Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Diclofenac Sodium and Diclofenac Potassium

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ABSTRACT: Literature data are reviewed regarding the scientific advisability of allowing a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing either diclofenac potassium and diclofenac sodium. Within the biopharmaceutics classification system (BCS), diclofenac potassium and diclofenac sodium are each BCS class II active pharmaceutical ingredients (APIs). However, a biowaiver can be recommended for IR drug products of each salt form, due to their therapeutic use, therapeutic index, pharmacokinetic properties, potential for excipient interactions, and performance in reported BE/bioavailability (BA) studies, provided: (a) test and comparator contain the same diclofenac salt; (b) the dosage form of the test and comparator is identical; (c) the test product contains only excipients present in diclofenac drug products approved in ICH or associated countries in the same dosage form, for instance as presented in this paper; (d) test drug product and comparator dissolve 85% in 30 min or less in 900 mL buffer pH 6.8, using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm; and (e) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1206–1219, 2009

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INTRODUCTION

A biowaiver monograph of diclofenac is presented based on literature data and new experimental data. Risks are evaluated in basing a BE assessment on *in vitro* study results (i.e., "biowaiving"), rather than *in vivo* study results, for the approval of new IR solid oral dosage forms containing diclofenac sodium and diclofenac potassium, for example, plain IR tablets, dispersable tablets and powders for oral solutions. This risk evaluation considers diclofenac sodium and diclofenac potassium biopharmaceutical and clinical properties, as they pertain to reformulated products and new multisource products. This evaluation concerns drug products containing diclofenac as the only API and does not concern combination drug products. This evaluation does not concern delayed release products or any other modified release formulations of diclofenac.

The purpose and scope of this series of monographs have been previously discussed.[1] Briefly, the aim is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of making an incorrect biowaiver decision, as well as the resulting consequences of such a decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver is advisable or not. This systematic approach to recommend for or to advise against a biowaiver is described in the recently published World Health Organization (WHO) Guideline.[2] These monographs do not intend to simply apply the WHO, FDA[3] and/or EMEA Guidance,[4] but aim to apply these guidances and further serve as a critical validation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),[5] acetazolamide,[6] aciclovir,[7] amitriptyline,[8] atenolol,[1] chloroquine,[9] cimetidine,[10] ethambutol,[11] ibuprofen,[12] isoniazid,[13] metoclopramide, prednisolone,[14] prednisone,[15] pyrazinamide,[16] propranolol,[1] ranitidine,[17] and verapamil.[1] They are also available on-line at www.fip.org/bcs. Although diclofenac is not on the present WHO List of Essential Medicines,[18] it was considered appropriate to include this widely used and important API in this series.

Literature Review

Published information was obtained from PubMed up to November 2007. Key words used were: diclofenac potassium, diclofenac sodium, NSAID, indication, therapeutic index, solubility, polymorphism, partition coefficient, pK_a, absorption, permeability, distribution, metabolism, excretion, excipients, bioequivalence and dissolution.

GENERAL CHARACTERISTICS

Name and Structure

The chemical name of diclofenac is 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid. Its structure is shown in Figure 1.

Therapeutic Indication, Side Effect and Therapeutic Index

Diclofenac is a well-known nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties, comparable or superior to other NSAIDs.[19] Diclofenac shows preferential inhibition of the cyclooxygenase-2

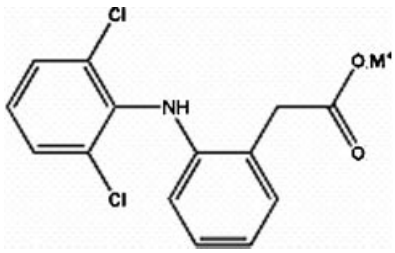

Figure 1. Structure of diclofenac, where M = K^+ or Na^+ for potassium or sodium salt, respectively.

