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A comprehensive review of diclofenac pharmacology

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Abstract

Diclofenac, the standard comparator for many studies that aim to evaluate the efficacy and safety of other non-steroidal anti-inflammatory molecules, is one of the most used drugs of its class due to its good efficacy *versus* safety profile. This article is a review of the most important information regarding the pharmaceutic, pharmacokinetic and pharmacodynamic properties, therapeutic indications and contraindications of diclofenac. A special attention is addressed to the oral and topical pharmaceutical forms that are the most comfortable and accepted by patients, consequently, the most used. The innovation in manufacturing technologies led to the emergence of new pharmaceutical forms that generated major changes in the pharmacokinetics of the active substance and, consequently, in its pharmacodynamics, mainly by increasing efficiency in rheumatic diseases. Thus, the innovative pharmaceutical forms of diclofenac bring about an improvement of some pharmacokinetic characteristics and parameters such as bioavailability following administration on different routes, preferential distribution at the site of action, faster elimination from plasma, along with long-term maintenance of active and effective concentrations in target tissues (synovia, muscles etc.). Finally, all these advances in pharmaceutical formulation increase therapeutic efficacy, treatment adherence and significantly reduce the risk of adverse reactions.

Keywords: diclofenac, oral, topical, pharmacokinetics, rheumatic diseases

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) is the class of drugs most used in inflammatory diseases and in the therapy of pain or pyrexia. There are more than 300 registered substances (INN) and more than 2,000 commercial names [1].

Diclofenac is the standard comparator for many studies that aim to evaluate the efficacy and safety of other non-steroidal anti-inflammatory molecules, and its consumption has currently reached over one billion patients/month. The market for diclofenac is expected to reach $6.1 billion in 2027 [2].

It was introduced in therapeutics in 1973 (more than half a century since it has been used), so it passed the test of time. Among the most prescribed NSAIDs in the world, being one of the most active NSAIDs with very good clinical tolerability, it is indicated in the treatment of acute and chronic pain of various etiologies, especially those of inflammatory cause, due to its analgesic and anti-inflammatory effects. It is also used as an antipyretic. It is used in the prevention or even the treatment of acute pancreatitis post-ERCP [3].

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Based on analysis of other non-steroidal anti-inflammatory drugs, it was supposed that an effective NSAID that can be used in rheumatic diseases should have the following characteristics: an acidity constant between 4 and 5, a partition coefficient of approximately 10, and two aromatic rings that can rotate in relation to each other [4].

Diclofenac is a derivative of acetic acid (belongs to the group of aryl-acetic acids). It is a weakly lipophilic organic acid with a pKa of 3.8 (it crosses the skin and biological membranes easily, reaching a high level in the synovial fluid). It is used in the form of salts, which at neutral pH are hydrophilic, and such formulations also allow its injectable administration. It has a partition coefficient of 13.4 (partial solubility in water, but also in hydrophobic liquids- octanol), which allows its administration in several ways: oral, topical (*e.g.*, cutaneous, ophthalmic, buccal), intrarectal, and injectable.

Among these routes of administration, oral and topical administration are the most comfortable and accepted by patients; consequently, they are the most used. The oral/internal route of administration is the most frequently used for systemic effects. After oral administration of diclofenac, the active substance is released in the digestive tract and then passes through a series of pharmacological processes to reach the place where it acts (hypothalamus, other central nervous system structures, synovia), producing the therapeutic effects. There are three phases described in the pharmacology of every drug orally administered, namely the biopharmaceutical phase, the pharmacokinetic phase and the pharmacodynamic phase (Wermuth, 2011) [5].

The biopharmaceutical phase

It consists of the release of the active substance from non-coated tablets, film-coated tablets, delayed-release tablets, dragees or capsules. After that, the dissolution of the active substance and its release in the gastrointestinal fluids of the digestive tract takes place. There are also some oral liquid formulations of diclofenac with a rapid onset of action, especially for the treatment of acute pain and pyrexia.

The pharmacokinetic phase

It consists of several steps:

- Absorption through the gastrointestinal membranes and passage into the entero-hepatic circulation with or without hepatic metabolism;
- Distribution in the body, through the general blood circulation;
- Elimination by metabolism (biotransformation, mainly in the liver);
- Excretion (mainly urinary, in a smaller amount biliary) (Altman *et al.*, 2015) [6].

