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REVIEW ARTICLE

Advances in NSAID Development: Evolution of Diclofenac Products Using Pharmaceutical Technology

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Abstract Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) of the phenylacetic acid class with anti-inflammatory, analgesic, and antipyretic properties. Contrary to the action of many traditional NSAIDs, diclofenac inhibits cyclooxygenase (COX)-2 enzyme with greater potency than it does COX-1. Similar to other NSAIDs, diclofenac is associated with serious dose-dependent gastrointestinal, cardiovascular, and renal adverse effects. Since its introduction in 1973, a number of different diclofenac-containing drug products have been developed with the goal of improving efficacy, tolerability, and patient convenience. Delayed- and extended-release forms of diclofenac sodium were initially developed with the goal of improving the safety profile of diclofenac and providing convenient, once-daily dosing for the treatment of patients with chronic pain. New drug products consisting of diclofenac potassium salt were associated with faster absorption and rapid onset of pain relief. These include diclofenac potassium immediate-release tablets, diclofenac potassium liquid-filled soft gel capsules, and diclofenac potassium powder for oral solution. The advent of topical formulations of diclofenac enabled local treatment of pain and inflammation while minimizing systemic absorption of diclofenac. SoluMatrix diclofenac, consisting of submicron particles of diclofenac free acid and a proprietary combination of excipients, was developed to provide analgesic efficacy at reduced doses associated with lower systemic absorption. This review illustrates how pharmaceutical technology has been used to modify the pharmacokinetic properties of diclofenac, leading to the creation of novel drug products with improved clinical utility.

Key Points

Since its introduction, the original diclofenac sodium drug product has been modified using pharmaceutical technology.

Alteration of the pharmacokinetic properties of oral diclofenac drug products produced a number of desirable characteristics, including more convenient dosing, improved absorption, and rapid onset of analgesia.

Development of topical diclofenac drug products improved tolerability and reduced systemic exposure to the drug, and improvements have been seen recently in diclofenac drug products for injection.

Recently, a new technology that reduces drug particle size has been used to develop low-dose oral diclofenac products that provide analgesic efficacy with low systemic exposures.

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1 Introduction

In recent decades, novel methods for chemical synthesis and improved analytical and screening technologies have spurred the creation of new nonsteroidal anti-inflammatory drug (NSAID) products [1–5]. In parallel, advances in pharmaceutics, along with the science of developing physical medicinal dosing forms such as tablets and capsules, have also been used to improve the pharmacological properties of these agents. These advances include development of controlled drug delivery systems and novel oral drug preparations such as flexible, dispersible, or multiparticulate dosage forms [6]. Furthermore, new manufacturing technologies that modify the particle size distribution of the active drug substance have enhanced the dissolution, bioavailability, and efficacy of oral drug products [7]. These improvements have provided clinical benefits such as reduced dosing frequency and improved adverse event profile.

Advances in NSAID pharmaceutics have recently been focused on the development of options to address serious dose-dependent gastrointestinal (GI), cardiovascular (CV), and renal adverse effects (AEs) associated with the use of NSAIDs [8–15]. Approaches to address these concerns have concentrated on modifications of pharmacological properties, novel modes of delivery, and co-administration with gastroprotective agents such as proton pump inhibitors, with the main goal of improving tolerability and, in some cases, supporting expanded indications.

Diclofenac is the most widely prescribed NSAID worldwide [14]. More than 10 million diclofenac drug product prescriptions were dispensed in the USA in 2012 [16]. Since its introduction in 1973 [17, 18], a number of new diclofenac-containing drug products have been approved for use and marketed in the USA (Table 1). The growth in NSAID prescriptions in the USA has been driven in part by the introduction of new diclofenac drug products [19]. These new products have varied pharmacokinetic (PK) properties and dosing regimens and are indicated for the treatment of a range of acute and/or chronic pain conditions [20, 21]. The development of diclofenac drug products demonstrates how pharmaceutical technology can be used to drive innovation, creating drug products with improved efficacy, safety, and increased clinical utility.

We review the history leading to the invention of NSAIDs, including diclofenac, and summarize advances in the development of diclofenac drug products, with primary emphasis on the modifications of the PK properties of diclofenac implemented to improve its efficacy and safety.

1.1 Search Strategy

We performed a literature search in National Library of Medicine/PubMed to identify potential articles during the period 1 January 1970 to 30 September 2014 using the following search terms alone or in combinations: NSAID, diclofenac, development, diclofenac sodium, diclofenac potassium, extended-release, enteric-coated, sustained-release, controlled-release, delayed-release, immediate-release, diclofenac topical, diclofenac epolamine, diclofenac free acid, ProSorb, SoluMatrix, submicron, milling technologies, dispersion technologies, diclofenac gel, diclofenac solution, diclofenac powder, diclofenac pharmacokinetics, diclofenac delivery, diclofenac dissolution, diclofenac potassium liquid-filled soft gelatin capsules, DPSGC, diclofenac AND gastroprotective agents, diclofenac AND proton pump inhibitors, diclofenac AND fixed dose combination, diclofenac AND misoprostol, and diclofenac AND omeprazole. Search terms with high sensitivity and low specificity were chosen to produce a comprehensive list of search results. Published articles and abstracts were reviewed to identify additional references that were considered relevant. Clinical studies cited in the review were those designed to characterize the biopharmaceutical properties or definitively characterize clinical efficacy in well-controlled phase III pivotal studies and are included for illustrative purposes. A comparison of clinical studies that were identified using this strategy with studies obtained using a broader search strategy did not identify additional relevant studies.

2 Development of Nonsteroidal Anti-Inflammatory Drugs and Diclofenac

The active compound of willow bark, salicin, an historical medicinal remedy, is metabolized to salicylic acid, which has antipyretic, analgesic, and anti-inflammatory properties [22–24]. In the late nineteenth century, salicylic acid was used throughout the world for a variety of ailments [22]. Because of its bitter taste and concomitant gastric irritation, there was a need for new, improved chemical derivatives of salicylic acid. In 1897, Felix Hoffman and Arthur Eichengrün acetylated the salicylic acid molecule to produce a weakly acidic acetylsalicylic acid with a more palatable taste, which was patented by Bayer (Berlin, Germany) as aspirin in 1899 [23, 25].

