DICLOFENAC IN OSTEOARTHRITIS: MECHANISTIC PERSPECTIVES, EVOLVING FORMULATIONS, AND COMPUTATIONAL ADVANCEMENTS

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Abstract

Diclofenac remains a widely used NSAID for osteoarthritis management due to its potent inhibition of cyclooxygenase-mediated prostaglandin synthesis. Beyond COX blockade, emerging evidence highlights its role in modulating oxidative stress, cytokines, and eicosanoid pathways. Advances in formulations—including controlled-release systems, topical preparations, prodrugs, and transdermal patches—have improved safety and patient compliance by reducing gastrointestinal and renal adverse effects. In parallel, computational approaches such as molecular docking, QSAR, and ADMET analyses have enhanced understanding of diclofenac–COX interactions and supported the rational design of safer, more effective derivatives, reinforcing its relevance in contemporary OA therapy.

Keywords: Diclofenac; Osteoarthritis; COX inhibition; Molecular modelling; QSAR; ADMET; Prodrugs; Hydrazones; Topical NSAIDs; Knee osteoarthritis

1. Introduction

Osteoarthritis represents the most prevalent chronic joint disorder, characterised by the progressive degeneration of articular cartilage, alterations in subchondral bone, osteophyte formation, and varying degrees of synovial inflammation. The resulting pain, stiffness, and functional disability significantly diminish the quality of life in affected individuals, particularly older adults and those with metabolic or mechanical risk factors [11]. NSAIDs remain the cornerstone of OA management, offering symptomatic relief through well-defined anti-inflammatory and analgesic pathways [12]. Among these, diclofenac has maintained clinical prominence since the 1970s due to its robust COX inhibitory activity, favourable therapeutic index, and availability in diverse dosage forms catering to acute and chronic phases of pain [1,3].

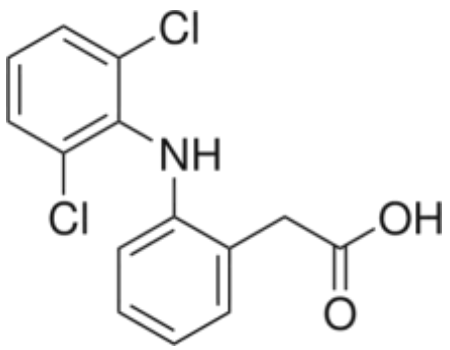

Fig. 1. Two-dimensional chemical structure of diclofenac, a phenylacetic acid derivative characterized by dichloro-substituted phenyl rings and a carboxylic acid group crucial for COX inhibition.

Despite its therapeutic efficacy, traditional oral diclofenac poses limitations due to dose-related GI toxicity, renal strain, and cardiovascular risks in susceptible populations [9,10,13]. These challenges have driven substantial innovation in medicinal chemistry and pharmaceutical formulation. Strategies to improve its safety have included modifying its molecular scaffold to yield less acidic or more selective derivatives, designing prodrugs to reduce gastric mucosal irritation, and employing delivery systems that minimise systemic exposure. Additionally, computational tools have accelerated drug optimisation by predicting pharmacokinetic behaviour and active-site interactions, supporting the development of safer and more effective analogues [7,8].This review therefore integrates classical pharmacology with modern innovations to present a comprehensive narrative on diclofenac in OA management.

2. Marketed Preparations of Diclofenac

2.1 Oral Preparations

Diclofenac sodium and diclofenac potassium remain the most widely used oral variants, typically available in strengths ranging from 25 mg to 100 mg per tablet [1]. Immediate-release diclofenac potassium offers rapid onset of analgesia, making it beneficial for acute flare-ups, whereas sustained- release and controlled-release diclofenac sodium tablets are intended for chronic OA pain where stable plasma concentrations are desired [1].

Fig . 2. Commonly available oral formulations of diclofenac include Voveran®, Voltaren®, Cataflam® and Diclofenac Potassium 50 mg which are widely used in osteoarthritis therapy.

Although these formulations effectively reduce pain and stiffness, systemic exposure is directly linked to GI

irritation, hepatotoxicity, renal compromise, and cardiovascular risk [13]. These concerns are more pronounced in elderly patients, individuals with comorbidities, or those taking concomitant antiplatelet or anticoagulant therapy. Newer oral formulations attempt to optimise pharmacokinetics, increase mucosal protection, or incorporate enteric coatings to minimise upper GI toxicity.

