COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ibuprofen

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ABSTRACT: Literature data are reviewed on the properties of ibuprofen related to the biopharmaceutics classification system (BCS). Ibuprofen was assessed to be a BCS class II drug. Differences in composition and/or manufacturing procedures were reported to have an effect on the rate, but not the extent of absorption; such differences are likely to be detectable by comparative *in vitro* dissolution tests. Also in view of its therapeutic use, its wide therapeutic index and uncomplicated pharmacokinetic properties, a biowaiver for immediate release (IR) ibuprofen solid oral drug products is scientifically justified, provided that the test product contains only those excipients reported in this paper in their usual amounts, the dosage form is rapidly dissolving (85% in 30 min or less) in buffer pH 6.8 and the test product also exhibits similar dissolution profiles to the reference product in buffer pH 1.2, 4.5, and 6.8. J Pharm Sci 94:2121–2131, 2005

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INTRODUCTION

A monograph based on literature data is presented on ibuprofen concerning its properties related to the biopharmaceutics classification system (BCS). Purpose, scope and working procedure for these monographs were discussed previously.[1] In brief, it is to evaluate data available from literature sources about ibuprofen and to come to a conclusion whether or not to recommend a biowaiver for immediate release (IR) solid oral dosage forms containing ibuprofen, both from the biopharmaceutical point of view and from the perspective of public health risks.

This paper reflects the scientific opinion of the authors and not the policies of regulating agencies.

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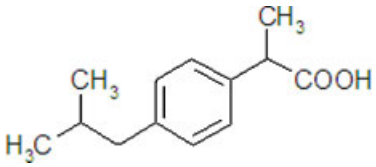

Figure 1. Structure of ibuprofen.

LITERATURE DATA

General Characteristics

Ibuprofens chemical name is (RS)-2-(4-Isobutylphenyl)propionic acid and its structure shown in Figure 1. The drug is usually administered as the racemic compound, but preparations containing only the S(+)-enantiomer (dexibuprofen) are available in some countries[2], for instance in Finland (FI).[3] Ibuprofen is usually given as the free acid but various salts, esters, and other complexes are also used. These include lysine and sodium salts, guaiacol and pyridoxine esters, isobutanolammonium and meglumine derivatives. In this monograph, ibuprofen is understood to be the free acid in the racemic form, unless otherwise indicated.

Therapeutic Indication and Therapeutic Index

Ibuprofen is a well-known and widely used nonsteroidal antiinflammatory drug (NSAID). The racemic compound is regarded a nonselective cyclooxygenase (COX)-inhibitor.[4–6] The S(+)-enantiomer was found to be a selective COX-1 inhibitor while R(−)-ibuprofen has little pharmacodynamic efficacy.[5] Racemic ibuprofen and the S(+)-enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhoea, headache, migrane, postoperative, and dental pain and in the management of spondylitis, osteo-arthritis, rheumatoid arthritis, and soft tissue disorders. Ibuprofen has also antipyretic properties.[4–6] Ibuprofen is regarded one of the safest NSAIDs available.[5,6]

Physicochemical Properties

Solubility

Solubility values are shown in Table 1. In the literature only data at 20°C or room temperature were found.[7,8] BCS classification requires data on the solubility at 37°C, these values were experimentally determined, for each media in triplicate. Ibuprofen drug substance was suspended in medium and stirred for 24 h at 37°C and then stored for a further 24 h without agitation. In each case sediment on the bottom of the flask was observed. The ibuprofen concentration in the clear supernatant was determined by UV-analysis. These results are also shown in Table 1.