(COX-2) enzyme.[20] Diclofenac sodium is mainly indicated in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Diclofenac potassium is claimed to dissolve faster, and hence absorbed faster, than the sodium salt and is recommended for the treatments that need short onset of action, mainly for its analgesic properties. Diclofenac potassium is also indicated for the treatment of primary dysmenorrheal and mild to moderate pain.[21,22] As with other NSAIDs, diclofenac is known to increase the risk of gastrointestinal bleeding and cardiovascular side effects.[21,22] However, diclofenac has a relatively high therapeutic index in comparison to other NSAIDs.[23]

PHYSICOCHEMICAL PROPERTIES

Salts, Esters, Polymorphs, Hydrates

Diclofenac is usually formulated as the sodium or potassium salt, but other salts are also used, such as hydroxyethylpyrrolidine salt for oral preparations, and diethylammonium and diethylamine for topical preparation.[24] This monograph refers to drug products containing the sodium or potassium salt of diclofenac only. Most "plain" tablets contain the potassium salt, whereas most dispersable dosage forms contain diclofenac sodium, see Tables 1 and 2. In this monograph, the term diclofenac without indicating the salt form refers to the sodium and potassium salts. Trihydrates and tetrahydrates exist for both of diclofenac potassium and diclofenac sodium,[25,26] but in pharmacopoeial drug products only the anhydrate is used.[27,28]

Solubility

Solubility values for diclofenac sodium taken from the literature[29] are shown in Table 3 and experimentally determined solubilities of diclofenac potassium are show in Table 4, respectively, together with the dose to solubility ratios (D/S) for several tablet strengths.

Polymorphism

Reports of diclofenac potassium or diclofenac sodium polymorphs were not found in the literature.

Partition Coefficient

Partition coefficient in *n*-octanol/aqueous buffer ($\log D$) are reported to be 1.4 and 1.1 for pH 6.8 and 7.4, respectively.[30–32] The experimental $\log P$ (*n*-octanol/water) and $C\log P$ values of diclofenac are 4.40 and 4.71, respectively,[33,34] which are larger than the corresponding values of 1.72 and 1.35 for the highly permeable marker drug metoprolol.[35]

pK_a

The pK_a of diclofenac is about 3.80 at 25°C.[36,37]

Strengths of Marketed Drug Products

Dosage form strength is expressed in mg of salt present, not equivalent of the free acid. In the United States (US) and in the EU, Marketing Authorizations (MAs), that is, registrations, exist for IR solid oral dosage forms for 12.5, 25, and 50 mg diclofenac salt, see Tables 1 and 2. Higher strengths of these drugs have been marketed, but only as delayed release solid forms or combination oral products; however, such products are outside the scope of this monograph.

PHARMACOKINETIC PROPERTIES

The majority of pharmacokinetic data concerns diclofenac sodium. Literature reports indicate that diclofenac sodium and diclofenac potassium are similar in terms of extent of oral absorption, pattern of distribution, metabolism, and elimination.[38]

Absorption and Permeability

Diclofenac is 100% absorbed after oral administration, compared to intravenous administration, based on urine recovery studies.[21,22] Only about 60% of drug reaches the systemic circulation due to first pass metabolism.[39,40] In some fasting volunteers, measurable plasma levels are observed within 10 min of dosing with diclofenac potassium, although peak plasma levels are generally achieved after 0.33–2 h.[21] For enteric-coated diclofenac sodium tablets, drug is released once the tablet reaches the duodenum, with subsequent rapid absorption.[30,41,42] Absorption of diclofenac occurs throughout the intestinal tract.[43–46] Diclofenac shows linear pharmacokinetics. The absolute BA of diclofenac potassium after oral administration did not differ significantly when 1×12.5- and 2×12.5-mg were dose in a randomized, three-way, crossover study in

Table 1. Excipients[a] Present in Diclofenac[b] IR Solid Oral Drug Products[c] With a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES), Sweden (SE), United Kingdom (UK) and the United States (US)[d], and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products With an MA in the USA[e]

