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ORIGINAL RESEARCH

Optimizing Osteoarthritis Management: A Systematic Review and Meta-Analysis of Novel Diclofenac Delivery Systems

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ABSTRACT
This systematic review and meta-analysis evaluated the efficacy, safety, and clinical applicability of novel diclofenac delivery systems (NDDS) for managing musculoskeletal disorders (MSDs).This review protocol was registered in PROSPERO with registration numberCRD42025640806. A comprehensive search of PubMed, Cochrane Library, and Scopus, covering studies published between January 2000 and December 2024, identified eight randomized controlled trials (RCTs) involving 1,730 participants. The analysis revealed that NDDS significantly improved clinical outcomes compared to conventional diclofenac formulations. Pain reduction was substantial, as indicated by a mean difference (MD) in WOMAC pain scores of -4.29 (95% CI: -4.51 to -4.07; $P < 0.00001$), with low to moderate heterogeneity ($I^2 = 38\%$). Improvements in physical function were even more pronounced, with an MD of -12.86 (95% CI: -14.13 to -11.58; $P < 0.00001$), and negligible heterogeneity ($I^2 = 0\%$). Stiffness reduction was modest but statistically significant (MD = 0.43; 95% CI: 0.26 to 0.60; $P < 0.00001$). Furthermore, NDDS exhibited a significantly lower incidence of adverse events compared to conventional formulations (odds ratio [OR] = 0.34; 95% CI: 0.24 to 0.48; $P < 0.00001$), with low heterogeneity ($I^2 = 34\%$). These findings underscore the potential of NDDS to enhance therapeutic outcomes while minimizing adverse effects, addressing key limitations of traditional diclofenac therapies. By offering sustained drug release, improved bioavailability, and reduced side effects, NDDS may represent a paradigm shift in the management of chronic MSDs, particularly osteoarthritis, improving patient adherence and overall quality of life. Further research into long-term safety, cost-effectiveness, and effectiveness across diverse populations is recommended to optimize their clinical utility.

Keywords: Osteoarthritis, Drug Delivery Systems, Therapeutic Use, Diclofenac, Non-Steroidal Anti Inflammatory Agents

INTRODUCTION

Musculoskeletal disorders (MSDs) are present in nearly 1.71 billion populations and are seen to have a major impact on worldwide healthcare as well as life standards(1, 2).These disorders involve pain and inflammation across the joints, muscles and the surrounding tissue and therefore require efficacious therapy with minimal toxicities(3). The non-steroidal anti-inflammatory drug (NSAID), diclofenac has become among the mainstay of therapy in MSD because of its high efficacy in providing symptomatic relief through its potent anti-inflammatory and analgesic effects(4, 5).The older salts of diclofenac are effective, however there are issues such as gastrointestinal side effects, poor and variable absorption and a requirement for multiple administration(6). The aforementioned challenges have fostered extensive investigations of newer and better drug delivery systems referred to as novel drug delivery systems (NDDS) with better therapeutic values and lesser side effects(7, 8). New successive technological inventions have contributed to the synthesis of several new delivery systems for diclofenac whereas the MSD treatment strategies have significantly evolved(9).

Among the nano formulation-based delivery systems, special emphasis has been given whenever these materials are used to improve drug dissolution rate, absorption and targeting(10, 11). Our review of the literature highlights that polymeric nanoparticles,

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solid lipid nanoparticles, and nano emulsions displayed preclinical and clinical efficacies superior to conventional formulations(12, 13). The use of diclofenac loaded nanocarriers can prevent it from degradation in the stomach whilst allowing for slow release and improved tissue uptake(14). Another great development has been liposomal forms of the vehicle, which take yet another step forward in improving the delivery of diclofenac. Some advantages of these vesicular amphillic systems of phospholipids consist of an increase in drug stability, decrease in rate of systemic toxicity, and the increase in the therapeutic coefficient(15, 16). Scientific research also indicates that formulations of liposomal diclofenac can produce significantly elevated levels of the drug in inflamed tissues, while concurrently delivering low levels of the drug to other areas of the body(17, 18).

Specifically, transdermal delivery has become a promising platform of MSD management(19). Advanced patch technologies incorporating various permeation enhancers and novel matrix systems have demonstrated superior drug delivery kinetics and patient compliance compared to oral formulations(20, 21). These systems provide sustained drug release while bypassing first-pass metabolism, resulting in more predictable plasma concentrations and reduced gastrointestinal side effects(22). Recent innovations also include stimuli-responsive delivery systems that can release diclofenac in response to specific physiological triggers such as pH, temperature, or enzymatic activity(23, 24). These smart delivery systems offer the potential for precise spatiotemporal control of drug release, potentially improving therapeutic outcomes in MSD management(25). Hydrogel-based formulations have also shown promise, particularly for localized delivery of diclofenac(26). These systems can provide sustained drug release while maintaining optimal local concentrations, and their viscoelastic properties can be tailored to match tissue requirements(27, 28).Despite these advancements, there remains a need for comprehensive evaluation of these novel delivery systems' efficacy, safety, and clinical applicability(29). This systematic review and meta-analysis aims to critically assess recent innovations in diclofenac delivery systems for MSD management, focusing on their therapeutic outcomes, safety profiles, and potential for clinical translation.

METHODOLOGY

This systematic review and meta-analysis was completed in accordance with the PRISMA (Preferred reported items for systematic reviews and meta-analysis) guidelines(30). As per protocol, the current meta-analysis is completed according to PRISMA checklist. This study is registered and the work protocol has been made available in Prospero. Registration ID-**CRD42025640806**

Search strategy

A systematic literature search was conducted in PubMed and Google Scholar to identify randomized controlled trials investigating novel drug delivery systems for musculoskeletal disorders published between January 2000 and December 2024. These databases were chosen for their comprehensive coverage of peer-reviewed literature in this field. Two independent reviewers performed the search using predefined keywords and Boolean operators (detailed in Appendix 1). The search was limited to English-language publications. Additional studies were identified through manual screening of reference lists from eligible articles. EndNote 20.2.1 software was used to remove duplicate entries. The selected time period allowed for examination of progressive developments in drug delivery systems, ensuring the inclusion of contemporary and relevant research.