Gosh et al.[9] reported a minimum solubility at pH 2.0. However, such a minimum was not re-

Table 1. Solubility Data at 20°C and 37°C (mg/mL) and Dose/Solubility Ratio's at 37°C (mL) of Two Strengths of Ibuprofen

	20°C			37°C		
					Dose/solubility ratio	
pH	Higgins et al.[7]	Stippler[8]	Calculated[7]	Experimental	For 400 mg	For 800 mg
1	<0.1		0.027	0.038	10526[a]	21053[a]
1.2		0.037				
2			0.027			
3	<0.1		0.028	0.043	9302[a]	18605[a]
4	<0.1		0.037			
4.5				0.084	4762[a]	954[a]
5			0.13			
5.5		0.0894		0.685	584[a]	1168[a]
6	1.0		1.1			
6.8		2.472		3.37	119	237
7			10			
7.2		4.52				
7.4				3.44	116	233
8	>100		80			

[a]Dose/solubility values outside the critical limit of <250 mL.

ported by other workers and is not in conformity with the molecular structure. The individual R(−) and S(+) isomers have greater solubility at pH 1.5 (9.5 mg/100 mL) than the racemate (4.6 mg/100 mL).[7] Complexation with β-cyclodextrin resulted in improved wettability and instantaneous dissolution.[10,11]

Polymorphism

Ibuprofen does not exhibit genuine polymorphism. However, it has a tendency towards slight crystal lattice modification, which may affect also its dissolution behavior.[7]

Partition Coefficient

Calculation of the octanol-water distribution coefficient gave log D values of 3.7, 3.6, 2.1, and 1.2 at pH values of 1, 4, 6, and 7, respectively.[7] Other workers estimated log *P* (n-octanol/water) and Clog *p* values of 3.68 and 3.14, respectively, using different methods based on atomic contributions to lipophilicity, wheras for the highly permeable marker drug metoprolol, using the same methodology, log *P* and Clog *p* values of 1.72 and 1.35 were calculated.[12]

pKa

The pKa of ibuprofen is in the range of 4.5–4.6.[7]

Dose Strength of Marketed Drug Products

Strengths of IR solid oral dosage form with a marketing authorization (MA) in Germany (DE) range from 200 to 800 mg.[13] The WHO List of Essential Medicines includes strengths of 200 and 400 mg.[14]

Pharmacokinetic Properties

Absorption and Permeability

Following oral administration of ibuprofen, maximum plasma concentrations are reached within 1–2 h in humans with an absolute bioavailability (BA) of about 100%.[6] Antacids like magnesium hydroxide accelerate the rate of absorption due to pH changes in the gastrointestinal (GI) system induced by the antacid. However, the extent of absorption, expressed as $AUC_{0\rightarrow 8}$, was not affected.[15] Also, ibuprofen absorption was much slower when concomitantly administered with aluminum hydroxide capsules than with sodium bicarbonate capsules. A rank order correlation was observed between dissolution parameters and the *in vivo* results that reflect rate of absorption, but no differences were noted in the AUC values.[16] Food intake also affects the absorption rate of ibuprofen, which is likely due to food induced pH elevation in the stomach resulting in earlier *in vivo* dissolution of ibuprofen.[17]

Rapid and complete absorption suggests a high permeability through the GI membrane.[2,4,6,18,19] Scintigraphic studies with sustained release products in humans indicate that ibuprofen absorption occurs throughout the GI tract following oral administration, which again supports a high permeability.[19] Rapid and complete absorption of ibuprofen was also reported from enteric coated microcapsules in humans administered as an oral suspension.[20]

Similar to other NSAIDs, high permeability of ibuprofen and its enantiomers has been observed in rats, where increased GI permeability was observed because NSAIDs promote their own transport.[21,22]This observation may possibly explain the GI side effects and the damage of the GI membrane following oral administration of high doses or upon long term oral usage of ibuprofen.

High permeability of ibuprofen and its enantiomers has been also observed in Caco-2 cell cultures. In a radiolabeled Caco-2 cell culture study, P-app of ibuprofen and propranolol were 53×10^{-6} and 27.5×10^{-6} cm/s, respectively.[23]

