Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Ketoprofen

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ABSTRACT: Literature and experimental data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate-release (IR) solid oral dosage forms containing ketoprofen are reviewed. Ketoprofen's solubility and permeability, its therapeutic use and therapeutic index, pharmacokinetic properties, data related to the possibility of excipient interactions, and reported BE/bioavailability (BA)/dissolution data were taken into consideration. The available data suggest that according to the current Biopharmaceutics Classification System (BCS) and all current guidances, ketoprofen is a weak acid that would be assigned to BCS Class II. The extent of ketoprofen absorption seems not to depend on formulation or excipients, so the risk of bioinequivalence in terms of area under the curve is very low, but the rate of absorption (i.e., BE in terms of peak plasma concentration, C_{max}) can be altered by formulation. Current *in vitro* dissolution methods may not always reflect differences in terms of C_{max} for BCS Class II weak acids; however, such differences in absorption rate are acceptable for ketoprofen with respect to patient risks. As ketoprofen products may be taken before or after meals, the rate of absorption cannot be considered crucial to drug action. Therefore, a biowaiver for IR ketoprofen solid oral dosage form is considered feasible, provided that (a) the test product contains only excipients present also in IR solid oral drug products containing ketoprofen, which are approved in International Conference on Harmonisation or associated countries, for instance, as presented in this paper; (b) both the test drug product and the comparator dissolve 85% in 30 min or less in pH 6.8 buffer; and (c) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8. When one or more of these conditions are not fulfilled, BE should be established *in vivo*. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:3593–3603, 2012

Keywords: ketoprofen; absorption; Biopharmaceutics Classification System (BCS); permeability; solubility; dissolution; regulatory science

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INTRODUCTION

Ketoprofen is an ibuprofen-type nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. A biowaiver monograph based on literature and some additional experimental data with respect to its Biopharmaceutics Classification System (BCS) classification, biopharmaceutical properties, and the risks associated with waiving *in vivo* bioequivalence (BE) testing in the approval of new immediate-release (IR) solid oral dosage forms containing ketoprofen ("biowaiving"), including both reformulated products and new multisource drug products, is presented. This evaluation refers to drug products containing ketoprofen as the only active pharmaceutical ingredient (API) and not to combination products. The purpose and scope of this series of monographs have been previously discussed.[1] As stated in previous article, "These monographs do not intend to simply apply the World Health Organization (WHO),[2] United States Food and Drug Administration (US FDA),[3] and/or European Medicine Agency (EMA) Guidance,[4] but aim also as a critical evaluation of these and other countries' regulatory documents." Biowaiver monographs have already been published for several APIs, and are also available online at www.fip.org/bcs.[5]

METHODS

Literature data were obtained from Web of Science, PubMed, Drugs.Com, and DrugBank databases up to May 2011. The keywords used for searching were ketoprofen, absorption, bioavailability, bioequivalence, log *P*, solubility, permeability, and dissolution. Information was also obtained from regulatory documents published by WHO,[2] US FDA,[3] and EMA.[4]

GENERAL CHARACTERISTICS

International nonproprietary name: Ketoprofen.[6] International Union of Pure and Applied Chemistry name: (RS)-2-[3-(benzoyl)phenyl]propanoic acid.[7] Its structure is shown in Figure 1.

Stereoisomers, Salts, and Polymorphs

Ketoprofen has one asymmetric carbon atom, giving rise to two enantiomers, both of which possess biological activity.[8,9] The majority of ketoprofen drug products contain the racemate.[10,11] Preparations containing a salt of the (S)-(+)-enantiomer, known as dexketoprofen, are also available,[10,11] claiming to reduce inflammation and pain,[12] whereas the (R)-(−)-enantiomer is used as a toothpaste additive to prevent periodontal disease.[13] The lysine salt and the sodium salt of ketoprofen are also known. These salts are used in dosage forms other than IR solid oral dosage forms such as suppositories and nonsystemic solutions.[10,11]

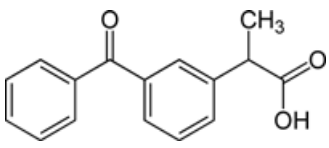

Figure 1. Ketoprofen structure formula.

Ketoprofen can exist as two polymorphs.[14] No data were found in the literature as to whether the polymorphic form of ketoprofen free acid affects dissolution performance or bioavailability (BA).

This monograph, which relates only to oral drug products, therefore considers only the free acid of ketoprofen in its racemate form.

