COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ciprofloxacin Hydrochloride

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of new multisource and reformulated immediate release (IR) solid oral dosage forms containing ciprofloxacin hydrochloride as the only active pharmaceutical ingredient (API) are reviewed. Ciprofloxacin hydrochloride's solubility and permeability, its therapeutic use and index, pharmacokinetics, excipient interactions and reported BE/bioavailability (BA) problems were taken into consideration. Solubility and BA data indicate that ciprofloxacin hydrochloride is a BCS Class IV drug. Therefore, a biowaiver based approval of ciprofloxacin hydrochloride containing IR solid oral dosage forms cannot be recommended for either new multisource drug products or for major scale-up and postapproval changes (variations) to existing drug products. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:22–33, 2011

Keywords: absorption; biopharmaceutics classification system (BCS); ciprofloxacin; dissolution; permeability; regulatory science; solubility

INTRODUCTION

A monograph based on literature data about ciprofloxacin hydrochloride monohydrate, with respect to its biopharmaceutical properties and the risk of waiving *in vivo* BE testing in the approval of immediate release (IR) solid oral dosage forms containing this active pharmaceutical ingredient (API), including both reformulated products and new multisource drug products is presented. The purpose and scope of this series of monographs have been previously discussed.[1] Briefly, the aims of the present study are to evaluate all pertinent data available from literature sources to assess the appropriateness of a biowaiver from both a biopharmaceutical and public health perspective. The progress in this series, hence the available monographs, can be followed on the FIP Website (http://213.206.88.26/www2/sciences/index.php?page=pharmacy_sciences&pharmacy_sciences = sciences_bioavail_groupbcs).

EXPERIMENTAL

A search in the PubMed Central and Scirus was conducted using the keywords ciprofloxacin and ciprofloxacin hydrochloride combined with: absorption, absolute bioavailability (BA), bioequivalence

A project of the International Pharmaceutical Federation FIP, Special Interest Group on BCS and Biowaiver, www.fip.org/bcs.

This article reflects the scientific opinion of the authors and not the policies of regulating agencies and the International Pharmaceutical Federation (FIP).

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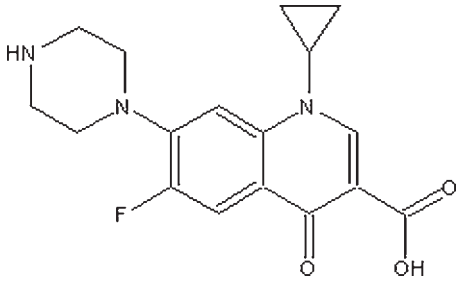

Figure 1. Structure of ciprofloxacin.

(BE), dissolution, excipients, partition coefficient, permeability, pharmacokinetics, polymorphism, oral, and solubility. Whenever possible, original literature was consulted and data from secondary sources were included for completeness or when original literature could not be located.

RESULTS

General Characteristics

Name

Ciprofloxacin (INN), structure shown in Figure 1.

Therapeutic Indications and Therapeutic Index

Ciprofloxacin is a broad-spectrum bactericidal anti-infective agent of the fluoroquinolone class. It is available in more than 100 countries, where it is approved for the treatment of 14 types of infections, especially urinary tract infections such as acute uncomplicated cystitis and chronic bacterial prostatitis, and lower respiratory infections.[2,3] The most frequent adverse reactions include nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness.[4] Rare allergic reactions such as hives and anaphylaxis have been described. Serious adverse effects include drug-induced psychosis, immunogenic hypersensitivity reaction, peripheral neuropathy, raised intracranial pressure, seizure, tendinitis, traumatic, or nontraumatic rupture of tendon.[4] Acute renal failure has also been described, mostly in cases related to overdose,[5,6] but sometimes at ciprofloxacin dosages within therapeutic schedules.[7,8] Because of its potency, broad-spectrum activity and general safety, ciprofloxacin is usually reserved as a drug of last resort to treat antibiotic-resistant infections.[3]

Chemical Properties

Salts, Isomers, and Polymorphs

The United States Pharmacopeia (USP)[9] contains a monograph for ciprofloxacin hydrochloride and the European Pharmacopeia (EP)[10] has a monograph for the anhydrous form of ciprofloxacin hydrochloride. The hydrochloride and the free base are in regular therapeutic use. Stoichiometric metallic complexes between ciprofloxacin and metals have been reported but they are not in regular therapeutic use.[11–13] Polymorphic forms and stereoisomers have not been reported.

Dissociation Constants

Ciprofloxacin is a zwitterionic molecule containing two proton-binding sites. At 37°C, values of pK_{a1} and pK_{a2} are 6.2 and 8.59, respectively, have been reported.[14] At 25°C, pK_a values of 6.8 and 8.73–8.76 were reported.[15,16]

Partition Coefficient

The *n*-octanol/pH 7.0 buffered solution partition coefficient ($\log P$) of ciprofloxacin was reported as −0.94 at 37°C,[16] −1.45 (temperature not given)[14] and −1.70 at 25°C and pH 7.2.[17] Similarly, calculations using fragmentation methods based on atomic contributions to lipophilicity employing the $C\log P^{®}$ gave values of −1.15 for $C\log P$ and 1.32 for $\log P$. These values are lower than the corresponding values of 1.35 ($C\log P$) and 1.72 ($\log P$) for the highly permeable marker drug metoprolol.[18]

Solubility

As other fluoroquinolones ciprofloxacin is zwitterionic and exhibits a "U" shaped pH-solubility profile, with high solubility at pH values below 5 and above 10, and minimum solubility near the isoelectric point, which is close to neutral. The USP[9] reports the aqueous unbuffered solubility of ciprofloxacin hydrochloride, which has a final acidic pH. The solubility in phosphate buffer was informed at pH 6.8 and 7.5 and 37°C.[19] Several pH-solubility profiles of ciprofloxacin hydrochloride have been reported at 25°C.[20–22] The data and the corresponding dose:solubility ratios (D/S) are summarized in Table 1 for the usual range of tablet strengths (see below). The intrinsic solubility of ciprofloxacin, that is, the solubility of the neutral form, also has been determined at different temperatures.[14,23]