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Benzoic acid	DK(1) NO(2) SE(3)	No data
Calcium hydrogen phosphate	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18) UK(19)	104–850
Calcium phosphate	DE(20) DK(21) FI(22) NL(23) NO(24) SE (25,26) US(27,28)	21–362
Carmellose sodium	DK(29) FI(30) NO(31) SE (32)	2.2–160
Cellulose	DE(20,33–36) DK(1,29,37) ES(38,39) FI(30,40) FR (41) NL(23,42,43) NO(2,31,44,45) SE (3,25,26,32,46,47) US(27,28,48,49)	4.6–1385[f]
Croscarmellose sodium	FI(40) US (48)	2–180
Crospovidone	DE(50,51)	4.4–792[f]
dimeticone	DE(33)	3.7
Glycerol	DK(29) FI(30,40) NO(31) SE (32)	0.14–198[f]
Glycerol dibehenate	DE(50,51)	5.7–14
Hypromellose	DE(34–36,50,51) DK(1,29,37) ES(38) FI(30,40) FR (41) NO(2,31) SE (3,32) US (28,48)	0.8–86
Lactose	DE(34–36) DK(1,29,37) ES(38,39) FI(30,40) FR (41) NL(42,43) NO(2,31,44,45) SE (3,32,46,47) US (28,48,49)	23–1020[f]
Lecithin	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18)	5–15
Macrogol	DE(20,33–36,50,51) DK(1,37) ES(38) FR (41) NL(23) NO(2) SE (3,25,26) US (27,28,48)	0.12–500[f]
Macrogol stearate	DK(1) NO(2) SE (3)	
Magnesium stearate	DE(4,20,33–36,50,51) DK(1,5–12,21,29,37) ES(38,39) FI(13,14,22,30,40) FR (41) NL(23,42,43) NO(2,15,16, 24,31,44,45) SE (3,17,18,25,26,32,46,47) UK(19) US (27,28,48,49)	0.15–401[f]
Maltodextrin	DE(35,36) DK(37) FR (41)	0.16–80
Mannitol	DE(50,51)	33–454
Octamethylcyclotetrasiloxane	DK(1) NO(2) SE (3)	No data
Polydextrose	US (48)	3.8–8.1
Polysorbate[g]	DK(37)	No data
Polysorbate 80	DE(35,36) FR (41)	2.2–418[f]
Poly(vinylalcohol)	DE(4) DK(5–8) FI(13,14) NO(15,16) SE (17,18)	0.7–20
Potassium hydrogen carbonate	DE(50,51)	12
Povidone	DE(4,20,33–36) DK(5–12,21,37) ES(38,39) FI(13,14,22) FR (41) NL(23,42,43) NO(15,16,24,44,45) SE(17,18,25,26,46,47) UK (19) US (27,28)	0.17–75
Silica	DE(4,20,34–36) DK(5–12,21,29,37) ES(38,39) FI(13, 14,22,30,40) FR (41) NL(23,42,43) NO(15,16,24,31,44,45) SE (17,18,25,26,32,46,47) UK (19) US (27,28,48)	0.65–99
Simethicone	DK(1) NO(2) SE (3)	0.0004–5.7
Sodium hydroxide	DE(33)	0.74–6.7
Sodium lauryl sulphate	DE(50,51) US (48)	0.65–50
Sodium starch glycolate	DE(4,20,33,35,36) DK(1,5–12,21,37) ES(38,39) FI(13,14,22) FR (41) NL(23,42,43) NO(2,15,16,24,44,45) SE (3,17,18,25,26,46,47) UK (19) US (27,28)	2–876[f]
Sorbic acid	DK(1) NO(2) SE (3)	0.94

(*Continued*)

Table 1. (*Continued*)

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Starch	DE(4,20,33–36) DK(1,5–12,21,29,37) ES(38,39) FI(13,14,22,30,40) FR (41) NL(23,42,43) NO(2,15,16,24,31,44,45) SE (3,17,18,25,26,32,46,47) UK(19) US (27,28)	0.44–1135[f]
Starch, pregelatinized	US (49)	6.6–600
Sucrose	DE(20,33) NL(23) SE (25,26) US (27)	12–900
Talc	DE(4,20,33,34) DK(1,5–12) ES(38) FI(13,14) NL(23) NO(2,15,16) SE (3,17,18,25,26)	0.26–220[f]
Triacetin	US (48)	0.72–15
Xanthan gum	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18)	14