Therapeutic Indication, Dose, Therapeutic Index, and Toxicity

Ketoprofen is an ibuprofen-type NSAID with analgesic and antipyretic properties. It is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and to alleviate moderate pain. Ketoprofen has pharmacologic actions similar to those of other NSAIDs, and these are thought to be associated with the inhibition of prostaglandin synthesis. Its anti-inflammatory effects are believed to be due to the inhibition of both cyclooxygenase-1 and cyclooxygenase-2.[15]

The highest single dose recommended for ketoprofen in IR solid oral dosage forms is 100 mg and for extended-release dosage forms 200 mg. Depending on the indication, the dosage regimen varies from 12.5 mg every 4–6 h (usual adult dose for fever) to 100 mg orally as an initial dose, followed by 50 mg every 6 h (usual adult dose for acute gout).[16] The recommended maximum dose should not exceed 300 mg/day.[16] Ketoprofen is considered to be a wide therapeutic index drug according to the US FDA definition,[17] and there is no need to monitor blood levels. It is also not mentioned in the Health Canada Critical dose drugs list[18] or the Japanese list of narrow therapeutic index drugs.[19]

Ketoprofen's LD_{50} is 62.4 mg/kg (rats, oral).[16] Overdose may cause adverse effects including breathing difficulty, coma, convulsions, drowsiness, high blood pressure, kidney failure, low blood pressure, nausea, sluggishness, stomach and intestinal bleeding, stomach pain, and vomiting.[15,16]

Generally, ketoprofen side effects are similar to other NSAIDs.[20] The most common side effects are rash, ringing in the ears, headache, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, heartburn, retention of fluid, and shortness of breath. Serious side effects are rare and mostly result from gastrointestinal (GI) damage. In fact, ketoprofen is one of the most ulcerogenic of the NSAIDs and its risk factor for serious GI complications against

reference drug ibuprofen is on average (95% confidence interval) 4.2 (2.7–6.4).[21]

PHYSICOCHEMICAL PROPERTIES

Partition Coefficient

The distribution coefficient (log *D*) of ketoprofen in *n*-octanol/aqueous buffer is reported to be 0.1 at pH 7.4[22] and 1.31 at pH 6.5.[23] Ketoprofen partition coefficient, log *P* and C log *P*, values are 3.31 and 2.76, respectively (ChemDraw Ultra 6.0, PerkinElmer Informatics, Cambridge, MA).[23] The experimentally measured log *P* has been reported as 3.2.[15] The calculated log *P* using ALOGPS (VCCLAB, Neuherberg, Germany) is 3.29 and 3.61 using ChemAxon Molconvert (ChemAxon, Budapest, Hungary).[15] Log *P* and C log *P* values are larger than the corresponding values for the highly permeable marker drug metoprolol, which are 1.72 and 1.35, respectively.[23] Generally, ketoprofen has a high log *P* like other NSAIDs.[24,25]

pK_a

Experimentally measured pK_a values of ketoprofen are reported to be 4.39, 4.45, and 4.76 at 25°C.[15,22,26] Its weak acid properties are associated with the carboxylic group.

Solubility

Ketoprofen is described in different pharmacopoeias as practically insoluble in water.[27–29] Ketoprofen's solubility in pure water at ambient temperature (22°C–24°C) was reported to be 0.010 mg/mL,[30] but other authors report the intrinsic solubility in water at 37°C as 0.253 mg/mL,[31] which is more in line with other published data. Solubility values for ketoprofen in different aqueous buffers taken from the literature are shown in Table 1, together with the dose to solubility ratios (*D*/*S*) for the highest dosage strength having a registration in International Conference on Harmonisation (ICH) countries (100 mg) and for the highest single oral dose administered (100 mg).[26,32,33]

The equilibrium solubility of ketoprofen at 37°C in McIlvaine buffer solutions of pH 4.0, 4.6, 6.0, and 6.8 is 0.28 ± 0.01, 0.49 ± 0.00, 3.68 ± 0.13, and 40.76 ± 0.01 mg/mL, respectively.[26] This trend in solubility with pH is commensurate with its weak acid properties. Other ketoprofen equilibrium solubility data, measured at pH 1.2 (0.1 N hydrochloric acid solution), 5.0 (0.02 M citric acid), and 7.4 (0.02 M Na_2HPO_4, 0.02 M NaH_2PO_4) at 37°C are 0.13, 0.38, and more than 1.4 mg/mL, respectively.[32] All equilibrium solubility data mentioned above were measured using shake-flask method at 37°C.

In addition to solubility measurements relevant to the biowaiver, further solubility data in the presence of artificial and natural surfactants have also been generated. The addition of sodium lauryl sulfate (SLS) in concentrations of 0.5%–2% significantly increases solubility of ketoprofen, especially at low pH: from about fivefold increase (for 0.5% SLS) to about 30 times increase (for 2% SLS) for pH 4.6.[26] The solubility of ketoprofen in fed-state simulated intestinal fluid (FeSSIF),[34] a biorelevant medium representing fed state conditions in the small intestine, is 0.84 mg/mL, which is about twofold higher than its solubility in pH 5.0 buffer without surfactants,[32] and its solubility in bile (diluted with phosphate buffer pH 6.5 1:1, v/v) and in pH 6.5 phosphate buffer was 8.36 and 3.31 mg/mL, respectively.[33]

Stability

No data on the stability of ketoprofen in human gastric and intestinal fluids were found in the literature. However, the complete absorption in humans[16,33] clearly indicates that the drug is stable in the GI tract.

