used as received without further purification.

B. Animals

Healthy adult Wistar rats of either sex, weighing 150-200g will be used as experimental animals. Animals will be obtained from the animal house of Adina Institute of Pharmaceutical Sciences, Sagar, M.P. The animals will be subjected to conventional settings, such as a 12-hour light-dark cycle, a temperature of 25°C, and a week of acclimatization before the experiment. The rats will be housed in appropriate cages and provided with a standard pellet diet (Lipton India Ltd, Mumbai, India) and water *ad libitum*. All experimental conditions and animal care will be adhere to IAEC and CCSEA guidelines.

C. Study Design

The experimental study was conducted using Complete Freund's Adjuvant (CFA)-induced rheumatoid arthritis in Wistar rats. Animals were randomly divided into 3 groups, each comprising 3 animals ($n = 3$). All treatments were administered orally once daily throughout the study period. Diclofenac sodium was suspended in 0.5% w/v carboxymethyl cellulose (CMC), while magnesium glycinate was dissolved in distilled water immediately before administration. The control groups received an equivalent volume of vehicle (0.5% CMC) [7-10].

Rheumatoid arthritis was induced by a single subplantar injection of 0.1 mL Complete Freund's Adjuvant into the left hind paw of animals in Groups I–III. Following arthritis induction, animals were treated according to their respective group allocations for 21 consecutive days.

Group I received diclofenac sodium at a dose of 10 mg/kg body weight. Group II received magnesium glycinate at a dose of 100 mg/kg body weight. Group III received a combination treatment consisting of diclofenac sodium (10 mg/kg) and magnesium glycinate (100 mg/kg) (Table 1).

The anti-arthritic efficacy of the treatments was evaluated by assessing paw edema, arthritis score, body weight changes, hematological parameters, inflammatory cytokines, oxidative stress biomarkers, radiographic alterations, and histopathological changes in joint tissues. The combination therapy was compared with monotherapy groups to determine the potential synergistic effects of magnesium glycinate as an adjunct to diclofenac in the management of rheumatoid arthritis [11-13].

D. Preparation of Doses

Diclofenac sodium and magnesium glycinate formulations were freshly prepared each day prior to administration to ensure stability and uniformity of dosing. The following dosages were made at 5 mL/kg (1 mL for 200g animal). 100mg of Diclofenac sodium was accurately weighed and suspended in 0.5% w/v carboxymethyl cellulose (CMC) solution prepared in distilled water (10ml) to obtain the 10mg/ml concentration for oral administration. The suspension was stirred continuously using a magnetic stirrer until a homogeneous dispersion was achieved [14].

1.0g of Magnesium glycinate was separately weighed and dissolved in distilled water (10ml) to obtain a clear solution corresponding to the 100mg/ml dose. In cases where complete dissolution was not achieved, the formulation was sonicated for 5–10 minutes to ensure uniform dispersion. The prepared solution was protected from direct light and used within the same day [15-16].

For the combination treatment group, diclofenac sodium suspension and magnesium glycinate solution were prepared separately and administered orally in sequence at their respective doses. The dosing volume was maintained at 10 mL/kg body weight for all experimental groups to ensure uniform administration conditions. Dose calculations were performed individually based on the most recent body weight measurements of each animal.

The doses selected for the study were 10 mg/kg body weight for diclofenac sodium and 100 mg/kg body weight for magnesium glycinate, administered once daily by oral gavage using a stainless-steel feeding needle. The formulations were gently shaken before each administration to maintain homogeneity and ensure accurate delivery of the intended dose [17]. All formulations were prepared under aseptic laboratory conditions and stored at room temperature until use on the day of preparation [18-19].

E. Analgesic Activity (Tail Flick Method)

An analgesiometer was used to measure the analgesic effect in rats. A nichrome wire within the instrument was heated by passing current through the bare nichrome wire at a consistent strength (4 Amps). The rat was restrained, with only its tail sticking out. The center of the tail was positioned on the platform. The animal's sudden, recognizable flick or tail rising in response was used to measure the animal's latency (reaction time). To prevent any tissue injury to the animal, cut-off duration of 10 seconds was planned [20-22]. On the seventh day following a one-week oral medication treatment, the response times for each animal were tested at 30, 60, 90, 120, and 180 minutes. Dose strength and dose volume for different groups given in Table 1.