Dosage Form Strength

Doses and strengths of ciprofloxacin hydrochloride are expressed in terms of its base.[24] The dose of ciprofloxacin (as hydrochloride) recommended by WHO is 250 mg.[25] Tablets of ciprofloxacin hydrochloride marketed in Argentina contain 100, 250, 500, and 750 mg (ciprofloxacin equivalent) strengths.[26] In most other countries, the same range of strengths has been registered; see Table 2.[27–36]

Table 1. Solubility of Ciprofloxacin Hydrochloride and Corresponding D/S Ratios for Three Usual Tablet Strengths

pH	°C	Medium	Solubility[a] (mg/mL)	References	D/S Ratio[b] (mL)		
					250 mg[c]	500 mg	750 mg
3–4.5	25	Water	10–30	[9]	8–25	17–50	25–75
4.5	25	Water + NaOH to indicated pH	3.5	[20]	71	143	214
6.8	25	Water + NaOH to indicated pH	0.0813	[20]	3075	6150	9225
6.8	37	Phosphate buffer	0.17	[19]	1470	2941	4412
6.84	25	Water + NaOH to indicated pH	0.088	[21,22]	2840	5682	8523
7.5	25	Water + NaOH to indicated pH	0.0702	[20]	3536	7072	10,608
7.5	37	Phosphate buffer	0.16	[19]	1562	3125	4687

[a]Expressed in mg of the ciprofloxacin base.
[b]Cut-off limit: ≤250 mL.[76–78]
[c]Highest strength on WHO list of essential medicines.[26]

Pharmacokinetic Properties

Bioavailability

The BA of ciprofloxacin was studied by several authors. Doses of 200 mg were given to 12 healthy volunteers orally in a randomized, crossover design, 1 week apart, and as a 10 min intraveneous (i.v.) infusion. Absorption was rapid, with peak concentrations in serum occurring at 0.71 ± 0.15 h. Absolute BA, defined as the ratio of the Area Under the Curve from 0 h to infinity ($AUC_{0-\infty}$) for the oral to the i.v. dose was $69 \pm 7\%$.[37] In other study, the AUC obtained after administration of a single oral dose of 500 mg was compared with that obtained with a single i.v. infusion of 400 mg over 60 min; $AUC_{oral}/AUC_{i.v.}$ was 0.74 ± 0.03; The absolute BA was 56%.[38] Other workers determined the pharmacokinetic parameters of ciprofloxacin after the oral administration of 50, 100, and 750 mg, as well as 50 and 100 mg i.v., over 15 min.[39] Serum and urine concentrations were determined with a bioassay. Absolute BA varied between $77 \pm 16\%$ and $63 \pm 15\%$ after oral administration of 50 and 100 mg. When normalized to 0.1 g of ciprofloxacin, the C_{max} and the $AUC_{0-\infty}$ after the 750 mg dosing were smaller than after the 50 or 100 mg oral dosing ($p < 0.05$) and the higher dosage tended towards a delay in absorption.[39]

Other authors found that the mean BA of ciprofloxacin at oral doses of 200 and 750 mg was nearly identical (69.0% and 69.1%). The BA of the 750 mg dose was, however, significantly more variable than observed with the 200 mg dose. But t_{max} was significantly longer with the 750 mg dose than with the 200 mg dose (1.38 h vs. 0.69 h). Also, $C_{max,}$ normalized to a dose of 750 mg, was significantly higher with the smaller dose (4.4 μg/mL vs. 3.0 μg/mL).[40] The slower absorption rate constant observed in the larger dose and the possible influence of changing gastrointestinal (GI) motility and blood flow may have contributed to this variability. The prolongation of absorption and the variability in BA observed in the larger dose most likely reflected variable disintegration/dissolution rate with the 750 mg tablet versus the 200 mg tablets.

Tartaglione et al.[41] reported mean C_{max} and AUC values to increase in proportion after sequential increasing oral dosing of 250, 500, 750, and 1000 mg. Interestingly, they observed that the absorption phase of their data were best fitted by a zero-order equation and suggested that events leading up to the absorption step could be which are rate limiting, thus forcing the absorption to appear to be zero order. This could be likely due to *in vivo* dissolution problems. Since ciprofloxacin is a zwitterionic drug and is probably absorbed by passive diffusion, intestinal pH changes suggest that rapid absorption may occur in the duodenum and proximal jejunum, whereas absorption may decrease in the distal portion of the intestine.[41] Other authors,[42] using HPLC methodology, could not detect dose disproportionality in ciprofloxacin kinetics after a single oral administration of 100, 250, 500, or 1000 mg. Nonetheless, no other reports on dose proportionality problems could be identified.

Except for an increase in the time to achieve C_{max}, significant food–drug interactions have not identified in the reviewed literature,[43,44] although when administered with calcium-fortified orange juice or dairy products a significant decrease in BA has been observed.[45,46]

Ciprofloxacin and other quinolones chelate with cations such as aluminum, magnesium, calcium, iron, and zinc. Clinically relevant drug–drug interactions between ciprofloxacin and metal cations have been extensively described.[47–49] Although the biopharmaceutical mechanism of this interaction is still not understood, a recent report clearly shows that the metal cations do not affect the solubility of fluoroquinolone and when they do, such solubility increases. So, a decrease in solubility cannot explain the lower BA observed when metal ions are coadministered.[50]

Table 2. Excipients* Present in Ciprofloxacin Hydrochloride IR Solid Oral Drug Products** 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), and the Minimal and Maximal Amount of that Excipient Present Pro-Dosage Unit in Solid Oral Drug Products With a MA in the US***