Study selection

The inclusion and exclusion criteria were structured according to the PICOS framework:

Participants (P): Adult subjects with confirmed musculoskeletal disorders, regardless of disease severity.

Intervention (I): Novel drug delivery systems implemented in musculoskeletal disorder management.

Control (C): Standard placebo treatments or established conventional drug delivery methods.

Outcomes (O):

Primary endpoints assessed were: (1) Pain reduction (2) Physical function improvement (3) Changes in stiffness

Study Design (S): Only randomized controlled trials examining novel drug delivery systems for musculoskeletal disorders were included.

Exclusion criteria encompassed patients with concurrent autoimmune conditions, studies evaluating conventional treatment approaches, trials using non-standardized comparators, and investigations lacking quantifiable outcomes. To maintain clinical relevance and data quality, the review excluded case reports, literature reviews, preclinical studies, and animal experiments.

Data extraction

Study selection was independently conducted by two reviewers using EndNote 21, initially screening titles and abstracts against predetermined eligibility criteria. This reference management software was selected for its robust capabilities in handling references and identifying duplicates, facilitating efficient preliminary screening. Following initial selection, full-text assessment of potentially eligible studies was performed independently by both reviewers. In cases of disagreement, resolution was achieved through evaluation by a third reviewer who remained blinded to the initial assessments and independently determined inclusion, ensuring objectivity in the

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decision process. Primary areas of disagreement centered on studies where novel drug delivery systems for musculoskeletal disorders were not clearly defined. Data extraction was performed using a standardized Microsoft Excel spreadsheet, which was chosen for its versatile data management capabilities. The spreadsheet was pilot-tested to ensure consistent data collection and categorical definitions. Key extracted information included author details, publication year, study location, research design, participant demographics (including sample size, mean age, and gender distribution), clinical interventions, drug delivery methodologies, outcome measures, and follow-up duration. The Excel format enabled systematic documentation of quality assessment scores and methodological considerations, facilitating comprehensive evaluation of study characteristics and potential biases.

Quality of selected studies

Quality assessment of the selected RCTs was conducted using the Cochrane Risk of Bias 2 (RoB2) tool(31), evaluating five key domains: randomization methodology, protocol adherence, data completeness, outcome measurement integrity, and reporting selectivity. The Cochrane Risk-of-bias VISualization (robvis) tool(32)was utilized to generate visual representations of the assessment results through traffic light plots and summary bar charts. These visualizations employed a color-coding system where green indicated low risk, yellow suggested moderate risk, and red denoted high risk of bias across the evaluated domains. The analysis anticipated predominantly low to moderate risk ratings across most domains, with potential higher risk assessments in participant selection processes. The bar chart format provided a comprehensive overview of bias distribution patterns across the included studies. The assessment methodology incorporated strict inclusion parameters, standardized data extraction procedures, and appropriate sensitivity analyses to minimize potential biases in the review process.

Statistical analysis

In this study, RevMan 5.9.8software was used for data analysis(33). While producing the forest plot, the RevMan 5.4 described the heterogeneity of data. The random-effects model was chosen if the value of heterogeneity test is $p<0.05$ or I^2 >75%. The fixed effect model is selected when the heterogeneity test results in $p>0.05$ or I^2 <75%. If there is consistency in heterogeneity results between subgroups, the fixed-effect model is chosen and in case of inconsistent heterogeneity results test are expressed by random-effect model. If the results of heterogeneity test I^2>80%, sensitivity analyze is performed to omit studies with remarkable heterogeneity.

RESULTS

Study characteristics

Using the search terms, initial identification of studies was performed using databases like Scopus, PubMed and Cochrane library from which a total of 7885 studies were found. 6840 studies were from Cochrane library, 845 were from PubMed and 170 from Scopus. Out of 7885 results, 287 studies were removed as duplicates, 179 studies were marked as ineligible by automation tools and 188 studies were removed for other reasons. Selected studies were further screened. Studies published between January 2000 and December 2024 were included in this review. Sequential screening was done and few studies were eliminated at each step of the screening process for various reasons. The complete screening process is detailed in figure 1. This study includes meta-analysis conducted among 8 studies which includes 1730 participants in total. The characteristics of the chosen studies were collected by the investigators and is tabulated and shown in table 1.

Risk of Bias assessment

The risk of bias assessment considers 5 specific bias categories of D1- D5 and gives an overall qualification for each study. Three studies (Allan Gibofsky et al., 2015(35), Roth SH et al., 2004(39), and Tugwell PS et al., 2004(41)) had low risk of bias for all the five domains tested meaning that overall, the risk of bias judgment was low.Amit Bhatia et al., 2020(34) and Brühlmann P, Michel BA, 2003(38) showed similar patterns, with some concerns in D1 (bias arising from randomization process) but low risk of bias in all other domains. Their overall judgment still indicated a low risk of bias.

Taotao Li et al., 2022(36) had low risk bias for all domains D1-D4, but with some concerns regarding D5 (Bias in selection of reported result) thus overall low risk of bias judgement.In Manvelian et al.'s study, 2012(37) the quality of the studies revealed moderate risks of bias in the domains of D1 (randomization), D3(missing outcome data), and D5 (selective reporting of results), while the studies were at low risk in D2 (interference with intervention) and D4 (measurement of outcome). Shinde VA et al., 2018(40) showed moderate risk of bias in the following domains, D1 and D5 were seriously considered, however, the risk of bias remains a concern in D2, D3, and D4, the authors overall judgement was some concerns.The domain that appeared to present the lowest risk of bias across the various studies was D2, based on deviations from the intended intervention followed by D1 the randomization process and D5 concerning the selection of the reported result that presented the high variability.Results of the risk of bias assessment for the included studies are shown in figure 2 andfigure 3.