In the early 1950s, the Geigy Company (Basel, Switzerland) discovered a new compound that formed water-soluble salts of aminophenazone, with potent anti-inflammatory and uric acid excretion-promoting activity [26, 27]. This compound, a pyrazolidine derivative named phenylbutazone, became the first non-salicylate NSAID

Table 1 Prescription diclofenac drug products approved by the US FDA

Generic name; commercial name	Description	Date of FDA approval	Recommended dosing regimen[a]	Indication
Diclofenac sodium; Voltaren®	DR (enteric-coated) tablets, 25, 50, and 75 mg	28 Jul 1988	25 mg qid; 50 mg bid, tid, qid; or 75 mg bid	Signs and symptoms of OA, RA, and AS [28]
Diclofenac potassium; Cataflam®	IR tablets, 25[b] and 50 mg	24 Nov 1993	50 mg bid, tid, or qid	Signs and symptoms of OA, RA, primary dysmenorrhea, and mild-to-moderate pain [29]
Diclofenac sodium; Voltaren®-XR	XR tablets, 100 mg	8 Mar 1996	100 mg od	Signs and symptoms of OA and RA [30]
Diclofenac sodium/misoprostol; ARTHROTEC®	Tablets, enteric-coated core containing 50 or 75 mg; outer mantle containing 0.2 mg misoprostol	24 Dec 1997	50 mg bid, tid, or qid; or 75 mg bid	Signs and symptoms of OA or RA in pts at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications [31]
Diclofenac sodium; SOLARAZE®	Topical gel 3 %	16 Oct 2000	15 mg diclofenac bid (0.5 g gel per 5 cm^2 skin)	Topical tx of actinic keratosis [32]
Diclofenac epolamine; FLECTOR®	Topical patch 1.3 %	31 Jan 2007	1 patch (180 mg) bid	Topical tx of acute pain due to minor strains, sprains, and contusions [33]
Diclofenac sodium; Voltaren®	Topical gel 1 %	17 Oct 2007	Maximum 32 g per day	OA pain of joints amenable to topical tx, such as the knees and hands [34]
Diclofenac potassium; CAMBIA®	Powder for oral solution, 50 mg sachet	17 Jun 2009	Single 50-mg dose	Acute tx of migraine attacks with or without aura in pts aged ≥18 years [35]
Diclofenac potassium; ZIPSOR®	Liquid-filled capsules, 25 mg	16 Jun 2009	25 mg qid	Mild-to-moderate acute pain [36]
Diclofenac sodium; PENNSAID®	Topical solution, 1.5 and 2 %	4 Nov 2009 (1.5 %) 16 Jan 2014 (2 %)	19.26 mg qid and 40 mg bid	Signs and symptoms of OA of the knee [37, 38]
Diclofenac free acid; ZORVOLEX®	Capsules, 18 and 35 mg	18 Oct 2013	18 mg tid 35 mg tid	Management of mild-to-moderate acute pain and OA pain [39]
Diclofenac sodium; Dyloject™	Solution for intravenous use, 37.5 mg in 1 mL vial	23 Dec 2014	37.5 mg by IV bolus injection qid, maximum 150 mg per day	Management of mild-to-moderate pain or moderate-to-severe pain alone or in combination with opioid analgesics [40]

AS ankylosing spondylitis, *bid* twice daily, *DR* delayed release, *FDA* US Food and Drug Administration, *IR* immediate release, *IV* intravenous, *NSAID* nonsteroidal anti-inflammatory drug, *OA* osteoarthritis, *od* once daily, *pts* patients, *qid* four times daily, *RA* rheumatoid arthritis, *tid* three times daily, *tx* treatment, *XR* extended release

[a] See prescribing information for specific dosing for each condition

[b] Discontinued: Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons

administered to patients with ankylosing spondylitis, gout, rheumatoid and psoriatic arthritis, and mixed connective tissue disease [27, 41]. The development of biological screening assays and preclinical models of inflammation represented a major advance in drug discovery and enabled screening of large numbers of chemical compounds for anti-inflammatory activity. This development led to the discovery of indomethacin, the first acetic acid derivative with anti-inflammatory properties, in the late 1950s, by Shen et al. [42]. It was not until 1971 that the molecular mechanism responsible for NSAID activity was discovered when John Vane demonstrated that acetylsalicylic acid and NSAIDs inhibited the activity of cyclooxygenase enzymes responsible for the conversion of arachidonic acid to prostanoids [43].

The discovery of the NSAID mechanism of action resulted in the development of a wide array of new NSAIDs, including propionic acid derivatives (e.g., ibuprofen) and fenamic acid derivatives (e.g., mefenamic acid) [44]. During this period, analysis of structural and physicochemical properties of the existing NSAIDs provided a theoretical basis for synthesis of new anti-inflammatory agents with enhanced efficacy [45]. Based on the results of this analysis, this hypothetical agent was postulated to have an acidity constant between 4 and 5; a partition coefficient of approximately 10; and two aromatic rings that were twisted in relation to each other [45, 46]. These specific physicochemical and spatial characteristics were anticipated to ensure efficient transport across biological membranes and to promote strong inhibition of the cyclooxygenase (COX)-dependent oxidation of the arachidonic acid molecule [45, 46].

Based on this information, diclofenac sodium was synthesized by Alfred Sallmann and Rudolf Pfister and first introduced by Ciba-Geigy (now Novartis AG, Basel, Switzerland) in 1973 [17, 18]. Diclofenac is a phenylacetic acid with an acidity constant of 4, establishing it as a weak acid, and a partition coefficient of 13.4, indicating partial solubility in both aqueous and hydrophobic environments. The structural features of the molecule, namely a phenylacetic acid group and a phenyl ring containing two chlorine atoms, produce maximal twisting of the phenyl ring (Fig. 1) and provide a good fit in the substrate-binding pocket of the COX enzyme [46, 47]. Subsequent experimental and clinical studies confirmed the theoretical considerations that led to the synthesis of diclofenac.

3 General Properties of Diclofenac

3.1 Mechanism of Action

Diclofenac belongs to a group of NSAIDs that inhibit both COX-1 and COX-2 enzymes. The binding of NSAIDs to COX isozymes inhibits the synthesis of prostanoids (i.e., prostaglandin [PG]-E_2, PGD_2, PGF_2, prostacyclin [PGI_2], and thromboxane [TX] A_2) [43, 48, 49]. PGE_2 is the dominant prostanoid produced in inflammation, and the inhibition of its synthesis by NSAIDs is believed to be the main mechanism of the potent analgesic and anti-inflammatory properties of these agents [49–51].

The human whole blood in vitro assay developed by Paola Patrignani and colleagues [52] has been used to measure the degree of selectivity of NSAIDs toward COX-2 or COX-1 by quantifying the inhibition of COX-2—dependent formation of PGE_2 produced by monocytes, following lipopolysaccharide (LPS) stimulation versus COX-1–dependent formation of TXB_2, the non-enzymatic hydrolysis product of TXA_2 produced by platelets [53]. Although diclofenac is commonly referred to as a traditional NSAID in the published literature, these assays have demonstrated that it has a higher selectivity for COX-2 than for COX-1, in contrast with most traditional NSAIDs. The degree of COX-2 selectivity demonstrated for diclofenac is comparable to that of celecoxib [51]. Diclofenac is more potent in inhibiting COX-2 than COX-1 isoenzymes. However, the estimated IC_{50} (concentration causing 50 % inhibition of activity) values for COX-1 and COX-2 of different COX inhibitors has been shown to vary

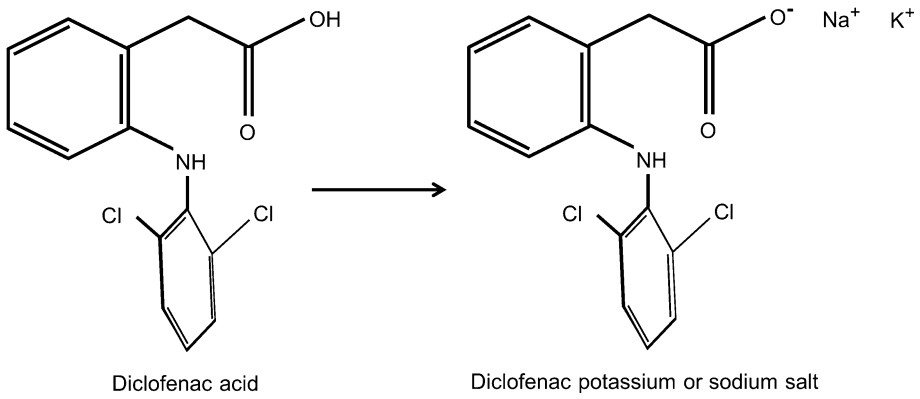

Fig. 1 Chemical structure of diclofenac drug products

between models, and selectivity is dose dependent in some cases [49, 54–56].