2.2 Topical Preparations

Topical diclofenac has gained significant clinical acceptance as a first-line option in knee and hand OA because it provides therapeutic drug levels at the site of inflammation with minimal systemic absorption [2,3].

Commercially available preparations include 1% diclofenac gel, 2–2.32% diclofenac topical solution containing dimethyl sulfoxide (DMSO), and diclofenac epolamine transdermal patches (Flector®) [5,9,48,49].

Fig. 3. Marketed topical diclofenac preparations—such as Voltaren® Gel, Pennsaid® topical solution, Voveran® Emulgel, and Dynapar® Gel—widely used for localized osteoarthritis pain management.

These formulations leverage both passive diffusion and penetration enhancers to improve dermal uptake. Metaanalyses demonstrate that topical diclofenac significantly reduces WOMAC pain scores, improves physical function, and shows a favourable safety profile compared with oral NSAIDs [6,8,9]. Because systemic exposure is minimal, topical diclofenac is preferred in older adults, patients with cardiovascular risk, and those with a history of peptic ulcer disease [12].

2.3 Parenteral Preparations

Intramuscular and intravenous diclofenac formulations are predominantly used for acute pain, perioperative analgesia, and acute musculoskeletal injuries [1].

Fig. 4. Injectable diclofenac preparations (e.g., Voveran® Injection, Dynapar AQ®, Diclomax®

Injection, and Dolonex® IM) commonly employed for acute musculoskeletal and perioperative pain.

Their rapid onset of action can be clinically useful; however, the invasive route, risk of systemic toxicity, and lack of clear benefit for chronic OA management make them unsuitable for long-term therapy.

2.4 Advanced Drug-Delivery Platforms

Recent drug-delivery advancements aim to enhance diclofenac's efficacy while reducing off-target effects. Nitrosothiol ester prodrugs have shown improved gastric tolerability by reducing direct mucosal irritation and modifying systemic COX-1 inhibition [21]. Similarly, amide-bond diclofenac analogues exhibit improved COX-2 selectivity, potentially lowering ulcerogenic risk [22,30]. Hybrid scaffolds and heterocyclic derivatives, including hydrazones and oxadiazoles, demonstrate superior anti-inflammatory potency and enhanced metabolic stability [23,24,27].

Fig. 5. Commercial diclofenac transdermal patch systems, including Flector® Patch, Olfen® Patch, Diclofenac Patch EG®, and Voltarol® 140 mg medicated patch, designed for sustained drug delivery in osteoarthritis.

Nanocarrier-based systems—including solid lipid nanoparticles, liposomes, ethosomes, and nanogels—have also improved skin penetration and sustained drug release, making them attractive for chronic OA management.

3. Mechanism of Action: COX Blockade and Auxiliary Pathways

Diclofenac's primary mechanism of action is the reversible and competitive inhibition of cyclooxygenase enzymes, COX-1 and COX-2, which catalyze the conversion of arachidonic acid into prostaglandins—key mediators of inflammation, pain, and fever [3,11,12]. By reducing prostaglandin biosynthesis, diclofenac attenuates peripheral sensitization of nociceptors, diminishes synovial inflammation, and alleviates the pain and stiffness associated with osteoarthritis [3,11]. Unlike highly COX-1-selective NSAIDs that are strongly ulcerogenic, diclofenac demonstrates a relatively balanced inhibition profile, exhibiting moderately higher affinity for COX-2 over COX-1. This selectivity contributes to potent anti-inflammatory effects while reducing —but not entirely eliminating—the risk of gastrointestinal adverse events [30,32].

Beyond classic COX blockade, emerging studies reveal that diclofenac also modulates auxiliary inflammatory pathways, contributing to its multimodal pharmacological profile. For instance, diclofenac can inhibit the lipoxygenase pathway, leading to decreased formation of leukotrienes, which are potent mediators

of leukocyte chemotaxis, vascular permeability, and tissue edema [4]. This additional pathway suppression helps attenuate inflammatory cascades that are not fully addressed by COX inhibition alone. Diclofenac has also been shown to downregulate pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-

1β), and interleukin-6 (IL-6) in synovial tissues, thereby reducing chronic inflammatory signaling in osteoarthritic joints [6,18].