Pharmacokinetics

Linear pharmacokinetics of ibuprofen have been reported in the dose range of 200–400 mg.[24] At doses higher than 400 mg nonlinearity has been reported, but this is more likely due to changes of plasma protein binding than reduced absorption.[25,26] Dose linearity in the absorption of S(+)-ibuprofen in the dose range of 200–600 mg has also been documented.[27] Ibuprofen is extensively bound to plasma proteins (>99%).[26,28] R(−)-ibuprofen undergoes systemic unidirectional inversion to S(+)-ibuprofen, which is known to be the main pharmacodynamically active moiety.[29,30] Besides the extensive enantiomeric metabolic inversion of R(−) to the active S(+)-ibuprofen, there are no known metabolites of ibuprofen, which are pharmacologically active.[31] Hepatic biotransformation results in two inactive main metabolites (+)-2-4′-(2-hydroxy-2-methylpropyl) phenylpropionic acid and (+)-2-4′-(2-carboxypropyl) phenylpropionic acid, which are excreted either free or as conjugates in urine.[4,6] Total urinary recovery of ibuprofen and its metabolites is

about 70%–90% of the administered dose. There is almost no unchanged ibuprofen detected in the first 24 h in urine.[5,6] About 10% of the administered dose is eliminated via faeces. Neither ibuprofen nor the metabolites accumulate after multiple dosing.[6]

Dosage Form Performance

The pharmacokinetic properties of two ibuprofen preparations were compared in a randomized crossover study on ten healthy volunteers; there was no statistically significant difference in the extent of absorption but ibuprofen peak plasma concentrations differed between the two preparations.[32] The influence of incorporation of various different binding agents on the *in vitro* dissolution rate of ibuprofen formulations was investigated by Ghosh et al., using a rotating basket. As dissolution media, 0.1 and 0.1N HCl containing various concentrations of sodium laurylsulphate were used.[9] Polyvinylpovidone-containing formulations showed the fastest *in vitro* dissolution, but no confirmatory pharmacokinetic study was carried out. In another study, the pharmacokinetic properties of a soft gelatin capsule and a film-coated tablet were compared to those obtained after the administration of liquid prepared from effervescent tablets. The fastest absorption was observed after the ingestion of the soft gelatin capsule; liquid and film-coated tablet produced longer absorption half-lives, lower peak concentrations in serum and greater t_{max} values, but also in this study, the AUCs were close to similar for all products.[33] In another study, ibuprofen containing capsules prepared either from hypromellose or gelatin were investigated *in vitro* and *in vivo*. Again, there were no differences found in the extent of absorption, but in the fasted state a shorter *in vivo* lag time was found for the gelatin capsule. No difference was observed in the fed state, probably due to the "normalizing" effect by delayed gastric emptying after meal intake. This shorter *in vivo* lag time was reflected in the *in vitro* dissolution in the paddle apparatus, operated at 50 rpm, both in phosphate buffer pH 7.2 and in TRIS buffer pH 7.2.[34]

The excipients used in IR solid oral dosage forms having a MA in DE, FI, and NL are shown in Table 2. Soft gelatin capsules containing ibuprofen in dissolved forms having a MA also exists, but these drug products are not included in this table. In previous monographs, MAs of solid oral dosage forms were taken as indicators that these drug products had successfully passed an *in vivo* bioequivalence (BE) test.[1] However, for ibuprofen drug products with a MA in DE, this cannot be assumed, because in 1998 a committee working for the regulatory authority of DE classified ibuprofen as an active pharmaceutical ingredient (API) for which *in vivo* BE testing is not always necessary, in view of its wide therapeutic index and non critical therapeutic use.[35] It is also possible that FI and NL might have granted MAs without requiring *in vivo* BE studies. So, these MAs indicate clinical efficacy and safety, not necessarily BE between these drug products with respect to rate of absorption, However, differences in rate of absorption of ibuprofen drug products did not preclude the regulatory authorities of DE, FI and NL to license such drug products. This can be derived from the MAs they granted to soft gelatin capsules into one summary of product characteristics (SmPC), together with IR tablets, although the soft gelatine capsules will show faster absorption than the tablets.

Dissolution

The current USP 27 specification for *in vitro* dissolution requires not less than 80% (Q) dissolved within 60 min in 900 mL phosphate buffer pH 7.2 at 50 rpm using the paddle apparatus.[36] A large number of IR drug products marketed in DE showed more rapid dissolution, using an agitation speed of 75 rpm at the same pH, although differences for some products were still obvious.[37] Under those test conditions, almost all drug products met the criteria for rapid dissolution as defined in BCS guidances, that is, 85% within 30 min.[38,39]