3.2 Adverse Events and Drug–Drug Interactions

Diclofenac, similar to other NSAIDs, is associated with an increased risk of serious dose-related GI, CV, and renal side effects [8, 10–13, 15]. The GI AEs occur due to reduced synthesis of prostanoids, limiting secretion of mucus and bicarbonate that normally protect the gastric mucosa from injury [44, 57]. Consistent with the hypothesis that NSAIDs associated with the highest COX-1 selectivity are more likely to be associated with an increased risk of GI toxicity [56, 58], diclofenac ranks low in terms of relative risk for GI complications, especially when administered at low doses (≤75 mg daily) [56, 59–61]. The GI toxicity of this agent is dependent on high diclofenac levels in the systemic circulation [58]. PGI_2, a major product of COX-2—mediated metabolism of arachidonic acid in vascular endothelial cells, serves a physiologic function as a potent vasodilator and platelet inhibitor [62]. Both preclinical and clinical evidence indicate that suppression of PGI_2 synthesis increases the risk for hypertension and thrombosis [9, 63, 64]. The dose-related risk of thrombotic events, especially following administration of high doses of diclofenac (≥150 mg daily), has been documented in observational studies [9, 58]. The CV hazard of diclofenac at doses ≥150 mg daily is estimated to be comparable to that of rofecoxib and celecoxib, as well as ibuprofen administered at high doses [9, 15]. The variable risk of myocardial infarction (MI) due to NSAIDs that do not completely inhibit COX-1 is largely related to their extent of COX-2 inhibition [55]. Because the incidence of AEs is dose dependent, a reduction of the diclofenac dose is advisable for patients with risk factors for the development of CV and GI adverse events [55].

Low-dose aspirin (75–150 mg daily) prevents the aggregation of platelets and is commonly used in the pharmacological prevention of CV disease [65]. An important clinical issue is the potential interference of NSAIDs with the antiplatelet effects of low-dose aspirin when co-administered with NSAIDs in patients with CV disease. The irreversible inhibition of platelet COX-1 activity by aspirin requires initial low-affinity anchoring to the Arginine-120 residue of the COX channel, which is a common docking site shared by other NSAIDs. Thus, NSAIDs that inhibit platelet COX-1, such as ibuprofen [66, 67] or naproxen [68, 69], could interfere with the antiplatelet effects of low-dose aspirin. In contrast, diclofenac and the selective COX-2 inhibitors rofecoxib and celecoxib do not interfere with aspirin action on platelets [66, 67]. Measurement of the extent of COX-1 acetylation in platelets by mass spectroscopy may shed additional light on the mechanistic aspects of this clinically relevant drug–drug interaction [70].

3.3 General Pharmacokinetic Properties of Diclofenac

Following oral administration, systemic absorption of diclofenac is generally rapid and directly proportional to the dose [71, 72]. The rate of diclofenac absorption may vary depending on the salt form, pharmaceutical composition, and timing of administration in relation to food intake. The absorption of diclofenac can be inconsistent, with variable maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}), as well as the presence of late or secondary plasma peaks in plots of diclofenac concentration versus time [73–77]. It has been proposed that these inconsistences in diclofenac absorption arise due to individual subject differences in GI pH [78], partial precipitation of the dose in the acidic conditions in the stomach [79, 80], variable timing in gastric emptying, and enterohepatic circulation [81, 82].

Approximately 60 % of the intact diclofenac reaches the systemic circulation due to first-pass metabolism [20, 71]. The main metabolite, 4′-hydroxydiclofenac, is known to retain weak anti-inflammatory and analgesic activities [83]. Following biotransformation to glucoroconjugated and sulphate metabolites, diclofenac is excreted in the urine [20, 71]. Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Approximately 65 % of the dose is excreted in the urine and 35 % in the bile as conjugates of unchanged diclofenac and its metabolites [28].

Acidic NSAIDs are highly bound to plasma proteins, mainly albumin. Diclofenac, similar to other acidic NSAIDs, concentrates not only in the systemic circulation, but also in inflamed tissues where the weak acidic environment reduces plasma protein binding, thereby increasing the free fraction of the drug and facilitating diffusion of diclofenac into the intracellular spaces where it can exert its therapeutic effect [26, 84, 85]. Diclofenac accumulates in synovial fluid at levels that eventually exceed plasma levels and that persist after the plasma levels have substantially decreased. Diclofenac administered as the sodium salt was detectable in synovial fluid for up to 11 h following administration of a 50-mg enteric-coated tablet [83] and up to 25 h following administration of a 100-mg slow-release tablet [83, 86, 87]. Whether diffusion into the synovial fluid of joints accounts for the therapeutic efficacy of diclofenac is unknown; its persistence at the site of inflammation, and its inhibition of COX-2 enzymes in the inflammatory cells,

could explain the duration of diclofenac therapeutic effect that extend beyond the plasma half-life. However, the prolonged therapeutic effect of diclofenac could also be related to its extended pharmacodynamic half-life after administration of high doses [56, 88]. Several studies have shown that treatment with diclofenac sodium significantly decreases the synovial fluid levels of PGE_2 [87] as well as those of inflammatory cytokines such as interleukin-6 and substance P [89].

Because of its short biological half-life (~2 h) [71, 72, 90] and fast elimination rate (mean elimination half-life 1.2–1.8 h) [20, 71, 90, 91], frequent administration of diclofenac is usually necessary to maintain its therapeutic concentration, which could in turn increase the risk for adverse events. However, the relatively short pharmacological half-life of diclofenac may be extended, since, at therapeutic doses, the C_{max} [88] is greater than that necessary to inhibit COX-2 by 80 % [56], indicating that efficacy could be achieved at lower diclofenac doses.

The requirement for frequent dosing due to the rapid elimination rate was anticipated to potentially compromise the tolerability of diclofenac. To minimize damage to the stomach and to make the dosing regimen of diclofenac safer and more convenient for patients, modified-release dosage forms have been introduced. Oral diclofenac sodium formulations available include enteric-coated tablets [90, 91], which have found their main therapeutic niche in the treatment of rheumatoid arthritis. Intravenous diclofenac formulations have been developed to treat moderate pain or more severe pain as an adjunct to more potent agents, such as opioids, for perioperative pain [40, 92]. Topical formulations, as liquid solutions, gels, or transdermal patches permitting dermal delivery, have been developed for the treatment of certain types of localized pain [93].