1. Eeze, filmovertrukne tabletter
2. Ezze 25 mg filmdrasjerte tabletter
3. Eeze 25/50 mg, filmdragerade tabletter
4. Diclac® Dolo 12.5 mg Filmtabletten (Mono)
5. Diclofenac Rapid "Actavis", filmovertrukne tabletter
6. Diclofenac Rapid "Copyfarm", filmovertrukne tabletter
7. Diclon Rapid, filmovertrukne tabletter
8. Diclopax, filmovertrukne tabletter
9. Fenaclo, filmovertrukne tabletter
10. Dictavis, filmovertrukne tabletter
11. Diclium, filmovertrukne tabletter
12. Fenacta, filmovertrukne tabletter
13. Diclofenac Rapid Actavis 25/50 mg tabletti, kalvopäällysteinen
14. Diclofenac Rapid Copyfarm 25/50 mg tabletti, kalvopäällysteinen
15. Diclofenackalium Actavis 25/50 mg tabletter, filmdrasjerte
16. Diclofenackalium Copyfarm 25/50 mg filmdrasjerte tabletter
17. Diklofenak T Actavis 25/50 mg filmdragerade tabletter
18. Diklofenak T Copyfarm 25 mg och 50 mg filmdragerade tabletter
19. Diclofenac potassium 12.5 mg tablets
20. Voltaren® K Migräne 50 mg überzogene Tabletten (Mono)
21. Voltaren Rapid, overtrukne tabletter
22. Voltaren Rapid 25/50 mg tabletti, päällystetty
23. Cataflam 25/50, omhulde tabletten 25/50 mg
24. CATAFLAM 50 mg drasjerte tabletter
25. Diklofenak T Sandoz 25/50 mg, tabletter
26. Voltaren T 25/50 mg, dragerade tabletter
27. Cataflam® tablet 50 mg, sugar-coated [Novartis Pharmaceuticals Corporation]
28. Diclofenac potassium tablets 50 mg, film-coated [TEVA Pharmaceuticals USA]
29. Diclofenac ratiopharm Rapid, filmovertrukne tabletter
30. Diclomex Rapid 25/50 mg tabletti, kalvopäällysteinen
31. DiclofenacKalium ratiopharm tabletter, filmdrasjert
32. Diclofenac T ratiopharm 25/50 mf filmdragerade tabletter
33. Diclofenac PB 50 mg Tabletten (Mono)[h]
34. Diclodoc® 50 Tabletten (Mono)[h]
35. Optalidon® Zahnschmerz mit Diclofenac Filmtabletten (Mono)
36. Voltaren® Dolo 12. mg Filmtabletten (Mono)
37. Voltaren Dolo, filmovertrukne tabletter
38. DICLOFENACO PENSA 50 mg comprimidos EFG[h]
39. Voltalgial 12.5 mg comprimidos

(*Continued*)

 DOI 10.1002/jps

Table 1. (*Continued*)

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
40.	Diclofenac Rapid ratiopharm 25/50 mg tabletti, kalvopäällysteinen	
41.	VOLTARENDOLO 12.5 mg cp enr	
42.	Voltaren K, omhulde tabletten 12.5 mg	
43.	Otriflu, omhulde tabletten 12.5 mg	
44.	CATAFLAM 12.5 mg tabletter, filmdrasjerte	
45.	Otriflu 12.5 mg tabletter, filmdrasjerte	
46.	Otriflu 12.5 mg filmdragerade tabletter	
47.	Voltaren T 12.5 mg filmdragerade tabletter	
48.	Diclofenac potassium tablets USP, 50 mg film-coated [Mylan Pharmaceuticals Inc.]	
49.	Diclofenac potassium tablets 50 mg, film-coated [Sandoz Inc.]	
50.	Diclo-CT akut 12.5 mg Filmtabletten (Mono)	
51.	Diclofenac-ratiopharm® Schmerztabletten 12.5 mg Filmtabletten (Mono)	

[a]Colourants, flavors and ingredients present in the printing ink are not included. Coating substances are excluded if in the SmPC the constituents of core and coating are stated separately.
[b]Diclofenac potassium and diclofenac sodium. Unless otherwise indicated the reported drug products contain diclofenac potassium.
[ac]Drug products containing more than one API are excluded. Soluble tablets, dispersible tablets and powders and tablets to prepare an oral solution are reported in Table 2.
[d]Sources of data: DE, www.rote-liste.de (assessed September 25, 2007); DK, www.dkma.dk (assessed September 20, 2007); FI, www.nam.fi (assessed September 25, 2007); FR, www.vidal.fr (assessed September 24, 2007); NL, www.cbg-meb.nl. (assessed September 20, 2007); NO, www.legemiddelverket.no (assessed September 24, 2007); ES, www.agemed.es (assessed September 21, 2007); SE, www. lakemedelsverket.se (assessed September 25, 2007); UK, www.mhra.gov.uk (assessed February 7, 2008); USA, http://dailymed.nlm.nih.gov (assessed February 6, 2008).
[fe]FDA's Inactive Ingredient Database: http://www.fda.gov/cder/iig/iigfaqweb.htm#purpose (version date November 1, 2007).
[f]The reported upper range value is unusually high. The authors doubt its correctness.
[g]Without specified grade.
[h]Contains diclofenac sodium.