The absorption of diclofenac contained in non-modified pharmaceutical forms is rapid, directly proportional to the dose. The absorption rate depends on the type of salt (sodium, potassium, epolamine). Sodium salt is better absorbed at the small intestinal level, potassium salt can be absorbed starting at the stomach level [7].

It also depends on the pharmaceutical composition (excipients and the pressing force of the machine that produced the tablets are of great importance), on the relationship with food (food can usually decrease absorption). Inconstant absorption is caused by inter-individual differences in gastrointestinal pH, partial precipitation in acidic stomach pH, variable gastric emptying times, and enterohepatic circulation [8].

Diclofenac is a weak acid compound that, after absorption, binds in a very high percentage to the plasma proteins (albumins). Many of its drug-drug interactions occur because of this process, those with other NSAIDs such as acetylsalicylic acid being the most important [9].

Diclofenac concentrates in the inflamed tissues where it detaches from the plasma proteins due to the local acidic pH, becomes liposoluble and thus ends up by diffusing more easily in the inter-cellular tissue spaces, and also intra-cellularly, resulting in an increase in the therapeutic effect. Diclofenac is rapidly distributed in the synovial fluid, reaching C_{max} in 2–4 hours after the plasma peak. It accumulates in synovial fluid at higher levels than in plasma and for longer periods of time [10].

Diclofenac sodium salt is detected in synovial fluid 11 hours after administration of a 50 mg enteric tablet and 25 hours after a 100 mg prolonged-release tablet [11]. The therapeutic effect of diclofenac at its site of action (in the inflamed tissue) is high, and it exceeds the plasma $T_{1/2}$ duration (which is approx. 1–2 hours). This is explained by the fact that diclofenac persists for a long time at the site of the inflammatory process ($T_{1/2}$ for elimination from joints is 3 times higher than the plasma $T_{1/2}$).

Also, diclofenac inhibits COX-2, an enzyme secreted by local inflammatory cells and decreases the level of PGE2 and proinflammatory cytokines (IL-6 and substance P). All these actions increase pharmacodynamic effect duration (longer time of the therapeutic effect after a single oral high dose of 100mg) [12].

It passes the placental barrier but does not accumulate in foetal tissues. The teratogenic risk is low [13]. It may pass into breast milk in very small amounts (6 hours after i.m. injection of 50 mg diclofenac in women immediately after they

gave birth, no diclofenac was detected in the milk) [14]. Other agents having more information published, and they are preferred especially while nursing a newborn or preterm infant [15]. In conclusion, diclofenac is not recommended for nursing mothers.

Biotransformation occurs in two stages. In the first step, 4-hydroxy-diclofenac, the main metabolite of diclofenac, has weak anti-inflammatory and analgesic effects. In the second step, glucuronide-conjugate and sulphate-conjugation metabolites result, which do not have any pharmacological activity (Davies & Anderson, 1997) [16]. Excretion of these inactive metabolites takes place approximately 65% via urine and approximately 35% via bile, entering the enterohepatic circuit [17]. Other aspects are presented in the item regarding the pharmacotoxicology of diclofenac.

The pharmacodynamic phase

It refers to the actions of the drug at the level of the entire body or tissues, and also to its molecular mechanisms of action. By acting on both cyclooxygenases, diclofenac, like other NSAIDs, can produce adverse reactions that constitute the pharmacotoxicologic component of the pharmacodynamic phase. Thus, the same mechanism could lead to adverse effects along with the therapeutic ones.

The main mechanism of action of Diclofenac is the inhibition of both cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). By inhibiting the constitutive COX-1, it produces a weak inhibition of platelet aggregation, but at therapeutic doses, it seems not to affect the bleeding time. The inhibition of COX-2, an enzyme induced in the inflammatory process, leads to blocking of the transformation of arachidonic acid into cyclic endoperoxides, inhibiting their downstream transformation into prostaglandins, prostacyclin and thromboxanes. Consequently, the formation of prostaglandins (*e.g.*, PGE2), prostacyclin (PGI2) and thromboxane (*e.g.*, TXA2) decreases. At doses lower than or equal to 150 mg/day, diclofenac preferentially inhibits COX-2 (acts like a COX-2-selective NSAID), which also means a lower risk of gastrointestinal damage (Altman *et al.*, 2015) [6] and a possible higher cardiovascular risk.