Table 1: Study Design and Grouping Details for Analgesic Activity

S. No.	Group	Drug to be administered	Dose & Route of Administration	No. of animals
Group I	Diclofenac-treated	Diclofenac sodium	10 mg/kg, oral (p.o.)	3
Group II	Magnesium Glycinate-treated	Magnesium glycinate	100 mg/kg, oral (p.o.)	3
Group III	Combination-treated	Diclofenac sodium + Magnesium glycinate	Diclofenac 10 mg/kg + Magnesium glycinate 100 mg/kg, oral (p.o.)	3

F. Anti-inflammatory Activity (Inflammation Induced using Carrageenan)

After one week of oral administration, all groups except the control group received 1% w/v carrageenan (0.1 mL) injection into the rat paw. After a gap of one hour interval up to 6 hours, a digital plethysmometer (UGO Basile, Italy, Model 7140) was used to measure the paw volume. Determining the anti-inflammatory activity by calculating the quantity of suppressed oedema in relation to the control group. The following formula was used to determine the percentage of oedema inhibition: oedema (% inhibition) = $(A-B)/A \times 100$ [23-24]. In this case, A represents the paw volume of the group under control, and B represents the paw volume of the group receiving the test drug. Dose strength and dose volume for different groups given in Table 2.

Table 2: Study Design and Grouping Details for Anti-inflammatory Activity

S. No.	Group	Drug to be administered	Dose & Route of Administration	No. of animals
Group I	Diclofenac-treated	Diclofenac sodium	10 mg/kg, oral (p.o.)	3
Group II	Magnesium Glycinate-treated	Magnesium glycinate	100 mg/kg, oral (p.o.)	3
Group III	Combination-treated	Diclofenac sodium + Magnesium glycinate	Diclofenac 10 mg/kg + Magnesium glycinate 100 mg/kg, oral (p.o.)	3

G. Anti-arthritis Activity (CFA-induced Arthritis)

After injecting 0.1 mL (0.1% w/v) of killed tuberculosis mycobacterium in paraffin into the hind paw, arthritis occurred. On the fifth day, a second CFA booster was administered. The drug treatment was started on day 1 and continued for 21 days [25]. Different parameters were taken into account to observe the arthritis. When the paw of an animal that had been injected swelled at least once, it was ruled that the animal had arthritis. A digital plethysmometer was used to measure the paw volume on various days 1, 7, 14, and 21 (Panlab, LE7500 model number). The proportion of oedema in treated animals was observed in comparison to the arthritic condition, which was interpreted as an anti-inflammatory effect [26-28]. Dose strength and dose volume for different groups given in Table 3.

Table 3: Study Design and Grouping Details for Anti-arthritis Activity

S. No.	Group	Drug to be administered	Dose & Route of Administration	No. of animals
Group I	Diclofenac-treated	0.1% w/v CFA + Diclofenac sodium	10 mg/kg, oral (p.o.)	3
Group II	Magnesium Glycinate-treated	0.1% w/v CFA + Magnesium glycinate	100 mg/kg, oral (p.o.)	3
Group III	Combination-treated	0.1% w/v CFA + Diclofenac sodium + Magnesium glycinate	Diclofenac 10 mg/kg + Magnesium glycinate 100 mg/kg, oral (p.o.)	3

H. Assessment of Parameters

Body weight, paw volume, joint diameter, and visual arthritic index were assessed at predetermined intervals to monitor the progression of CFA-induced arthritis and treatment response. Relative body weight was calculated as $RBW (\%) = [BW/IB] \times 100$. Paw edema was measured using a plethysmometer, while joint diameter was measured using a Vernier caliper. Arthritis severity was scored on a 0–5 visual scale based on the extent of joint and paw inflammation, with cumulative scores representing the overall arthritic index [29-30].

On day 21, blood samples were collected under anesthesia for WBC and rheumatoid factor analysis, and serum was separated by centrifugation and stored at -80°C . At the end of the study, ankle joints were collected, fixed in 10% formalin, decalcified, processed, and stained with H&E. Histopathological examination was performed to evaluate inflammatory infiltration, synovial changes, edema, cartilage damage, and overall joint architecture [31-33].