10 subjects.[39] The systemic absorption of diclofenac as a function of the dose is proportional within the range 25–150 mg,[39,44] which suggests that the low drug solubility at low pH is not limiting absorption.

Administration with food can extend the lag time (t_{lag}) of drug absorption, thereby increasing the time to maximum concentration (t_{max}) and decreasing the maximum concentration (C_{max}). Food does not have a significant effect on the extent of oral absorption of diclofenac sodium or diclofenac potassium.[22,38,47,48] Diclofenac's rapid and complete absorption suggests a high permeability through the intestinal membrane.[43,44] This observation of high permeability throughout the intestinal tract is also supported by reports of rapid absorption of diclofenac from effervescent tablets[45] and the high permeability of diclofenac in the colon after administration of the drug as a suppository.[46]

In a Caco-2 cell monolayer experiment, the permeability of diclofenac from apical-to-basolateral ($P_{A–B}$) and basolateral-to-apical ($P_{B–A}$) directions were 20.2×10^{-6} and 21.3×10^{-6} cm/s, respectively, while metoprolol permeability was $43.4 \pm 0.7 \times 10^{-6}$ and $34.1 \pm 0.6 \times 10^{-6}$ cm/s in the two directions, respectively.[49] Metoprolol is 90–95% absorbed from the intestinal tract and is often used as a reference for the lower limit of a highly permeable drug.[3,35,50] In an artificial membrane model, P_{am} of diclofenac, metoprolol and propanolol were 53.3×10^{-6}, 5.67×10^{-6}, and 13.7×10^{-6} cm/s, respectively.[51]

Distribution

The apparent volume of distribution is 1.3 L/kg for diclofenac potassium[21] and 1.4 L/kg for diclofenac sodium.[22] Circulating diclofenac is known to be greater than 99% bound to human serum protein, primarily to albumin.[30,52] However, this binding has been described as pharmacokinetically insignificant due to the rapid association–dissociation of diclofenac to albumin, such that the drug readily dissociates and permeates across the vascular membrane to the tissues.[38]

Table 2. Excipients[a] Present in Diclofenac[b] IR Soluble Tablets, Dispersable Tablets and Powders for Oral Solution[c] With a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Norway (NO), Spain (ES), Sweden (SE) and United Kingdom (UK)[d], and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products With an MA in the USA[e]

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Castor oil hydrogenated	DE(1–4) DK(5) ES(6) UK (7)	0.93–37.6[f]
Cellulose	DE(1–4,8,9) DK(5) ES(6) UK (7)	4.6–1385[f]
Citric acid	DE(8,9)	2.6–78
Croscarmellose sodium	DE(1–4) DK(5) ES(6) UK (7)	2–180
Crospovidone	DE(8,9) ES(10)	4.4–792[f]
Glycerol dibehenate	DK(11) NO(12) SE (13)	5.7–14
Lactose	DE(8,9)	23–1020[f]
Magnesium stearate	DE(8,9) ES(10)	0.15–401[f]
Mannitol	DK(11) NO(12) SE (13)	33–454
Potassium hydrogen carbonate	DK(11) NO(12) SE (13)	12
Povidone	DE(1–3) ES(6)	0.17–75
Silica	DE(1–4,8,9) DK(5) ES(6) UK (7)	0.65–99
Sodium starch glycolate	DE(1–4) DK(5) ES(6) UK (7)	2–876[f]
Starch	DE(8,9)	0.44–1135[f]
Talc	DE(1–4) DK(5) ES(6) UK (7)	0.26–220[f]

1. Diclofenac AbZ 50 mg Trinktabletten (Mono)[g]
2. Diclofenac-CT 50 mg Trinktabletten (Mono)[g]
3. Diclofenac-ratiopharm® 50 mg Disperstabletten Tabletten zur Herstellung einer Suspension zum Einnehmen (Mono)[g]
4. Voltaren® Dispers Tabletten (Mono)[g]
5. Voltaren, opløselige tabletter[g]
6. DICLOFENACO RCA 50 mg comprimidos dispersables EFG[g]
7. Voltarol Dispersible Tablets 50 mg[g]
8. Diclac® Dispers Tabletten (Mono)[g]
9. Diclo dispers® Tabletten zur Herstellung einer Suspension zum Einnehmen (Mono)[g]
10. DICLOFENACO NORMON 50 mg Comprimidos Dispersables EFG[g]
11. Voltaren Rapid, pulver til oral opløsning[h]
12. CATAFLAM 50 mg dosepulver til mikstur, oppløsning[h]
13. Voltaren 50 mg pulver till oral lösning, dospåse[h]