At the level of the gastrointestinal tract, PGE2 has a protective role by increasing the synthesis of mucus and bicarbonate and facilitating the physiological restoration process of the gastric mucosa. The decrease in PGE2 synthesis by inhibiting COX can lead to adverse gastrointestinal reactions, such as pyrosis, erosive gastropathy, ulcers etc. At the renal level, PGE2 produces vasodilation and favours glomerular filtration. Decreased PGE2 synthesis by COX inhibition increases the risk of water and salt retention, arterial hypertension, nephropathy etc. At the cardiovascular level, PGI2 (formed in vascular endothelial cells) produces vasodilation and inhibits platelet aggregation.

PGE2 is the main prostaglandin responsible for the pathological manifestations of the inflammatory process: *rubor*, *tumor*, *calor*, *dolor*, *functio laesa*. Prostaglandins, prostacyclins and thromboxanes are also involved in many beneficial physiological processes [12].

Orally administrated pharmaceutical forms are indicated:

- In the long-term treatment of inflammatory and degenerative rheumatic diseases, such as rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the spine, abarticular rheumatism etc.;
- In the short-term treatment, in the acute stage of the following clinical situations: acute articular and abarticular inflammations (bursitis, capsulitis, synovitis, tendinitis or tenosynovitis); lumbago; radiculitis; microcrystalline arthritis; acute episodes of gout; post-traumatic and post-operative pain, inflammation and oedema, *e.g.* after dental or orthopaedic surgery; painful and/or inflammatory conditions in gynaecology, for example, primary dysmenorrhea or adnexitis; adjuvant in severe painful inflammatory infections of the ear, nose, or throat, *e.g.* pharyngotonsillitis, otitis; cold and flu symptoms, including fever, sore throat and catarrh; acute migraine attack.

Orally administrated pharmaceutical forms are contraindicated in:

- Hypersensitivity to diclofenac or to any of the drug excipients;
- Active gastric or duodenal ulcer, haemorrhage or perforation or history of gastrointestinal bleeding or perforation related to previous NSAID treatment;
- Disorders of haematopoiesis of unspecified aetiology;
- Recent rectal bleeding;
- The third trimester of pregnancy;
- Liver failure;
- Renal failure;
- Congestive heart failure (classes NYHA II-IV);
- Ischemic cardiac disease;
- Peripheral arteriopathy and/or cerebrovascular disease;

- In patients whose asthma attacks, urticaria or nasal polyposis/acute rhinitis were aggravated by acetylsalicylic acid or other NSAIDs;
- Children and adolescents under 14 years of age [18].

Oral pharmaceutical forms

The following pharmaceutical forms of diclofenac are on the market: gastro-resistant dragees, film-coated tablets, gastro-resistant tablets, extended-release tablets, and extended-release capsules. (Table 1). Tablets are the most common oral pharmaceutical forms, but they often face bioavailability issues due to incomplete absorption of the active substance. The bioavailability is increased from dragees and tablets (almost equal) to capsules. The best absorption would be for oral (drinkable) solutions [5].

Diclofenac is an excellent example of how innovation in pharmaceutical engineering can contribute to the creation of new pharmaceutical forms using older active molecules whose pharmacological properties could be considerably improved by increasing their bioavailability, efficacy, tolerability, and safety. Such benefits lead to higher treatment adherence.

Simple tablets (uncoated) are oral solid pharmaceutical forms, obtained from agglomerated or aggregated and compacted solid particles, from which the active substance is available for absorption after a certain time required for the medicine to disintegrate, first, into coarse particles, then into fine particles which can be dissolved and absorbed.