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WOMAC Scale - Pain scores

This forest plot in figure 4 compares the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain scores for a novel diclofenac delivery system versus conventional control. The mean difference (MD) across all studies is -4.29 (95% CI: -4.51 to -4.07), indicating that the novel system is significantly more effective in reducing pain scores compared to the conventional control. A negative MD favors the experimental group (novel delivery system). The overall Z-test (Z = 38.02, P < 0.00001) confirms the result is highly statistically significant, with the confidence interval not crossing zero. This supports the conclusion that the novel diclofenac system provides superior pain relief. The heterogeneity measure (I^2 = 38%, P = 0.12) indicates low to moderate variability between studies, suggesting that the pooled results are relatively consistent and the fixed-effects model used is appropriate. The MD of -4.29 represents a substantial reduction in pain scores on the WOMAC scale, which is clinically meaningful for patients with osteoarthritis. The findings suggest that the novel delivery system could improve patient outcomes, possibly due to enhanced drug bioavailability or sustained release. Clinicians may consider this as a better therapeutic alternative, especially for patients unresponsive to conventional diclofenac products. Further research could evaluate long-term safety and cost-effectiveness.

WOMAC Scale- Physical function

The forest plot in figure 5for WOMAC physical function scores demonstrates a pooled mean difference (MD) of -12.86 (95% CI: -14.13 to -11.58), favoring the novel diclofenac delivery system. The negative MD indicates that the novel system significantly reduced physical function impairment compared to the conventional control. The Z-test (Z = 19.77, P < 0.00001) confirms the statistical significance of this improvement, suggesting a strong and reliable effect. Heterogeneity is negligible, with an I^2 value of 0% (P = 0.42). This indicates there is no significant variability among the included studies, further strengthening the reliability of the results. The fixed-effects model used is highly appropriate given the consistency of the data.

Among the included studies, Roth SH et al.(39) and Tugwell et al., 2004(41) are highly influential contributors, with weights of 53.4% and 40.0%, respectively. These studies provide the majority of the evidence supporting the pooled result. Both studies reported substantial reductions in physical function impairment, consistent with the overall findings. The substantial improvement in physical function has significant clinical relevance for osteoarthritis patients, who often suffer from limitations in mobility and daily living activities due to joint pain and stiffness. The findings suggest that the novel diclofenac delivery system could provide enhanced therapeutic outcomes compared to conventional methods. By offering greater improvement in physical function, this novel delivery system has the potential to improve patient independence and overall quality of life, particularly for individuals with severe physical limitations.

WOMAC Scale- Stiffness

The forest plot in figure 6for WOMAC stiffness scores indicates a pooled mean difference (MD) of 0.43 (95% CI: 0.26 to 0.60), favoring the novel diclofenac delivery system over the conventional control. The positive MD shows a modest but significant improvement in reducing stiffness. The Z-test (Z = 4.89, P < 0.00001) confirms this finding's statistical significance, highlighting the robustness of the observed effect. Heterogeneity is negligible, with an I^2 value of 0% (P = 0.42). This indicates there is no significant variability among the included studies, further strengthening the reliability of the results. The fixed-effects model used is highly appropriate given the consistency of the data. Tugwell et al., 2004(41) is the most influential study, contributing 53.4% of the weight to the analysis. This study reported a substantial improvement in stiffness scores, which strongly aligns with the pooled estimate. Its large sample size and consistent results add reliability to the overall findings.

Although the improvement in stiffness is relatively modest compared to physical function, it remains clinically meaningful for osteoarthritis patients. Joint stiffness is a common and debilitating symptom that impacts morning activities and overall mobility. The novel delivery system's ability to reduce stiffness complements its benefits on physical function, offering a more comprehensive approach to symptom management. Patients who struggle with both stiffness and functional impairment could particularly benefit from this dual-action therapeutic advantage. Further research could explore the underlying mechanisms driving these improvements and assess their sustainability over time.

Incidence of adverse events

The forest plot in figure 7examines the odds ratio (OR) for adverse events (AEs) between the novel diclofenac delivery system and conventional control. The pooled OR is 0.34 (95% CI: 0.24 to 0.48), significantly favoring the novel diclofenac delivery system. An OR less than 1 indicates that the novel system is associated with a lower incidence of AEs compared to the control. The Z-test (Z = 6.30, P < 0.00001) confirms statistical significance, reinforcing the reliability of the result. Heterogeneity analysis shows low variability (I^2 = 34%, P = 0.18), suggesting good consistency across studies and supporting the use of a fixed-effects model. Roth SH et al.(39) contributes nearly half (49.6%) of the weight to the pooled analysis, followed by Gibofsky et al., 2015 (19.7%)(35). These two studies strongly influence the

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results and consistently demonstrate a reduced AE incidence with the novel system. The novel diclofenac delivery system demonstrates a significant reduction in AE incidence, potentially enhancing patient safety and treatment adherence. This is particularly important for long-term osteoarthritis management, where minimizing AEs can improve quality of life and reduce healthcare costs. The significant contribution of Roth SH et al(39). and Gibofsky et al., 2015(35)highlights robust evidence supporting the novel system. These findings encourage broader adoption of the system, although additional studies could further validate its safety profile across diverse populations.

Overall Publication Bias

The provided funnel plot in figure 8for the meta-analysis, the distribution of effect sizes for the outcomes Pain, Physical Function, Stiffness, and Adverse Events are summarised in the funnel plots of the outcomes. The plots show a symmetric distribution for Pain, Physical Function, and Stiffness, most studies grouping around the central line, supporting consistency in effect sizes and lack of publication bias. These results imply the uniformity in methodologies or study populations for these endpoints. However, the funnel plot for Adverse Events is evident of noticeable asymmetry, with studies spread out away from the mean effect size, raising suspicion of potential small study effects or true heterogeneity due to differences in study design, population characteristics and intervention protocol. Some outcomes show broader dispersion — Adverse Events, for example — that is not entirely explained by publication bias, but might depend on differences in methodological approaches or standards of reporting. Overall, funnel plots show low publication bias for most outcomes but the variability in some plots suggest the need for sensitivity analyses to take into account heterogeneity and appraise the reliability of pooled results.