[a] Colourants, flavors and ingredients present in the printing ink only are not included.
[b] Diclofenac potassium and diclofenac sodium. The salt form present is indicated for each product.
[c] Drug products containing more than one API are excluded.
[d] Sources of data: DE, www.rote-liste.de (assessed October 24, 2007); DK, www.dkma.dk (assessed October 24, 2007); NO, www.legemiddelverket.no (assessed September 20, 2007); ES, www.agemed.es (assessed October 24, 2007); SE, www. lakemedelsverket.se (assessed October 24, 2007); UK, www.medicines.org.uk (assessed February 7, 2008).
[e] FDA's Inactive Ingredient Database, http://www.fda.gov/cder/iig/iigfaqweb.htm#purpose (version date November 1, 2007).
[f] The reported upper range value is unusually high. The authors doubt its correctness.
[g] Contains diclofenac sodium.
[h] Contains diclofenac potassium.

Metabolism

Diclofenac undergoes extensively hepatic biotransformation involving aromatic hydroxylations and conjugations.[53,54] Five diclofenac metabolites have been identified.[22,41,54] One metabolite has a very weak pharmacological activity.[22]

Excretion

Approximately 65% of diclofenac is excreted in the urine, largely as metabolites, and 35% in bile as conjugates of unchanged diclofenac and metabolites.[22] Very little drug is eliminated in the unchanged form in urine.[44] The terminal half-life of unchanged diclofenac is approximately 2 h.[22,30]

Table 3. Solubility of Diclofenac Sodium from Literature Data[19] and the Corresponding Dose/Solubility (D/S) Ratio's for Three Tablet Strengths

			D/S^a (mL)		
pH	Medium	Solubility (mg/mL) (23 ± 2°C)	12.5 mg	25 mg	50 mg[b]
1.2	0.1 N HCl	0.0012	12500[c]	25000[c]	50000[c]
2.0	0.01 N HCl	0.0017	7353[c]	14706[c]	29412[c]
3.0	0.001 N HCl	0.28	45	89	179
4.1	Acetate buffer	0.0033	3788[c]	7576[c]	15152[c]
4.5	Acetate buffer	0.0036	3472[c]	6944[c]	13889[c]
5.5	Acetate buffer	0.036	347[c]	694[c]	1389[c]
5.8	Phosphate buffer	0.14	89	179	357[c]
6.0	Phosphate buffer	0.15	83	167	333
6.8	Phosphate buffer	0.67	19	37	75
7.0	Phosphate buffer	1.36	9	18	37
7.4	Phosphate buffer	5.15	2	5	10
7.8	Phosphate buffer	12.00	1	2	4
8.0	Phosphate buffer	12.14	1	2	4

[a]Critical limit: <250 mL.[2–4]
[b]Highest tablet strength of IR solid oral dosage forms on USA and EU market.
[c]Exceeds critical limit.

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

Excipients present in diclofenac sodium and diclofenac potassium IR solid oral drug products with an MA in the US and some European countries are shown in Table 1. These products are "plain" tablets and are intended to be swallowed intact. In Table 2, the same information is shown for IR soluble tablets, dispersible tablets and powders for oral solution. In view of the MAs, it is presumed that these drug products successfully met the *in vivo* BE criteria. Unlike other APIs, diclofenac products were not exempted from *in vivo* BE studies for some time by the German Regulatory Authorities.[55] Moreover, diclofenac is not on the list of except APIs from *in vivo* BE studies by the Dutch Regulatory Authorities.[56]

In Vivo Bioequivalence

Several studies demonstrated BE among diclofenac potassium IR products.[39,52,57,58] In a randomized, single dose, two-way crossover study in 66 subjects, a 12.5 mg diclofenac potassium tablet formulation was shown to be bioequivalent in terms of log transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ to its reference, Voltarol Dolo 12.5 mg tablets (Norvatis, Basel, Switzerland).[57] Dissolution profiles of test product were reported to be similar to the reference products marketed in various European countries.[57]

Table 4. Solubility of Diclofenac Potassium at Room Temperature and the Corresponding Dose/Solubility (D/S) Ratio's for Three Tablet Strengths

			D/S^b (mL)		
pH	Medium	Solubility (mg/mL)[a]	12.5 mg	25 mg	50 mg[c]
4.5	Acetate buffer	0.0014 (0.0001)	8929[d]	17857[d]	35714[d]
6.8	Phosphate buffer	0.7167 (0.0165)	17	35	70
7.4	Phosphate buffer	2.341 (0.016)	5	11	21

[a]Between brackets: standard deviation of mean.
[b]Critical limit: <250 mL[2–4].
[c]Highest tablet strength of IR solid oral dosage forms on USA and EU market.
[d]Exceeds critical limit.

