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Research Article

BIOWAIVER MONOGRAPH FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS: OFLOXACIN

SOMNATH SAKORE*, SUNIL CHOUDHARI, BHASWAT CHAKRABORTY

[1,2]Cadila Pharmaceuticals Limited, 1389, Trasad Road, Dholka-387810, Ahmedabad, Gujarat. India
Email: drb.chakraborty@cadilapharma.co.in

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ABSTRACT

Literature and experimental data relevant to the decision to allow a waiver of in vivo bioequivalence testing for the approval of immediate release (IR) solid oral dosage forms containing ofloxacin have been reviewed. According to the current Biopharmaceutics Classification System (BCS), ofloxacin should be assigned to Class I. Therapeutic use, therapeutic index, pharmacokinetic properties, reported BE/bioavailability (BA) and data related to the possibility of excipient interactions studies of Ofloxacin were also taken into consideration in order to ascertain whether a biowaiver can be recommended. Ofloxacin seems not to be critical with respect to a risk for bioinequivalence, as no examples of bioinequivalence have been identified. However; if (a) the test product contains only excipients in their usual amounts present in ofloxacin solid oral IR drug products approved in ICH or associated countries, for instance as presented in this article; and (b) the comparator and the test product both are very rapidly dissolving a biowaiver for IR ofloxacin solid oral drug products is considered justified for all tablet strengths.

Keywords: Absorption, Biopharmaceutics Classification System (BCS), Ofloxacin, Permeability, Solubility.

INTRODUCTION

A biowaiver monograph of ofloxacin based on literature data together with some additional experimental data has been presented here. A biowaiver implies that bioequivalence (BE) assessment studies would be waived for marketing authorizations (MA) by Health Authorities for a new tablet or capsules, or a new formulation of an existing immediate release (IR) dosage form, and hence the product is considered bioequivalent to its reference product, without carrying out a bioequivalence (BE) study. The risks of waiving in vivo BE testing for the approval of new and/or reformulated immediate release (IR) solid oral dosage forms containing ofloxacin, including both reformulated products and new multi source products, are evaluated in consideration of their biopharmaceutical and clinical properties. The scientific basis for a waiver request for ofloxacin tablets has been developed according to Biopharmaceutical Classification System (BCS)[1] .

The BCS states that three major factors govern the rate and extent of drug absorption of IR solid oral dosage forms: dissolution rate, solubility and intestinal permeability. For IR dosage forms containing active pharmaceutical ingredients (APIs) showing high solubility, high intestinal permeability, and rapid dissolution, a waiver from performing BE studies (biowaiver) can be scientifically justified. In the regulatory domain this is adopted by both the US FDA and the European CPMP in their guidances for industry, Waiver of In Vivo Bioavailability (BA) and BE Studies for Immediate-Release Solid Oral Dosage Forms Based on a BCS [2] and the Note for Guidance on the Investigation of BA and BE [3] respectively, have been together referred to as the Guidances in this article. In particular, the US FDA document describes in detail the data that are necessary for a successful application for a biowaiver. To explore the scope and the possibilities of gathering BCS related data from scientific literature, and in order to set up such BCS-monographs, a literature search was carried out on ofloxacin.

The aim of this monograph is to evaluate all pertinent data available from literature sources for ofloxacin to assess the risks associated with a biowaiver. For these purposes risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of an incorrect biowaiver decision in terms of public health and individual patient risk. On the basis of these considerations, a recommendation can be made as to whether a biowaiver is advisable or not for ofloxacin solid oral dosage forms. This systematic approach to recommend or advice against a biowaiver decisions is referred to in recently published World Health Organization (WHO) Guideline.

General characteristics of Ofloxacin

Chemical, Pharmaceutical and Pharmacokinetic BCS-related information on ofloxacin was obtained by means of a literature search. The following data-fields were defined in order to standardize the dataset: indication, solubility, dissolution, poly-morphism, partition coefficient, pKa, available dose, permeability, stereospecificity, pharmacokinetic properties. Literature data was accessed from PubMed, PubChem, Medicines Complete, WHO search engine, WHOLIS, the BIAM, 16 ROTE LISTE, and VIDAL databases. Key words used for searching were: Ofloxacin, bioequivalence, bioavailability, biowaiver, solubility, permeability, dissolution, excipient, toxicity, polymorphism, and pharmacokinetics.