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)
Carmellose sodium	NL (1)	2.2–160
Cellulose	DE (2–25) DK (26–51) ES (52–98) FI (99–108) FR (109–125) NL (1, 126–139) NO (140–145) SE (146–158) UK (159) US (160–165)	4.6–1385[a]
Croscarmellose sodium	DE (2, 3, 7, 8, 12, 15, 23, 24) DK (26, 27, 31, 33, 35, 37) ES (73, 86, 94) FI (99–102) FR (114, 116, 119, 122) NL (127, 130, 131, 133–135, 139) NO (144) SE (148–150, 155) US (164)	2–180
Crospovidone	DE (5, 6, 10, 11, 13, 14, 16, 18–22, 25) DK (28–30, 32, 34, 36, 38–51) ES (52, 54, 58, 59, 61, 63, 66, 69–71, 74, 76–78, 80–82, 90, 91, 93, 95, 96, 98) FI (104–108) FR (109–113, 115, 117, 120, 121, 123–125) NL (126, 128, 129, 132, 136–138) NO (140, 141, 143, 145) SE (146, 147, 151, 153, 154, 156–158) UK (159) US (160, 162, 166)	4.4–792[a]
Disodium edetate	DE (17) ES (85, 87–89, 97)	0.21–4
Hydroxypropylcellulose	DE (167–170)	4–132
Hypromellose	DE (2–21, 23–25, 167–170) DK (28, 29, 32, 34, 36, 38–41, 43–51) ES (52, 56, 57, 60, 61, 63, 70, 73, 74, 76, 77, 80, 83–89, 91, 92, 94, 95, 97) FI (101, 104–106) FR (109, 110, 112–114, 119–121, 123–125) NL (1, 126, 128, 131, 135, 137, 171, 172) NO (140, 142, 143, 145) SE (146, 153, 154, 158) US (160, 161, 163–166)	0.8–86
Lactose	DE (12) NL (171, 172)	23–1020[a]
Macrogol	DE (2–22, 25, 167–170) DK (28, 29, 32, 34, 36, 38–41, 43–51) ES (52, 55, 57, 61, 65, 73, 76, 77, 80, 85–89, 91, 94, 95, 97) FI (101, 104–106) FR (109, 112–114, 120, 121, 123–125) NL (126, 128, 137, 171, 172) NO (140–143, 145) SE (146, 153, 154, 158) US (160–166)	0.12–500[a]
Magnesium stearate	DE (2–25, 167–170) DK (26–51) ES (52–98) FI (99–108) FR (109–125) NL (1, 126–139) NO (140–145) SE (146–158) UK (159) US (160–166)	0.15–401[a]
Polydextrose	DE (19) DK (41) US (165)	3.8–8.1
Polysorbate 80	ES (56, 60, 92)	2.2–418[a]
Poly (vinylalcohol)	DE (22) NO (141) US (162)	0.7–20
Povidone	DE (2, 3, 7, 8, 12, 15, 23, 24) DK (26, 27, 31, 33, 35, 37) ES (53, 55, 57, 64, 65, 67, 68, 72, 79) FI (99–102) FR (114, 116, 119, 122) NL (1, 127, 130, 131, 133–135, 139, 171, 172) NO (142, 144) SE (148–150, 155) US (161, 164)	0.17–75
Propylene glycol	DE (23, 24) ES (55, 56, 60, 65, 92) FR (119) NL (1, 131, 135)	1.5–52
Silica	DE (2–11, 13–25) DK (26–51) ES (52–54, 56–64, 66–98) FI (99–108) FR (109–115, 117–125) NL (1, 126–139) NO (140–145) SE (146–158) UK (159) US (160–166)	0.65–99
Sodium citrate	DE (12)	18–275
Sodium lauryl sulphate	ES (73, 86, 94)	0.65–50
Sodium starch glycolate	DE (2–4, 7–9, 15, 17, 23, 24, 167–170) DK (31, 33, 35, 37) ES (55, 56, 60, 62, 63, 65, 69–71, 74, 75, 78, 83–85, 87–90, 92, 93, 97, 98) FI (99, 102, 103) FR (110, 114, 118, 119) NL (1, 127, 131, 133–135, 139, 171, 172) NO (142) SE (149, 150, 152) US (161, 163, 165)	2–876[a]
Sodium stearyl fumarate	NL (171, 172)	1.2–26
Starch	DE (4–6, 9, 17, 19, 21, 22) DK (28, 29, 36, 41, 42) ES (53, 54, 56–60, 62, 64, 66–68, 72, 73, 75, 76, 79, 82–89, 91, 92, 94, 96, 97) FI (103, 108) FR (109, 111, 115, 117, 118, 125) NL (126, 129, 138) NO (141, 145) SE (147, 151, 152, 156–158) UK (159) US (160, 162, 163)	0.44–1135[a]
Starch, pregelatinized	DE (19, 22) DK (41, 42) ES (52, 61, 77, 80, 81, 95) FR (111, 115, 117) NL (129, 138) NO (141) SE (147, 151, 156, 157) US (165)	6.6–600

Table 2. (*Continued*)

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)
Stearic acid	DE (2, 3, 7, 8, 15) DK (33, 37) FI (102) FR (114) NL (127, 133, 134) NO (142) SE (149)	0.9–72[a]
Succinic acid	US (166)	65
Talc	DE (2–4, 7, 8, 15, 17, 22–24) ES (55, 56, 60, 62, 65, 73, 75, 85–89, 92, 94, 97) FI (103) FR (114, 118, 119) NL (1, 131, 135) NO (141, 142) SE (152) US (162, 163, 165)	0.25–220[a]
Triacetin	DE (19) DK (41) ES (63, 70, 74) FR (110) US (165)	0.72–15