4 Oral Preparations of Diclofenac Sodium

4.1 Diclofenac Sodium Enteric-Coated Tablets for the Treatment of Chronic Pain

Introduced in the late 1980s, diclofenac sodium enteric-coated (delayed-release) tablets (Voltaren®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) was the first diclofenac drug product aimed at reducing gastric exposure. A polymeric coating was developed to modify the final site of drug delivery in the digestive system. The pH-sensitive barrier applied to these tablets resisted dissolution in the acidic environment of the stomach, but allowed release of diclofenac on reaching the higher pH environment of the small intestine [21, 94]. Enteric coating involves a fine balance: the higher pH required for dissolution of the coating could lead to inconsistent release of the active diclofenac ingredient. Furthermore, although bypassing the gastric mucosa could potentially reduce the risk of gastroduodenal ulcers, the possibility of transferring the direct mucosal effects of the drug to distal parts of the gastrointestinal tract is still of potential clinical concern [78].

Diclofenac absorption following administration of enteric-coated diclofenac sodium tablets is usually delayed by approximately 0.5–2 h, although some tablets may remain in the stomach void for up to 24 h [79]. Once the active ingredient is released in the stomach, C_{max} is usually attained within 0.5–1.5 h after ingestion of a 50-mg tablet [78, 79] (Table 2).

A number of clinical studies have confirmed the anti-inflammatory and analgesic efficacy of diclofenac sodium enteric-coated tablets in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gout. Diclofenac sodium enteric-coated tablets were, at one time, considered the benchmark for pharmacological treatment for osteoarthritis [95–97]. In randomized controlled studies in patients with osteoarthritis of the hip and/or knee, treatment with enteric-coated tablets provided better pain relief and substantial functional improvement compared with placebo [98]. Diclofenac sodium was non-inferior to indomethacin [99], ibuprofen [100], naproxen [101, 102], and other NSAIDs [98].

Adverse events reported for diclofenac enteric-coated tablets were generally similar to those reported for other NSAIDs. The most frequent GI AEs included abdominal pain, constipation, diarrhea, indigestion, and nausea [20]. Diclofenac sodium enteric-coated tablets caused fewer digestive (nausea, vomiting, abdominal discomfort) and central nervous system-associated (headache, dizziness) side effects than aspirin or indomethacin [20, 103, 104] and were associated with fewer endoscopically confirmed hemorrhagic and erosive lesions in the GI mucosa than naproxen [104, 105].

4.2 Diclofenac Sodium Extended-Release Tablets for Treatment of Chronic Pain

Diclofenac sodium extended-release tablets (Voltaren®-XR, Novartis Pharmaceuticals Corporation) were introduced in the late 1990s [106, 107]. This drug product was designed to continuously release active diclofenac over an extended period of time, permitting once-daily dosing with the 100-mg tablet in patients with chronic pain associated with osteoarthritis and rheumatoid arthritis [30, 108]. Extended-release diclofenac sodium tablets consisted of a multilayer matrix, with the outer layer of hydroxypropylmethylcellulose alternating with drug substance [88]. The outer layer of these tablets

Table 2 Pharmacokinetic characteristics of oral diclofenac drug products summarized from clinical studies in healthy volunteers under fasting conditions

Generic name; commercial name	Formulation	Dose	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-t} (ng·h/mL)	$t_{½}$ (h)	References
Diclofenac sodium; Voltaren and Voltarol	Delayed-release (enteric-coated) tablets	25	626.8 ± 288.9	2.25 (1.125–4)	–	296–1179[a] (8 h)	–	[80]
		50	1126.2 ± 224.4	1.125 (1.125–3)	–	1107–2286[a] (8 h)	–	
		50	1364 ± 335	2.0 (0.5–3.67)	1262 ± 220	–	–	[74]
		50	1497 (761–2708)	2.75 (0.33–4.03)	–	1297.7[b] (740–2101) (5 h)	–	[82]
		50	2000 ± 700	2.5 ± 1.1	1670 ± 440	–	1.8 ± 2.1	[90]
Diclofenac sodium; DOLOTREN	Delayed-release (enteric-coated) tablets	100	1880.8 ± 867.3	4.00 (3–8)	4375.4 ± 756.5	–	2.8 ± 1.9[c]	[73]
Diclofenac sodium; Voltaren Retard	Slow-release tablets	100	408 ± 152	3.0 (1–8)	–	2528 ± 837 (24 h)	–	[109]
Diclofenac sodium; Voltaren Retard		100	438 ± 231	5.5 (2–9)	–	2400 ± 920 (24 h)	–	
Diclofenac sodium; Voltaren SR		100	960 ± 140	4.88 ± 0.53	–	3430 ± 260 (24 h)	–	[110]
		100	453.1 ± 217.6	3.0 ± 2.6	5756.6 ± 3950.3	–	–	[111]
Diclofenac sodium; ZOLTEROL SR		100	511.3 ± 272.5	3.0 ± 3.2	5275.7 ± 3996.4	–	–	
Diclofenac potassium	Film-coated tablets	25	940.2 ± 387.0	0.354 ± 0.119	611.81 ± 144.76	–	–	[75]
		50	1766.7 ± 1020.2	0.489 ± 0.366	1267.67 ± 356.46	–	–	
Diclofenac potassium; Cataflam	Immediate-release tablets	50	1071 ± 451	0.625 (0.25–4.0)	1214 ± 348	119 3 ± 350 (12 h)	1.034 ± 0.38	[112, 113]
		50	1316 ± 577	0.80 ± 0.50	1511 ± 389	–	1.92 ± 0.38	[114]
		50	1168 ± 657	1.26 ± 0.99	1175 ± 396	1131 ± 391 (6 h)	0.85 ± 0.43	[112]
		50	1169 ± 528	0.93 ± 0.85	1144 ± 282	1133 ± 297 (10 h)	1.45 ± 0.74	
Diclofenac potassium; ZIPSOR	Liquid-filled soft gelatin capsules (DPSGC)	50	1989 ± 921	0.60 ± 0.47	1262 ± 473	1230 ± 459 (6 h)	0.97 ± 0.40	
		25	1125 ± 486	0.45 ± 0.13	603 ± 163	579 ± 162 (10 h)	1.35 ± 0.80	
		50	2035 ± 725	0.48 ± 0.20	1232 ± 296	1197 ± 301 (10 h)	1.84 ± 1.25	
		25 process A	1023 (39 %)[d]	0.42 (0.33–1.0)	607 (26 %)	585 (26 %)[d]	1.10 (25 %)[d]	[115]
		25 process B	1087 (39 %)[d]	0.5 (0.33–1.0)	597 (25 %)	577 (26 %)[d]	1.07 (27 %)[d]	
Diclofenac potassium; CAMBIA®	Granulate for oral solution	50	2213 ± 743	0.228 ± 0.037	1362 ± 358	–	–	[76]

Table 2 continued

Generic name; commercial name	Formulation	Dose	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-t} (ng·h/mL)	$t_{½}$ (h)	References
Diclofenac potassium; VOLTAFAST	Granulate for oral solution sachets	50	2213 ± 743	0.250 (0.167–0.267)	1362 ± 358	–	1.148 ± 0.52	[113]
Diclofenac free acid; ZORVOLEX	Low-dose, SoluMatrix capsules	18	656 ± 300	0.62 ± 0.35	593 ± 163	–	1.52 ± 0.31	[114, 116]
		35	1347 ± 764	0.59 ± 0.20	1225 ± 322	–	1.85 ± 0.45	
		18	495.8 ± 202.93	1.0 (0.5–4.5)	499.2 ± 105.51	490.2 ± 105.09	1.9 ± 0.50 (0.92–3.04)	
		35	868.7 ± 352.83	1.0 (0.5–4.0)	1001.1 ± 229.74	1004.7 ± 242.75	2.1 ± 0.49 (1.20–3.35)	