Nomenclature

Ofloxacin (INN) It's chemical name is (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. [4]

Its structure is shown in below Fig 1.

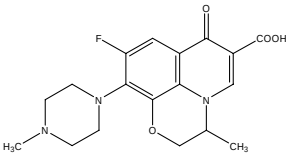

Fig. 1: Structure of ofloxacin

Therapeutic indications

Ofloxacin is a new fluoroquinolone with a spectrum of activity similar to other fluoroquinolones with activity which includes Chlamydia trachomatis, Mycobacterium spp., Mycoplasma spp. and Legionella pneumophila. Ofloxacin may be less susceptible to the development of resistance from Staphylococcus aureus commonly seen with currently available fluoroquinolones[5].

It is also used in chlamydial infections including nongonococcal urethritis in treating mycobacterial infections such as leprosy. Ofloxacin tablets are indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of the designated microorganisms in the infections listed below [6].

- Acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenzae or Streptococcus pneumoniae.
- Community-acquired Pneumonia due to Haemophilus influenzae or Streptococcus pneumoniae.
- Uncomplicated skin and skin structure infections due to methicillin-susceptible Staphylococcus aureus, Streptococcus pyogenes, or Proteus mirabilis.Acute, uncomplicated urethral and cervical gonorrhea due to Neisseria gonorrhoeae.
- Nongonococcal urethritis and cervicitis due to Chlamydia trachomatis.
- Mixed Infections of the urethra and cervix due to Chlamydia trachomatis and Neisseria gonorrhoeae.
- Acute pelvic inflammatory disease (including severe infection) due to Chlamydia trachomatis and/or Neisseria gonorrhoeae.
- Uncomplicated cystitis due to Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, or Pseudomonas aeruginosa.
- Complicated urinary tract infections due to Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter diversus, or Pseudomonas aeruginosa.
- Prostatitis due to Escherichia coli (http://www.rxlist.com/floxin-drug.htm)

Therapeutic index and toxicity

An adult oral or intravenous dose ranges from 200 mg daily to 400 mg twice daily depending on the severity and the nature of the infection. Oral doses up to 400 mg may be given as a single dose, preferably in the morning. For intravenous use a 0.2% solution is infused over 30 minutes or a 0.4% solution over 60 minutes. A dose of 400 mg daily or intermittently by mouth has been recommended by WHO as part of alternative multidrug therapy regime for leprosy [7].

The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and intravenous formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences. In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of ofloxacin: nausea 3%, insomnia 3%, headache 1%, dizziness 1%, diarrhea 1%, vomiting 1%, rash 1%, pruritus 1%, external genital pruritus in women 1%, vaginitis 1%, dysgeusia 1%. Information on overdosage with ofloxacin is limited. One incident of accidental overdosage has been reported. In this case, an adult female received 3 grams of ofloxacin intravenously over 45 minutes. A blood sample obtained 15 minutes after the completion of the infusion revealed an ofloxacin level of 39.3 µg/mL. In 7 h, the level had fallen to 16.2 µg/mL, and by 24 h to 2.7 µg/mL. During the infusion, the patient developed drowsiness, nausea, dizziness, hot and cold flushes, subjective facial swelling and numbness, slurring of speech, and mild to moderate disorientation. All complaints except the dizziness subsided within 1 h after discontinuation of the infusion. The dizziness, most bothersome while standing, resolved in approximately 9 h. Laboratory testing reportedly revealed no clinically significant changes in routine parameters in these patient. Thus, ofloxacin does not have a narrow therapeutic index [6].

Chemical properties

Stereoisomers and polymorphs

Ofloxacin chemically a fluorinated corboxyquinolone, and it's the racemate [6] Polymorphic forms have not been reported in the literature.

Partition coefficient (logP)

The n-octanol/water partition coefficient (log P) of ofloxacin was reported as -0.48 [8].

pKa

Ofloxacin is an amphoteric drug with two protonation sites[9,10]. Its pKa are 6.05 for the carboxylic group and 8.22 for the piperazine nitrogen given in figure 2.