(1) Ciprofloxacine ratiopharm 250 mg/500 mg/750 mg tabletten; (2) Cipro—1 A Pharma® 100 mg Filmtabletten (Mono); (3) Cipro—1 A Pharma® 250 mg/500 mg/750 mg Filmtabletten (Mono); (4) CIPRO BASICS 250 mg/500 mg Filmtabletten (Mono); (5) Ciprobay® 250 mg/500 mg/750 mg Filmtabletten (Mono); (6) Ciprobay® Uro Filmtabletten (100 mg) (Mono); (7) Ciprobeta® 250 mg/500 mg/750 mg Filmtabletten (Mono); (8) Ciprobeta® Uro 100 mg Filmtabletten (Mono); (9) Ciprofloxacin 250 mg/500 mg DeltaSelect Filmtabletten (Mono); (10) Ciprofloxacin AbZ 100 mg/250 mg/500 mg Filmtabletten (Mono); (11) Ciprofloxacin AL uro 100 mg/Ciprofloxacin AL 250 mg/500 mg/750 mg Filmtabletten (Mono); (12) Ciprofloxacin AWD® 250 mg/500 mg Filmtabletten (Mono); (13) Ciprofloxacin-ratiopharm® 100 mg/250 mg/500 mg/750 mg Filmtabletten (Mono); (14) Ciprofloxacin Sandoz® 100 mg Filmtabletten (Mono); (15) Ciprofloxacin Sandoz® 250 mg/500 mg/750 mg Filmtabletten (Mono); (16) Ciprofloxacin STADA® 100 mg/250 mg/500 mg/750 mg Filmtabletten (Mono); (17) Ciprofloxacin TAD 250 mg/500 mg Filmtabletten (Mono); (18) Ciproflox-CT 100 mg/250 mg/500 mg Filmtabletten (Mono); (19) CIPROFLOX-PUREN® 100 mg/250 mg/500 mg Filmtabletten (Mono); (20) CiproHEXAL 100 mg Filmtabletten (Mono); (21) CiproHEXAL 250 mg/500 mg/750 mg Filmtabletten (Mono); (22) Cipro-Q® 250 mg/500 mg/750 mg Filmtabletten (Mono); (23) Cipro-saar® 250 mg/500 mg Filmtabletten (Mono); (24) Gyracip® 250 mg/500 mg/750 mg Filmtabletten (Mono); (25) Keciflox® 100 mg/250 mg/500 mg/750 mg Filmtabletten (Mono); (26) Ciprofloxacin "Teva" filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (27) Ciprofloxacin "BMM Pharma," filmovertrukne tabletter 250 mg/500 mg/750 mg; (28) Ciprofloxacin "Copyfarm," filmovertrukne tabletter 250 mg/500 mg/750 mg; (29) Ciprofloxacin "Pharmathen," filmovertrukne tabletter 250 mg/500 mg/750 mg; (30) Ciprofloxacin "Ratiopharm," filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (31) Ciprofloxacin "Alternova," filmovertrukne tabletter 250 mg/500 mg/750 mg; (32) Ciprofloxacin "Actavis," filmovertrukne tabletter 250 mg/500 mg/750 mg; (33) Ciprofloxacin "1A Farma," filmovertrukne tabletter 250 mg/500 mg/750 mg; (34) Ciprofloxacin "Sandoz," filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (35) Ciprofloxacin "Krka" filmovertrukne tabletter 250 mg/500 mg/750 mg; (36) Ciproxin, filmovertrukne tabletter 250 mg/500 mg/750 mg; (37) Ciprofloxacin "HEXAL," filmovertrukne tabletter 250 mg/500 mg/750 mg; (38) Ciprofloxacin "Pharmafile," filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (39) Ciprofloxacin "Multipharma," filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (40) Ciproscope, filmovertrukne tabletter 100 mg/250 mg/500 mg; (41) Ciprofloxacin "Merck NM," filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (42) Ciprofloxacin "Arrow," filmovertrukne tabletter 250 mg/500 mg/750 mg; (43) Ciproten, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (44) Cidelta, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (45) Ciprotabs, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (46) Cifin, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (47) Myrciprox, filmovertrukne tabletter 100 mg/250 mg/500 mg; (48) Ciprodane, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (49) Cispharm, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (50) Sancipro, filmovertrukne tabletter 100 mg/250 mg/500 mg/750 mg; (51) Ciprodis, filmovertrukne tabletter 100 mg; (52) CIPROACTIN® 250 mg/500 mg/750 mg comprimidos recubiertos; (53) CIPROFLOXACINO ACOST 250 mg/500 mg comprimidos recubiertos con película EFG; (54) CIPROFLOXACINO QUALIGEN 250 mg/500 mg/750 mg comprimidos; (55) ESTECINA "250"/"500"/"750" Comprimidos recubiertos; (56) FELIXENE® 500; (57) BAYCIP® 250 mg/500 mg/750 mg, comprimidos; (58) BELMACINA 250 mg/500 mg/750 mg comprimidos recubiertos; (59) CIPROFLOXACINO BEXAL 250 mg/500 mg/750 mg COMPRIMIDOS RECUBIERTOS EFG; (60) CETRAXAL 250 mg/500 mg/750 mg comprimidos recubiertos; (61) CIPROACTIN® 250 mg/500 mg/750 mg comprimidos recubiertos; (62) CIPROFLOXACINO COMBIX 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (63) CIPROFLOXACINO EDIGEN 250 mg/500 mg/750 mg, comprimidos recubiertos EFG; (64) CIPROFLOXACINO GRAPA 250 mg/500 mg COMPRIMIDOS RECUBIERTOS CON PELÍCULA EFG; (65) CIPROFLOXACINO NORMON 250 mg/500 mg/750 mg Comprimidos Recubiertos EFG; (66) CIPROFLOXACINO TEVA 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (67) CIPROFLOXACINO UR 250 mg/500 mg comprimidos recubiertos EFG; (68) CIPROFLOXACINO VIR 250 mg/500 mg COMPRIMIDOS RECUBIERTOS CON PELÍCULA EFG; (69) CIPROFLOXACINO ALTER 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (70) CIPROFLOXACINO JUVENTUS 250 mg/500 mg/750 mg Comprimidos recubiertos con película EFG; (71) CIPROFLOXACINO KERN PHARMA 500 mg comprimidos EFG; (72) CIPROFLOXACINO LAREQ 250 mg/500 mg COMPRIMIDOS RECUBIERTOS CON PELÍCULA EFG; (73) CIPROFLOXACINO MABO 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (74) CIPROFLOXACINO MERCK 250 mg/500 mg/750 mg comprimidos recubiertos EFG; (75) Ciprofloxacino Ranbaxy 250 mg/500 mg/750 mg comprimidos; (76) Ciprofloxacino Sandoz 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (77) CIPROFLOXACINO TAUCIP 250 mg/500 mg/750 mg comprimidos recubiertos EFG; (78) CIPROFLOXACINO WINTHROP 250 mg/500 mg comprimidos EFG; (79) DORIMAN 250 mg/500 mg COMPRIMIDOS RECUBIERTOS CON PELÍCULA; (80) GLOBUCE 250 mg/500 mg/750 mg comprimidos recubiertos; (81) PIPROL 250 mg/500 mg/750; (82) RIGORAN 250 mg/500 mg/750 mg comprimidos; (83) SEPCEN 250 mg/500 mg/750 mg comprimidos recubiertos; (84) TAM 250 mg/500 mg/750 mg comprimidos recubiertos; (85) CIPROCTAL 250 mg/500 mg/750 mg comprimidos recubiertos con película; (86) Ciprofloxacino cinfamed® 250 mg/500 mg/750 mg comprimidos recubiertos EFG; (87) CIPROFLOXACINO CUVE 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (88) CIPROFLOXACINO DAVUR 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (89) CIPROFLOXACINO KORHISPANA 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (90) CIPROFLOXACINO STADA 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (91) CIPROFLOXACINO SUMOL® 250 mg/500 mg/750 mg comprimidos recubiertos con película EFG; (92) ULTRAMICINA 250 mg/500 mg comprimidos recubiertos; (93) CIPROFLOXACINO BELMAC 250 mg/500 mg/750 mg comprimidos EFG; (94) Ciprofloxacino cinfa® 250 mg/500 mg/750 mg comprimidos recubiertos; (95) Ciprofloxacino ratiopharm 250 mg/500 mg/750 mg comprimidos recubiertos EFG; (96) Ciprofloxacino Tarbis 250 mg/500 mg/750 mg comprimidos EFG; (97) Ciprofloxacino Rimafar 250 mg/500 mg/750 mg comprimidos EFG; (98) Ciprofloxacino Farmabion 250 mg/500 mg/750 mg comprimidos recubiertos con película; (99) Ciprofloxacin Alternova 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (100) Ciprofloxacin BMM Pharma 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (101) Ciprofloxacin Enna 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (102) Ciprofloxacin HEXAL 250 mg/500 mg/750 mg kalvopäällysteinen tabletti; (103) Ciprofloxacin Ranbaxy 250 mg/500 mg tabletit; (104) Ciprofloxacin ratiopharm 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (105) Ciprofloxacin Sandoz 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (106) Ciprofloxacin STADA 250 mg/500 mg/750 mg kalvopäällysteinen tabletti; (107) Cipromed 250 mg/500 mg/750 mg tabletti; (108) CIPROXIN® 250 mg/500 mg/750 mg tabletti, kalvopäällysteinen; (109) CIFLOX 250 mg/750 mg cp pellic mg/500 mg cp pellic séc; (110) CIPROFLOXACINE ALTER 250 mg/500 mg cp pellic; (111) CIPROFLOXACINE ARROW 250 mg/500 mg/750 mg cp pellic; (112) CIPROFLOXACINE BIOGARAN 250 mg cp pellic mg/500 mg cp pellic séc; (113) CIPROFLOXACINE EG 250 mg/500 mg cp pellic; (114) CIPROFLOXACINE G GAM 250 mg/500 mg cp pellic séc; (115) CIPROFLOXACINE MERCK 250 mg/750 mg cp pellic mg/500 mg cp pellic séc; (116) CIPROFLOXACINE PANPHARMA 500 mg cp pellic; (117) CIPROFLOXACINE QUALIMED 250 mg cp pellic mg/500 mg cp pellic séc; (118) CIPROFLOXACINE RANBAXY 500 mg cp pellic; (119) CIPROFLOXACINE RATIOPHARM 250 mg cp pellic mg/500 mg cp pellic séc; (120) CIPROFLOXACINE RPG 250 mg cp pellic mg/500 mg cp pellic séc; (121) CIPROFLOXACINE SANDOZ 250 mg cp pellic mg/500 mg cp pellic séc; (122) CIPROFLOXACINE TEVA 250 mg/500 mg cp pellic séc; (123) CIPROFLOXACINE WINTHROP 250 mg cp pellic mg/500 mg cp pellic séc; (124) CIPROFLOXACINE ZYDUS 250 mg cp pellic mg/500 mg cp pellic séc; (125) UNIFLOX 500 mg cp pellic séc; (126) Ciproxin 100 mg/250 mg/500 mg/750, tabletten 100 mg/250 mg/500 mg/750 mg; (127) Ciprofloxacine Sandoz 250 mg/500 mg/750 mg, filmomhulde tabletten; (128) Ciprofloxacine 100 mg/250 mg/500 mg/750 mg Katwijk, tabletten; (129) Ciprofloxacine Merck 250 mg/500 mg, filmomhulde tabletten; (130) Ciprofloxacine 100 mg/250 mg/500 mg/750 mg PCH, filmomhulde tabletten; (131) Ciprofloxacine 250 mg/500 mg//750 mg filmomhulde tabletten, filmomhulde tabletten; (132) Ciprofloxacine Actavis 250 mg/500 mg/750 mg, filmomhulde tabletten; (133) Ciprofloxacine 250 mg/500 mg/750 mg, filmomhulde tabletten [Betapharm]; (134) Ciprofloxacine 100 mg/250 mg/500 mg/750 mg, filmomhulde tabletten [Hexal AG]; (135) Ciprofloxacine 250 mg/500 mg/750 PCH, filmomhulde tabletten 250 mg/500 mg/750 mg; (136) Ciprofloxacine-ratiopharm 100 mg/250 mg/500 mg/750 mg, filmomhulde tabletten; (137) Ciprofloxacine CF 100 mg/250 mg/500 mg/750 mg, filmomhulde tabletten; (138) Ciprofloxacine 250 mg/500 mg/750 mg, filmomhulde tabletten [Arrow Generics];