DISCUSSION

Solubility

The several reports on the solubility at 20°C are in reasonable agreement with each other and also support our experimental values at 37°C, being somewhat higher than the values at 20°C, as can be expected. Solubility for biowaiver purposes should be determined at 37°C and at that temperature, at pH values below pH 5.5 their dose/solubility ratio exceeds the critical value of 250 mL for both strengths considered.[38,39] So, ibuprofen is insoluble in acid and consequently not "highly soluble" as defined according to the present BCS guidances.[38,39]

Table 2. Excipients[a] Present in Ibuprofen IR Solid Oral Drug Products[b] With an Marketing Authorization (MA) in Germany (DE), Finland (FI), and The Netherlands (NL)

Acacia	DE(1) NL(2–10)
Acesulfame potassium	DE(11)
Acetylated monoglyceride	DE(1)
Alginic acid	DE(12,13) NL(14,15)
Aluminium hydroxide	DE(16–18)
Beeswax	NL(3–6,8–10)
Calcium behenate	DE(19)
Calcium carbonate	NL(3–6,8–10,20–25)
Calcium sulphate	DE(1)
Carmellose sodium	DE(1,12,13,26–36) NL(2,7,25,37)
Carmoisine	NL(38)
Carnauba wax	DE(1,12,13) NL(3–6,8–10,14,15,20–24)
Carrageen	DE(39)
Castor oil	DE(40)
Cellulose	DE(11–13,18,19,26,28–36,39,41–60) NL(6,14,15,38,61–70) FI(71–79)
Copolymer of acrylate and methacrylate	DE(31,80)
Copovidone	DE(12,13,81,82) NL(14)
Croscarmellose sodium	DE(11,19,31,39,47–50,56,58,83–89) NL(2,6–8,38,61,65–70,90,91) FI(71–73,75–79,92,93)
Crospovidone	DE(11)
Dextrates	NL(90)
Dimeticone	DE(18)
Erythrosine	DE(16–18,94–96) NL(3–6,8–10,20–22,25,37,61,63,64,66–70,97–101)
Ethylcellulose	DE(82)
Gelatin	DE(56) NL(14,15,25) FI(73,77)
Glucose, liquid	DE(59,60)
Glycerol	FI(72,73,76–78)
Hydroxyethylcellulose	DE(40)
Hydroxypropylcellulose	DE(38,55) NL(38,62,64)
Hypromellose	DE(11,16–19,26–30,32–36,41–58,80,83–89,94–96,102–119) NL(37,38,61–70,91,97–101,120) FI(71–79,92,93)
Indigo carmine	NL(97,101)
Iron oxide	DE(26,36,44,84,86,89,106) NL(23,61,91) FI(92,93)
Kaolin	DE(59,60)
Lactose	DE(11,19,26,28,30,31,33,42,43,45,46,48,49,53,56) NL(3–5,8–10,25,61,65–70,97,101) FI(71,73,75,77,79)
Lactulose	DE(121)
Lecithin	NL(61,91)
Macrogol	DE(11,16–18,26–35,40–55,57–60,80,83–89,94–96,102–119) NL(2,7,20–25,37,38,62,64,91,97,98,100,101) FI(73,74,77,79,92,93)
Macrogolglycerol ricinoleate	NL(6)
Magnesium stearate	DE(12,13,16,17,26–36,39,40,47–51,54,55,59,60,80,82,94–96,102–119,121) NL(3–6,8–10,14,15,25,37,61,62,64–70,90,97,101,120) FI(71–79)
Maize starch	DE(1,12,13,16–18,26–30,32–36,39,40,47–51,54,57,58,80,83–87,94–96,102–114,116–119,121) NL(3–5,8–10,14,15,20–25,37,63,65–70,91,97–101) FI(79)
Maize starch, pregelatinised	DE(1,88,89) NL(8,63,97,98) FI(74)
Maltodextrin	DE(39)
Methylcellulose	NL(3–5,9,10)
Montanglycol wax	DE(59,60)
Polydextrose	**FI**(74)
Polysorbate	NL(20–22,24)
Polysorbate 80	DE(51,109,110) NL(23) FI(72,73,76–78)
Polyvinyl acetate phthalate	NL(3–5,10)
Potato starch	DE(110) FI(75)

(*Continued*)