I. Statistical Analysis for Analgesic, Anti-inflammatory and Antiarthritic Activity

The average of six animals represents all the data (mean $\pm$ SD). Group differences were examined using a one-way ANOVA, then Dunnett's multiple range test. Significant differences were reported with a, b, and c, where a indicating $p < 0.0001$, b indicating $p < 0.001$, c imply $p < 0.05$ significant differences between healthy and arthritic animals [34-35].

III. RESULTS AND DISCUSSION

A. Analgesic Activity (Tail Flick Test)

The analgesic effects of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination in CFA-induced arthritic rats are summarized in Table 4 and Figure 1. Baseline tail flick latency was comparable among the treatment groups. Diclofenac sodium significantly increased tail flick latency from 60 min, with the maximum response at 120 min. Magnesium glycinate also produced a significant increase in latency, indicating a potential role in pain modulation. The combination treatment produced the greatest increase in tail flick latency, with a significant response observed from 30–60 min and a maximum effect at 120 min that remained elevated up to 180 min. These findings indicate enhanced analgesic activity with the combined treatment compared with either agent alone.

Table 4. Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Tail Flick Latency in CFA-Induced Arthritic Rats

Group	Treatment	0 min	30 min	60 min	90 min	120 min	180 min
I	Diclofenac sodium (10 mg/kg)	1.82 ± 0.30	2.15 ± 0.34*	2.78 ± 0.42**	3.52 ± 0.46***	4.85 ± 0.51****	3.96 ± 0.48***
II	Magnesium glycinate (100 mg/kg)	1.81 ± 0.27	2.01 ± 0.29	2.34 ± 0.36*	2.89 ± 0.41**	3.68 ± 0.45***	3.21 ± 0.39**
III	Diclofenac sodium (10 mg/kg) + Magnesium glycinate (100 mg/kg)	1.83 ± 0.29	2.42 ± 0.37**	3.41 ± 0.44***	4.68 ± 0.49****	6.12 ± 0.56****	5.24 ± 0.53****

*Values are expressed as Mean ± SD (n = 3). Statistical significance was considered at $p < 0.05$, $p < 0.01$, $*p < 0.001$, and $**p < 0.0001$ compared with the arthritic control group. Tail flick latency was recorded at different intervals following treatment.

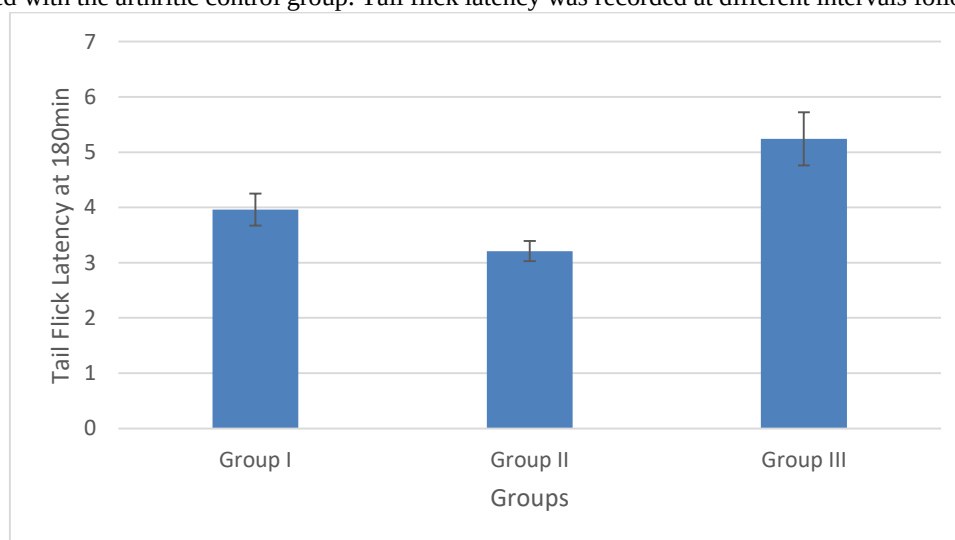


Figure 1: Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Tail Flick Latency in CFA-Induced Arthritic Rats