Coated tablets are covered with one or more layers of mixtures of various substances such as: natural/synthetic resins, gums, gelatine, inactive and insoluble diluents, sugars, plasticizers, polyols, waxes, colouring matter, flavouring substances and also the pharmacodynamic active substances. If the coating is a thin polymer film, the tablets are called film-coated tablets. If the coating is thick and made of sugar, they are named dragees. In order to release the medicinal substance, the coating must first be removed. These coatings are quickly destroyed and release the active substance. Film-coated tablets should disintegrate in the digestive liquid within 30 minutes.

Coated tablets, other than film-coated tablets, must disintegrate within 60 minutes (*e.g.*, dragees). They have been in clinical practice since the 1980s in order to provide superior protection to the gastric mucosa against the irritating action of the active substance. These are gastro-resistant tablets/capsules designed to resist the action of gastric juice and release the active substance only in the intestinal environment (delayed release).

In laboratory tests simulating a gastric acid environment, gastro-resistant tablets/capsules should last two hours (sometimes three hours), but never less than one hour. After this, in an environment simulating the intestinal one (pH=6.8), they must dissolve in no more than 60 minutes. Gastro-resistant tablets are generally prepared from granules or particles already covered with a gastro-resistant coating or by covering the tablets with a gastro-resistant coating.

Absorption is delayed by 0.5–2 hours compared to the forms in which the active substance is released in the stomach, which means that the time

Table 1. Treatments using diclofenac, oral route, in adults, in Romania (some products could be used in children over 14 years old).

Generic name/generic names of drugs for combinations	Commercial name	Pharmaceutical form
Diclofenac sodium	Diclofenac 50 mg gastroresistant tablets	Gastroresistant tablets
Diclofenac sodium	Diclofenac Arena 25 mg/50 mg gastroresistant tablets	Gastroresistant tablets
Diclofenac sodium	Diclofenac Helcor 50 mg gastroresistant tablets	Gastroresistant tablets
Diclofenac sodium	N-Diclofenac	Gastroresistant dragee
Diclofenac potassium	Raplon 12,5 mg film coated tablets	Film coated tablets
Diclofenac sodium	Diclofenac Duo Pharmaswiss 75 mg	Extended-release capsules
Diclofenac sodium	Dicloreum 150 mg extended-release capsules	Extended-release capsules
Diclofenac sodium	Diclotard 100 mg	Extended-release tablets
Diclofenac sodium	Refen Retard 100 mg	Extended-release tablets

elapsed until reaching C_{max} is longer, and the pain relief is not rapidly established. However, the effectiveness in arthrosis is similar to that of indomethacin, naproxen, ibuprofen and other NSAIDs. Delayed-release pharmaceutical forms are also recommended for chronic pain.

Gastro-resistant tablets reduce the risk of gastrointestinal ulcers, but the action of the active substance on the digestive mucosa could be transferred to the distal segments of the gastrointestinal tract. Diaphragm disease, a rare small or large intestine endoscopic finding, could be retrieved in the intestinal exploration of patients with chronic treatment with NSAIDs [19]. Diaphragm disease is a rare complication of chronic NSAIDs therapy with lesions comprising multiple (3–70), thin (2–4 mm), concentric, septa-like mucosal projections that may result in narrowing of the intestinal lumen [20].

There are also pharmaceutical forms capable of releasing the active substance in well-defined places of the intestinal tract. They have been introduced into clinical practice since 1990s in order to offer the possibility of a better control of prolonged pain from rheumatic joint diseases, like osteoarthritis, spondylarthritis, rheumatoid arthritis.

These technologies use a multilayer matrix containing diclofenac. The outer layer of the matrix is much less soluble than the inner one, but it can self-expand in the intestinal environment, which offers the possibility of gradual and continuous release of the active substance as the underlying layers solubilize. In this way, the administration of a single dose of 100 mg of diclofenac can maintain its effectiveness for almost 24 hours. If diclofenac immediate-release tablets or dragees are used, 2–3 administrations per day would be required to maintain efficacy over the entire 24-hour interval, as diclofenac has quite a rapid systemic clearance. Despite comparable bioavailability to gastro-resistant tablets, extended-release tablets have a lower C_{max} and a delayed Tmax. Therefore, for faster control of acute pain, it is necessary to administer an additional dose of 25–50 mg of rapid-release diclofenac.