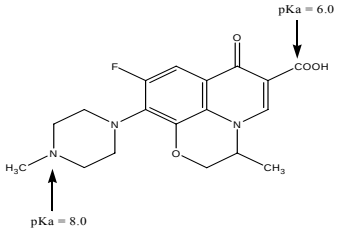

Fig. 2: The molecular structure of ofloxacin with the approximate pKa values.

Solubility

Ofloxacin is freely soluble in acetic acid, slightly soluble in water, methanol, ethanol or acetone[8].

Dosage form strengths

The WHO Essential Medicines List (EML) lists Ofloxacin Tablet strengths from 200 to 400 mg (WHO drug information, 2007) Ofloxacin tablet dosage form existing in different countries through out world on different brand names by different marketing authorization[7] . In the United States, NDA exists for strengths in the range of 200 to 400 mg[3] .

Pharmacokinetic properties

Permeability and absorption

One of the permeability studies for ofloxacin drug substance was carried out with Caco-2 assay method. This cell culture model was previously evaluated and determined to be a suitable method according to the BCS Guidance as it demonstrated a rank-order correlation between in vitro permeability and human extent of absorption for the model drugs, with a clear segregation between high and low permeability drug substances[11]. Based on the previous reports of human absolute bioavailability, it was expected that ofloxacin would be classified as a highly permeable (HP) drug[12,13] **.** Also, in the Caco-2 permeability assays, ofloxacin was classified as HP drugs. Thus, the in vitro results matched human in vivo data based on absolute bioavailability. In addition, there was evidence that ofloxacin underwent some active transport as its permeability apparent values decreased with concentration [14] .

Following oral administration, there is rapid and extensive oral absorption from the gastrointestinal tract achieving peak serum concentration within 1 – 3 h and levels in excess of 100 g/ml in the urine and bladder [8].

The pharmacokinetics of ofloxacin are characterised by almost complete bioavailability (95 to 100%), peak serum concentrations in the range of 2 to 3 mg/L after a 400mg oral dose and an average half-life of 5 to 8h. Ofloxacin is rapidly and well absorbed from the gastrointestinal tract[5].Oral bioavailability is almost 100% and a peak plasma concentration of 3 to 4 µg/mLis achieved within 1 to 2 hours after a dose of 400 mg by mouth. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected [7] .

Distribution

About 25% of ofloxacin is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. Relatively high concentration is achieved in bile [7] .

Metabolism and excretion

There is limited metabolism to desmethyl and N-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 75 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites. From 4 to 8% of a dose may be excreted in the faeces. Only small

amount of ofloxacin are removed by Dialysis [7] . In comparison with other available quinolones, elimination is more highly dependent on renal clearance, which may lead to more frequent dosage adjustments in patients with impaired renal function[6].

Food and excipients interaction

Ofloxacin interacts with multivalent cation-containing products, such as aluminum- or magnesium-containing antacids and products containing calcium, iron, or zinc. Concomitant use invariably results in marked reduction of oral absorption of this antimicrobial. The mechanism of this interaction is formation of insoluble chelation complexes in the gastrointestinal tract that inhibit drug absorption [15,16] .

Multivitamin preparations that contain minerals should be avoided. Similar adverse effects on fluoroquinolone absorption were observed with concomitant administration of ferrous sulfate (iron), with decreases in bioavailability of the antibiotic of 19-66 %.[17,18] .

Although it is usually recommended that concomitant intake of calcium-rich foods (e.g., milk) be avoided because of the potential for chelation effects, the actual influence of dairy products on fluoroquinolone absorption varies[19,20] . Milk did not alter the rate or extent of absorption of ofloxacin or its elimination [21] .

Sucralfate significantly interferes with oral absorption of fluoroquinolones. It decreased the bioavailability of these drugs by up to 98% when given within 2 hours of antibiotic administration. The mechanism of this interaction has been attributed to both the aluminum content of the sucralfate salt and direct binding of the fluoroquinolone by the sucralfate itself [22,23]. The degree to which fluoroquinolones are absorbed is not significantly affected by food. Studies involving ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin consistently reported alterations in drug absorption rates without change in the extent of absorption [24].