B. Anti-inflammatory Activity (Paw Edema)

Diclofenac sodium (10 mg/kg) significantly reduced paw edema in the carrageenan-induced inflammation model, with the effect becoming evident from Day 7 and progressively increasing through Days 14 and 21. Magnesium glycinate (100 mg/kg) also reduced paw swelling, suggesting potential anti-inflammatory and antioxidant activity. The combination of diclofenac sodium and magnesium glycinate produced the greatest reduction in paw edema, with significant inhibition from Day 7 onward and the highest inhibition on Day 21 ($p < 0.0001$), indicating an enhanced anti-inflammatory effect compared with either treatment alone.

Table 5. Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Paw Volume in Carrageenan-induced Inflammation model.

Group	Treatment	Baseline Paw Volume (mL)	Day 7 (mL)	Day 14 (mL)	Day 21 (mL)	% Inhibition on Day 21
Group I	Diclofenac Sodium (10 mg/kg)	0.52 ± 0.03	0.72 ± 0.04*	0.79 ± 0.05**	0.84 ± 0.04****	28.81±1.2
Group II	Magnesium Glycinate (100 mg/kg)	0.53 ± 0.04	0.76 ± 0.05*	0.86 ± 0.05**	0.92 ± 0.05***	22.03±1.5
Group III	Diclofenac Sodium (10 mg/kg) + Magnesium Glycinate (100 mg/kg)	0.52 ± 0.03	0.65 ± 0.04**	0.70 ± 0.04***	0.72 ± 0.03****	38.98±2.1

Values are expressed as Mean ± SD (n = 3). Statistical significance is denoted as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$ compared with the control group.

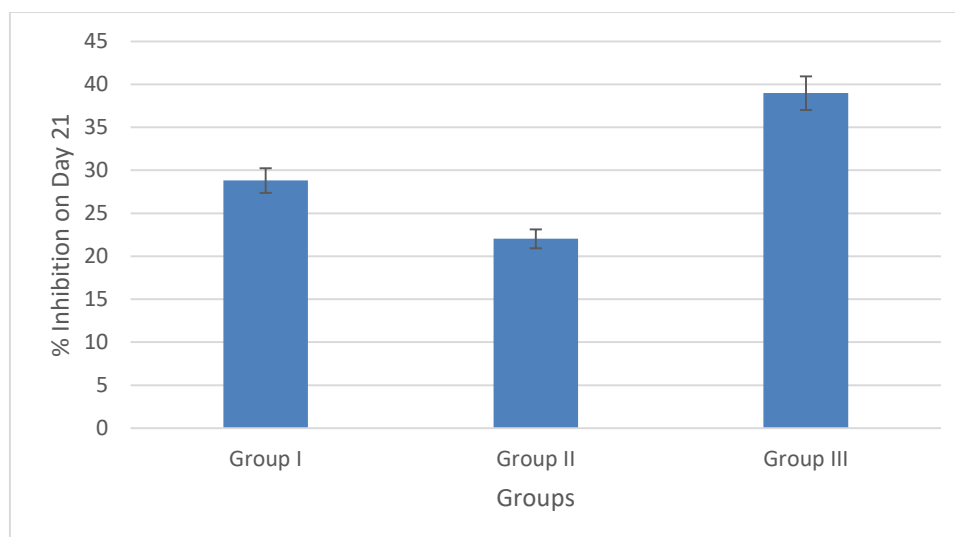


Figure 2: Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Paw Volume in Carrageenan-induced Inflammation model

C. Anti-arthritis Activity

Treatment with diclofenac sodium (10 mg/kg) moderately improved body weight compared with the CFA-induced arthritic control group, while magnesium glycinate (100 mg/kg) produced a more noticeable improvement during the later treatment period. The combination of diclofenac sodium and magnesium glycinate produced the greatest increase in body weight, becoming significant from Day 14 and reaching maximum improvement on Day 21 ($p < 0.001$). This improvement may reflect better control of inflammation and overall recovery in the combination-treated animals.