Pharmacokinetics of an oral innovative formulation of diclofenac: 150 mg prolonged release capsule

In therapeutic use, there is a significantly improved pharmaceutical form of 150 mg diclofenac extended-release capsule based on the use of multilayer pellets in which the active substance is "trapped" between the polysaccharide core (sugar spheres/sucrose granules) and the two layers that cover it on the outside (hard-soluble paraffin and insoluble methacrylic polymer).

The sugar spheres (Macrogol 4000) act as inert cores upon which the diclofenac sodium powder is deposited. These inert carriers provide a uniform substrate for drug loading and subsequent layering, ensuring consistent granule and drug distribution [18, 21].

The diclofenac sodium is layered onto the sugar spheres, and Macrogol 4000 functions as an adhesive agent, ensuring that the active ingredient adheres uniformly to the sugar cores. On top of these active granules, there is a first layer of a paraffin solution in methylene chloride. This layer prevents immediate dissolution in gastric fluids, thus protecting the gastric mucosa from direct exposure to diclofenac sodium. It also contributes to the initial modulation of drug release by slowing down water penetration into the core. The first paraffin layer is coated with the second layer of methacrylic acid polymers, which acts as a pH-sensitive retarding agent along the gastrointestinal tract. This polymer remains intact in acidic conditions (stomach), preventing drug release. In the higher pH environment of the gut, the polymer gradually expands and dissolves, permitting drug release, its diffusion and absorption [18, 22].

In summary, for this innovative oral formulation, the release of diclofenac sodium active ingredient into the intestinal lumen becomes possible due to the concentration gradient and the pH gradient after self-expansion of the outer layer into the weak intestinal acid environment and the solubilization of the underlying paraffin layer [18].

In this way, 50 mg of diclofenac is released in the first hour (rapid/immediate release) after which the pH gradient reaches equilibrium and modulates the release of the remaining 100 mg for the next 23 hours (prolonged release) due to the concentration gradient.

Consequently, adherence to treatment is superior for this kind of prolonged-release diclofenac pharmaceutical forms that require one single daily administration in comparison to fast-release ones that require 2 or 3 administrations per day. Besides an increased patient adherence, 150 mg prolonged-release diclofenac pharmaceutical forms improve efficacy and safety, keeping as much as possible the plasma concentrations within the therapeutic window.

A single daily administration of a 150 mg prolonged-release diclofenac pharmaceutical form is followed by a single plasma concentration peak and a steady state concentration within the synovial fluid (maximum efficacy).

Pharmacotoxicology of diclofenac (adverse reactions)

Although diclofenac presents a much lower risk of severe gastrointestinal complications (*e.g.*,

gastro-duodenal ulcers, digestive bleeding, perforations) at therapeutic doses, due to more selective inhibition of COX-2 isoenzymes, this gastrointestinal risk cannot be ruled out.

The pharmacokinetics of diclofenac also depend on gene polymorphism, which can increase its risk of hepatopathy, leading to acute hepatitis in those with higher catalytic activity of UGT2B7 (uridylic glucuronic transferase 2B7). The hepatotoxic effect of diclofenac is produced by a decrease in ATP concentration due to the drug and also by a reduction in ATP synthesis, together with the useless consumption of NADPH [23]. Diclofenac can induce a severe liver injury because of reactive quinone imine and acyl glucuronide metabolites that deplete hepatic glutathione [24].

The cardiovascular risk, which is dose-dependent, is not to be neglected. Decreased PGI2 synthesis by COX-2 inhibition may increase the risk of arterial hypertension and thrombosis (this effect was especially described with COXibs, *e.g.*, rofecoxib, withdrawn from the market for this reason) (Sibbald, 2004) [25].

Topical-cutaneous pharmaceutical forms

Several topical-cutaneous pharmaceutical forms containing diclofenac in different concentrations are registered in Romania:

- Ointment – contains approx. 80% oil in water;
- Cream – contains "oil in water" or "water in oil";
- Gel – does not contain oil (non-greasy formulation), but cellulose, alcohol and water;
- Cutaneous foam – does not contain oil (non-greasy formulation), but macrogol-6 glycerol caprylocaprate, alcohol, Phospholipon® 80 H and water.