(139) Ciprinol 250 mg/500 mg/750 mg, filmomhulde tabletten; (140) Ciprofloxacin Actavis 250 mg/500 mg tabletter; (141) Ciprofloxacin Arrow tablett, filmdrasjert 250 mg/500 mg/750 mg; (142) CIPROFLOXACIN HEXAL 250 mg/500 mg/750 mg tablett, filmdrasjert; (143) Ciprofloxacin ratiopharm 250 mg/500 mg/750 mg filmdrasjerte tabletter; (144) Ciprofloxacin Teva 100 mg/250 mg/500 mg/750 mg filmdrasjerte tabletter; (145) Ciproxin 250 mg/500 mg/750 mg tabletter, filmdrasjerte; (146) Ciprofloxacin Actavis 250 mg/500 mg/750 mg filmdragerade tabletter; (147) Ciprofloxacin Arrow 250 mg/500 mg/750 mg filmdragerad tablett; (148) Ciprofloxacin BMM Pharma 250 mg/500 mg/750 mg filmdragerad tablett; (149) Ciprofloxacin HEXAL 100 mg/250 mg/500 mg/750 mg filmdragerade tabletter; (150) Ciprofloxacin Krka 250 mg/500 mg/750 mg filmdragerad tablett; (151) Ciprofloxacin Merck NM 100 mg/250 mg/500 mg/750 mg filmdragerade tabletter; (152) Ciprofloxacin Ranbaxy 250 mg/500 mg/750 mg filmdragerade tabletter; (153) Ciprofloxacin Sandoz 250 mg, 500 mg eller 750 mg filmdragerade tabletter; (154) Ciprofloxacin STADA 250 mg/500 mg/750 mg filmdragerad tablett; (155) Ciprofloxacin Teva 100 mg/250 mg/500 mg/750 mg filmdragerade tabletter; (156) Ciprofloxbact 100 mg/250 mg/500 mg/750 mg filmdragerade tabletter; (157) Ciprofloxbiotic 100 mg/250 mg/500 mg/750 mg filmdragerade tabletter; (158) Ciproxin 250 mg/500 mg/750 mg tablett; (159) Ciproxin Tablets 100 mg/250 mg/500 mg/750 mg; (160) Cipro (ciprofloxacin hydrochloride) tablet, film coated (250, 500, and 750 mg) [Schering-Plough Corporation]; (161) Ciprofloxacin (Ciprofloxacin hydrochloride) tablet, film coated (250, 500, and 750 mg) [Aurobindo Pharma Limited]; (162) Ciprofloxacin (ciprofloxacin hydrochloride) tablet, film coated (100, 250, 500, and 750 mg) [Cobalt Laboratories]; (163) Ciprofloxacin (ciprofloxacin hydrochloride) tablet, film coated (250, 500, and 750 mg) [Ranbaxy Pharmaceuticals Inc.]; (164) Ciprofloxacin (Ciprofloxacin) tablet, film coated (250, 500, and 750 mg) [TEVA PHARMACEUTICALS, USA]; (165) Ciprofloxacin hydrochloride (Ciprofloxacin hydrochloride) tablet (250, 500, and 750 mg) [Ivax Pharmaceuticals, Inc.]; (166) Cipro (ciprofloxacin) tablet, film coated (500 and 1000 mg) [Bayer Pharmaceuticals Corporation]; (167) Ciprodoc 250 mg/500 mg Filmtabletten (Mono); (168) Ciprofat® 250 mg/500 mg Filmtabletten (Mono); (169) CIPROFLOXACIN axcount® 250 mg/500 mg Filmtabletten (Mono); (170) Ciprofloxacin real 250 mg/500 mg/750 mg Filmtabletten (Mono); (171) Ciprofloxacine 250 mg/500 mg/750 A, filmomhulde tabletten 250 mg/500 mg/750 mg; (172) Ciprofloxacine 250 mg/500 mg/750 Focus, filmomhulde tabletten 250 mg/500 mg/750 mg.