Moreover, diclofenac exerts effects on nitric oxide (NO) synthase pathways and oxidative stress markers, which can further modulate inflammation and tissue injury. By reducing inducible nitric oxide synthase (iNOS) activity and reactive oxygen species production, diclofenac protects against oxidative damage and secondary inflammatory amplification [6,18]. Preclinical studies also suggest that diclofenac may inhibit nuclear factor kappa B (NF-κB) activation, a transcription factor that regulates expression of numerous inflammatory mediators, further contributing to its anti-inflammatory and analgesic properties [18].

These multimodal actions—COX inhibition, lipoxygenase interference, cytokine modulation, and oxidative stress regulation—collectively account for diclofenac's superior analgesic potency relative to many other NSAIDs and support its continued use as a first-line therapeutic agent in osteoarthritis [3,4,6,30,32]. In addition, ongoing medicinal chemistry efforts, including hydrazone and oxadiazolederivatives, aim to enhance COX-2 selectivity and further refine the anti-inflammatory profile, potentially reducing adverse effects while maintaining efficacy [27,25].

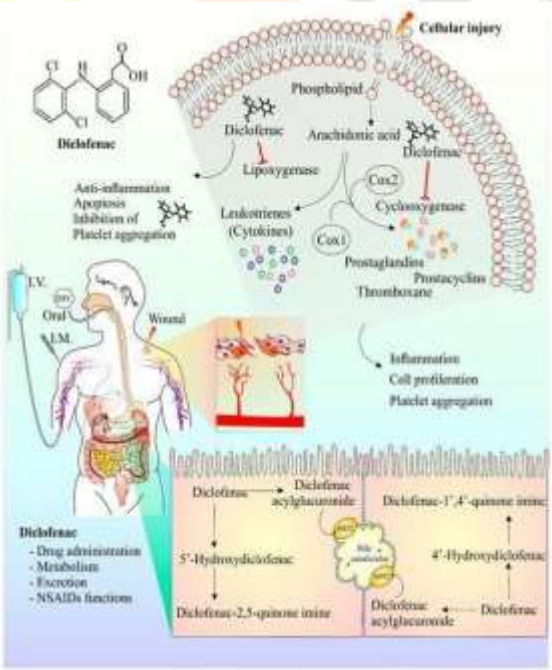

Fig . 6. A schematic representation of Diclofenac-mediated inhibition of the cyclooxygenase (COX-1 and COX2) enzymes, leading to reduced conversion of arachidonic acid into prostaglandins
responsible for pain, inflammation, and swelling in osteoarthritis.

4. Computational Modelling Approaches

4.1 Molecular Docking

Molecular docking has played a central role in elucidating diclofenac's binding orientation and energetics within COX enzymes. Studies using AutoDock Vina, CB-Dock, and COX crystal structures consistently show strong binding affinity driven by hydrophobic interactions between diclofenac's aromatic rings and the COX hydrophobic channel, alongside stabilising hydrogen bonds formed by the carboxylate group [34,36]. Enhanced docking scores for hydrazone and oxadiazole derivatives stem from additional heteroatoms capable of forming stronger hydrogen-bond networks, thereby improving interaction stability and potentially increasing COX-2 selectivity [23,9]. Docking predictions align closely with in vivo anti-inflammatory outcomes, strengthening confidence in modelling-guided drug design [23].