Table 2. (*Continued*)

Potato starch (acetylated)	NL(23)
Potato starch (oxidized and acetylated)	NL(20–22,24)
Povidone	DE(1,11–13,51,57–60,104,105,116) NL(15,20–25,120)
Propylene glycol	DE(36,39,56) NL(63) FI(75)
Quinoline yellow	NL(97,101)
Shellac	DE(1) NL(3,4,6,61,91)
Silica	DE(1,11–13,26,28–36,39–41,44,47–52,54–60,83–89,104,105,109–111,116,117,121) NL(2–4,6,7,14,15,20–25,38,61–70,90,91,97–101) FI(71–79,92,93)
Sodium acetate	NL(61)
Sodium benzoate	DE(1) NL(3–6,8–10)
Sodium citrate	NL(2,7)
Sodium lauryl sulphate	NL(7,38,61,91,97,101) FI(71,74)
Sodium starch glycolate	DE(16–18,26,28,30,33,40–46,48,49,51–53,55,59,60,80,94–96,102–119,121) NL(2–5,9,10,62–64,97–101,120)
Sodium stearyl fumarate	DE(11)
Starch	DE(36)
Starch, pregelatinised	NL(6,20–24,91,99–101) FI(72,76,78,93)
Stearic acid	DE(1,26,28–31,33–36,41,46–50,52–54,57,83–85,87–89) NL(2,5,7,10,20–24,63,91,98–100) FI(74,92,93)
Stearic palmitic acid	DE(32,42–45,86)
Sucrose	DE(1,12,13,59,60) NL(2–10,14,15,20–25) FI(72,73,76–78)
Talc	DE(12,13,18,27–35,40–54,57–59,80,81,95,102,103,106,109–111,117,121) NL(2–10,14,15,20–25,38,61,63,91,97–101,120) FI(71,75)
Titanium dioxide	DE(1,11–13,16–18,26–36,40–54,56–60,70,80,81,83,85–89,94–96,102–106,109–111,115–117) NL(2–10,14,15,20–24,37,38,61,63,64,66–70,91,97–101,120) FI(71–74,77,78,92,93)
Triacetin	DE(11,65,66) NL(67–70)

1. Migränin 400 mg Ibuprofen Dragees.
2. Nurofen 200 mg/–400 mg tablet, omhulde tabletten 200/–400 mg.
3. Ibuprofen Sandoz 200 mg, dragees 200 mg.
4. Ibuprofen Sandoz dragee 200 mg/–400 mg, omhulde tabletten 200 mg/–400 mg.
5. Ibuprofen Dagra 200 mg, omhulde tabletten.
6. Ibuprofen 200 mg/–400 mg Katwijk, dragees.
7. Nurofen 200 mg tablet ovaal, omhulde tabletten 200 mg.
8. Ibuprofen 400 mg, dragees (MA holder: Katwijk Farma).
9. Ibuprofen 200 mg/–400 mg, dragees (MA holder: Delphi).
10. Actifen 400 mg, omhulde tabletten 400 mg.
11. Ibumerck® 400 mg/–600 mg/–800 mg Filmtabletten.
12. Aktren® Dragees.
13. Dolgit® 200 mg/–400 mg/–600 mg überzogene Tabletten.
14. Femapirin, dragees 200 mg.
15. Actifen 200 mg, omhulde tabletten 200 mg.
16. Ibuprofen 400 mg medphano Filmtabletten.
17. Ibuprofen-mp 600 mg Filmtabletten.
18. Optalidon® 200 mg Filmtabletten.
19. ibuTAD® akut Tabletten.
20. Ibuprofen 200 mg/–400 mg PCH, omhulde tabletten.
21. Ibuprofen dragees 200 mg Samenwerkende Apothekers, omhulde tabletten.
22. Sterke Ibuprofen dragees 400 mg Samenwerkende Apothekers, omhulde tabletten.
23. Advil, dragees 200 mg.
24. Ibuprofen 200 mg/–400 mg, omhulde tabletten (MA holder: Pharmachemie).
25. Ibuprofen, dragees 200 mg/–400 mg (MA holder: Lagap BNL).
26. Aktren® Forte Filmtabletten.
27. Contraneural® 400 mg/–600 mg Filmtabletten.
28. Ibu 400–1 A Pharma Filmtabletten.
29. Ibu 600/–800–1 A Pharma Filmtabletten.
30. Ibu 400 akut–1 A Pharma Filmtabletten.
31. Ibu Eu Rho® 400 mg Filmtabletten.
32. IbuHEXAL® 400 mg/–600 mg/–800 mg Filmtabletten.
33. IbuHEXAL® akut 400 gegen Schmerzen Filmtabletten.