Doses are presented in mg unless otherwise indicated. Data are presented as mean ± SD or median (range) unless otherwise indicated

AUC_{0-t} area under the concentration–time curve from time 0 to the time of the last quantifiable concentration, $AUC_{0-\infty}$ area under the concentration–time curve from time 0 extrapolated to infinity, C_{max} maximum plasma concentration, *DPSGC* diclofenac potassium soft gelatin capsules, *SD* standard deviation, *SR* sustained release, $t_{½}$ terminal elimination half-life, t_{max} time to maximum plasma concentration

[a] Only range was published

[b] Median (range)

[c] This value was published as 2.754/h^{-1}

[d] Coefficient of variation was given instead of SD

expands during dissolution but is not subjected to erosion and acts as a barrier that regulates drug release. The inner, erodible layer enables progressive dissolution of the active drug substance, thus extending the time of release and drug delivery [106]. Extended-release diclofenac delivers the total drug content slowly over the course of 8–10 h [83]. The dissolution behavior of this drug product may vary depending on physiological conditions or physical stress [117]. Despite similar bioavailability compared with enteric-coated tablets, the extended-release diclofenac sodium tablets are associated with a lower C_{max} and delayed t_{max} [66, 85–87] (Table 2).

In patients with rheumatoid arthritis or osteoarthritis, the efficacy of diclofenac sodium sustained-release formulation was comparable to that of nabumetone [118] and meloxicam [119]. Furthermore, in patients with chronic pain due to osteoarthritis of the hips and/or knees, diclofenac sodium extended-release tablets were shown to be as effective as controlled-release tramadol, an opioid analgesic [120]. Significantly more patients with osteoarthritis receiving diclofenac 75-mg sustained-release tablets twice daily experienced "good" (defined as ≥90 %) compliance compared with patients receiving enteric-coated 50-mg tablets three times daily [121].

Although the relative risk of serious GI complications with diclofenac was estimated as low compared with other NSAIDs [122], the hazard of developing gastric/duodenal ulcers and upper GI perforation and bleeding was not eliminated with the use of enteric-coated or extended-release tablets [123]. More recent data from observational studies suggest that administration of diclofenac drug products with extended half-lives (i.e., slow- or extended-release forms) are associated with an elevated risk of serious GI and CV events [30, 55]. It is postulated that persistent inhibition of COX-1 and COX-2 in the systemic circulation may limit the opportunity for recovery by endogenous COX enzymes [84].

5 Diclofenac Sodium and Gastroprotective Therapies

Endoscopic evaluation of patients with rheumatoid arthritis or osteoarthritis who used NSAIDs continuously over a period of 6 months revealed clinically significant gastroduodenal lesions in 37 % and ulceration in 24 % of cases [124]. To reduce the risk for serious GI AEs associated with long-term use of diclofenac sodium, combination therapies based on co-administration of diclofenac along with gastroprotective agents such as prostaglandin analogs or proton pump inhibitors were developed.

5.1 Diclofenac Sodium and Misoprostol Fixed-Dose Combination

A fixed-dose combination diclofenac sodium-misoprostol (ARTHROTEC®, G.D. Searle LLC Division of Pfizer Inc., New York, NY, USA) [31] sequential-release tablet was approved by the US FDA in 1997 for the treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at high risk for developing NSAID-induced gastric/duodenal ulcers and related complications. The tablet is composed of an enteric-coated diclofenac sodium core (50 or 75 mg) and an outer shell containing misoprostol (200 μg), a synthetic prostaglandin analog, with gastric antisecretory and mucosal protective properties [108].

Studies reported that diclofenac and misoprostol do not interact with each other, exhibit similar absorption rates, display elimination half-lives of <2 h, and do not accumulate in plasma after recommended doses [125]. Pharmacokinetic properties of diclofenac sodium in the fixed-dose combination with misoprostol were generally similar to those of enteric-coated diclofenac sodium when administered as monotherapy [125]. On average, mean C_{max} was approximately 1.5 or 2.0 μg/mL for 50 or 75-mg doses, respectively, and was usually attained within 2 h after dosing [31].

A fixed-dose combination of diclofenac sodium/misoprostol was shown to be as efficacious as indomethacin, diclofenac, ibuprofen, naproxen, or piroxicam in the relief of signs and symptoms of rheumatoid arthritis or osteoarthritis [126, 127]. In endoscopic studies, a lower incidence of both gastric and duodenal ulcers was noted in the groups receiving diclofenac/misoprostol therapy compared with sodium diclofenac treatment alone. GI and duodenal ulcers were significantly less frequent in patients with osteoarthritis of the hip or knee and previous history of gastric ulcers after 6 weeks of therapy with a fixed-dose combination of diclofenac 50 mg/misoprostol 200 μg three times daily (8 %), diclofenac 75 mg/misoprostol 200 μg twice daily (7 %), or placebo (4 %) compared with patients receiving enteric-coated diclofenac sodium 75 mg twice daily (17 %) [128]. In a study in a similar patient population at risk for NSAID-induced ulcers, fewer patients administered enteric-coated diclofenac/misoprostol combination for 12 weeks developed gastroduodenal ulcers (4 %) compared with diclofenac-treated patients (11 %; $P = 0.034$) [127]. The combined incidence of endoscopically confirmed gastric and duodenal ulcers was also significantly lower in the diclofenac/misoprostol therapy group (4 %) than in the nabumetone-treated group (11 %) [129].

Adverse events following administration of diclofenac/misoprostol generally did not differ between the active treatment groups, except for higher rates of flatulence and diarrhea in patients receiving misoprostol [128]. These findings were consistent with earlier clinical studies that reported that misoprostol was associated with dose-dependent GI AEs, the most common of which included diarrhea and abdominal cramps, at the dose of 200 μg four times daily [130, 131]. Lower doses of misoprostol were better tolerated, but were less effective at preventing endoscopically confirmed gastric ulcers [132]. Despite the impact on reducing the risk of endoscopically proven ulcers, the presence of these unpleasant GI effects has limited the general acceptance of the diclofenac/misoprostol combination.

5.2 Diclofenac Sodium and Omeprazole Combination

Although no fixed-dose combinations of diclofenac and proton pump inhibitors have been developed to date, several clinical studies have evaluated the efficacy and safety of co-administration enteric-coated or extended-release sodium diclofenac with omeprazole in patients with osteoarthritis or rheumatoid arthritis who had developed gastroduodenal ulcers after long-term treatment with diclofenac or other NSAIDs.

No drug–drug interactions were demonstrated for omeprazole and diclofenac. Omeprazole administered 20 mg daily had no significant influence on the pharmacokinetic properties of enteric-coated diclofenac sodium 50-mg tablets [133].