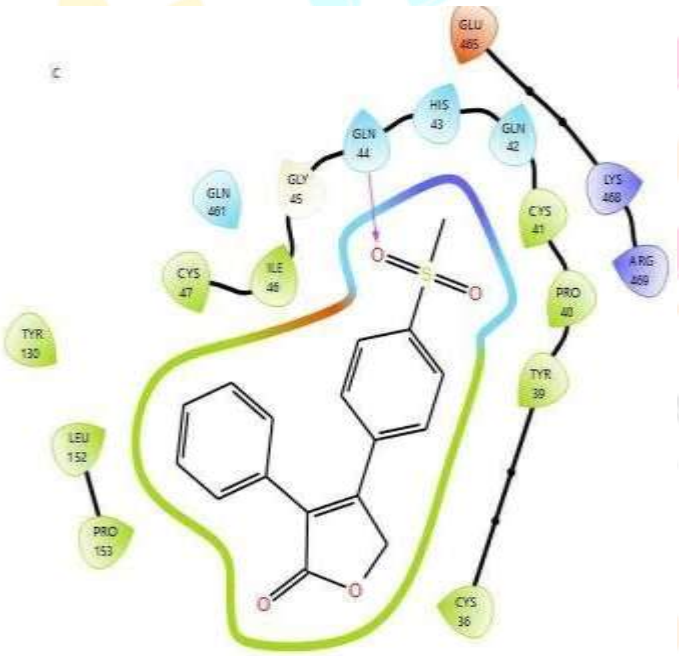

Fig . 7. A 3D docking visualization illustrating the interaction of Diclofenac with key residues in the COX-2 catalytic pocket, highlighting hydrogen bonding and hydrophobic interactions responsible for its selective inhibitory potential.

4.2 QSAR and Structure–Activity Relationships

QSAR analyses reveal that diclofenac's pharmacological activity is highly sensitive to modifications in its carboxylate group, aromatic substituents, and linker chemistry. Introduction of hydrazide or hydrazone functional groups enhances both lipophilicity and binding site complementarity, leading to superior COX affinity and anti-inflammatory properties [27]. Inclusion of oxadiazole or azetidinone rings introduces additional sites for hydrogen bonding, while side-chain modifications—such as alanyl conjugation—can reduce gastric irritation by masking the acidic centre [31]. Bulky substituents near the dichlorophenyl ring often correlate with increased COX-2 selectivity and reduced GI risk [25,30].

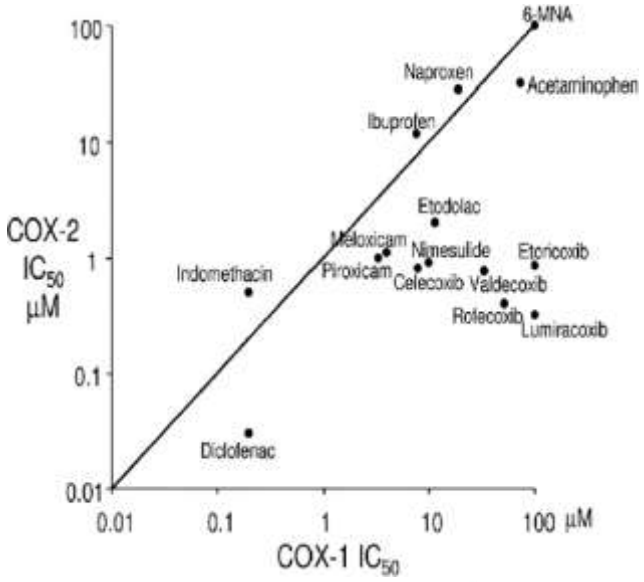

Fig. 8. Potency of NSAIDs in inhibiting COX-1 and COX-2 enzymes. Concentrations required to inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) by 50% (IC50).

4.3 ADMET Modelling

In silico ADMET predictions consistently affirm that diclofenac possesses adequate lipophilicity for membrane penetration and maintains suitable oral bioavailability parameters [39]. For newer prodrug variants, these models suggest reduced gastric mucosal irritation and improved pharmacokinetic stability, supporting GIsparing properties observed in preclinical settings [21,23]. Hydrazone derivatives also demonstrate acceptable ADME profiles with predictions indicating lower toxicity and improved metabolic compatibility, ensuring their ential suitability for chronic OA therapy.

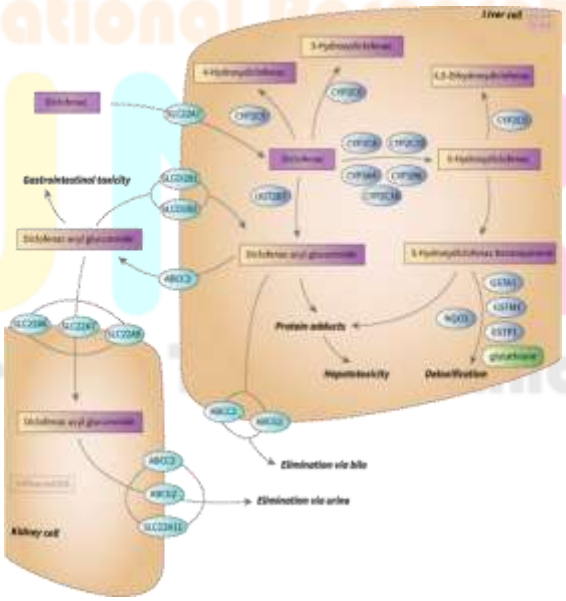

Fig. 9. Schematic representation of ADME/ADMET parameters illustrating absorption, distribution, metabolism, excretion, and toxicity processes relevant to Diclofenac and its derivative prodrugs.