(*Continued*)

Table 2. (*Continued*)

34. ibuTAD® 200 mg gegen Schmerzen Filmtabletten.
35. ibuTAD® 400 mg/−600 mg/−800 mg Filmtabletten.
36. Jenaprofen® 600 mg Filmtabletten.
37. Ibuprofen 600 mg, omhulde tabletten (MA holder: Katwijk Farma).
38. Ibuprofen Dumex 200 mg/−400 mg/−600 mg, tabletten.
39. Ibuprofen Sandoz® 400 mg/−600 mg Filmtabletten.
40. Jenaprofen® 400 mg Filmtabletten.
41. Dolgit® 800 Filmtabletten.
42. DOLO-PUREN® 400 T Filmtabletten.
43. DOLO-PUREN® 600 Filmtabletten.
44. DOLO-PUREN® forte Filmtabletten.
45. dolo sanol® 200 mg/−400 mg Filmtabletten.
46. Ibu-acis® 600 mg Filmtabletten.
47. Ibubeta® 200 akut Filmtabletten.
48. Ibubeta® 400 akut Filmtabletten.
49. Ibubeta® 400 akut Filmtabletten.
50. Ibubeta® 600 mg/−800 mg Filmtabletten.
51. Ibuflam 800 mg Lichtenstein Filmtabletten.
52. Ibu KD® 800 Filmtabletten.
53. Ibuprofen Klinge® 400/−600 Filmtabletten.
54. IbuHEXAL® akut 200 gegen Schmerzen Filmtabletten.
55. Ibuprofen PB 400 mg Filmtabletten.
56. Kontagripp Sandoz® 200 mg Filmtabletten.
57. Parsal® 600 Filmtabletten.
58. Tabalon® Filmtabletten.
59. Urem® Dragees.
60. Urem® forte Dragees.
61. Brufen 400 mg/−600 mg, tabletten 400 mg/−600 mg.
62. Ibuprofen 200 mg/−400 mg/−800 mg PCH, omhulde tabletten 200 mg/−400 mg/−800 mg.
63. Ibuprofen Gf 600 mg, omhulde tabletten.
64. Ibuprofen Sandoz 200 mg/−400 mg, tabletten 200 mg/−400 mg.
65. Ibuprofen 200 mg, tabletten (MA holder: Sanofi-Synthelabo).
66. Ibuprofen 200 mg/−400 mg/−600 mg, tabletten (MA holder: GenRx).
67. Ibuprofen 200 mg/−400 mg/−600 mg, tabletten 200 mg/−400 mg/−600 mg.
68. Ibuprofen 200 mg Hexal, omhulde tabletten/Ibuprofen 400 mg/−600 mg, tabletten.
69. Ibuprofen 200 mg/−400 mg/−600 mg FLX, tabletten.
70. Ibuprofen Merck 200 mg/−400 mg/−600 mg, omhulde tabletten.
71. Brufen® 400 mg/−600 mg tabletti.
72. Burana 200 mg/−400 mg tabletti, kalvopäällysteinen.
73. Burana 600 mg/−800 mg tabletti, kalvopäällysteinen.
74. IBUMAX® 400 mg/−600 mg kalvopäällysteinen tabletti.
75. IBUMETIN® 400 mg/−600 mg tabletti, kalvopäällysteinen.
76. Ibusal 200 mg/−400 mg tabletti, kalvopäällysteinen.
77. Ibusal 600 mg/−800 mg tabletti, kalvopäällysteinen.
78. Ibutabs 400 mg tabletti, kalvopäällysteinen.
79. Solpaflex 400 mg tabletti, kalvopäällysteinen.
80. Ibu Eu Rho® 200 Filmtabletten.
81. ibu-Attritin, 400 mg Dragees.
82. ibu-Attritin forte, 600 mg Filmtabletten.
83. Ibu 200 mg AbZ Filmtabletten.
84. Ibu 400 mg/−600 mg/−800 mg AbZ Filmtabletten.
85. ibuprofen 200 von ct Filmtabletten.
86. ibuprof 200/−400/−600/−800 von ct Filmtabletten.
87. IBU-ratiopharm® 200 akut/−400 akut Schmerztabletten Filmtabletten.
88. Ibu-ratiopharm® 400 akut Filmtabletten.
89. Ibu-ratiopharm® 600 akut/−800 akut Filmtabletten.
90. Ibuprofen Chefaro 200 mg, tabletten.
91. Advil Ovaal 400 mg, filmomhulde tabletten 400 mg.
92. Ibuprofen-ratiopharm 200 mg/−400 mg/−600 mg/−800 mg kalvopäällysteinen tabletti.
93. Ibuxin 200 mg/−400 mg/−600 mg/−800 mg tabletti, kalvopäällysteinen.
94. Ibuprofen PB 600 mg Filmtabletten.
95. Togal® Ibuprofen 400 mg Filmtabletten.
96. Ibu-Hemopharm 400 mg Filmtabletten.
97. Ibuprofen Gf 400 mg, omhulde tabletten.
98. Ibuprofen 200 mg, omhulde tablet (MA holder: Healthypharm).
99. Ibuprofen CF 200 mg, omhulde tabletten.
100. Ibuprofen CF 400 mg/−600 mg, omhulde tabletten.
101. Ibuprofen Gf 200 mg, omhulde tabletten.
102. Dismenol® N Filmtabletten.