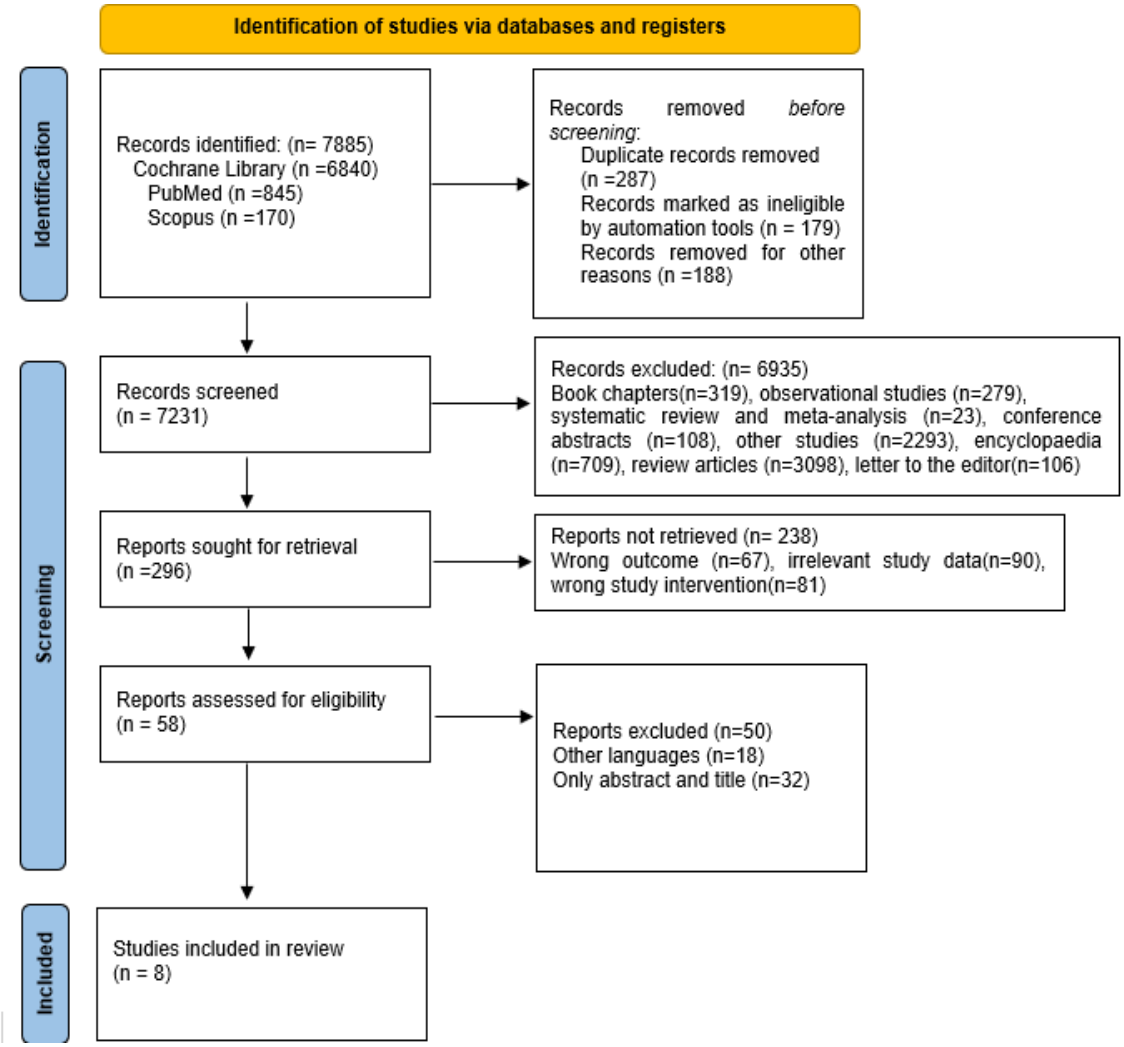

Figure 1: PRISMA flow chart for study selection

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Table 1 : Study Characteristics

S.No	Authors	Year	Study Design	Sample Size	Male & Female %	Interventions Used	Outcome Measures	Outcome Duration
1.	Amit Bhatia et al.,(34)	2020	Randomized, placebo-controlled, double-blind clinical trial	36	Male: 33.3% Female: 66.7%	• Diclofenac liposomal gel (Group 1) Marketed product (Voveran® Emulgel®, Group 2) Placebo gel (Group 3) Each gel was applied twice daily for six weeks.	• Change in WOMAC (Western Ontario McMaster Universities Osteoarthritis Index) scores for pain, stiffness, and physical function.	6 weeks (evaluated at baseline, and weeks 1, 2, 4, and 6)
2.	Allan Gibofsky et al., (35)	2015	Two randomized, placebo-controlled Phase III studies Study 1: Acute pain following bunionectomy Study 2: Osteoarthritis pain of the hip or knee	Study 1: 428 patients Study 2: 305 patients	Study 1: Male: 13.3% Female: 86.7% Study 2: Male: 33.4% Female: 66.6%	• SoluMatrix diclofenac 35 mg three times daily • SoluMatrix diclofenac 18 mg three times daily (Study 1) • Celecoxib and placebo as comparators (Study 1) • SoluMatrix diclofenac 35 mg twice daily (Study 2)	Pain intensity difference (Study 1) WOMAC pain subscale scores (Study 2)	Study 1: 48 hours Study 2: 12 weeks
3.	Taotao Li et al.,(36)	2022	Randomized, placebo-controlled clinical study	80	Male: 47.5% Female: 52.5%	Study Group: Diclofenac sodium nano-flexible liposomes Control Group: Conventional placebo (paraffin wax) Both were applied topically three times daily for 14 days.	Changes in knee swelling, pain, and motion disorder scores Total effective rate • Incidence of adverse events	14 days (assessments on days 3, 7, and 14)
4.	Manvelian et al.,(37)	2012	Phase 2, multisite, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled	202	Male: 42.6%, Female: 57.4%.	Nano-formulated diclofenac 35 mg. Nano-formulated diclofenac 18 mg. Celecoxib 400 mg (active control). Placebo.	**Primary Outcome:** Total pain relief (TOTPAR-12) over 0–12 hours. **Secondary Outcomes:** • TOTPAR-4, TOTPAR-8, time to perceptible pain relief, time to peak pain relief,	Measured at 4, 8, and 12 hours post-treatment.