Co-administration of omeprazole reduced the risk of ulcer formation [134] and bleeding from recurrent ulcers [135] and accelerated healing of the existing ulcers in patients with a previous history of gastric or duodenal ulcers associated with long-term NSAID administration [136]. Omeprazole-related side effects were mostly mild and transient and included diarrhea and dry mouth [136]. Because of their efficacy and good tolerability, proton pump inhibitors are the main acid-reducing medication used to prevent ulcers related to NSAIDs [137]. However, the proton pump inhibitors do not protect against injury to the lower GI tract [71, 78, 138].

6 Oral Preparations of Diclofenac Potassium

The unpredictable absorption profile of diclofenac sodium was initially suggested to explain delays in the analgesic onset and efficacy of the drug [115]. Diclofenac potassium salt is more water soluble and was considered to provide more rapid dissolution and faster absorption than sodium salt, leading to more uniform absorption and shortened time to onset of analgesia [81]. These characteristics of diclofenac potassium products were confirmed by several

pharmacokinetic and clinical studies (Table 2) [21, 76, 112, 113, 115].

As a reflection of the rapid absorption kinetics, diclofenac potassium is usually indicated for conditions that require a rapid onset of analgesia. A number of diclofenac potassium drug products are available in the USA, including immediate-release tablets [139], liquid-filled soft gelatin diclofenac capsules [140], and diclofenac powder for oral solution [141].

6.1 Diclofenac Potassium Immediate-Release Tablets

Diclofenac potassium immediate-release sugar-coated tablets (Cataflam®, Novartis Pharmaceuticals Corporation) were developed in the early 1980s [139] with the aim of releasing the active drug in the stomach to permit rapid uptake and prompt pain relief [139]. Pharmacokinetic studies in healthy volunteers showed that the differences in the absorption characteristics between immediate-release potassium and enteric-coated sodium diclofenac tablets were notable. The C_{max} achieved after administration of a diclofenac potassium immediate-release 50-mg tablet was slightly lower (Table 2), but the t_{max} was substantially shorter (range 0.63–1.26 h) than that of a diclofenac sodium enteric-coated 50-mg tablet (range 1.13–2.75 h; Table 2) [76, 112, 113, 115]. In some studies, secondary diclofenac absorption peaks were not observed [76, 115].

Clinical studies evaluated the efficacy and safety of diclofenac potassium immediate-release tablets in various conditions characterized by the acute onset of pain, such as pain following removal of impacted molars [140], ankle sprains [141–143], episiotomy [144], and dysmenorrhea [145]. The analgesic efficacy of diclofenac potassium immediate-release tablets in the treatment of ankle sprains was superior to that of placebo, ibuprofen, and piroxicam [141–143]. Generally, AEs were infrequent, and no serious AEs were reported in these studies. The most common AEs were GI disorders, with diarrhea reported most often by the patients in active treatment groups [141–143]. Diclofenac potassium immediate-release tablets were approved by the FDA in 1993 and are indicated for the relief of acute and chronic signs and symptoms of osteoarthritis and rheumatoid arthritis and the relief of mild-to-moderate pain and treatment of primary dysmenorrhea [29]. In comparison with diclofenac sodium enteric-coated tablets, a single oral dose of diclofenac potassium immediate-release provided significantly faster analgesia in patients with moderate-to-severe postoperative pain [21].

Diclofenac potassium immediate-release tablets were also evaluated in patients with acute migraine headaches. The rapid and effective analgesia reported for diclofenac in studies in other acute pain conditions and the potent anti-inflammatory activity of diclofenac were considered to be potentially beneficial in preventing neurogenic inflammation, one of the major causes underlying migraine attacks [146, 147]. In clinical studies, diclofenac potassium immediate-release tablets were reported to be effective in relieving migraine pain and provided significant pain relief 1–2 h following initial dosing [147, 148]. In one study, diclofenac potassium immediate-release tablets appeared to be as efficacious as, but better tolerated than, the serotonin agonist sumatriptan, a first-line agent commonly prescribed for the relief of migraine headache [147]. Diclofenac-potassium immediate-release doses 50 and 100 mg were well tolerated, with reduced incidence of nausea compared with placebo or sumatriptan 100 mg. Furthermore, a larger proportion of patients evaluated the overall tolerability of diclofenac-potassium immediate-release tablets as better than that of sumatriptan [147]. These data suggest that diclofenac potassium was likely to find a role in the treatment of migraine headaches.

6.2 Diclofenac Potassium Powder for Oral Solution for Treatment of Migraine Headaches

Early studies of diclofenac sodium demonstrated rapid absorption when administered in liquid solution [71, 79]. The diclofenac potassium powder for oral solution (CAMBIA™, Depomed, Inc., Newark, CA, USA) consists of diclofenac potassium salt, sweeteners, and flavoring agents, and a dynamic bicarbonate buffering agent that could prevent diclofenac potassium from precipitating in the stomach under acidic conditions [35]. When dissolved in water and ingested, diclofenac potassium powder for oral solution results in rapid diclofenac absorption into the systemic circulation [76]. In the initial PK study in healthy volunteers, peak plasma concentrations were attained within 10–15 min after dosing (Table 2) [76]. Furthermore, the prompt absorption of diclofenac potassium was accompanied by the presence of only a single plasma diclofenac peak [76].

In patients with migraine headaches, diclofenac potassium powder for oral solution demonstrated improved analgesia, with the onset of pain relief as early as 15 min following administration, compared with 60 min following administration of diclofenac potassium immediate-release tablets. These results suggest that administration of the drug as an oral solution may have contributed to more rapid onset of absorption and pain relief [149, 150]. Significant reduction in headache intensity and sustained relief were also demonstrated when compared with diclofenac immediate-release tablets and placebo [150]. Adverse events related to treatment with diclofenac potassium powder for oral solution that were reported in >1 % of study participants included nausea, dyspepsia, vomiting, and

dizziness [150]. Diclofenac potassium powder for oral solution is the only FDA-approved NSAID indicated for the acute treatment of migraine attacks with or without aura in adults [35] (Table 1).

6.3 Diclofenac Potassium Liquid-Filled Soft Gelatin Capsules

Diclofenac potassium liquid-filled capsules (ZIPSOR®, Depomed, Inc.) were developed using the patented ProSorb® dispersion technology that combines a mixture of liquid formulation of diclofenac potassium with solubilizing and dispersing agents to maximize the absorption of diclofenac from the stomach and to reduce variability in the absorption pattern. The main concept of this technology relies upon the fact that weakly acidic drugs admixed with solubilizing and dispersing agents will be absorbed from the stomach at accelerated rates [151].

The inactive ingredients in this formulation are predominantly non-aqueous and include polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, hydrochloric acid, isopropyl alcohol, and mineral oil [152]. As a result, the product can be manufactured and administered as an oral dosage form comprising the liquid fill in soft gelatin capsules [36]. The capsule shells contain gelatin, sorbitol, isopropyl alcohol, glycerin, and mineral oil [36].