There are other topical-cutaneous pharmaceutical forms containing diclofenac in different concentrations (some innovative): solutions, transdermal skin systems (TDDS-transdermal drug delivery systems) – *e.g.*, medicated patches. (Table 2).

Table 2. Topical cutaneous preparations of diclofenac in Romania (for adults and children over 14 years of age).

Generic name/generic names of drugs for combinations	Commercial name	Pharmaceutical form
Diclofenac sodium	Clafen 10 mg/g	Cream
Diclofenac sodium	Clafen 10 mg/g	Gel
Diclofenac sodium	Clafen forte 50 mg/g	Gel
Diclofenac sodium	Clafen rapid 11.6 mg/g	Gel
Diclofenac sodium	Diclac 10 mg/g	Emulsion gel
Diclofenac sodium	Diclac 50 mg/g	Gel
Diclofenac sodium	Diclofenac Chirmis 10 mg/g	Gel
Diclofenac sodium	Diclofenac Dr. Max 50 mg/g	Gel
Diclofenac sodium	Diclofenac Fiterman 10 mg/g	Cream
Diclofenac sodium	Diclofenac Fiterman 10 mg/g	Ointment
Diclofenac sodium	Diclofenac MCC 10 mg/g	Cream
Diclofenac sodium	Diclofenac MCC 10 mg/g	Gel
Diclofenac sodium	Diclofenac MCC 50 mg/g	Gel
Diclofenac sodium	Diclofenac Rompharm 10 mg/g	Cream
Diclofenac sodium	Diclofenac Slavia 10 mg/g	Gel
Diclofenac sodium	Diclofenac Terapia 10 mg/g	Cream
Diclofenac sodium	Diclofenac Terapia 10 mg/g	Gel
Diclofenac sodium	Diclofenac Terapia 50 mg/g	Gel
Diclofenac sodium	Diclofenac Tis 10 mg/g	Gel
Diclofenac	Dicloreum 30 mg/g Cutaneous foam	Cutaneous foam
Diclofenac sodium	Diclosal 10 mg/g	Cream

Table 2. Continued.

Generic name/generic names of drugs for combinations	Commercial name	Pharmaceutical form
Diclofenac sodium	Diclosal 10 mg/g	Gel
Diclofenac sodium	Diclosal 50 mg/g	Gel
Diclofenac sodium	Diclosin 10 mg/g	Gel
Diclofenac sodium	Diclosin 50 mg/g	Gel
Diclofenac sodium	Volini 50 mg/g	Gel
Diclofenac sodium	Volini 10 mg/g	Gel
Diclofenac	Voltaren 140 mg	Medicated patches
Diclofenac diethylamine	Voltaren Actipro 11.6 mg/g	Gel
Diclofenac diethylamine	Voltaren Forte 23.2 mg/g	Gel

In localized inflammatory conditions, the topical administration of diclofenac (as well as NSAIDs in general) presents several advantages, the most important of them being maximization of therapeutic effects, decrease of systemic adverse effects, and increase of patient adherence.

Variability factors of the bioavailability of an active substance after topical-cutaneous application are: the degree of hydration of the epidermis, the thickness of the *stratum corneum* which influences transdermal diffusion, the degree of vascularization of the dermis by vasodilation, a better dispersion of the active substance from the application site (which is favoured by the method of application of the medicinal preparation repetitively, under an occlusive dressing, by local massage, or by ultrasound penetration) [26]. Various pharmaceutical forms and vehicles are used to facilitate transcutaneous penetration of the active substance (foam has the highest penetrability, followed by gel, cream and ointment, for similar concentrations).

A finding from a clinical study was that after topical administration of diclofenac on the surface of one gonarthrotic knee, the active substance was distributed by the blood flow to the contralateral knee [27].

Topical diclofenac diethylamine 2.32% w/w gel penetrated into the osteoarthritic knee after repeated application and remained detectable in synovial tissue and fluid at the end of the final 12 h dosing cycle [28].

In the past 5–10 years, new techniques of evaluation of *stratum corneum* permeability for diclofenac and excipients such as propylene glycol and butylene glycol were developed for medicated patches. Actinic keratosis is a new possible indication of diclofenac with topical administration [29].