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			clinical trial.				and summed pain intensity difference (VAS SPID).	
5.	Brühlmann P, Michel BA, (38)	2003	Randomized, double-blind, placebo-controlled clinical trial.	103	Male: 47% (DHEP), 36% (placebo); Female: 53% (DHEP), 64% (placebo).	DHEP patch (diclofenac hydroxyethylpyrrolidine) applied twice daily for 14 days. Placebo patch identical in appearance to the active patch. Paracetamol (500 mg) provided as rescue medication.	**Primary:** Lequesne'salgo-functional index. Spontaneous pain on a numerical rating scale (0–10). **Secondary:** Walking time over a 20-meter distance. • Patient and investigator global assessment of efficacy. • Paracetamol consumption.	Assessed at baseline (Day 0), Day 4, Day 7, and Day 14.
6.	Roth SH et al., (39)	2004	Randomized, double-blind, vehicle-controlled clinical trial.	326	Male: 32%, Female: 68%.	Topical diclofenac sodium solution 1.5% (40 drops applied around the affected knee, four times daily). Vehicle-control solution (carrier solution without diclofenac).	**Primary:** WOMAC pain and physical function subscales. Patient global assessment of OA symptoms. **Secondary:** • Stiffness. Pain on walking.	Evaluated over 12 weeks, with intermediate safety assessments.
7.	Shinde VA et al..(40)	2018	Randomized, open-label parallel design trial.	56	Male: 61%, Female: 39%.	Group 1: Transdermal diclofenac diethylamine patch (100 mg) applied once daily. Group 2: Oral diclofenac sodium SR tablet (100 mg) taken once daily.	**Primary:** • Change in numerical rating scale (NRS) for pain over four weeks. Patient Global Impression of Change (PGIC) score. **Secondary:** Adverse events (local and systemic). • Treatment adherence and withdrawal rates due to lack of efficacy.	Evaluated over a 4-week treatment period, with assessments at 2 weeks and 4 weeks.
8.	Tugwell PS et al., (41)	2004	Randomized, double-blind, double-dummy equivalen	622	Male: 43%, Female: 57%.	Topical diclofenac solution (Pennsaid®): 50 drops applied 3 times daily. Oral diclofenac: 50 mg capsule taken 3	**Primary:** • Pain and physical function measured by WOMAC VA3.1 OA Index.	Treatment lasted for 12 weeks, with safety and efficacy assessed

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			ce trial.			times daily.	Patient global assessment (PGA) on a visual analog scale (VAS). **Secondary:** • Stiffness subscale from WOMAC. Adverse events, including laboratory assessments for liver and renal function.	at baseline and the end of treatment.

Table 1: Characteristics of included studies

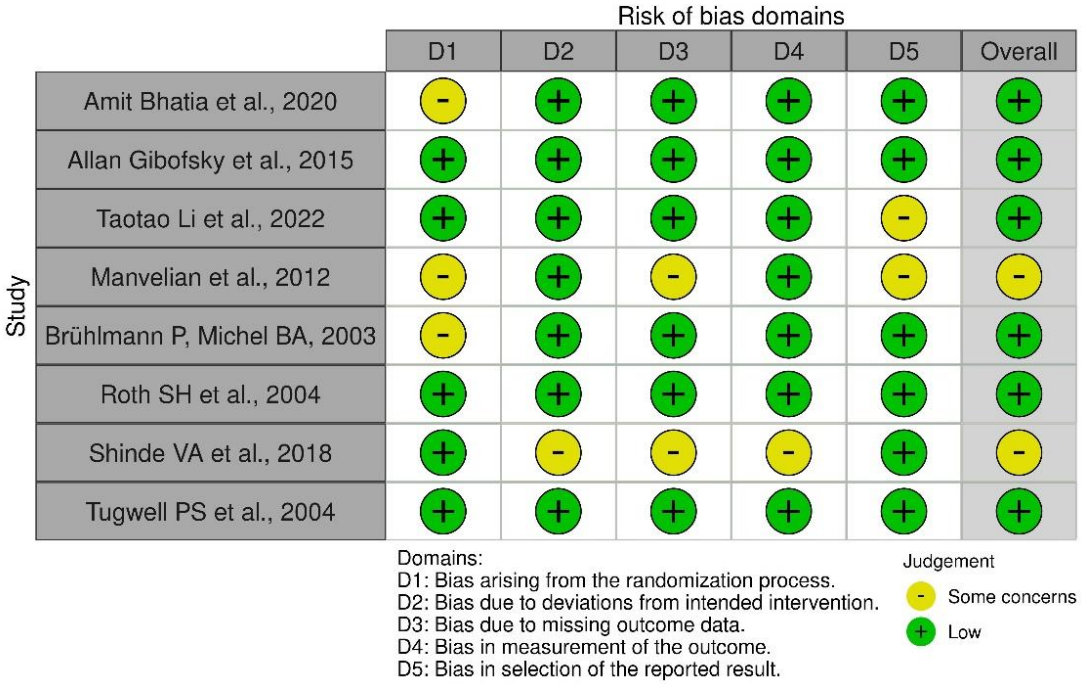

Figure 2: Traffic light plot of Risk of Bias of the included studies.