In phase I studies in healthy volunteers, diclofenac potassium liquid-filled soft gelatin capsules demonstrated rapid and predictable absorption with shorter time to C_{max} compared with diclofenac potassium immediate-release tablets [115] (Table 2). A 50-mg dose achieved significantly shorter t_{max} and higher C_{max} than the 50-mg diclofenac potassium tablet, and the C_{max} following the 25-mg dose was equivalent to that following administration of the 50-mg diclofenac potassium tablet. Plasma diclofenac concentration–time courses for the diclofenac potassium 50-mg tablet produced multiple peaks compared with one peak obtained for diclofenac potassium liquid-filled soft gelatin capsules (Table 2) [112].

Diclofenac potassium liquid-filled capsules 25 mg, administered every 6 h, provided significantly faster onset of analgesia than placebo in patients with acute pain following third molar extraction [153, 154] or bunionectomy surgery [155, 156]. Diclofenac potassium liquid gel-filled capsules were generally well tolerated. In the study of patients following bunionectomy, fewer patients in the active treatment group (20.6 %) than in the placebo group (44.4 %) reported AEs. The most commonly reported AEs in this study included nausea, headache, vomiting, and constipation [155]. The generally high proportion of patients reporting AEs in the placebo group was attributed to the significantly increased number of patients requiring opioid-containing rescue medication. Diclofenac potassium liquid-filled soft gelatin capsules were approved by the FDA in 2009 for the relief of mild-to-moderate acute pain in adults [36].

7 Topical Formulations of Diclofenac Sodium or Epolamine Salt for Local Treatment

Topical diclofenac sodium preparations were developed with the aim of treating local pain and inflammation while limiting diclofenac systemic exposure and potentially minimizing the risk of AEs associated with treatment with systemic NSAIDs. As an organic acid, diclofenac is lipophilic, while its salts are water soluble at neutral pH. The combination of these two properties renders diclofenac capable of penetrating through cell membranes, including the synovial lining of diarthrodial joints and the skin [47]. Studies performed in 1997 and 2001 reported that diclofenac had excellent transdermal penetration properties [157, 158]. Based on the favorable permeation properties along with strong inhibition of PGE_2 synthesis, diclofenac was expected to exert potent anti-inflammatory activity when applied topically [47, 158]. Several diclofenac formulations have been developed for transdermal delivery, including diclofenac sodium gels, diclofenac sodium topical solutions, and a diclofenac epolamine patch [93].

Although topical NSAIDs are widely used outside the USA [159, 160], diclofenac sodium is the only NSAID approved by the FDA for topical use in the treatment of pain associated with osteoarthritis. The dispensed prescriptions for topical diclofenac products constituted approximately 3 % of the total annual prescriptions for NSAIDs in the USA in 2012 [19]. Topical diclofenac drug products include diclofenac sodium topical gel 1 % (Voltaren® Gel, Novartis Consumer Health, Inc., Parsippany, NJ, USA) [34], approved by the FDA in 2007 and indicated for the relief of pain of osteoarthritis of joints amenable to topical treatment such as the knees and hands, and diclofenac sodium topical solution 1.5 and 2 % (PENNSAID® Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO, USA), indicated for the treatment of signs and symptoms of osteoarthritis of the knee [37], approved in 2009 (1.5 %) and 2014 (2 %) (Table 1). The American College of Rheumatology and the American Academy of Orthopedic Surgeons guidelines have recently recommended use of topical NSAIDs for treatment of osteoarthritis of the hand or knee, especially in patients older than 75 years or those with increased GI risk [161–164].

NSAIDs administered topically usually achieve only 3–5 % of total systemic absorption for oral diclofenac products. On the other hand, interstitial concentrations of diclofenac in the muscle tissue are usually higher after

topical treatment than after oral administration of NSAIDs [165]. PK studies in healthy volunteers who received topical diclofenac and other topical NSAID preparations available in Europe demonstrated that peak plasma levels constituted less than 10 % of the C_{max} achieved following oral administration [166]. The maximal plasma concentrations were achieved approximately ten times later following topical diclofenac administration compared with administration of an equivalent oral dose of diclofenac.

The analgesic and anti-inflammatory efficacy of diclofenac sodium topical preparations have been documented in several clinical studies. The efficacy of 1 % diclofenac sodium topical gel in patients with osteoarthritis of the knee treated for 3–12 weeks was superior to placebo in reducing pain intensity and average pain on movement and in improving physical function [167, 168]. In patients with knee osteoarthritis, treatment with diclofenac sodium 1.5 % topical solution combined with dimethyl sulfoxide led to significant reduction in pain and improvement in physical function, as well as relief of joint stiffness, compared with placebo or dimethyl sulfoxide vehicle [169, 170]. In two studies, efficacy of diclofenac sodium 1.5 % topical solution was comparable to that of oral diclofenac [171].

Because patients with osteoarthritis of the knee are likely to use topical NSAIDs over the course of many years, it is important to gain an understanding of their long-term safety. Diclofenac gel or topical solution administration in long-term studies (up to 52 weeks' duration) were generally well tolerated, and the most frequent reported AEs were dry skin at the application site (25.3 % of patients), contact dermatitis (13.0 %), and contact dermatitis with vesicles (9.5 %) [172]. Due to lower circulating diclofenac levels, patients administered diclofenac sodium topical solution experienced fewer GI-associated AEs than did patients treated with oral diclofenac (6.5 vs. 23.8 %) [173]. Serious GI AEs associated with topical diclofenac treatments are rare [166, 174].

Compared with diclofenac sodium and potassium salts, the epolamine salt of diclofenac demonstrates detergent-like properties with improved solubility in both water and organic solvents, facilitating enhanced epidermal penetration [47, 175]. Clinical studies in patients experiencing acute pain from minor soft tissue injuries or ankle sprains reported that diclofenac epolamine topical patches provided rapid and effective local analgesia compared with placebo and were generally safe and well tolerated [176–178]. Diclofenac epolamine (FLECTOR® IBSA Institut Biochimique SA, Lugano, Switzerland) 1.3 % patches (10 × 14 cm) containing 180 mg of diclofenac were approved by the FDA in 2007. They are indicated for topical treatment of acute pain due to minor strains, sprains, and contusions, with the recommended twice-daily changes of the patch [33]. In patients with acute musculoskeletal conditions or osteoarthritis, treatment for 2–3 weeks with diclofenac epolamine patches did not lead to any serious AEs in the GI tract, kidneys, or liver. The majority of AEs included skin reactions, most commonly pruritus in both placebo-treated and diclofenac epolamine patch-treated patients. A comparison with diclofenac gel suggested that pruritus was most likely secondary to the presence of the plaster component of the patch [47].

Altogether, these data suggest that topical NSAID preparations are suitable for treatment of a subset of patients with acute pain following injury or osteoarthritis amenable to local application of gel or solution, but not for management of inflammation of multiple joints that may be difficult to access or for systemic treatment of inflammation.