5. Advances in Formulation and Therapeutic Optimization

5.1 Oral Dosage Forms

Oral diclofenac continues to be a mainstay in osteoarthritis management due to its wellcharacterized pharmacokinetics, predictable systemic absorption, and consistent analgesic and anti-inflammatory effects [14,15,19]. Clinical trials and meta-analyses indicate that daily doses of 100–150 mg provide comparable or superior pain relief and functional improvement relative to other commonly used NSAIDs such as ibuprofen, naproxen, and etoricoxib, with favorable global assessment scores [16,19]. Modified-release and sustainedrelease oral formulations of diclofenac maintain steady plasma concentrations, thereby reducing peak-related adverse events, minimizing fluctuations in analgesic effect, and improving patient adherence [14,16].

Entericcoated tablets protect diclofenac from acidic degradation in the stomach, reducing direct gastric irritation and lowering the risk of upper GI complications, especially in elderly or high-risk populations [13,14,16]. In addition, controlled-release matrices facilitate flexible dosing schedules and may limit systemic exposure to high peak concentrations, contributing to improved safety while retaining therapeutic efficacy [14, 15].

5.2 Topical Diclofenac in Knee OA

Topical diclofenac formulations—including gels, solutions, and transdermal patches—offer targeted delivery to affected joints, enabling effective local concentrations while limiting systemic absorption (typically 5–7% of oral exposure) [2,5,6,8,48,49]. Randomized controlled trials and meta-analyses consistently demonstrate that topical diclofenac significantly improves pain scores, physical function, and patient-reported quality of life in knee and hand OA [1,2,5,6,7].