Dose Strength of Marketed Drug Products

Ketoprofen is not listed in the WHO Model List of Essential Medicines.[35] In Russia, Marketing Authorizations (MA) exist for IR solid oral dosage forms for 50 mg capsules and 25 and 100 mg tablets.[10] The USA currently lists MA for 50 and 75 mg ketoprofen IR capsules, and 12.5 mg oral films.[11] Higher strengths

Table 1. Solubility Values for Ketoprofen in Different Aqueous Buffers at 37°C Together with the Dose to Solubility Ratios (*D*/*S*) for the Highest Dosage Strength (100 mg) Having a Registration in ICH Countries

Reference	pH	Medium	Solubility (mg/mL)	*D*/*S* (mL)	Acceptance Criterion (*D*/*S* ≤ 250 mL) for "Highly Soluble" Drugs (Yes/No)
26	4.0	McIlvaine buffer (0.1 M citric acid, 0.2 M disodium phosphate, water)	0.28 ± 0.01	357	No
	4.6		0.49 ± 0.00	204	Yes
	6.0		3.68 ± 0.13	27.2	Yes
	6.8		40.76 ± 0.01	2.4	Yes
32	1.2	0.1 N hydrochloric acid	0.13	769.2	No
	5.0	0.02 M citric acid	0.38	263.2	No
	7.4	0.02 M Na_2HPO_4, 0.02 M NaH_2PO_4	>1.4	<71.2	Yes
33	6.5	Phosphate buffer	3.31	30.2	Yes
	6.5	Bile–phosphate buffer [pH 6.5, 1:1 (v/v)]	8.36	11.96	Yes

(up to 200 mg) of these drugs have also been marketed, but only as extended-release solid oral dosage forms.[10,11] Ketoprofen in IR formulations (tablets and capsules) is marketed in the European Union in 25, 50, 75, and 100 mg dosages. One hundred milligrams is a general maximum strength with exception for Iceland (200 mg) and France (150 mg).[36–51] The analysis performed in the current work is based on a maximum strength of 100 mg. In addition, several rapidly disintegrating solid oral dosage forms of ketoprofen (e.g., solid dispersions in pellets) are being developed, but as they do not have MA yet,[52,53] they are beyond the scope of this monograph.

PHARMACOKINETIC PROPERTIES

Absorption and Permeability

Ketoprofen's absolute BA versus intravenous (i.v.) BA for 100 mg capsules is on average 92%.[29] After oral administration, the fraction dose absorbed has also been reported as 90%.[16,33] Ketoprofen, like many other drugs, is mainly absorbed in the small intestine.[26] Peak plasma concentrations (C_{max}) are reached within 1–2 h (T_{max}) after administration of a single dose.[16,54] Ketoprofen shows dose linearity for the R and S enantiomers over a dose range of 50–200 mg after administration of racemic ketoprofen.[54]

This complete oral absorption of ketoprofen is supported by *in vivo*, *in situ*, and *in vitro* permeability data. The permeability of ketoprofen studied by intestinal perfusion in humans ($P_{\text{eff } in\ vivo}$) is $8.4 \pm 3.3 \times 10^{-4}$ cm/s, which is significantly faster than the high permeability marker metoprolol ($P_{\text{eff } in\ vivo}$ 1.34×10^{-4} cm/s).[23]

Rat perfusion studies and *in vitro* cell layer studies have consistently illustrated the high permeability of ketoprofen in relation to well-established marker compounds.[55–58]

Ketoprofen is also mentioned in the US FDA BCS Guidance (Attachment A) as a highly permeable reference drug substance.[3]

Distribution

Ketoprofen is more than 99% bound to plasma proteins, mainly to albumin.[16] Its volume of distribution varies from 7 to 14 L (about 0.1–0.2 L/kg).[16,22]

Metabolism and Excretion

The metabolic fate of ketoprofen is glucuronide conjugation to form an unstable acyl glucuronide.[16] In addition, it undergoes hydroxylation of benzoyl ring by CYP3A4 and CYP2C9.[59] There are no known active metabolites of ketoprofen. Ketoprofen has been shown not to induce drug-metabolizing enzymes.[16] Less than 1% of the dose administered is excreted unchanged in urine, whereas the glucuronide-conjugated metabolite accounts for nearly 65%–75%.[60]

The plasma clearance of ketoprofen is approximately 0.08 L/(kg h) (5.7 L/h).[16,22] It has been demonstrated that in elderly subjects following multiple doses (50 mg every 6 h), the ratio of conjugated-to-parent ketoprofen area under the curve (AUC) was 30% and 3%, respectively, for the S-(+) and R-(−) enantiomers.[16] The elimination half-life of ketoprofen has been reported to be 2.05 ± 0.58 h (range 2–4 h).[1654]