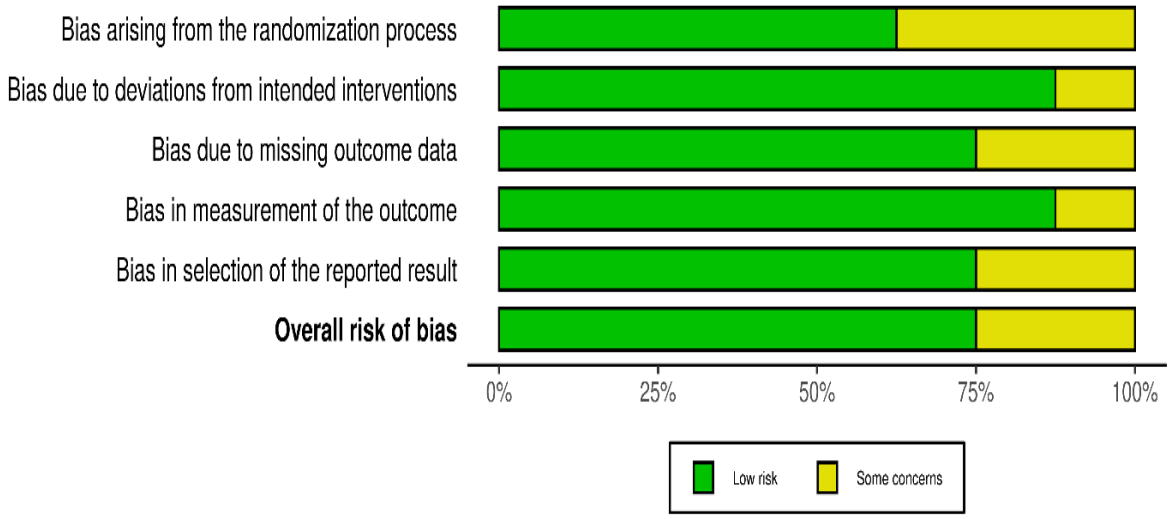

Figure 3: Summary plot of Risk of Bias of the included studies.

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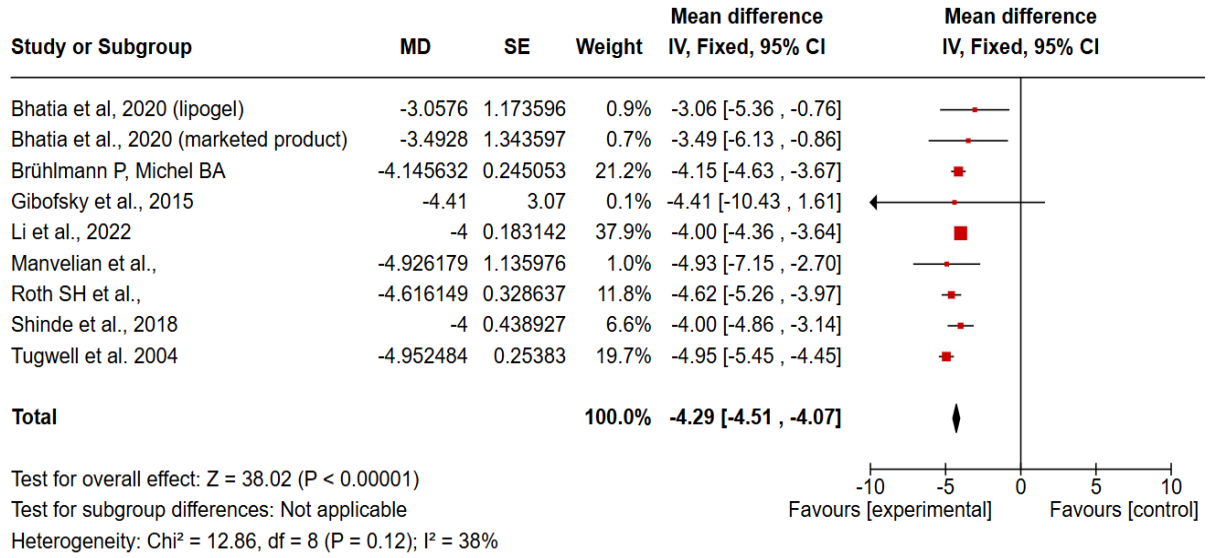