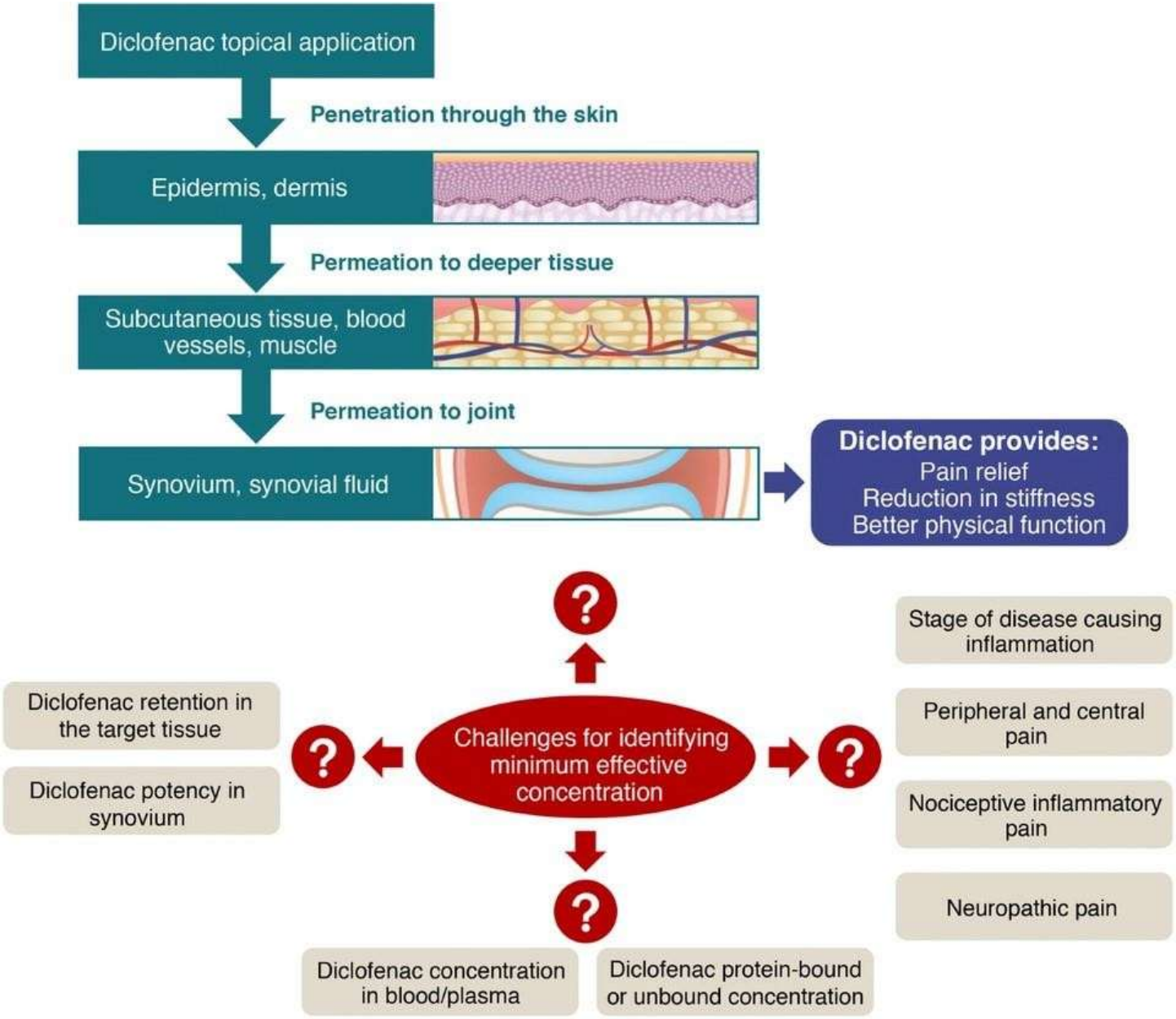

Fig . 10. Topical diclofenac gel and its transdermal delivery pathway.

5.3 Gastroprotective Prodrug Development

To address the dose-limiting gastrointestinal toxicity of conventional diclofenac, significant efforts have focused on the development of gastroprotective prodrugs and molecularly modified derivatives. Nitrosothiol ester prodrugs release nitric oxide locally in the gastric mucosa, enhancing mucosal blood flow, promoting epithelial repair, and mitigating ulceration, while preserving potent anti-inflammatory activity [21]. Non-acidic aminoalkyl diclofenac analogues and hydrazone derivatives exhibit reduced gastric irritation, improved aqueous solubility, and comparable or enhanced efficacy relative to parent diclofenac [23,27]. These structural modifications not only lower ulcerogenic potential but also enable

safer long-term therapy in OA patients, potentially expanding treatment options for high-risk populations [21,23,27].

5.4 Novel Derivatives and Nano-enabled Systems

Recent medicinal chemistry efforts have produced novel diclofenac derivatives and advanced nanocarrier systems aimed at optimizing therapeutic outcomes while minimizing adverse effects. Hydrazone and oxadiazole derivatives demonstrate high binding affinity to COX isoenzymes, strong anti-inflammatory and analgesic activity, and reduced ulcerogenic potential in preclinical models [24,25,27]. Concurrently, nano-enabled delivery platforms—including nanoemulsions, nanostructured lipid carriers, transfersomes, and polymeric nanoparticles—improve dermal penetration, achieve sustained release, and maintain local drug concentrations in synovial tissue [29,50]. These systems reduce systemic exposure, decrease dosing frequency, and enhance patient adherence, offering a dual advantage of efficacy and safety for topical OA therapy. Additionally, hybrid scaffolds and molecularly optimized analogues under investigation provide opportunities to fine-tune COX-2 selectivity, further mitigating GI and cardiovascular risks while maintaining robust analgesic effects [24,25,27]. Collectively, these advances in formulation, prodrug development, and nanotechnology represent a multidimensional strategy to enhance diclofenac therapy, particularly for long-term management of osteoarthritis.