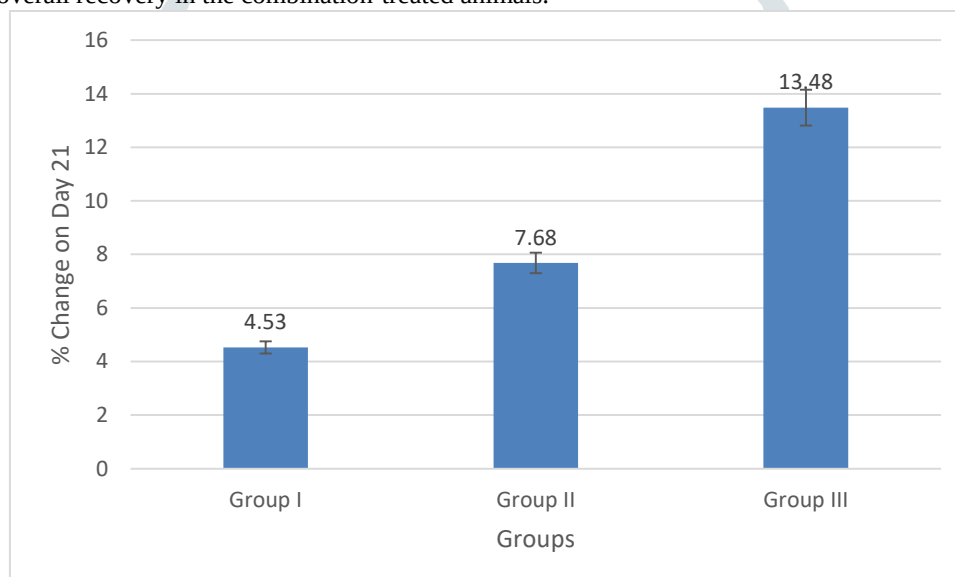


Figure 3: Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Body Weight in CFA-Induced Arthritic Rats

The anti-arthritis activity of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination was assessed by measuring paw oedema using a digital plethysmometer in CFA-induced arthritic rats (Table 7.4; Figure 7.4). Diclofenac sodium significantly reduced paw oedema, particularly on Days 14 and 21 ($p < 0.001$), while magnesium glycinate produced a significant reduction from Day 14 onward, indicating attenuation of inflammatory responses. The combination treatment produced the greatest reduction in paw oedema, with highly significant effects on Days 14 and 21 ($p < 0.0001$) and maximum inhibition at the end of the study, demonstrating enhanced anti-inflammatory and anti-arthritis activity compared with either treatment alone.

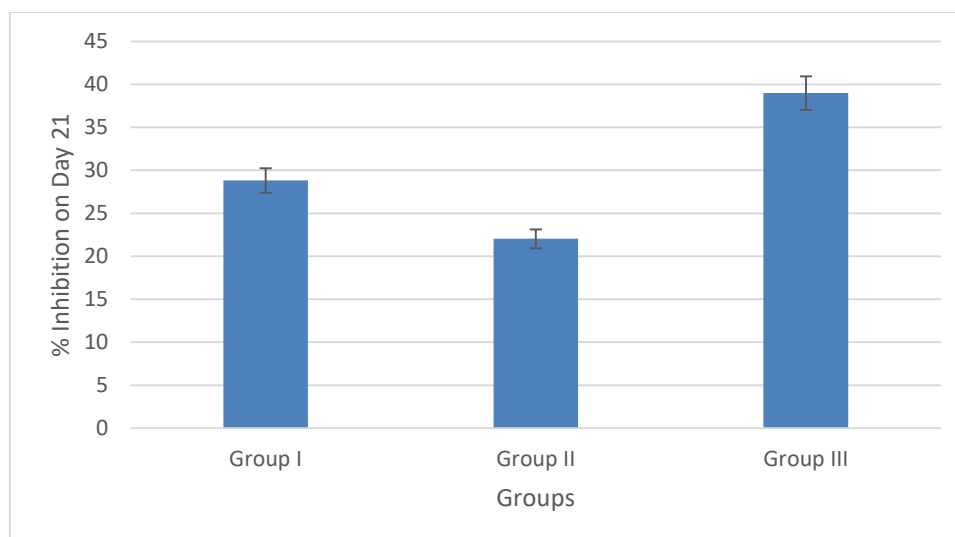


Figure 4: Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Paw Oedema in CFA-Induced Arthritic Rats.