(*Continued*)

Table 2. (*Continued*)

103. Esprenit® 400 mg/−600 mg Filmtabletten.
104. EUDORLIN® Extra Ibuprofen-Schmerztabletten Filmtabletten 400 mg.
105. EUDORLIN® Migräne Filmtabletten.
106. Gyno-Neuralgin® Filmtabletten.
107. Ibudolor® 200 mg/−400 mg Filmtabletten.
108. Ibudolor® Migräne Filmtabletten.
109. Ibuflam 400 mg Lichtenstein Filmtabletten.
110. Ibuflam 600 mg Lichtenstein Filmtabletten.
111. Ibu KD® 400 mg/−600 mg Filmtabletten.
112. Ibumerck® 200 mg Filmtabletten.
113. Ibuprofen AL 400 mg/−600 mg/−800 mg Filmtabletten.
114. Ibuprofen STADA® 400 mg/−600 mg Filmtabletten.
115. Ibutop® Rückenschmerztabletten Filmtabletten.
116. MENSOTON® gegen Regelschmerzen Filmtabletten.
117. Opturem® 400 mg/−600 mg Filmtabletten.
118. Pfeil Zahnschmerz-Tabletten®.
119. Pfeil Zahnschmerz-Tabletten® forte.
120. Nurofen Omhulde Tabletten 200 mg, omhulde tabletten 200 mg.
121. Dolodoc® 200 mg Filmtabletten.

Sources of data: DE: www.rote-liste.de; FI: www.nam.fi; NL: www.cbg-meb.nl.
[a]Ingredients present in printing inkt only are not included.
[b]Excluded are: oromucosal preparations and dosage forms that are swallowed by the patient in liquid form: soft gelatin capsules filled with a solution, oral lyophilisates, soluble tablets, effervescent tablets, dispersible tablets, oral powders and oral granulates. Drug products containing more then one API are also excluded.

Absorption and Permeability

The BA of about 100% already classifies ibuprofen as "highly permeable" according to the present BCS Guidances.[38,39] This classification is supported from both *in vivo* as well as *in vitro* data. Absorption of ibuprofen occurs throughout the GI tract. A P-app exceeding 10×10^{-6} cm/s is considered to imply high permeability.[23] The results reported from Caco-2 studies exceed this value, in line with the higher P-app found for ibuprofen than for propranolol; propranolol is recommended as a high permeability reference substance for Caco-2 permeability in the FDA guideline.[38]

Also, the partition coefficient of ibuprofen, being higher than of metoprolol, supports its high permeability. In the referred study, metoprolol was chosen as the reference compound for permeability since 95% of the drug is known to be absorbed from the GI tract.[12] Hence, the *in vitro* results are consistent with the observation of complete absorption *in vivo*.