Drug amounts in the *stratum corneum* increased with time of application up to 6 h and no further increase was observed when the administration was prolonged to 12 h. When the plaster was removed after 6 h of wear, diclofenac cleared relatively slowly from the *stratum corneum* suggesting that drug was bound at this level with a slow off-rate.

This fact implies that diclofenac in medicated patches is useful in dermatologic diseases in doses administered at 12 hours interval and the clearance of the cutaneous absorbed diclofenac is slow. The problem is that the active substance and the vehicles (propylene glycol, butylene glycol) had a divergent pharmacokinetic behaviour. The study concluded that the various pharmaceutical forms of diclofenac administered cutaneous might have great differences in absorption only after a slight modification of excipients. Consequently, the efficacy in dermatologic and inflammatory diseases or other related pathologies is unpredictable in various topical pharmaceutical forms of diclofenac [30].

Diclofenac cutaneous foam (5%) was topically administered on the thigh, in a dose of 80 mg/200 cm^2 twice daily for a period of 7 days in healthy volunteers (n=12). On Day 8, 2 microdialysis probes were inserted into skeletal muscle tissue beneath the application site and a dose of 80 mg was administered cutaneous. Concentration *versus* time profiles in plasma and skeletal muscle were followed for 10 hours. Mean C_{max} in plasma was 18.75±4.97 ng/ml. Corresponding interstitial concentrations in skeletal muscle were significantly higher (more than ten times), 219.68± 66.36 ng/ml (p=0.01). (Müller *et al.*, 1998) [31]

Diclofenac foam 30 mg/g is an innovative non-greasy topical-cutaneous pharmaceutical form with probably the highest skin penetrability due to the use of Phospholipon® 80 H, a special transcellular phospholipid vehicle which is increasing the penetrability of the diclofenac molecule through the *stratum corneum* of the skin by approximately 6 times compared to a gel formulation that does not contain such a facilitating vehicle.

According to the SPC of Diclofenac foam 30 mg/g approved in Romania [32], after cutaneous administration the interstitial concentrations of the active substance in the muscle tissue are higher than those recorded with the same oral dose. After topical-cutaneous application of this foam, only a very small part of the absorbed diclofenac reaches the systemic circulation, while obtaining a plasma concentration of approximately 100 times lower compared to that obtained after oral administration of the same dose of diclofenac.

Topical – cutaneous administrated pharmaceutical forms are indicated in local symptomatic treatment in adults and children over 14 years old in the following pathologies:

- Muscular or osteoarticular pain and inflammation of rheumatic cause;
- Post-operative and post-traumatic oedemas;
- Muscular or osteoarticular pain and inflammation of traumatic nature (*e.g.* minor injuries of tendons, muscles, ligaments);
- Localized forms of abarticular rheumatism: tendinitis (*e.g.* lateral epicondylitis), bursitis, shoulder-hand syndrome and periarthritis.

Topical – cutaneous administrated pharmaceutical forms are contraindicated in:

- Hypersensitivity to diclofenac, to other NSAIDs or to any of the drug excipients;
- Patients with a history of bronchial asthma, urticaria or nasal polyposis to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs;
- Skin lesions, such as: eczema, infected lesions, burns, wounds;
- Patients with peptic ulcer;
- The third trimester of pregnancy;
- Children and adolescents under 14 years of age (see SPC Dicloreum foam 30 mg/g) [32].

Other topical pharmaceutical forms of diclofenac

Administration of diclofenac sodium in ocular instillations has numerous indications: inhibition of miosis during cataract surgery, treatment of inflammation and postoperative pain after cataract surgery or other types of surgical interventions (surgical correction of strabismus, after surgical correction of refractive disorders or after other surgical interventions at the level of the anterior pole of the eye), control of inflammation and post-traumatic pain after non-penetrating trauma, improving the signs and symptoms of seasonal allergic conjunctivitis, pre- and postoperative prevention of cystoid macular oedema associated with cataract extraction and artificial lens implantation, postoperative pain after photorefractive radial keratectomy, non-infectious inflammatory conditions of the anterior pole of the eye (chronic non-infectious conjunctivitis).