In another single dose study in 24 healthy volunteers, a diclofenac potassium 50 mg sachet formulation containing excipients such as potassium hydrogen carbonate, mannitol, aspartame, saccharin sodium, glyceryl dibehenate, and flavors proved to be bioequivalent to the reference tablet formulation Voltfast in terms of $AUC_{0-\infty}$, although C_{max} was twofold larger from the sachet formulation.[58] No dissolution studies were performed because the test formulation is a powder for oral solution.

Neuvonen[59] reported no significant change in the pharmacokinetics of diclofenac when coadministered with magnesium hydroxide, but this study was carried out with enteric coated tablets and hence of very limited value for IR dosages forms.

Dissolution and *In Vitro*/*In Vivo* Correlation

For diclofenac potassium tablets, the USP30 dissolution specification is not less than 80% (*Q*) of the labeled amount to be dissolved within 60 min in 900 mL simulated intestinal fluid (without enzyme) at 50 rpm in the paddle apparatus.[27] The Ph.Eur and the BP do not contain monographs for IR diclofenac tablets. No *in vitro*/*in vivo* correlations were identified in the literature for diclofenac IR solid oral dosage forms.

DISCUSSION

Solubility

Tables 3 and 4 show the dose/solubility ratio (*D*/*S*) of each salt at pH 6.0 and above to be less than the critical limit of 250 mL for *highly soluble* according to the present BCS Guidances.[2,3,60] The solubility reported by Kincl et al.[29] at pH 3.0 in 0.001 N HCl appears unexplainably high. All other data show diclofenac to be below pH 4.5 (or pH 5.8, depending on the tablet strength) to be not *highly soluble*. Although most solubility data have been collected at room temperature, it is unlikely that solubility values would be much different at 37°C to change the interpretation in terms of the BCS classification.

Absorption and Permeability

The complete 100% absorption classifies diclofenac as *highly permeable*.[2,3,60] This classification is supported by *in vitro* data. Some reports indicate that a permeability coefficient of more than 1×10^{-6} cm/s in Caco-2 model is considered to imply high permeability and/or complete absorption.[49,61,62] Others report that a permeability coefficient over 10×10^{-6} cm/s implies high permeability[11] or >70% absorption in humans.[63] Diclofenac exceeds both criteria. The artificial membrane permeability data and the partitioning data further support the classification of diclofenac as being *highly permeable*.

BCS Classification

According to all Guidances, the data presented above classify diclofenac in BCS Class II.[2–4] Using the disposition characteristics of the API as an estimate for its permeability, Wu and Benet[64] assigned diclofenac to Class II in a Biopharmaceutics Drug Disposition Classification System (BDDCS).

Risk for Drug Products to be Bio*in*equivalent

Tables 1 and 2 show excipients and their quantity limits used in diclofenac IR products with MAs in a number of countries. By virtue of their MAs, it may be assumed that these drug products passed *in vivo BE* studies. Hence, it is inferred that none of the excipients tabulated in these tables has had a significant effect on the extent nor the rate of diclofenac absorption. It is worthy of note that some drug products contain sodium lauryl sulfate, which has been reported to improve drug dissolution of poorly soluble drugs.[65] However, it appears that even if there was improved dissolution, sodium lauryl sulfate did not lead to the drug product to be bio*in*equivalent. It is deduced that these excipients in these reported limits do not cause interactions that result in bio*in*equivalence for diclofenac.

