COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Doxycycline Hyclate

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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 immediate release (IR) solid oral dosage forms containing doxycycline hyclate are reviewed. According to the Biopharmaceutics Classification System (BCS), doxycycline hyclate can be assigned to BCS Class I. No problems with BE of IR doxycycline formulations containing different excipients and produced by different manufacturing methods have been reported and hence the risk of bio*in*equivalence caused by these factors appears to be low. Doxycycline has a wide therapeutic index. Further, BCS-based dissolution methods have been shown to be capable of identifying formulations which may dissolve too slowly to generate therapeutic levels. It is concluded that a biowaiver is appropriate for IR solid oral dosage forms containing doxycycline hyclate as the single Active Pharmaceutical Ingredient (API) provided that (a) the test product contains only excipients present in doxycycline hyclate IR solid oral drug products approved in the International Conference on Harmonization (ICH) or associated countries; and (b) the comparator and the test products comply with the BCS criteria for "very rapidly dissolving" or,

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alternatively, when similarity of the dissolution profiles can be demonstrated and the two products are "rapidly dissolving." © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:1639–1653, 2010

Keywords: absorption; biopharmaceutics classification system (BCS); doxycycline hyclate; permeability; regulatory science; solubility

INTRODUCTION

A biowaiver monograph for doxycycline hyclate based on literature data, together with some additional experimental data, is presented. The risks of waiving *in vivo* bioequivalence (BE) testing for the approval of new multisource and/or reformulated immediate release (IR) solid oral dosage forms containing doxycycline hyclate are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing doxycycline hyclate, which is the hemiethanolate hemihydrate form of doxycycline hydrochloride, as the single Active Pharmaceutical Ingredient (API). The purpose and scope of this series of monographs have been previously discussed.[1] Briefly, the aim of these monographs is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver is advisable or not. This systematic approach to recommend or advise against a biowaiver decision is referred to in the recently published World Health Organization (WHO) Guideline.[2] These monographs do not intend to simply apply the WHO,[2] US FDA,[3] and/or EMEA Guidance,[4] but aim to apply these guidances and further serve as a critical evaluation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (paracetamol),[5] acetazolamide,[6] aciclovir,[7] amitriptyline hydrochloride,[8] atenolol,[1] chloroquine (phosphate, sulfate, and hydrochloride),[9] cimetidine,[10] diclofenac (sodium and potassium),[11] ethambutol dihydrochloride,[12] ibuprofen,[13] isoniazid,[14] metoclopramide,[15] prednisolone,[16] prednisone,[17] propranolol hydrochloride,[1] pyrazinamide,[18] quinidine sulfate,[19] ranitidine hydrochloride,[20] rifampicin,[21] and verapamil hydrochloride.[1] They are also available online at http://www.fip.org/bcs.[22]

GENERAL CHARACTERISTICS

Name

INN name: Doxycycline;[23,24]
INNM name: Doxycycline hyclate;[23,24]
Chemical name: [4S-(4α,4aα,5α,5aα,6α,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, compound with ethanol (1:0.5), hemihydrate;[25]
(4S,4aR,5S,5aR,6R,12aS)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride, compound with ethanol (1:0.5), hemihydrate;[25]
6-Deoxy-5β-hydroxytetracycline hydrochloride;[26]
4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.[27]

Doxycycline hyclate is official in the JP XV[28] where it is named "doxycycline hydrochloride hydrate." The Martindale[26] uses the name "doxycycline hydrochloride" for doxycycline hyclate.

The molecular weight of doxycycline hyclate is 512.9 and its melting point is 201°C.[29] The structure of doxycycline hyclate is shown in Figure 1.

Therapeutic Indication and Dose

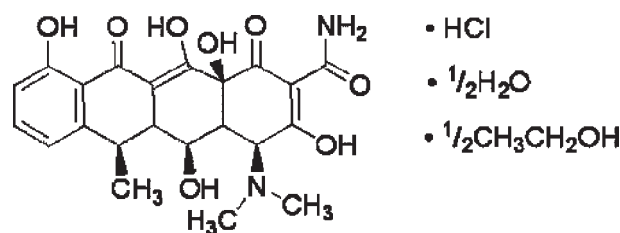Doxycycline is bacteriostatic against a wide variety of organisms, both Gram-positive and

Figure 1. Structure of doxycycline hyclate.