Food Effects

Prescribing information states that ketoprofen can be administered with food to minimize GI adverse effects. When ketoprofen is administered with food, its total BA (AUC) is not altered; however, the rate of absorption from IR dosage form is slowed down. After oral administration of IR ketoprofen capsules, food intake reduces C_{max} by approximately one-half and increases the T_{max} from 1.2 h for fasting subjects (range 0.5–3 h) to 2 h for fed subjects (range 0.75–3 h). Ketoprofen plasma levels may also be influenced by circadian changes in the absorption process: ketoprofen has a greater rate and particularly extent of BA when it is given in the morning than in the evening.[1654] The GI irritation is reduced when ketoprofen is taken with food.[15] It is mentioned in the prescribing information that ketoprofen may be taken with food or milk to prevent upset stomach.[16]

DOSAGE FORM PERFORMANCE

Excipients

Excipients present in ketoprofen IR solid oral drug products with an MA in ICH and associated countries are shown in Table 2.[36–51,61,62]

It can be assumed that these drug products successfully passed an *in vivo* BE study, clinical trial or were judged by other appropriate means by the regulatory authority to provide adequately similar clinical safety and efficacy. Excipients present in these drug products seem, therefore, to be safe and not to detrimentally affect BE of ketoprofen when present in amounts usual for IR tablets.

BA and BE Studies

No literature data devoted to BE studies of IR solid oral dosage forms of ketoprofen were found but several related publications were identified. Neuvonen[63] studied the effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen, and diclofenac. This study was conducted on six healthy women who received 50 mg ketoprofen tablets (Orudis; Rhone-Poulenc, Copenhagen, Denmark) either with 150 mL water only or with water containing 850 mg magnesium hydroxide. Neither the rate nor the extent of

Table 2. Excipients* Present in Ketoprofen IR Solid Oral Drug Products† with a Marketing Authorization (MA)‡ in Canada (CA), Czech Republic (CZ), Germany (DE), Denmark (DK), Spain (ES), Finland (FI), France (FR), Hungary (HU), Iceland (IS), The Netherlands (NL), Norway (NO), Portugal (PT), Romania (RO), Sweden (SE), Slovakia (SK), United Kingdom (UK), and the USA (US)§ and the Minimal and Maximal Amount of that Excipient Present Prodosage Unit in Solid Oral Drug Products with a MA in the USA

Excipient	Drug Products Containing that Excipient with a MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with a MA in the USA (mg)
Calcium hydrogen phosphate	FR(1–5)	104–850
Castor oil, hydrogenated	FI(6)	0.93–38[a]
Cellulose, microcrystalline	FI(6–8) RO(9)	4.6–1385[a]
Cellulose, powdered	FI(10)	44–170
Croscarmellose sodium	CA(11) CZ(12) FI(7,10) FR(13–15) HU(16) RO(9)	2–180
Ethylcellulose	IS(17)	1.0–121[a]
Gelatin	DE(18) FI(7,10) FR(5,19) NL(20)	1–756[a]
Glycerol	FI(6)	0.13–224
Hydroxyethylcellulose	FR(1–5)	2–12
Hypromellose	CZ(12) FI(6) FR(13–15) HU(16)	0.8–537
Lactose	CA(11) CZ(12,21–23) DE(18,24–27) DK(28) ES(29,30) FI(31) FR(1–5,13–15,19) HU(16,32) NL(20) NO(33) PT(34) RO(9,35,36) SE(37,38) SK(39,40) UK(41) US(42–45)	23–1020[a]
Macrogols	CZ(12) FR(13–15) HU(16)	0.12–961[a]
Magnesium stearate	CA(11) CZ(12,21–23) DE(18,24–27) DK(28) ES(29,30) FI(7,8,10,31) FR(1–5,13–15,19) HU(16,32) NL(20) NO(33) PT(34) RO(9,35,36) SE(37,38) SK(39,40) UK(41) US(42–45)	0.15–401[a]
Mannitol	FI(8)	33–992
Povidone	CZ(22) RO(35,36) SK(40)	0.17–80
Propylene glycol	US(42–44)	1.5–148
Riboflavin sodium phosphate	FR(5)	
Shellac	IS(17) US(43,44)	4.4–25
Silica	CA(11) CZ(12,21,22) DE(18,25) FI(7,10) FR(1-5,13–15,19) HU(16) IS(17) NL(20) NO(33) RO(9,35) SE(38) SK(39,40) US(42–44)	0.50–100
Sodium laurilsulfate	CA(11) DE(24,26,27) FI(6) US(42–45)	0.65–52
Sodium starch glycolate	FI(8) US(42–44)	2–876[a]
Starch	CZ(12,22) DE(18,27) FI(7,8,10) FR(1–5,13–15,19) HU(16) IS(17) NL(20) NO(33) RO(35,36) SE(38) SK(40) US(42–44)	0.44–1135[a]
Starch, pregelatinised	CZ(12) FI(6) FR(13–15) HU(16) RO(9)	5.0–600
Sucrose	IS(17)	12–900
Talc	CZ(22) ES(29) FI(7,10) IS(17) RO(35) SK(40)	0.10–220[a]