BCS Classification

According to the present regulations, ibuprofen is a BCS class II drug, showing high permeability and pH-dependent solubility, that is, a high solubility according to BCS requirements only above a certain pH value. The assignment of ibuprofen to BCS Class II is supported by an observed *in vitro-in vivo* correlation (IVIVC) where a rank order was found between dissolution characteristics and the rate of absorption,[16] since IVIVC's are predicted for BCS Class II drugs.[40] Other workers classified ibuprofen as BCS Class II also. One research group based its classification on solubility values, measured by the saturation-flask method, at different pH-values, and absorption/permeability literature data[41]; an other reseach group based its classification on the solubility of ibuprofen in water, without taking into account the pH-dependency, and calculated partition coefficients; the latter were shown to correlate with human intestinal permeability.[12]

Both of the current BCS Guidances allow the possibility for a biowaiver exclusively for BCS class I drugs.[38,39] The limited solubility of ibuprofen at acid pH thus excludes it from the present biowaiver criteria. However, at pH values near neutral, the solubility of ibuprofen is sufficient to comply with criterion for high solubility: a dose/solubility quotient of less than 250 mL.[38,39] As these pH values are closer to those at the absorption sites in the small intestine they are therefore more relevant in terms of systemic absorption of ibuprofen.

Accordingly, ibuprofen may also fit in the newly proposed "intermediate solubility class" suggested for acids and bases that are highly soluble at either physiologically relevant pH 1.2 or 6.8.[42,43] Current publications also suggest pH-dependent soluble, highly permeable, weak acidic ionizable drug compounds should be handled like BCS class I drugs.[44,45] This evaluation is supported by Rinaki et al.[46] who emphasized the dynamic character

of the absorption process, as drug dissolution is promoted by high permeability for highly permeable acidic NSAIDs like ibuprofen.

Risk on Bioinequivalence and the Performance of Surrogate Techniques for *In Vivo* BE

Literature data do not report formulation effects on the extent of absorption. But with respect to rate of absorption, not all ibuprofen IR solid dosage forms with a MA are necessarily bioequivalent to each other, since pH-regulating excipients and surfactants in the formulation may increase the rate of absorption of ibuprofen. However, there is some evidence that such differences could be detected by comparative dissolution testing *in vitro* at a discriminatory pH. Dissolution studies were reported in 0.1N HCl, despite the low solubility of ibuprofen in acidic media[9] and testing under that extreme nonsink conditions was able to revealed very small differences between formulations. But also dissolution testing at pH 7.2, that is, at a less discrimatory pH, was able to predict differences *in vivo*.[34] Dissolution testing at a slightly lower pH, for example, pH 6.0 or 6.5, can be expected to be more discriminatory than testing at pH 7.2 as per USP.

Patient's Risks Associated with Bioinequivalence

When considering a biowaiver for a drug substance, its therapeutic index also needs to be taken into account.[38,39] Ibuprofen has a wide therapeutic range between 10 and 50 mg/L, the toxic concentration being >100 mg/L and has no life-threatening indication.[5,6] So, the use of *in vitro* methodology as a surrogate for *in vivo* BE studies involves little therapeutic risk. The risks to public health are further reduced if a biowaiver is given only to drug products formulated with the excipients shown in Table 2, being present in drug products, which can be assumed to have an acceptable clinical performance.

CONCLUSION

A biowaiver for IR ibuprofen solid oral dosage form is scientifically justified, provided that

- the dosage form is rapidly dissolving (85% in 30 min or less) in pH 6.8 buffer [38,39]
- the test product shows dissolution profile similarity to the reference product in pH 1.2, 4.5, and 6.8[38,39]
- the test product contains only the excipients shown in Table 2, in amounts that are usual for IR solid oral dosage forms. The range of the amounts present in dosage forms with a MA in the USA can be obtained from the FDA Inactive Ingredients Database.[47]

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