Gram-negative. It is used mainly for the treatment of urinary tract, respiratory tract, and gastrointestinal (GI) tract infections.[30] The usual initial dose of doxycycline is the equivalent of 200 mg doxycycline base (equal to 230.8 mg of doxycycline hyclate) as a single dose or in divided doses over the first day. This initial dose is followed by 100 mg (equivalent to 115.4 mg of doxycycline hyclate) daily.[26] For children weighing less than 45 kg an initial dose of approximately 4 mg/kg/day followed by 2 mg/kg/day may be given, whereby the effects of drug on teeth and bones should be taken into consideration.[26,30] In severe cases, for example, in patients with sensitive gonococcal infections, a dosage of 200 mg doxycycline is maintained throughout the course of treatment.[26] Occasionally, as in the case of syphilis, a daily dose of 300 mg may be given for 15 days.[26]

According to the Essential Medicines List of the WHO (EML, 15th ed., March 2007), 100 mg doxycycline (hydrochloride) capsules or tablets can be used as an antibacterial.[31] In case of malaria, 100 mg doxycycline as capsules (hydrochloride) or dispersible tablets (monohydrate) can be used in combination with quinine for curative treatment, and for malarial prophylaxis 100 mg doxycycline (hydrochloride) capsules or tablets can be prescribed.[31]

Therapeutic Index and Toxicity

Doxycycline is considered to be a wide therapeutic index drug according to the US FDA definition,[32] and there is generally no need to monitor blood levels. An LD_{50} of 262 mg/kg was reported in rats.[33] No serious adverse effects of doxycycline have been reported. Disturbances of the GI tract are commonly observed following oral administration of tetracycline antibiotics in therapeutic doses; however, doxycycline shows the least GI adverse effects among the tetracycline antibiotics.[26] On the other hand, of all the tetracycline antibiotics, doxycycline hyclate, especially in capsule form, is most likely to cause esophageal ulceration.[26,34–36] Doxycycline monohydrate may be an alternative to doxycycline hyclate in patients with high risk of suffering from esophageal lesions because it has less acidic properties than the hyclate salt.[37]

As for other tetracycline antibiotics, doxycycline can accumulate in calcium-rich tissues such as bones and teeth during their formation, and may cause yellow and brown discoloration and enamel hypoplasia in developing teeth in children.[26] Photosensitivity reactions (mostly phototoxic and in rare cases photoallergic) due to accumulation of doxycycline in the skin have also been reported.[30,38,39]

In general, tetracycline antibiotics should not be used in patients who have renal disease, specifically, renal insufficiency or renal failure. However, if therapy with a tetracycline proves necessary for such a patient, doxycycline or minocycline are preferred due to their minimal renal clearance.[26] Studies to date have indicated that at usual recommended doses of doxycycline, the drug does not accumulate in patients with renal impairment.[26,40]

It is contraindicated to give doxycycline to patients with porphyria.[26,41]

Symptoms including nausea, vomiting, and diarrhea are commonly observed with overdosage of tetracycline antibiotics including doxycycline.[26] Occasionally, overdosage of doxycycline has led to liver and kidney damage as well as pancreatitis.[42] Treatment for overdosage with the oral preparation of doxycycline should be symptomatic and gastric lavage may be considered.

PHYSICOCHEMICAL PROPERTIES

Salt, Stereoisomers, and Polymorphs

Salts of doxycycline for pharmaceutical preparations listed in the pharmacopoeias include doxycycline monohydrate (free base), doxycycline hyclate (in some pharmacopoeias under the name "hydrochloride," see above), and doxycycline calcium.[28,43–46] The USP 32 has monographs for doxycycline monohydrate, doxycycline hyclate and doxycycline calcium, although the latter salt is used only for oral solutions.[43] The European Pharmacopoeia (Ph.Eur., 5th ed.) has monographs on doxycycline monohydrate and doxycycline hyclate.[44,46] The International Pharmacopoeia (Ph.Int., 4th ed.),[46] the British Pharmacopoeia (BP 1993)[45] as well as the Japanese Pharmacopoeia (JP XV)[28] include only doxycycline hyclate. Oral products with Marketing Authorizations (MAs) in Germany (DE),[42] contain either the hyclate or the monohydrate. This monograph pertains only to the hyclate salt.

No polymorphism of doxycycline hyclate has been reported.