When fluoroquinolones are administered with food, peak concentration times are usually slightly delayed, and maximum plasma concentrations (C_{max}) are decreased 8-16%. The area under the plasma concentration versus time curve (AUC) is invariably unchanged and alterations in absorption rates are considered to be clinically insignificant[21].

Dosage form performance

Bioavailability and bioequivalence

Bioavailability of oral and intravenous ofloxacin was investigated after the administration of multiple doses of 400 mg every 12 h to 20 healthy male volunteers in a randomized, crossover, open-label study. Ofloxacin concentrations in plasma were evaluated after 4 days of oral or intravenous (1-h infusion) dosing with a 3-day wash-out period between regimens. As expected, delivery to the systemic circulation took slightly longer after the oral dosing (time to maximum concentration of drug in serum of 1.7 h) relative to the 1-h intravenous infusion, but the systemic availabilities of ofloxacin by the two routes of administration were equivalent (area under the concentration-time curve from 0 to 12 h ratio of 95%)[25].

Excipients

Ofloxacin interact with multivalent cations present in fillers, binders and lubricants. Table 2 shows the excipients present in ofloxacin IR solid drug products in US market. It can be inferred that these drug products successfully passed an in vivo BE study. In Table 2 the amounts of various excipients found in single API ofloxacin products, along with the ranges specified by the FDA for oral drug products in general, are given [3] .

Excipients present in IR ofloxacin tablets with US MA are summarized in Table 3. In vivo comparisons of different formulations were not reported. Therapeutic inequivalence between brand-name drug products and FDA-approved generic drug products has not been reported and there have been no reports of bioinequivalence of IR tablets with an approval in India.

Table1: Excipients present in Ofloxacin IR solid oral drug with a Marketing Authorization United States (IIG Limits)

Excipients	Max. amount present in solid oral dosage forms with a MA in the USA (mg)
Lactose Anhydrous	735.20
Modified corn starch	433.32
Hydroxy propyl cellulose	46.00
Hypromellose	54.00
Magnesium stearate	400.74
Polyethylene Glycol	0.12
POLYSORBATE 80	21.25
Sodium starch Glycolate	876.00
Purified Talc	91.20
Titanium dioxide	27.00

Different countries having ofloxacin with following brand names:

Germany: Floxacil, Gyroflox, Oflo, Oflodura, Oflohexal, Oflox, Ofloxbeta, Tanvid, Uro Tanvid.

Finland : Excin,Tanvid

Netherlands: Tanvid, Trafloxal.

USA: Floxin.

Details of excipients used in the Ofloxacin tablet formulation from different countries were not available for studying.

Dissolution

The present biowaiver criteria state that, in addition to similarity of dissolution profiles, the test and the comparator drug product should both be rapidly dissolving , which is defined as: not less than 85% of API releases within 30 min employing the dissolution conditions decribed therein [2,3] The Office of Generic Drugs (OGD), USFDA recommended dissolution medium is 0. 1 N HCl of 900ml, using USP-II apparatus at 100 rpm with time points 10,20,30 & 45 minutes and specification for ofloxacin tablets is: not less than 80% (Q) should be dissolved in 45 mins.

MATERIALS AND METHODS

Solubility

The solubility of Ofloxacin as a function of pH is shown in Table 2. The solubility of ofloxacin was determined and all the solibility tests were conducted in triplicate. The media used were water media of various pH as 1.2, 4.5, 5.0, 6.0, 6.8, 7.2, 7.5, 8.2, and pH 9.2 and the temperatures were maintained at 37±0.5 ◦C.

Table 2: Experimental solubility data (mg/ml) for ofloxacin and the corresponding dose/solubility (d/s) ratios for highest tablet strengths

S No	pH	pH after adittion of ofloxacin	Calculated solubility in mg/ml	Dose/solubility (D/S) ratios for highest tablet strengths (mg)		
				200	300	400
1	1.2	1.94	37.09	5.30	8.09	10.81
2	Water	7.15	2.66	75.19	112.81	150.38
3	4.5	5.20	14.62	13.69	20.53	27.38
4	5.05	6.0	16.49	30.82	46.22	61.63
5	6.0	6.32	5.04	39.68	59.52	79.37
6	6.8	6.80	4.57	43.76	65.64	87.53
7	7.2	7.15	2.85	70.18	105.26	140.35
8	7.5	7.30	2.80	71.43	107.14	142.86
9	8.2	7.87	3.64	54.95	82.42	109.90
10	9.2	8.85	4.32	46.30	69.44	92.60