1, KETOPROFENE ARROW 150 mg cp séc; 2, KETOPROFENE BIOGARAN 150 mg cp séc; 3, KETOPROFENE EG 150 mg cp séc; 4, KETOPROFENE TEVA 150 mg cp séc; 5, PROFEMIGR 150 mg cp séc; 6, KETO 25/50/100 mg tabletti, kalvopäällysteinen; 7, Ketomex 50/100 mg kalvopäällysteiset tabletit; 8, Ketorin 50 mg kapseli, kova; 9, KETOPROXIN 50/100 mg, comprimate filmate; 10, Ketomex 25 mg kalvopäällysteinen tabletti; 11, Ketoprofen Capsules BP 50 mg; 12, PROFENID 100 mg, potahované tablety; 13, KETOPROFENE RANBAXY 100 mg cp pellic; 14, KETUM 100 mg cp pellic; 15, PROFENID 100 mg cp pellic; 16, Profenid 100 mg filmtabletta; 17, Orudis, 200 mg for Đahylki, hart; 18, Gabrilen® GS gegen Schmerzen Tabletten 25 mg; 19, TOPREC 25 mg cp; 20, Rilies®, tabletten 25 mg; 21, Ketonal, tvrdé tobolky 50 mg; 22, Ketonal forte, potahované tablety 100 mg; 23, PROFENID 50 mg, tvrdé tobolky; 24, Alrheumun® Kapseln 50 mg; 25, Gabrilen® 50/100 mg Hartkapseln; 26, Spondylon® Kapseln 100 mg; 27, Alrheumun®-forte Kapseln 100 mg; 28, Orudis, hårde kapsler 50 mg og 100 mg; 29, Ketoprofeno ratiopharm 50 mg cápsulas; 30, Orudis 50 mg cápsulas; 31, Ketorin 100 mg kapseli, kova; 32, Profenid 50 mg kapszula; 33, ZON 50 mg kapsler, harde; 34, PROFENID 100 mg cápsulas; 35, KETONAL FORTE 100 mg COMPRIMATE FILMATE; 36, RUBIFEN 100 mg, comprimate filmate; 37, Orudis 50/100 mg kapsel, hård; 38, Zon 50 mg, kapsel, hård; 39, Ketonal 50 mg, tvrdé kapsuly; 40, Ketonal forte 100 mg, filmom obalené tablety; 41, Orudis 50/100 mg; 42, KETOPROFEN capsule 50/75 mg (Physicians Total Care, Inc., Tulsa, OK); 43, KETOPROFEN capsule 50/75 mg (Mylan Pharmaceuticals Inc., Canonsburg, PA); 44, KETOPROFEN capsule 50/75 mg (Rebel Distributors Corporation, Thousand Oaks, CA); 45, KETOPROFEN capsule 50/75 mg (TEVA Pharmaceuticals USA Inc., Miami, FL).

*Colorants and ingredients present in the coating and/or the printing ink are not included; of capsules, the gelatin of the shell is not included.

†Excluded are enteric-coated tablets and powder for oral solution.

‡The approval of a drug product by the local regulatory authority. Also the terms drug approval and registration are used.

§Abbreviations of the countries: see text.

[a]The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

absorption of ketoprofen or diclofenac was changed significantly by magnesium hydroxide.

In another study, the relative BA of ketoprofen from a liquid formulation was compared with a tablet formulation after a single oral dose. Sixteen healthy male volunteers received 25 mg of ketoprofen as tablet or liquid formulation administered as single dose in a randomized, crossover design. Although the extent of absorption expressed by AUC was nearly the same (about 95%), pronounced differences in the shape of concentration–time profiles between the two formulations were found, with higher C_{max} (by about 70%) and earlier T_{max} (by 15 min) values for the ketoprofen solution.[64]

A comparative pharmacokinetic study of ketoprofen suspension versus solution following oral dose administration conducted in four mongrel dogs in fasted state did not show any statistical significant differences in C_{max} and AUC.[65] The fraction absorbed was shown not to be significantly affected by different dissolution profiles in a simulation study.[22]

Dissolution

The USP30-NF25 has no specification for ketoprofen IR solid oral dosage forms, but monograph 1090 "*In vivo* bioequivalence guidances" states that not less than 80% (*Q*) of the labeled amount of ketoprofen should be dissolved within 30 min in 1000 mL of 0.05 M phosphate buffer (pH 7.4) at 50 rpm using United States Pharmacopeia (USP) Apparatus II at 37°C.[29] The British Pharmacopoeia has a monograph for ketoprofen capsules. Dissolution specification is: 900 mL of phosphate buffer pH 7.5, paddle at 50 rpm, and not less than 75% of substance should release at 45 min.[28]

In an experimental *in vitro* dissolution study comparing two different capsule formulations previously performed at the Institute of Clinical Pharmacology in Moscow, equivalent dissolution performance was shown at pH 4.5 and 6.8, whereas profiles differed at pH 1.2. The different dissolution at acidic pH was possibly because of the use of a solubilizing excipient (sodium lauryl sulfate) contained in one of the test preparations.[66]