6. SAFETY AAND TOLERABILITY OF DICLOFENAC IN OSTEOARTHRITIS

6.1 Gastrointestinal Safety

Gastrointestinal toxicity is the most frequent limitation of systemic diclofenac therapy, ranging from dyspepsia to severe complications such as ulcers, bleeding, and perforation [9,10,13]. Diclofenac- induced GI injury is primarily due to COX-1 inhibition, which reduces protective prostaglandin synthesis, impairs mucosal blood flow, and disrupts epithelial repair [3,11,12]. Strategies to reduce GI risk include co-administration with proton pump inhibitors or H2 receptor antagonists, use of topical preparations, and novel molecular approaches such as nitrosothiol ester prodrugs and non-acidic diclofenac analogues, which maintain antiinflammatory efficacy while minimizing mucosal damage [21,23,27].

6.2 Cardiovascular Safety

Long-term diclofenac therapy has been associated with increased risk of cardiovascular events, including myocardial infarction, stroke, and hypertension, particularly at high doses or in patients with pre-existing cardiovascular conditions [9,10,47]. This is thought to result from an imbalance in COX- 1/COX-2-mediated thromboxane and prostacyclin pathways, promoting platelet aggregation and endothelial dysfunction [10,30,32]. Short-term or low-dose therapy carries minimal cardiovascular risk, and careful dose management can mitigate long-term adverse outcomes [10,30].

6.3 Renal and Hepatic Safety

Renal adverse effects include reduced glomerular filtration, fluid retention, peripheral edema, and, in severe cases, acute kidney injury, particularly in patients with pre-existing renal impairment [46]. Hepatotoxicity is uncommon but may manifest as transient elevations in liver enzymes, with rare cases of clinically significant liver injury [14,15]. Routine monitoring of renal and hepatic function is recommended in high-risk patients, elderly individuals, or those on prolonged therapy [46].

6.4 Hypersensitivity and Dermatologic Reactions

Hypersensitivity reactions are rare (<0.1%) and may include urticaria, rash, angioedema, or bronchospasm [40]. Topical diclofenac may occasionally cause transient local irritation, erythema, or pruritus, generally selflimiting and not requiring discontinuation [1,2,48,49].

6.5 Advances in Safety Optimization

Recent strategies to improve diclofenac safety include molecular modifications such as hydrazone derivatives, nitrosothiol prodrugs, and non-acidic analogues, which reduce ulcerogenic potential while retaining COXinhibitory efficacy [21,23,27]. Advanced drugdelivery systems, including gels, patches, liposomes, and nanoenabled formulations, allow targeted delivery to inflamed tissues with minimal systemic exposure [2,6,29,50]. Adjunctive therapy with gastroprotective agents or natural anti- inflammatory compounds such as curcumin (BCM-95) further improves tolerability [17]. Personalized approaches, including pharmacogenomic screening for CYP2C9 and other metabolizing enzymes, may optimize dosing and reduce adverse events, enhancing overall safety in OA management [31,32].

7. EVIDENCE-BASED CLINICAL STUDIES OF DICLOFENAC IN OSTEOARTHRITIS MANAGEMENT

A substantial body of clinical evidence positions diclofenac as one of the most effective and widely validated NSAIDs for osteoarthritis (OA). Data from randomized trials, meta analysis, post-marketing studies, and formulation-based advancements consistently highlight its strong analgesic activity, favourable safety–

efficacy balance, and versatile use across different OA patient profiles [2,4,5,6,8,9,10,13,16,17,19,21,23,24,27,30,32].

7.1 Comparison of Topical and Oral Diclofenac

Randomized studies in knee OA have shown that topical diclofenac gel provides pain and stiffness relief comparable to oral diclofenac therapy (100–150 mg/day). Importantly, topical application leads to far lower systemic exposure—only about 5–7% of oral levels—resulting in fewer gastrointestinal complications and better overall tolerability, particularly in older adults or patients with digestive sensitivities [2,5,8].

7.2 Diclofenac Versus COX-2 Selective NSAIDs

Evidence from several controlled trials and network analyses demonstrates that diclofenac produces equal or better improvements in pain reduction, mobility, and global assessment compared with COX- 2-selective agents such as celecoxib and etoricoxib [4,19]. While maintaining strong anti-inflammatory action, its balanced COX profile avoids the extreme COX2 selectivity associated with elevated cardiovascular risk, though routine monitoring remains necessary [9,10,13].