We conclude that the low solubility of diclofenc at pH values of 4.5 and below does not pose a substantial risk for bio*in*equivalence. This may be the result of diclofenac high permeability, as well as the dynamic character of the uptake processes.[66]

Surrogate Techniques for *In vivo* BE Testing

The rate-limiting step in the absorption of diclofenac from a drug product is gastric emptying, disintegration *in vivo* or dissolution *in vivo*. Comparative *in vitro* dissolution testing in

discriminatory media is a sensible technique to detect significant differences in disintegration *in vivo* or dissolution *in vivo* between a test drug product and comparator. *In vitro* dissolution testing in SIF (pH 6.8) without enzyme is suggested by USP and FDA for IR diclofenac potassium drug products as the quality control test.[27,67] SIF without pancreatin and SIF without pancreatin with 1% (w/v) Tween 20 has been suggested as discriminatory dissolution media for diclofenac sodium prolonged release tablets.[68] Dissolution in these media can be considered as discriminatory dissolution test for IR dosage forms. The BCS Guidance prescribes comparative *in vitro* dissolution testing between test and comparator in pH 1.2, 4.5, and 6.8 buffers and also provides criteria for the assessment of dissolution profile similarity.[2–4] In media pH 1.2 and pH 4.5, no dissolution is expected, providing evidence that no dissolution enhancers are present.

Since diclofenac permeability is high, intestinal absorption is not limiting. An excipient interaction with the permeation process is unlikely. This risk of interaction is even lower if the test product contains excipients that are known to exert no such influence, that is, the excipients tabulated in Tables 1 and 2.

Patient's Risks Associated With Bio*in*equivalence

Bio*in*equivalence with respect to AUC can cause subtherapeutic drug level, resulting in low analgesic efficacy, or supra-bioavailability, which may lead to cardiovascular and gastrointestinal side-effect risks. However, diclofenac products are used for non-life-threatening conditions, which require achieving minimal effective plasma concentration. The issue of supra-bioavailability is not critical, as diclofenac is a relatively safe drug with wide therapeutic range[69,70] Most diclofenac drug products carry a leaflet in which patients are advised to observe and report back any signs or symptoms related to cardiovascular and gastrointestinal events to the physician.

CONCLUSION

According to the current FDA and EMEA BCS Guidances, only BCS class I APIs are eligible for the biowaiver,[3,60] and diclofenac would not qualify for such a biowaiver. However, the recent WHO Guidance[2] opens a possibility for biowaiving of drug products containing BCS Class II APIs with weak acidic properties. This viewpoint for highly permeable acidic APIs has been supported for NSAIDS generally.[49] Certain conditions must be fulfilled, such as requirements with respect to *in vitro* dissolution; the excipients should be critically evaluated; and the risk of an incorrect biowaiver decision need to be assessed in terms of public health and risks to individual patients.[2] Diclofenac fulfills these criteria.

The question regarding the acceptability of biowaiving between pharmaceutical alternatives requires further discussion. Pharmaceutical alternatives are drug products containing the same molar amount of the same API, but differing in dosage form (e.g., tablet vs. capsule; "plain" tablet vs. dispersable tablet), or chemical form (e.g., different salts, different esters), delivering the same active moiety by the same route of administration.[2]

In *in vivo* BE testing, different salt forms of the API present in test and comparator are potentially allowed if there is no safety concerns.[60,71] However, in *in vitro* BE testing, a more conservative approach is prudent in granting biowaivers between different salt forms of an API. Moreover, these two salts sometimes have different therapeutic indications, as diclofenac potassium is sometimes claimed to be absorbed faster than the sodium salt and hence recommended for the treatments that need short onset of action. Hence, we recommend against a biowaiver when the test and comparator do not contain the same salt form of diclofenac.

The FDA, EMEA, and WHO Guidance provide some possibility for *in vivo* BE testing between pharmaceutical alternatives that differ in dosage form, such as IR tablets versus IR capsules.[60,71] Available diclofenac IR solid oral dosage forms include plain tablets, dispersible tablets, and powders for solution which are different dosage forms. As above, a more conservative approach is prudent in granting biowaivers between different solid oral dosage forms of an API. We recommend against a biowaiver when the test and comparator do not contain the same dosage form of diclofenac.

In summary, a biowaiver for IR solid oral dosage forms of diclofenac potassium and diclofenac sodium are scientifically justified, provided that: (a) test and comparator contain the same diclofenac salt; (b) the dosage form of the test and comparator is identical; (c) the test product contains only excipients present in diclofenac drug products approved in ICH or associated

countries in the same dosage form, such as those shown in Tables 1 and 2, in amounts that are usual for that dosage form; (d) test drug product and comparator dissolve 85% in 30 min or less in 900 mL buffer pH 6.8, using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm; and (e) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8.

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