*Colourants, water and ingredients present in the coating and/or the printing ink are not included. Substances were excluded if could be assumed that the constituents are only present in the coating/polish.

**Excluded are oral powders, oral granulates and powder for oral solution.

***FDA's Inactive Ingredient Database, http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose (version date 04-04-2008).

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

Distribution and Elimination

Ciprofloxacin is widely distributed throughout the body. Penetration in bile, prostatic tissue, gingival fluid, and lung tissue is higher than the concentration achieved in plasma.[42,51–54] The values for the volumes of distribution have been reported to be 2.27 and 2.44 L/kg for doses of 100 and 200 mg, respectively.[55] Ciprofloxacin is cleared by both renal and nonrenal mechanisms. One-third to one-half of the serum clearance of ciprofloxacin is accounted for by nonrenal mechanisms. Four metabolites have been characterized. Each of these compounds has limited microbiologic activity, usually one-quarter to one-half of the activity of the parent drug.[56] Elimination half-life for ciprofloxacin vary from 3 to 4 h when it is administered i.v. at doses ranging from 100 to 200 mg; in this dose range, ciprofloxacin pharmacokinetics are independent of dose.[57,58] With oral administration, however, Tartaglione [41] observed a noticeable trend in the increasing half-life with increasing dose from 250 to 1000 mg and suggested as a possible explanation a slow continuous absorption phase due to pH-dependent phenomena and a decreased fraction absorbed with the higher doses. This hypothesis was also supported by urinary recovery data since they found a lower elimination after administration of 1000 mg. Similar results were obtained by Plaisance et al.[40]

Absorption and Permeability

No human jejunal perfusion studies were identified. The absorption of ciprofloxacin from different regions of the human GI tract was investigated in four healthy males using a special drug-releasing device (hf-capsule) by measuring the AUC after release of 180 mg ciprofloxacin–betaine in stomach, jejunum, ileum, and ascending colon. Significant differences in AUC were observed in the control study (oral administration of ciprofloxacin solution without the hf-capsule = 100%) and after release of ciprofloxacin in the jejunum (geometric mean: 37%), the ileum (mean: 23%), the ascending colon (mean: 7%) and the descending colon (mean: 5%). Ciprofloxacin release in the stomach resulted in the greatest AUC (mean: 140%). Based on that, the authors suggested that the main absorption site of ciprofloxacin is the upper GI tract, up to the jejunum.[59] However, the incomplete dissolution of ciprofloxacin in other intestinal region different from the stomach, may have played a role.

The permeability of ciprofloxacin was measured in an *in vitro* Caco-2 assay with previously demonstrated suitable method.[60] Metoprolol and atenolol were used as high- and low-reference standard and labetalol as the high-permeability internal standard. Ciprofloxacin was classified as *not highly permeable* since its permeability was lower than labetalol and close to atenolol.[60]

Several reports were identified on ciprofloxacin rat intestinal permeability. As a general fact, ciprofloxacin is absorbed by passive diffusion and subjected to a possible intestinal secretion.[61–63] It seems, however, that the secretion process has little significance in the overall absorption of ciprofloxacin.[64–66]

Similar to the data reported with Caco-2 cells, the permeability of ciprofloxacin from the mucosal to the serosal side, measured through the rat small intestine in side-by-side diffusion chambers, was low compared with the low-permeability marker fluorescein.[62]

A summary of the permeability values of ciprofloxacin estimated in Caco-2 cells and rat intestine are presented in Table 3.