Formulation dissolution study

The release rate of Ofloxacin was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus II (Paddle method). The dissolution test was performed in 900 ml of 0.1N HCl, in acetate buffer of pH 4.5 and simulated intestinal fluid pH 6.8, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at intervals of 10, 20, 30 and 45 minutes and the samples were replaced with fresh dissolution medium. The samples were diluted to a suitable concentration with dissolution media. Absorbance of these solutions was measured at 294nm using a UV/Visible spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve shown in table 3.

Table 3: Dissolution profiles of formulations of 200 mg, 300 mg and 400 mg of Ofloxacin

Time	0.1 N HCl (OGD-Media)			pH 4.5			pH 6.8		
(min)	400 mg (%)	300 mg (%)	200 mg (%)	400mg (%)	300mg (%)	200 mg (%)	400 mg (%)	300mg (%)	200mg (%)
10	64.0	71.3	70.7	56.1	61.5	72.0	55.0	63.8	55.0
20	94.1	89.6	95.2	94.4	83.7	94.0	73.4	76.4	85.0
30	98.5	96.5	100.0	98.4	92.8	98.0	80.3	83.7	94.0
45	99.0	98.1	101.3	101.4	97.2	100.0	85.0	88.0	98.0

The present biowaiver criteria state that, in addition to similarity of dissolution profiles, the test and the comparator drug product should both be ''rapidly dissolving,'' which is defined as not less than 85% of API releases within 30 minutes, employing the dissolution conditions described therein. The same dissolution method was employed for evaluating randomly selected IR Ofloxacin drug products having a marketing authorization in USA and in India and we found that both formulations showing above 85% drug release within 30 minutes. Thus, it was found that the Ofloxacin drug products exhibited rapidly dissolving characteristics within the BCS limits.

DISCUSSION

Solubility

The USFDA defines ''highly soluble drugs'' exhibiting a dose/solubility (D/S) of <250 ml over the pH range 1–7.5, (3)(CDER, Guidance for Industry, 2000) while the EU and the recently revised WHO Guidelines limit the requirements to the pH range of 1–6.8. It was recently suggested that the USFDA should also redefine the solubility boundaries for BCS Class I (i.e high solubility and high permeability) to pH 1.2–6.8 (http://www.fda.gov/cder/foi/label/2007). At 25^0C, all tablet strengths conform to the criterion of 250 mL for the dose/solubility ratio at pH 6.8 and below (Table 1). At pH 7.5, the WHO recommended dose comply with this dose/solubility ratio criterion but higher tablet strengths do not. However, these data refer to 25^0C, not at 37^0C, as required by the Guidances[3].

The solubility values found in the literature were not assessed under conditions specified for the Biopharmaceutics Classification System (BCS) classification .Therefore new solubility determinations were carried out by us. The minimum solubility of Ofloxacin was about 2.66 mg/ mL. The corresponding dose/solubility (D/S) ratio, calculated for the highest commercially available tablet strength on the US market and on the WHO EML, was 150.38 mL or lower in the relevant pH range (Table 1). An API is ''highly soluble'' if its D/S ratio is below 250 mL [3]. (WHO, Proposal to waive in vivo bioequivalence requirements, 2006). Thus, ofloxacin can be regarded as ''highly soluble".

Permeability

According to BCS, a drug showing high solubility and high permeability is considered as Class-1 drug. Ofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is almost 100% and a peak plasma concentration of 3 to 5 µg/mL is achieved 1 to 2 hours after a dose of 400 mg by mouth. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected. The plasma half life ranges from 4 to 7 h in renal impairment values of 15 to 60 h have been reported. About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in bile.

There is limited metabolism to desmethyl and N-oxide metabolites: demethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65% to 80% of a dose is excreted unchanged in the urine over 24 to 48 h resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites.

From 4 to 8% of a dose may be excreted in the faces (USFDA Drug approved information[26, 27].