The effects of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination on paw diameter were evaluated using a digital Vernier caliper in CFA-induced arthritic rats (Table 7.5; Figure 7.5). Diclofenac sodium significantly reduced paw swelling on Days 10, 15, and 21 ($p < 0.001$), while magnesium glycinate also produced a progressive reduction, particularly during the later stages of treatment. The combination treatment produced the greatest reduction in paw diameter, with significant inhibition from Day 10 onward and maximum effects on Days 15 and 21 ($p < 0.0001$), indicating enhanced suppression of arthritic inflammation compared with the individual treatments.

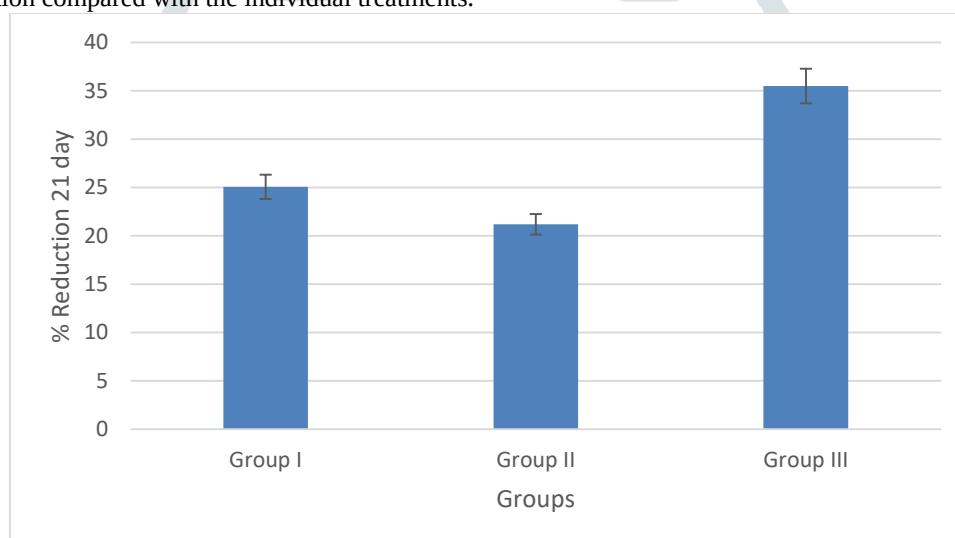


Figure 5. Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Paw Diameter in CFA-Induced Arthritic Rats

The anti-arthritic effects of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination were evaluated using a standardized visual arthritis scoring system over 21 days (Table 7.6; Figure 7.6). Diclofenac sodium significantly reduced arthritis severity at all observation intervals ($p < 0.05$), while magnesium glycinate produced a gradual reduction in arthritis scores from Day 10 onward. The combination treatment demonstrated the greatest improvement, with significant reductions on Days 10, 15, and 21 ($p < 0.0001$) and maximum improvement on Day 21, indicating enhanced control of arthritis progression compared with the individual treatments.

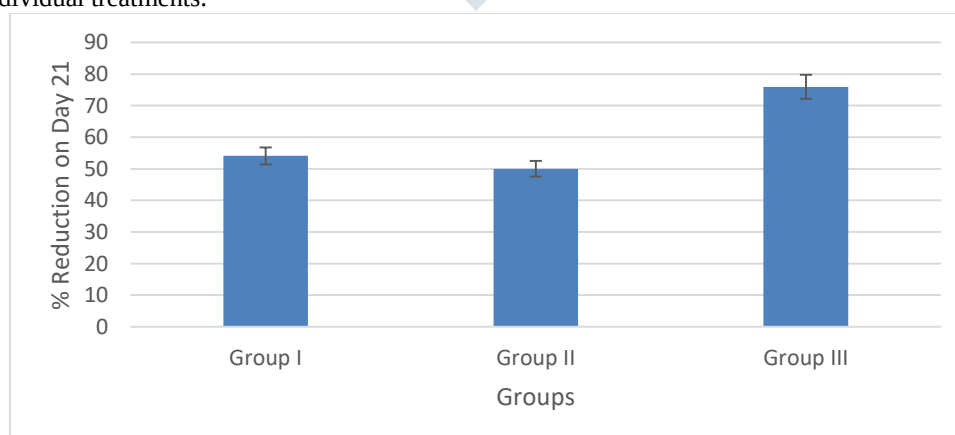


Figure 6. Graphical presentation of Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on Visual Arthritis Score in CFA-Induced Arthritic Rats