In humans, after instillation into the conjunctival sac, diclofenac sodium is absorbed into the aqueous humour and enters the anterior chamber of the eyeball. After topical ophthalmic administration of diclofenac 1 mg/ml, the systemic absorption of the active substance is practically negligible, no measurable levels of diclofenac being detected. Repeated and/or prolonged instillations of diclofenac 1 mg/ml may induce a systemic passage of diclofenac, but clinically insignificant (SPC Diclofenac eyedrops) [33].

Diclofenac as a mouthwash is indicated for the symptomatic treatment of irritation or inflammation states of the oropharyngeal cavity, associated with pain (*e.g.* gingivitis, stomatitis, pharyngitis, conservative dental treatments, or tooth extractions). Spectro-fluoroscopy indicated that diclofenac concentrates in the oral mucous membrane and then it is gradually absorbed, thus producing low plasma concentrations (SPC of a Diclofenac mouthwash, Glimbax 0.074 g/mL, Romania) [34].

Other systemic pharmaceutical forms of diclofenac

Suppositories

Although diclofenac in suppositories is rapidly absorbed, the absorption rate is lower than with oral tablets. After administration of a 100 mg suppository, the maximum plasma concentration is reached within one hour and is around 2 mg/l. The pharmacokinetics of diclofenac do not change after repeated dosing. There is no accumulation of the medicinal product if it is administered in the recommended doses and at the recommended intervals: maximum 150 mg per day, one suppository per day in the evening (SPC Clafen 100 mg suppositories, Romania) [35].

Injectable forms

Injectable preparations of diclofenac are used for faster onset of action (or in other conditions when oral NSAIDs could not be administered) as a single agent in acute or moderate pain, or in combination with opioids in moderate to severe pain, for example in postoperative pain. They can also be used by this route of administration in febrile syndromes and severe osteoarticular inflammatory diseases (gout, osteoarthritis).

Injectable preparations of diclofenac are conditioned in the form of sodium salts and with a solubilizing agent – hydroxypropyl-β-cyclodextrin

(HPβCD), or in the form of solutions with benzyl alcohol and propylene glycol. These pharmaceutical forms can be administered intramuscularly, but additional precautions are necessary for intravenous administration.

Unlike HPβCD-diclofenac, propylene-glycol and benzylic acid diclofenac must be diluted, buffered, and administered by infusion over 30–120 minutes. HPβCD-diclofenac, but not other injectable forms, can be administered also to patients with mild or moderate renal impairment or mild hepatic impairment, without dose adjustments [36]. Regarding the products with propylene-glycol and benzylic acid, these are contraindicated in severe renal or hepatic impairment [37].

Regarding the preparation with HPβCD, the clearance and the distribution parameters after injectable route are not significantly modified by the presence of mild renal insufficiency (50–80 ml/min creatinine clearance), and some did not change even in moderate renal insufficiency (30–50 ml/min clearance to creatinine). Half-life time ($T_{1/2}$) was 1.9±0.3 h in healthy volunteers and 2.1±0.44 h in those with moderate renal impairment. Apparent volume of distribution (V_d) was 50 l in healthy volunteers and 70 l in those with moderate renal impairment [36].

Conclusions

Diclofenac is a standard NSAID molecule in terms of efficacy and safety and has stood the test of time (more than 50 years after its introduction into medical practice).

The innovation in manufacturing technologies led to the emergence of new pharmaceutical forms that generated major changes in the pharmacokinetics of the active substance and, consequently, in its pharmacodynamics, mainly by increasing efficiency in rheumatic or other inflammatory diseases. Thus, the innovative pharmaceutical forms of diclofenac bring about an improvement of some pharmacokinetic characteristics and parameters such as bioavailability following administration on different routes, preferential distribution at the site of action, faster elimination from plasma along with long term maintenance of active and effective concentrations in target tissues (synovia, muscles etc.).

Finally, all these advances in pharmaceutical formulation increase therapeutic efficacy, treatment adherence and significantly reduce the risk of adverse reactions.

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Conflict of interest

The authors declare no conflict of interest.

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