7.3 Combined Use of Diclofenac and Curcuminoids

Studies involving diclofenac used together with BCM-95 curcumin have reported enhanced overall pain relief and reduced gastrointestinal discomfort relative to diclofenac alone [17]. The improved safety is attributed to curcumin's antioxidant and anti-inflammatory properties. Although promising, larger trials are needed to validate routine use of this combination in OA care.

7.4 Modified-Release and Enteric-Coated Diclofenac Formulations

Extended-release and enteric-coated diclofenac tablets have been shown to provide smoother plasma drug levels, improved day-long symptom control, and fewer peak-related adverse reactions versus immediate-release tablets [16,19]. These formulations are particularly beneficial for chronic OA patients requiring continuous pain relief.

7.5 Nanotechnology-Based and Enhanced Topical Diclofenac Delivery Systems

Recent clinical and experimental work indicates that nanoemulsions, lipid carriers, transfersomes, and other nano-enabled delivery systems significantly improve skin penetration, accelerate symptom relief, and may reduce dosing frequency [23,24,27]. Such formulations enhance local action while decreasing systemic risks, making them especially useful for individuals with cardiovascular or GI comorbidities [6].

7.6 Gastroprotective Diclofenac Prodrugs

Research on nitrosothiol-diclofenac compounds and hydrazone-based derivatives has shown that these

modified molecules retain strong anti-inflammatory activity while greatly reducing gastric irritation [21,23,27]. Nitric oxide–releasing diclofenac improves gastrointestinal mucosal blood flow, while hydrazone derivatives demonstrate selective COX-2 activity and reduced ulcerogenic potential— indicating future potential for safer long-term use.

7.7 Diclofenac Compared with Paracetamol

Comparative clinical evidence consistently reports that diclofenac provides greater pain reduction, faster onset of relief, and superior functional improvement than paracetamol in moderate OA [4,16]. Due to paracetamol's limited efficacy in inflammatory pain, diclofenac is considered the more effective choice for symptomatic OA.

7.8 Post-Marketing Observations and Real-World Safety

Large real-world surveillance datasets confirm that diclofenac delivers meaningful symptom relief with predictable and manageable adverse event patterns when used at recommended doses [9,10,13]. The safety profile is especially favourable for topical formulations, which show substantially fewer severe GI events and are widely recommended for high-risk OA patients [2,6].

7.9 Network Meta-Analyses Ranking Diclofenac Among Leading NSAIDs

High-quality network meta-analyses consistently rank diclofenac—particularly at 150 mg/day— as one of the most effective NSAIDs for both pain reduction and improvement in physical functioning [4,19]. Its performance is comparable or superior to ibuprofen, naproxen, celecoxib, and etoricoxib, reinforcing its status as a first-line analgesic for OA.

7.10 Integrative Approaches Using Diclofenac

Current clinical guidelines advocate the use of topical diclofenac in combination with physiotherapy, structured exercise, and lifestyle modifications such as weight reduction to optimize functional outcomes in OA [6,16]. Topical formulations are the preferred option for older adults and patients with renal, cardiovascular, or gastrointestinal risks.

8. Conclusion

Diclofenac continues to be a cornerstone in OA therapy due to its powerful COX inhibition and welldocumented analgesic and anti-inflammatory performance across diverse patient populations [3,4,19]. Its extensive clinical validation, combined with a broad range of traditional and advanced formulations, supports its ongoing value in both acute and chronic symptom management [1,2,5]. Developments in medicinal chemistry — including GIsparing prodrugs, hydrazone derivatives, and structurally optimised analogues — have demonstrated reduced ulcerogenic potential and preserved or enhanced COX-2 affinity, offering promising alternatives to conventional oral diclofenac [21,23,27].

Computational approaches such as docking, QSAR, and ADMET modelling have further refined understanding of diclofenac–COX interactions and accelerated rational design of safer derivatives [34,36,39].Topical preparations, particularly gels and epolamine patches, remain especially valuable in knee OA, delivering clinically significant pain relief with minimal systemic exposure and superior safety profiles compared to oral NSAIDs [2,6,48].

As formulation science, molecular modelling, and clinically guided optimisation continue to advance, diclofenac's therapeutic relevance in osteoarthritis is expected to persist, with future derivatives likely to deliver improved efficacy, tolerability, and long-term safety for chronic OA management [11,12,30].

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