DISCUSSION

Solubility

Experimental solubility data, reported by Sheng et al.[26] and Yazdanian et al.,[32] were determined at 37°C using shake-flask method, recommended for solubility determination; therefore, these data are valid according to current BCS Guidances. Solubility criteria stated in present BCS Guidances for classifying an API as "highly soluble" require the highest dosage strength (US FDA)[3] or the highest single dose administered (EMA and WHO)[2,4] to be soluble at 37°C in 250 mL aqueous buffer solution over the pH range of 1.2–6.8 according to WHO Guidance (three buffer media pH 1.2, 4.5, and 6.8), pH 1.0–6.8 according to EMA Guidance (three recommended buffer media pH 1.2, 4.5, and 6.8), or pH 1.0–7.5 according to the US FDA Guidance.[2–4] Ketoprofen's *D*/*S* ratio for the highest dosage strength and for the highest single dose administered at low pH (1.2–4.0) exceeds the critical limit of 250 mL, but meets the acceptance criteria at pH 4.6 and higher (including pH 6.8). Thus, according to all current BCS Guidances, ketoprofen should be classified as a "low soluble" API, although it meets the criteria for "high" solubility at pH 4.6 and 6.8.

Being a weak acid, ketoprofen's solubility increases with pH. Ketoprofen is completely ionized and highly soluble at intestinal pH, leading to complete dissolution of the dose in biorelevant volumes. This is because the average pH in upper small intestine is around 5.8–6.5, which is at least one unit higher than the drug pK_a, increasing the apparent solubility of ketoprofen by 10–100-fold.[26] The WHO BCS Guidance defines that the biowaiver can be extended to BCS Class II weak acids if the API has a *D*/*S* ratio of 250 mL or less at pH 6.8.[2] Therefore, ketoprofen meets the solubility requirements of the WHO Guidance for biowaiving of BCS Class II weak acids. However, neither the EMA nor the US FDA has accepted this extension of the biowaiver as yet.

Absorption and Permeability

When an API is absorbed to an extent of 85% or more (WHO, EMA)[3] or 90% (US FDA),[4] based on a mass balance determination or in comparison with an i.v. comparator dose, it is considered "highly permeable." Human *in vivo* data may be supported by *in situ* (intestinal perfusion in rats) and *in vitro* (Caco-2 cells) studies. Although log *P* values can be broadly correlated with human permeability,[50] log *P* has no regulatory acceptance as a permeability criterion.

Ketoprofen is considered to be "highly permeable" because the absolute BA versus i.v. in humans exceeds 90%. Surrogate methods (Caco-2 studies, intestinal perfusion in rats log *P*) support the classification of ketoprofen as a "highly permeable" compound, and indeed it has been recommended as a highly permeable compound for Caco-2 studies by the US FDA[3].

The Biopharmaceutics Drug Disposition Classification System (BDDCS), developed by Wu and Benet,[67] classifies an API as "highly" permeable, if its extent of metabolism exceeds 70% (or 90%).[68] The extensive metabolism of ketoprofen also suggests that it is "highly permeable."

In summary, ketoprofen fulfills all current permeability criteria[2–4] and can be clearly classified as a "highly permeable" API.

BCS Classification

According to all guidances, ketoprofen is a BCS Class II drug substance.[2–4] Yazdanian et al.[32] classified ketoprofen as BCS Class I, but this was based only on pH 7.4 solubility.[32] Wu and Benet[67] also assigned ketoprofen to BDDCS Class I with regard to its disposition characteristics to estimate permeability. Another opinion is that ketoprofen is a borderline case between BCS Classes I and II.[69] On the basis of the data presented in this monograph, ketoprofen is assigned to BCS Class II.

Risks with Respect to Excipient and/or Manufacturing Variations

The extent of ketoprofen absorption seems to be very robust and not dependent on formulation or excipients (at least for IR formulations), so the risk of bioinequivalence in terms of AUC is very low. The risks can be further mitigated if products contain only excipients present in ketoprofen IR solid oral dosage forms approved in ICH or associated countries, as

shown in Table 2, and if these excipients are used in similar quantities to those products.

By contrast, the rate of absorption (i.e., BE in terms of C_{max}) can be altered by formulation because pharmaceutical factors, for example, surfactants in concentrations which improve wetting or solubilize the API; formulation components which increase the pH in the stomach; and solid state forms which create supersaturation, could increase the dissolution rate in the stomach, and thereby, potentially increase the absorption rate. It has already been discussed under the section "Food Effects" that the T_{max} is increased when given with food, indicating a slower rate of absorption. But it is unlikely that the rate of absorption and C_{max} are critical for ketoprofen efficacy, as it can be given with or without meals.