The effects of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination on rheumatoid factor (RF) levels were evaluated in CFA-induced arthritic rats (Table 7.7). Both diclofenac sodium and magnesium glycinate significantly reduced RF levels compared with the arthritic control group ($p < 0.001$), indicating attenuation of inflammatory and immunological responses. The combination treatment produced the greatest reduction in RF levels, with a highly significant effect ($p < 0.0001$), suggesting enhanced immunomodulatory and anti-inflammatory activity when magnesium glycinate was administered alongside diclofenac sodium.

The effects of diclofenac sodium (10 mg/kg), magnesium glycinate (100 mg/kg), and their combination on total WBC count were evaluated in CFA-induced arthritic rats (Table 7.8). Diclofenac sodium and magnesium glycinate significantly reduced WBC counts compared with the arthritic control group ($p < 0.001$), indicating attenuation of systemic inflammatory responses. The combination treatment produced the greatest reduction in WBC count, with a highly significant effect ($p < 0.0001$), suggesting enhanced anti-inflammatory and immunomodulatory activity compared with the individual treatments.

Table 6. Effect of Diclofenac Sodium, Magnesium Glycinate, and Their Combination on White Blood Cell Count in CFA-Induced Arthritic Rats

Group	Treatment	WBC Count ($\times 10^3$ cells/mm ³)	% Reduction vs Arthritic Control
Group I	Diclofenac Sodium (10 mg/kg)	9.12 $\pm$ 0.96***	45.88
Group II	Magnesium Glycinate (100 mg/kg)	10.38 $\pm$ 1.04***	38.40
Group III	Diclofenac Sodium (10 mg/kg) + Magnesium Glycinate (100 mg/kg)	7.85 $\pm$ 0.88****	53.41

D. Histopathological Evaluation

Histopathological examination of ankle joints showed that diclofenac sodium (10 mg/kg) and magnesium glycinate (100 mg/kg) reduced inflammatory cell infiltration and preserved cartilage and bone architecture compared with the CFA-induced arthritic control. The combination treatment produced the most pronounced protective effect, with near-normal joint architecture, minimal inflammation, reduced pannus formation, preserved joint space, and marked protection against cartilage destruction and bone erosion. These findings suggest enhanced suppression of inflammation and structural joint damage with the combined treatment.

IV. CONCLUSION

The present study demonstrated that magnesium glycinate, when administered as an adjunct to diclofenac sodium, produced enhanced analgesic and anti-arthritic effects in CFA-induced arthritic rats. Diclofenac sodium and magnesium glycinate individually improved arthritis-associated parameters, including paw oedema, paw diameter, visual arthritis score, body weight, rheumatoid factor, and WBC count. However, their combination produced the most pronounced improvements, with greater reduction in inflammatory and arthritic manifestations, improved physiological status, and enhanced pain relief. Histopathological findings further supported these observations, showing better preservation of joint architecture, reduced inflammatory-cell infiltration, and protection against cartilage and bone damage in the combination-treated group.

Overall, the findings suggest that magnesium glycinate may provide complementary anti-inflammatory, antioxidant, and immunomodulatory effects when used alongside diclofenac sodium, thereby enhancing the overall therapeutic response in experimental arthritis. The proposed adjunctive approach may have potential for improving symptomatic management while warranting further investigation. However, the observed combination effect should be interpreted as enhanced activity in the experimental model rather than established clinical synergy. Further studies involving dose optimization, mechanistic biomarkers, pharmacokinetic evaluation, long-term safety assessment, and well-designed clinical trials are required to establish the therapeutic relevance of magnesium glycinate as an adjunct to conventional NSAID therapy in rheumatoid arthritis.

V. ACKNOWLEDGMENT

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