Dosage Form Performance

Bioequivalence

Eight *in vivo* BE studies for IR tablets of 250,[67,68] 500,[69–72] and 750 mg[73,74] from different manufac-

Table 3. Permeability of Ciprofloxacin

Method	C_0 (mg/mL)[a]	Papp M → S[b] ($\times 10^6$ cm/s)	Papp S → M[c] ($\times 10^6$cm/s)	Efflux Ratio[d]	Internal Standard	References
Caco-2	3	2.49 ± 0.43	11.41 ± 2.19	4.6	Metoprolol, atenolol, and labetalol[e]	60
	0.3	0.42 ± 0.06	—	—	Metoprolol, atenolol, and labetalol[e]	60
	0.03	1.82 ± 0.41	—	—	Metoprolol, atenolol, and labetalol [e]	60
Caco-2	0.05	3.32 ± 0.33	6.47 ± 0.24	1.9	Not reported	61
	0.02	2.99 ± 0.29	5.95 ± 0.37	2.0	Not reported	63
	5×10^{-4}	3.08 ± 3.71	6.68 ± 1.34	2.2	Not reported	61
Rat jejunum	0.2	3.2 ± 0.1	12.2 ± 0.8	3.8	Fluorescein[f]	62
	0.02	4.1 ± 0.9	9.9 ± 1.4	2.4	Fluorescein[f]	62
In situ rat jejunum perfusion	0.05	11.1 ± 4.43	—	—	Not reported	61
	0.02	12.0 ± 2.34	—	—	Not reported	63
	5×10^{-3}	12.0 ± 3.92	—	—	Not reported	61
In situ rat perfusion whole intestine	5×10^{-4}	8.25 ± 3.05	—	—	Not reported	61
In situ rat perfusion proximal intestine	5×10^{-4}	7.90 ± 2.18	—	—	Not reported	61
In situ rat perfusion medium intestine	5×10^{-4}	13.3 ± 3.1	—	—	Not reported	61
In situ rat perfusion distal intestine	5×10^{-4}	16.5 ± 7.22	—	—	Not reported	61

All values: mean ± SD
[a] C_0: initial concentration of ciprofloxacin on the donor side.
[b] Mucosal to serosal permeability.
[c] Serosal to mucosal permeability.
[d] Papp (S → M)/Papp (M → S).
[e] Metoprolol: M → S Papp ($\times 10^6$) = 29.88 ± 3.17 cm/s, atenolol: M → S Papp ($\times 10^6$) = 1.86 ± 0.47 cm/s, labetalol: M → S Papp ($\times 10^6$) = 18.05 ± 1.90 cm/s.
[f] Paracellular permeability marker. Papp ($\times 10^6$) ~3–5 cm/s.

turers were identified. Detailed compositions of the formulations tested were not given. The comparator was in all cases the innovator' product (Ciproxin, Bayer®). Crossover designed studies were performed in 14–28 fasted healthy volunteers. Plasma samples were collected until 12–32 h posttreatment. The pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were evaluated for BE after log-transformation of data. The 90% confidence intervals of the mean values for the test: reference geometric mean ratios were within the BE acceptance range of 0.80–1.25, thereby meeting the BE criteria of the FDA,[75] WHO,[76] and EMEA.[77] Comparative *in vitro* dissolution testing, using the USP conditions, was once reported, in which no differences between the profiles were found.[78] Therapeutic inequivalence between brand-name drug products and FDA-approved generic drug products has not been reported.

Excipients

Excipients present in IR ciprofloxacin hydrochloride tablets with marketing authorization (MA), in a number of countries, are summarized in Table 2.

Dissolution

The USP 32 specification for ciprofloxacin hydrochloride tablets is not <80% (Q) dissolved in 30 min in 900 mL 0.01 N HCl in the paddle apparatus, operated at 50 rpm.[9] Some *in vitro* comparative dissolution studies of different formulations were identified. Commercially available ciprofloxacin tablets and capsules from nine different manufacturers in China were investigated for dissolution in the basket apparatus. All the products showed a cumulative release >75% within 45 min. However, no all the dissolution profiles complied with the f_2 similarity factor and, when transformed to Weibull functions, showed statistical significant differences, as multivariate analysis of variances did.[78]

Recently, the dissolution profile of commercial ciprofloxacin hydrochloride 250 mg tablet was reported in BCS-pH 6.8 phosphate buffer.[79] The dissolution was not complete within 120 min, most probably due to the limited solubility of the API at this pH.

The *in vitro* dissolution efficiency[80] of six commercial brands of ciprofloxacin hydrochloride tablets was evaluated in 0.1 N acetic acid and phosphate buffer pH 7.4 and the results were used to predict a rank order in BA.[81] The dissolution of the six brands varied widely in these two media and the dissolution efficiency in 0.1 N acetic acid of five of the six brands fell within 60–75% at 30 min, whereas one of them fell below 40%. These results were reported to be an indication that the five brands were bioequivalent but one was most likely not.[81] However, this was not confirmed by an *in vivo* BE study. Also, *in vitro* dissolution in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) without enzymes was used to predict the BA of seven brands of ciprofloxacin

floxacin hydrochloride tablets marketed in Nigeria versus the innovator.[82] Again, the results varied widely. The dissolution in SGF indicated that four brands were probably bioequivalent to the innovator, whereas the dissolution in SIF appeared to be more discriminatory because it allowed only two of these four brands to be declared as being probably bioequivalent to the innovator.[82] Once again, these findings were not confirmed by an *in vivo* BE study.

DISCUSSION

Solubility

Ciprofloxacin hydrochloride is highly soluble at acidic pH, however, at intestinal pH like 6.8 and 7.5, its solubility is far lower. Table 1 shows D/S ratios for different tablet strengths. An API is defined as *highly soluble* if its D/S ratio at 37°C is below 250 mL, over the pH range 1.0–7.5 according to FDA;[75] 1.2–6.8 according to WHO[76] or within the range of pH 1–8, preferably at or about pH 1.0, 4.6, and 6.8 according to EMEA.[77] Although most of the data were reported at 25°C, not 37°C, it is evident that ciprofloxacin hydrochloride is not *highly soluble*.

Permeability

The FDA defines *highly permeable* as having a fraction dose absorbed of not <90%.[75] The WHO Guideline sets a limit of not <85% of the fraction dose absorbed.[76] The EMEA Note for Guidance presently in force is less precise. It states that "linear and complete absorption indicating high permeability reduces the possibility of an IR dosage form influencing the BA.[77]" With respect to the linearity of absorption: the data are somewhat conflicting. Some authors report a nonlinear increase of AUC, C_{max} and/or t_{max} with dose [39–42], other authors could not detect dose disproportionality in ciprofloxacin kinetics after a single oral administration.