The *in vivo* information about ketoprofen in the literature is limited. However, above-mentioned statements are strongly supported by different *in vivo* and *in vitro* studies of BCS Class II weak NSAID acids with similar biopharmaceutical and physicochemical properties.[70–77] For example, the analysis of 25 BE studies of ibuprofen IR tablets from 200 to 600 mg in Germany showed that 14 studies did not demonstrate BE because of the C_{max} differences, but were equivalent in terms of AUC.[70] Several other comparative BA studies of other NSAIDs (sulindac, indomethacin, flurbiprofen, lornoxicam, diclofenac potassium, and piroxicam) have also shown differences in T_{max} and C_{max}, between different formulations, whereas AUC was not different.[72–77] Thus, across the different NSAIDs, all being BCS Class II acid drugs with high solubility at intestinal similar to ketoprofen, the pattern is surprisingly consistent with no influence of formulations on AUC, but some influence on C_{max} possible. Interestingly, dissolution testing at close to neutral pH was not discriminating for some of the differences detected in C_{max}.[71,72]

Surrogate Techniques for *In Vivo* BE Testing

US Food and Drug Administration comparative dissolution technique for ketoprofen capsules is 1000 mL 0.05 M phosphate buffer (pH 7.4) using USP Apparatus II (paddle method) at 50 rpm, time points are 10, 20, 30, and 45 min; and for ketoprofen tablets, the method is Simulated Intestinal Fluid without enzymes, pH 7.4, 900 mL, using USP Apparatus II (paddle method) at 50 rpm, time points are 10, 20, 30, 45, and 60 min.[78] The WHO BCS Guidance prescribes comparative *in vitro* dissolution studies between test and reference products in three media (pH 1.2, 4.5, and 6.8) and also provides criteria for the evaluation of dissolution profile similarity.[2] In addition, US FDA recommends Apparatus II (paddle method) at 50 rpm, whereas WHO uses the same apparatus at 75 rpm. The increase in rpm reduces the forming of a mound of tablet material at the bottom of the beaker, which often occurs at 50 rpm and results in an artificially slow dissolution rate.

Dissolution studies in three buffer media covering physiological range seem to be more discriminatory than approaches described in the previous section because comparative dissolution kinetics at low pH, especially 1.2, are more discriminating with respect to solubility-enhancing formulation approaches. For example, in an *in vitro* dissolution study, a discrimination in dissolution performance at pH 1.2 but not at higher pH was shown for drug products with and without solubilizers. Dissolution testing at close to neutral pH for other NSAIDs did not predict some of the differences in C_{max} observed between the formulations.[71,72] Therefore, testing at acidic pH is likely to capture most of the differences depending on pharmaceutical factors. However, a challenge of testing at acidic pH is that for the high-strength products without any solubility-enhancing excipients, only a few percent of the drug substance is dissolved, making it difficult to distinguish between similar and not similar profiles according to the f2 factor.

Patient's Risks Associated with Bioinequivalence

Therapeutic index, therapeutic indications, and adverse effects also need to be taken into account when considering a biowaiver for APIs.[2] Bioinequivalence with respect to AUC can cause subtherapeutic drug levels, leading to low analgesic and anti-inflammatory action. In contrast, supra-BA may heighten the risk of GI side-effect risks.

Applying these concepts specifically to ketoprofen, it should be remembered that oral ketoprofen drug products are used for non-life-threatening conditions, and that it has a wide therapeutic index (it is not mentioned in US FDA, Canadian, or Japanese lists of narrow therapeutic drugs).[17–19] In addition, ketoprofen was considered unproblematic in terms of BA, and for the time was exempted from *in vivo* BE studies in Germany.[79]

As noted above, *in vitro* dissolution tests may or may not detect differences in absorption rate for BCS Class II drugs with high solubility at intestinal pH; therefore, biowaivers for such substances may be acceptable only if clinical effect/safety consequences of potentially altered plasma peak levels with unaffected extent are not critical. Famaey[80] reported that ketoprofen plasma concentrations vary greatly in patients treated with the drug and that no correlation can be established between plasma levels and the clinical effects of this drug. Orme[81] also published that there is no clear evidence of plasma concentration–clinical response relationship for NSAIDs, but indicated that some NSAIDs exhibit a correlation between plasma level and inhibition of prostaglandin production. Yet, other authors report that the clinical effect is correlated with plasma concentration for

Table 3. Comparison of Biopharmaceutical Properties of Ibuprofen and Ketoprofen

	Biopharmaceutical Property							
			Experimental Solubility at 37°C (mg/mL)					
API	pK_a	Log P (Octanol–Water)	pH 1.0–1.2[a]	pH 4.5–4.6[b]	pH 6.8	$P_{\text{eff } in\ vivo}$ (cm/s) (Human Permeability Studies)	P_{app} (cm/s) (Caco 2 Cells Studies)	F_a (%)
Ibuprofen[18]	4.5–4.6	3.68	0.038	0.084	3.37	8×10^{-4}	53×10^{-6}	About 100
Ketoprofen	4.4–4.8	3.1–3.2	0.13	0.49	40.76	$8.4 \pm 3.3 \times 10^{-4}$	40.6×10^{-6}	More than 90

[a] pH 1.0 for ibuprofen, pH 1.2 for ketoprofen.
[b] pH 4.5 for ibuprofen, pH 4.6 for ketoprofen.

ketoprofen preparations. Pain was at its lowest 2 h after the plasma level of ketoprofen was at its highest. Within the 10-h observation period, the maximum reduction in pain increased as the maximum plasma level rose.[82]

Risks associated with differences in C_{max} of NSAIDs are more critical for therapy of acute than chronic pain. Ketoprofen is used for both acute (pain relief) and chronic therapy (inflammatory diseases).[16] However, the prescribing information states that ketoprofen can be administered with food to minimize GI adverse effects. As mentioned above, when ketoprofen is taken with food, its C_{max} can be reduced by up to one-half, whereas AUC is not altered. This shows that patient risks associated with variations in the absorption rate and C_{max} are not critical to the therapeutic outcome.