8 Injectable Diclofenac

Injectable diclofenac drug products have been available in the UK since 1997 and are available globally [179, 180]. These drug products often consist of ampules containing diclofenac 75 mg and used propylene glycol and benzyl alcohol as solubilizing agents and have required a lengthy infusion time when administered intravenously [181]. An injectable diclofenac drug product has been developed and approved in the USA for use in patients with moderate pain or as part of a multimodal analgesic regimen for control of perioperative pain [40, 181]. This diclofenac formulation (Dyloject™, Hospira Inc., Lake Forest, IL, USA) contains diclofenac sodium 37.5 mg and includes hydroxypropyl-β-cyclodextrin (HPβCD) to enhance solubility (333 mg per mL of water), along with pH modifiers and monothioglycerol [40, 181]. Unlike other diclofenac sodium for-injection drug products, HPβCD-diclofenac is propylene glycol-free, and the improved solubility allowed convenient preparation of HPβCD-diclofenac and a shorter infusion period [181]. HPβCD-diclofenac administration intravenously or via intramuscular injection provided equivalent bioavailability compared with intravenous or intramuscular administration of an injectable diclofenac sodium drug product containing propylene glycol (Voltarol®, Novartis Pharmaceuticals UK Ltd, Camberly, UK) in healthy volunteers [181]. HPβCD-diclofenac 75 mg provided rapid pain relief in patients with postoperative pain following impacted molar extraction compared with placebo [182] and also provided significantly greater reductions in pain intensity and improved tolerability compared with a 75-mg dose of injectable diclofenac sodium drug product containing propylene glycol (Voltarol®) in a similar study of patients with postoperative dental pain [183]. HPβCD-diclofenac administered intravenously

produced significantly greater reductions in pain intensity and lower rates of opioid-rescue medication use compared with placebo in patients experiencing pain following orthopedic surgery [184]. These results suggest that diclofenac sodium injection for intravenous use is a suitable option for patients experiencing acute postoperative pain or as part of a multimodal analgesic strategy to achieve perioperative pain control.

9 SoluMatrix Diclofenac Acid

SoluMatrix diclofenac (ZORVOLEX®, Iroko Pharmaceuticals LLC, Philadelphia, PA, USA) was approved in the USA in 2013. Unlike other diclofenac drug products that contain sodium, potassium, or epolamine salts of diclofenac, the active ingredient in SoluMatrix diclofenac is the diclofenac molecule in its neutral, un-ionized (free carboxylic acid) form (Fig. 1) [39]. Thus, SoluMatrix diclofenac capsules are not interchangeable with other diclofenac products containing diclofenac potassium or sodium salts.

Salt forms of the drug, which are soluble in water at neutral pH, will precipitate in acidic conditions such as those that are found in the stomach. Without modification of the starting material, subsequent dissolution of the active ingredient may be variable or slow due to the presence of large or agglomerated particles [185, 186]. SoluMatrix® Fine Particle Technology™ is a proprietary process that produces drug particles that are 200–800 nm in diameter without altering the chemical properties of the active therapeutic ingredient [116]. The dry milling process increases drug particle surface area relative to mass, resulting in improved dissolution properties compared with diclofenac potassium immediate-release tablets, promoting rapid absorption [187].

SoluMatrix diclofenac capsules were developed to produce efficacy at reduced doses, aligned with recommendations by health authorities including the FDA and the European Medicines Agency that NSAIDs should be prescribed at the lowest effective dose for the shortest possible duration [188]. SoluMatrix diclofenac 18 and 35-mg doses contain 20 % less active ingredient on a molar basis than 25 and 50-mg diclofenac potassium immediate-release tablets, respectively. Under fasting conditions, a single dose of SoluMatrix diclofenac 35 mg achieved a 23 % lower overall systemic exposure (area under the concentration–time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$]) and lower C_{max} but similar t_{max} compared with the diclofenac potassium immediate-release tablets 50 mg (Table 2) [116, 189].

The analgesic efficacy of low-dose SoluMatrix diclofenac has been investigated in two phase III studies. In patients experiencing pain following bunionectomy, SoluMatrix diclofenac 18 or 35 mg administered three times daily provided rapid and significantly greater pain relief over 48 h than did placebo [189]. In patients with osteoarthritis of the hip or knee, treatment with SoluMatrix diclofenac 35 mg administered three times daily over 12 weeks significantly reduced pain measures (at rest or associated with usual activities) and improved composite indices of pain, function, and stiffness compared with placebo [182]. Based on the cumulative daily dose of 18 mg three times daily, SoluMatrix diclofenac represents the lowest-dose diclofenac option for the systemic treatment of acute pain.

In both controlled phase III studies, all doses of SoluMatrix diclofenac capsules were generally well tolerated, and AEs were generally of mild-to-moderate intensity [189, 190]. In the bunionectomy study, the most frequent non-procedure–related AEs (>5 %) included nausea, headache, dizziness, vomiting, and constipation [189]. In the 12-week osteoarthritis study, the most frequent AEs (>5 %) for diclofenac 35 mg three times daily included nausea, diarrhea, and headache [190]. Few serious GI, CV, or renal AEs were reported in these studies [189, 190]. SoluMatrix diclofenac is indicated for the management of acute and osteoarthritis pain [39].

10 Conclusions

Continuous improvements in biopharmaceutical properties of diclofenac have led to the creation of a broad array of drug products designed to treat multiple inflammatory and painful conditions. The development of diclofenac drug products began with a molecule with physicochemical and steric properties considered to represent the ideal NSAID. The first diclofenac drug product, diclofenac sodium enteric-coated tablets, was developed with the aim of reducing the risk of GI AEs commonly associated with the use of NSAIDS. Subsequent efforts focused on improving dosing convenience through development of an extended-release diclofenac sodium preparation. The development of a fixed-dose combination of diclofenac sodium and a gastroprotective agent, misoprostol, a synthetic prostaglandin, or co-administration of a diclofenac enteric-coated tablet with proton pump inhibitors provided an alternative approach to enhance GI tolerability. The enhanced dissolution and absorption kinetics of diclofenac potassium led to the development of several diclofenac potassium-containing drug products, with the ultimate goal of shortening the time to clinically meaningful analgesia. These include diclofenac potassium immediate-release tablets, diclofenac potassium powder for oral solution, and diclofenac potassium liquid-filled soft gelatin capsules. The development of

topical diclofenac preparations permitted local treatment of pain and inflammation in the subset of patients with readily accessible sites of osteoarthritis, and improved the safety profile of diclofenac by minimizing its systemic exposure. SoluMatrix diclofenac is a new drug product consisting of submicron drug particles with enhanced dissolution properties designed to provide efficacy at reduced doses and constitutes the lowest dose treatment option for the systemic treatment of acute pain. Diclofenac is as an excellent example of how pharmaceutical technology can create new drug products that continue to be useful in clinical practice, using existing molecules.

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Conflict of interest Dr. Altman has participated in advisory boards for Iroko Pharmaceuticals, LLC; has served as a consultant for Pfizer, Teva Pharmaceutical Industries Ltd., Petah Tikva, Oletec, Novartis, and Johnson & Johnson; and has consulted for and been a member of a speaker's bureau for Ferring Pharmaceuticals and Iroko Pharmaceuticals, LLC. Dr. Bosch is an employee of and stockholder in iCeutica Operations, LLC; he is also listed as a co-inventor on patents relating to Zorvolex® and SoluMatrix Fine Particle Technology. Dr. Patrignani reports grants from AIRC, from Ministero Dell'Istruzione, Dell'Università e della Ricerca, and MUIR; she received personal fees from Bayer and Iroko Pharmaceticals, LLC outside the submitted work. Dr. Brune declared no conflicts of interest. Dr. Young is an employee of and stockholder in Iroko Pharmaceuticals, LLC.

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