The draft revision to that Guidance says that an extent of absorption ≥85% is generally related to high permeability.[83] The data suggest that the fraction of dose absorbed in humans is somewhat lower than these cut-off limits. Ciprofloxacin permeability results obtained from rat jejunum by perfusion appear to be higher than the Caco-2 data, but are still below the cut-off value of 2×10^{-4} cm/s defined for human intestinal jejunal permeability.[84] For drug transport in Caco-2 monolayers, a cut-off point of Papp = 10^{-5} cm/s for *highly permeable* APIs was proposed to ensure a fraction dose absorbed higher than 95%.[85] Similarly, a cut-off limit of Papp from 2×10^{-6} to 10^{-5} cm/s as a boundary of *highly permeable* was proposed by Rinaki et al.[86]

Other workers proposed that a cut-off limit of Papp of 2×10^{-6} cm/s in the Caco-2 model is commensurate with 100% absorption.[87] Some of the results shown in Table 3 just exceeds this cut-off limit, others just do not meet. The $C\log P$ and $\log P$ values are lower than the corresponding values of metoprolol, which is usually taken as the compound having cut-off permeability.[18] Taking all evidence together, the dataset classifies ciprofloxacin hydrochloride as not *highly permeable*.

BCS Classification

Data on solubility, oral absorption, and permeability conclusively show ciprofloxacin to be BCS Class IV. Lindenberg et al.[88] provisionally classified ciprofloxacin as BCS II/IV. Similarly, Breda et al.[79] classified ciprofloxacin as BCS IV. Wu et al., using the disposition characteristics of the drug for classification, assigned ciprofloxacin to Class IV as per the Biopharmaceutics Drug Disposition Classification System.[89] Other provisional assignment of ciprofloxacin in BCS Class III was based on its nonbuffered aqueous solubility at 25°C and hence not according to the criteria of the BCS Guidelines.[90]

Risk of Bioinequivalence Caused by an Excipient and/or Manufacturing Effect

Perhaps, surprisingly for an API of BCS Class IV, there was not any report neither of a bioinequivalent formulation nor of a formulation failing to meet the present BE criteria.[a] On the other hand, eight studies reported the investigated formulations to be bioequivalent and there are 172 drug products having a registration. Most probably, these 172 drug products do not correspond to 172 different formulations, because many drug products will have a registration in more than one country. Also, it cannot be taken for granted that every registered drug product successfully passed an *in vivo* BE study versus the innovator. In theory, some could have been approved on a bibliographic application without the need of showing BE, others could have failed to show BE and completed the development with clinical studies justifing that such a difference in BA was clinically irrelevant, etc. However, balancing these remote possibilities against the overwhelming evidence of 172 drug products, of different composition, all having a registration, in a number of countries, it seems safe to conclude that the risk of bioinequivalence caused by an excipient and/or manufacturing variable(s) for IR

[a]Bio*in*equivalence implies that the regulatory defined confidence interval of one, or more, BE attributes (AUC, C_{max}, T_{max}) falls fully outside of their regulatory acceptance range, whereas failure to meet BE criteria implies that the regulatory defined confidence interval of one, or more, BE attributes does not fully fall inside their regulatory acceptance range.[91]

ciprofloxacin hydrochloride solid oral dosage forms is low.

Surrogate Techniques for *In Vivo* BE Testing

The USP 32 *in vitro* dissolution test for ciprofloxacin hydrochloride tablets uses diluted acid.[9] This acidic medium is poorly discriminating and it is questionable if this test is capable to assure batch-to-batch BE. It could be expected that dissolution testing in a media with a pH in which the solubility of ciprofloxacin is lower assures a more discriminating outcome, however, there are no data to demonstrate this postulate to be correct. Moreover, currently there are not regulatory accepted surrogate techniques available that are responsive to differences in permeability causing bioinequivalence.

Patient Risks Associated With Bioinequivalence

Ciprofloxacin has a broad therapeutic index. The Argentine Health Authority classified ciprofloxacin as a low health-risk drug, which means that adverse reactions arising from plasma concentrations outside the therapeutic window are not very serious.[26] Ciprofloxacin is nevertheless used for some critical therapeutic indications, such as multidrug-resistant tuberculosis. Such considerations led the German regulatory authorities in the past to categorize ciprofloxacin as an API for which biowaivers could not be granted.[92] Subtherapeutic levels arising from products that are substandard in their BA could increase the emergence of ciprofloxacin-resistant bacteria. So, the risk for the patient of a bioinequivalent drug product with respect to AUC or C_{max} that results in sub-therapeutic blood levels during a treatment for a life-threatening infection, does not seem to be acceptable.

CONCLUSION

Ciprofloxacin hydrochloride is a BCS class IV drug. The FDA,[75] the WHO,[76] and EMEA[77] Guidance do not allow biowaivers for BCS Class IV drugs and thus a biowaiver is not permitted to ciprofloxacin hydrochloride IR solid oral formulations. The risk that an IR drug product formulated only with the excipients shown in Table 3 could be bioinequivalent is considered to be low, especially if the products have met comparative *in vitro* dissolution specifications in pH 1.2; 4.5; and 6.8. But considering that the lack any report neither of a bioinequivalent formulation nor of a formulation failing to meet the present BE criteria maybe caused by publication bias, it is prudent to be conservative. In addition, ciprofloxacin is used for some serious therapeutic conditions. Hence, we conclude that a biowaiver based approval of ciprofloxacin hydrochloride containing IR solid oral dosage forms, for either new multisource drug products should not be granted. Changes in approved drug products, like changes in the manufacturing formula, in the manufacturing process, in manufacturing sites and/or equipment also necessitate demonstration of BE. If small, such changes may be approved without an *in vivo* BE study. The FDA describes such postapproval changes as SUPAC levels 1 and 2.[93] The EU has a comparable system.[94] When a change to an approved ciprofloxacin hydrochloride solid oral IR drug product falls into such category, the data presented in this monograph (including the excipient table for products with an MA) can be helpful to assess the criticality of the change.

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