Ofloxacin is an amphoteric drug with two protonation sites. Its pKas are 6.05 for the carboxylic group and 8.22 for the piperazine nitrogen [28]. The log P value (octanol/water partition coefficient) is 0.33 [29]. At blood pH, 87% of the drug is in the zwitterionic neutral form $HQ^{+/-}$ [28].This form of the molecule is the most hydrophobic and can readily diffuse through membrane lipids [30] . Fluoroquinolones could have a common transporter in the intestine and, according to their affinities, compete with each other for binding when coadministered [31]. investigated the effect of P-glycoprotein blockers on intestinal ofloxacin elimination in rats. P-glycoprotein is an energy-dependent drug-efflux system located at several sites, particularly at the plasma apical membrane of intestinal cells [31, 32]. This transport molecule seems to protect intestinal cells from plant alkaloids and other cytotoxic hydrophobic compounds [33]. The stereoselectivity and saturability of intestinal ofloxacin secretion in vivo [34].

Ofloxacin is a moderately lipophilic quinolone with an octanol-water partition coefficient of 0.41 at pH 7.0, 0.33 at pH 7.2, and 0.28 at pH 7.3 [35 ,36].After administration of ofloxacin 200mg I.V. Infusion the ratios OF AUC_{CSF}/AUC_s (csf: cerebro spinal fluid & s: serum) and AUC_{CSF} 0-∞/AUCs0-∞ there was a high level of penetration of ofloxacin into CSF (0.59 to 0.81 and 0.53 to 0.79, respectively [37].

Ofloxacin is excellently absorbed and has a biological half-life of 3 to 3.5hr, high volume of distribution, predominant renal elimination, and only limited biotransformation[38] **.** In vitro Caco-2 assay results concluded that ofloxacin was classified as high permeable drug [39]. In TC7 cells, ofloxacin displayed concentration-dependent permeability and was actively absorbed [40].

BCS classification

Ofloxacin is ''highly soluble.''Data on its oral absorption and permeability are not fully conclusive but suggest this API to be a BCS Class III drug, with permeability properties approaching the border to BCS Class I. It should be noted that the cut-off for ''highly permeable'' varies with regulatory authority. The FDA sets a limit for the fraction of dose absorbed of not less than 90%, the EMEA requires ''high permeability'' but does not define a limit for the fraction of dose absorbed and the WHO requires not less than 85% fraction of dose absorbed. Up to now, the FDA does not accept biowaivers for BCS Class III APIs, which would exclude ofloxacin from biowaiving. On the other hand, the recently revised WHO guidance extended the possibility of a biowaiver approval to BCS Class III APIs under certain conditions. Therefore ofloxacin is a candidate for biowaiver according to the WHO guidance.

Surrogate techniques for in vivo bioequivalence testing

Ofloxacin is ''highly soluble'' and the pure drug shows ''very rapid dissolution''. Furthermore bioinequivalence of ofloxacin formulations was reported neither in vivo nor in vitro and is unlikely to occur for this very soluble API. Hence, the stricter dissolution methodology for biowaiving of BCS Class III drugs according the WHO Guidance, that is, ''very rapid dissolution'' over the pH range of 1.2–6.8, should be capable of detecting poor quality of formulations. A caveat to the use of dissolution tests as surrogates for in vivo BE testing is that in vitro dissolution tests are not able to detect excipient influences on permeability and/or GI transit time which may cause bioinequivalence [3] .

Risks of bioinequivalence caused by excipients and/or manufacturing

Since no report of a bioinequivalent drug product has appeared in the accessible literature, the risk of bioinequivalence of ofloxacin IR dosage forms seems to be low. The risk of bioinequivalence caused by an excipient interaction is further reduced if the test product contains only excipients present in drug products having a MA in an ICH or associated country. The excipients present in a number of European countries are listed in Table 1. Patient risks associated with bioinequivalence of ofloxacin IR dosage forms can lead to decreased antibiotic efficacy. However, the risk of bioinequivalence of ofloxacin IR dosage forms appears to be relatively low, especially if the test product is formulated only with excipients shown in Table 2 and complies with the criteria for ''very rapidly dissolving.''

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