Therefore, it can be concluded that the risk of adverse patient experiences related to either supra-BA or sub-BA in terms of C_{max} is low. The risk of bioinequivalence with respect to AUC is also low and therefore the resultant risks to the patient are also low.

Previous Conclusions Related to BCS Class II Weakly Acidic NSAIDS

The BCS Guidance, issued by the US FDA, recommended the biowaiver only for drug products containing Class I compounds.[2] Discussions at scientific workshops after the guidance became available and in subsequent publications recommended that biowaiver could be extended to drugs containing Classes II and III APIs.[83–85] Subsequently, the WHO issued a Guidance that included the possibility of biowaivers for Class III as well as for Class I drugs and also for Class II drugs that are highly soluble at pH 6.8, arguing that such substances can practically behave as Class I drugs because of the high solubility at the site of absorption. Yazdanian et al.[32] also proposed that the "high solubility" definition may be too strict for acidic drugs and suggested that BCS-based biowaivers should also be applicable to weak acids with high solubility at pH 7.4. The BCS and Biowaiver focus group of the International Pharmaceutical Federation has prepared biowaiver monographs for IR solid oral dosage forms containing ibuprofen and diclofenac, both of which are BCS Class II weak acids and both of which were considered to be scientifically justified biowaiver candidates.[24,25] The biopharmaceutical properties relevant to the biowaiver decision are similar for ibuprofen and ketoprofen BCS (see Table 3).

Subsequent to the biowaiver recommendation for ibuprofen, a study describing efforts to develop an ibuprofen tablet appeared in the literature.[71] It concludes that the biowaiver dissolution testing procedure may not be adequate to detect differences in C_{max} for multisource ibuprofen products and BCS Class II drugs generally. A series of four *in vivo* BE studies were conducted. In all cases, AUC passed. However, in two of the four cases, the lower confidence limit of C_{max} failed to achive BE (i.e., too low). Several limitations of the report hinder broad application of the stated conclusion. First, although dissolution data at both 50 and 75 rpm were presented at biowaiver pH of 1.2, 4.5, and 6.8, no comparison of f2 values is given, so it is not possible to draw a conclusion regarding BE from the dissolution data. Second, as the clinical study did not demonstrate bioinequivalence, but rather was inconclusive, increasing the power of the study would have been necessary to come to a statistically reliable assessment of the BE status of the product. Third, the reference product contained SLS, whereas the test product in development did not. This difference in excipient composition would preclude application of the biowaiver to the test product, as per the recent EMA Guidance and probably the WHO Guidance.

Tubic-Grozdanis et al.[22] applied GI simulation techniques to five BCS Class II weak acids (ibuprofen, ketoprofen, diclofenac, mefenamic acid, and piroxicam). On the basis of simulation data, they proposed that all evaluated drugs, except mefenamic acid, are potential biowaiver candidates. Recommendations made in recent BE and BCS workshops related to such APIs were that biowaivers may be appropriate if complete dissolution is observed before reaching mid-jejunum.[85]

In summary, as ketoprofen is highly soluble at intestinal pH, is highly permeable, is effective over a wide range of C_{max} plasma levels (can be given before or after food), and has a wide therapeutic range, there are few, if any, arguments against applying the biowaiver for approval of IR oral solid products of this API.

CONCLUSIONS

Ketoprofen is a typical BCS Class II weak acid with "low solubility" in acidic media, "high solubility" at pH above 4.6, and "high permeability." Such APIs may be acceptable for biowaiver when patient risks associated with bioinequivalence in terms of C_{max} are not critical. In consideration of these BCS properties and its clinical indications and experience, the biowaiver procedure can be recommended for IR ketoprofen solid oral dosage form, provided that (a) the test product contains only excipients present also in ketoprofen containing IR solid oral drug products approved in ICH or associated countries, for instance, as presented in this paper; (b) if critical excipients are used, these should be qualitatively the same and present in quantitatively similar amounts in the test and reference product, (c) the test drug product and comparator must dissolve 85% in 30 min or less in a buffer at pH 6.8; and (d) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8. When one or more of these conditions is not fulfilled, BE should be established *in vivo*.

Additional research work is recomended to more generally assess the discriminatory power of multiple pH *in vitro* dissolution testing of ketoprofen and other similar BCS Class II acids.

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