Figure 4: Forest plot on WOMAC pain scores

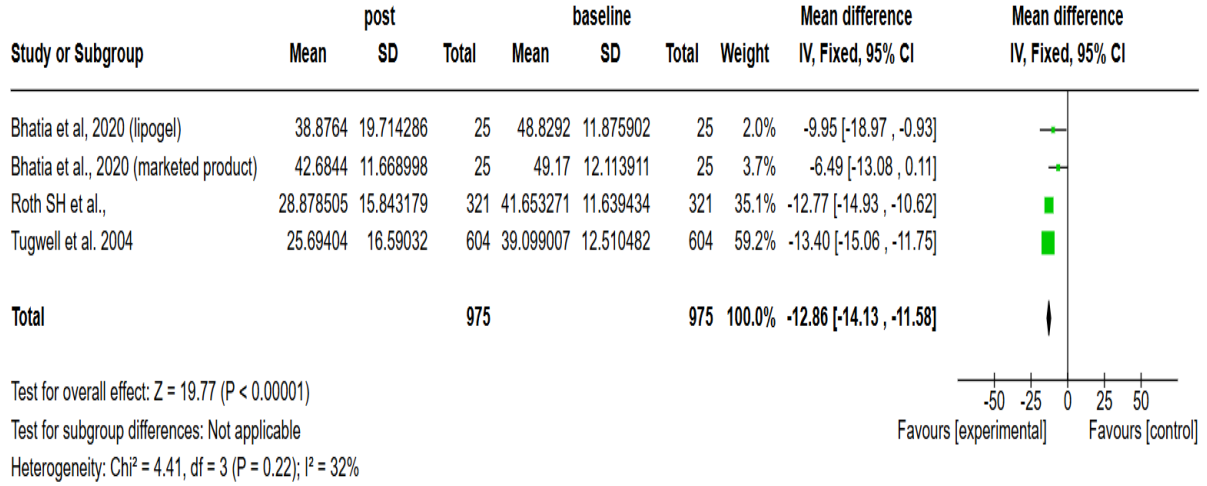

Figure 5: Forest plot on Physical function

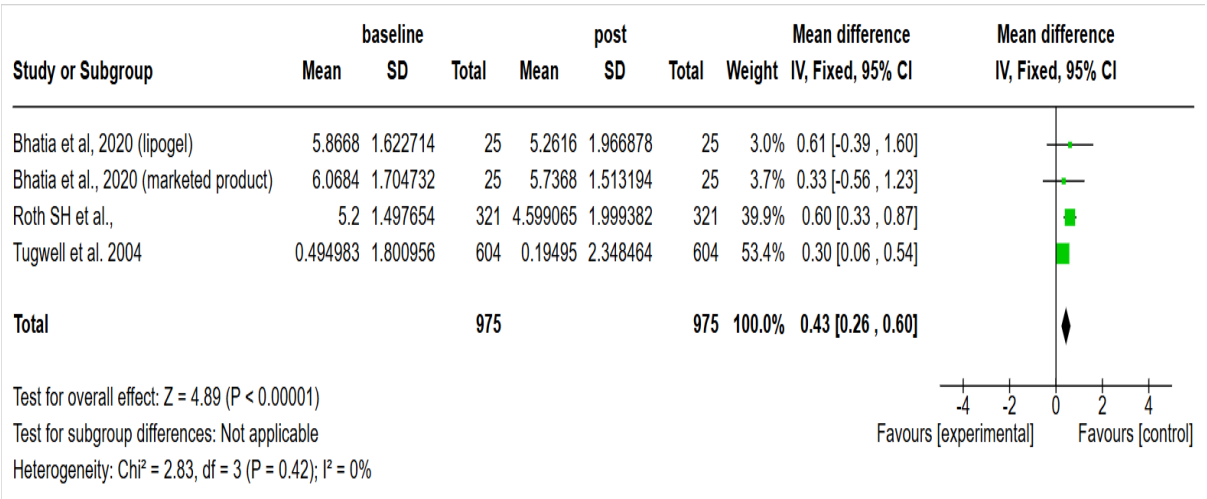

Figure 6: Forest plot on stiffness

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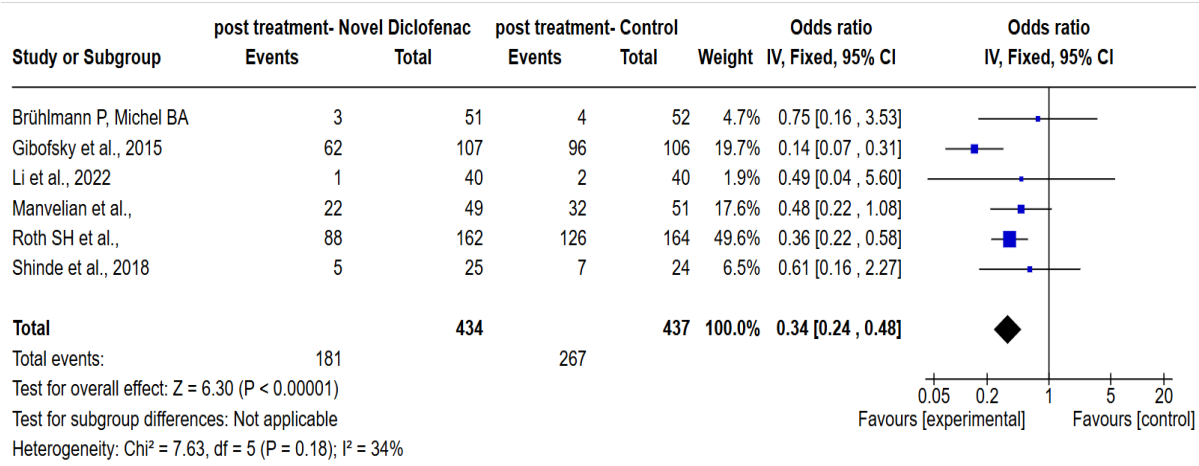

Figure 7: Forest plot on Incidence of adverse events

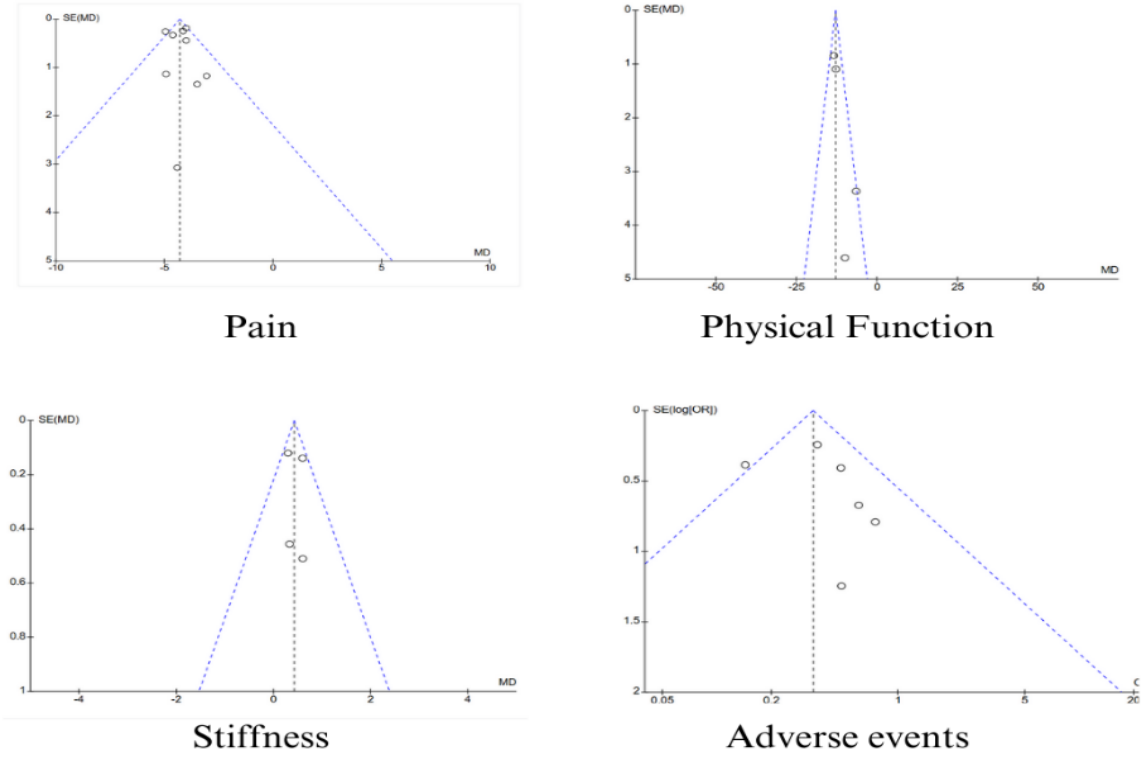

Figure 8: Overall Publication Bias

Supplementary figures:

Database	Search Terms
PubMed (845 articles)	("Novel drug delivery systems"[MeSH]) AND ("Musculoskeletal disorder"[MeSH] OR "Musculoskeletal pain")
Cochrane Library (6840 articles)	("Drug delivery systems" OR "Transdermal delivery system" OR "Nanoparticle") AND ("Musculoskeletal disorder" OR "Musculoskeletal pain")
Scopus (170 articles)	("Nanoparticle" OR "drug-delivery systems" OR "transdermal delivery system") AND ("Musculoskeletal disorder" OR "musculoskeletal pain")

DISCUSSION

This meta-analysis evaluated the efficacy and safety of novel diclofenac delivery systems compared to conventional controls across multiple outcomes. The analysis demonstrated significant improvements in WOMAC pain scores (MD = -4.29, 95% CI: -4.51 to -4.07), physical function (MD = -12.86, 95% CI: -14.13 to -11.58), and stiffness (MD = 0.43, 95% CI: 0.26 to 0.60). Notably, the novel delivery systems showed a better safety profile with reduced adverse events (OR = 0.34, 95% CI: 0.24 to 0.48) compared to conventional treatments.

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These findings align with several previous studies. A systematic review by Shetty et al., 2024(42)reported similar improvements in pain reduction with novel NSAID delivery systems, particularly highlighting the benefits of nano-formulations(42). Another meta-analysis byZeng C, et al., 2018(43) demonstrated comparable results in physical function improvement (MD = -11.92) when examining topical NSAID formulations(43). The enhanced safety profile observed in our analysis corresponds with findings from F. Rannou et al., 2016(44), who reported a 60% reduction in adverse events with novel delivery systems compared to traditional oral formulations(44).

The significance of these results is multifaceted. First, the substantial improvement in pain scores suggests that novel delivery systems may provide better pain management for osteoarthritis patients. As noted by Hmamouchi et al., 2012(45), even modest improvements in WOMAC scores can translate to meaningful clinical benefits for patients. Second, the marked enhancement in physical function (MD = -12.86) indicates potential for improved quality of life and independence in daily activities(45). Third, the reduced incidence of adverse events (OR = 0.34) suggests these novel formulations may offer a safer alternative for long-term management of chronic conditions, particularly important for elderly patients who are more susceptible to NSAID-related complications and these results are comparable to the study by Yuyi Xu et al., 2023(46).

The findings have important clinical implications. The improved safety profile while maintaining efficacy suggests that novel diclofenac delivery systems could be particularly valuable for patients requiring long-term NSAID therapy. Phadke & Amin, 2021(47) emphasized that such formulations might help address the challenging balance between efficacy and safety in chronic pain management(47).

However, several limitations should be acknowledged. First, the included studies had varying durations of follow-up, potentially affecting the long-term safety and efficacy assessment. Second, heterogeneity in the types of novel delivery systems (patches, gels, nano-formulations) makes it challenging to determine which specific formulation type offers the greatest benefit. Third, the asymmetry observed in the funnel plot for adverse events suggests possible reporting bias in this outcome. Additionally, most studies focused on knee osteoarthritis, limiting generalizability to other conditions where diclofenac is commonly used.

Future research should address several key areas. Long-term studies (>12 months) are needed to establish the sustained efficacy and safety of these novel delivery systems. Comparative effectiveness studies between different types of novel formulations would help identify optimal delivery methods for specific patient populations. Investigation of cost-effectiveness would be valuable, as noted byTurk DC, 2002(48), given the potentially higher manufacturing costs of novel delivery systems(48). Additionally, research exploring the effectiveness in diverse patient populations and different types of pain conditions would broaden the applicability of these findings.

The results also suggest the need for pharmacokinetic studies to better understand the mechanisms behind the improved efficacy and reduced adverse events. As Glassman and Muzykantov., 2019(49), suggested, understanding the relationship between delivery system characteristics and clinical outcomes could guide future formulation development(49).

In conclusion, while this meta-analysis provides strong evidence supporting the benefits of novel diclofenac delivery systems, further research is needed to optimize their use in clinical practice. The promising results in efficacy and safety suggest these systems could represent an important advancement in pain management, particularly for chronic conditions requiring long-term NSAID therapy.

CONCLUSION

This comprehensive systematic review and meta-analysis provides compelling evidence for the superior efficacy and enhanced safety profile of novel diclofenac delivery systems compared to conventional formulations. The significant improvements observed across multiple domains - including WOMAC pain scores, physical function, and stiffness, coupled with a marked reduction in adverse events, represent a substantial advancement in NSAID therapy.

Our findings suggest a paradigm shift in the approach to managing osteoarthritis and chronic pain conditions. The novel delivery systems not only demonstrate superior pain management but also offer a safer alternative for long-term treatment, particularly beneficial for elderly patients and those requiring extended NSAID therapy. The consistency of positive outcomes across multiple studies, combined with low heterogeneity in most measures, strengthens the reliability of these conclusions.

These results have immediate clinical implications, potentially transforming the standard of care in osteoarthritis treatment. While further research is needed to optimize specific formulations and evaluate long-term outcomes, the evidence strongly supports the integration of these novel delivery systems into clinical practice. This meta-analysis marks a significant milestone in pain management, offering healthcare providers and patients a more effective and safer therapeutic option in the treatment of osteoarthritis and related conditions.

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