Solubility

Doxycycline hyclate is classified as soluble[33] or freely soluble[44] in water. An aqueous solubility of 50 mg/mL has been reported, but without specifying the temperature.[47] Doxycycline hyclate aqueous solution, containing 1% doxycycline, has a pH of 2–3.[43,48] Solubility of doxycycline hyclate in SGF_{sp}, pH 1.2 and in SIF_{sp}, pH 6.8 at room temperature was reported as about 40 and 28 mg/mL,[49] corresponding to dose/solubility (D/S) ratios of 5.77 and 8.24 mL (based on a 230.8 mg dose of doxycycline hyclate), respectively. The values are far less than the D/S cut-off of 250 mL for the "high solubility" biowaiver criterion.[2,3]

To confirm the "high solubility" properties of doxycycline hyclate, further experimental data for doxycycline hyclate solubility in compendial buffers pH 1.0, 1.2, 4.5, 6.8, and 7.5 were obtained[a] at 37°C using the standard shake-flask method.[50] The experiment was performed by adding 461.6 mg doxycycline hyclate powder, equivalent to 400 mg doxycycline, to 250 mL buffer. In all cases the powder went immediately into solution, demonstrating that doxycycline hyclate has "high solubility" at all five pHs representing the GI conditions at 37°C.

Partition Coefficient

$Log P$ values of −1.90 and 0.63 were reported for doxycycline hyclate and doxycycline free base, respectively.[40,51] Calculations using fragmentation methods based on atomic contributions to lipophilicity and by using the $C \log P$ program (version 3.0, Biobyte Corp., Claremont, CA, http://www.biobyte.com) yielded values of −0.60 ($C \log P$) and −3.66 ($\log P$).

pK_a

Doxycycline is an amphoteric compound with three pK_a values.[52,53] At 20°C, pK_a values of 3.5 (tricarbonyl system), 7.7 (ketophenolic system), and 9.5 (dimethylammonium group) have been reported.[54]

Dosage Form Strengths

Dosage form strengths of doxycycline are expressed as mg free base. The WHO EML lists 100 mg doxycycline (capsules or tablets).[31] Table 1 shows IR doxycycline hyclate tablets with MAs in Germany (DE),[42] Denmark (DK),[55] Finland (FI),[56] France (FR),[57] the Netherlands (NL),[58] Norway (NO),[59] Spain (ES),[60] Sweden (SE),[61] the United Kingdom (UK),[62] and the United States (US).[63] These MAs cover a range of strengths corresponding to 20, 50, 100, and 200 mg doxycycline base.

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Among tetracycline antibiotics, doxycycline is reported to have the best absorption.

The absolute bioavailability (BA) of doxycycline administered orally at a dose of 100–200 mg is 90–100%.[30,40,64] The average percent fraction doxycycline absorbed in humans ($F_a\%$) was reported to be 95%.[40] Doxycycline is rapidly absorbed; it can be detected in the blood within 15 min of administration.[65] The absorption primarily occurs in the duodenum.[40] A secondary peak of doxycycline in plasma is normally observed due to enterohepatic cycling.[37,66] Linear pharmacokinetics of orally administered doxycycline have been demonstrated in the dose range 100–600 mg.[40] A peak plasma doxycycline concentration of about 2.6 µg/mL is reached within approximately 2–3.5 h after a dose of 200 mg.[26,40,42] Different salt forms demonstrated no significant influences on doxycycline absorption.[37,40,65]

Unlike tetracycline, food only slightly reduces the area under the plasma concentration–time curve (AUC) and the mean plasma concentrations of doxycycline.[54,67,68] The mean serum concentrations of doxycycline obtained during a multiple-dosage regimen of 200 mg/day in the fasted and fed states (regardless of the meal type) were found to be in the therapeutic range (4.4 µg/mL vs. 4.0 µg/mL), indicating little or no clinical significance of the food effect.[67] Although milk and dairy products reduce the exposure of several tetracycline antibiotics significantly, this is not the case for doxycycline.[26] Dairy products have at most a minor influence on doxycycline absorption.[26] Nevertheless, it is recommended to take doxycycline product separately from drugs containing di and/or trivalent cations, for example, antacids

Table 1. Excipients[*] Present in Doxycycline Hyclate IR Solid Oral Drug Products[**] with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), the Netherlands (NL), Spain (ES), the United Kingdom (UK) and the United States (US)[***], and the Minimal and Maximal Amount of that Excipient Present Per Dosage Unit in Solid Oral Drug Products with an MA in the US[,†]

Excipient	Drug Products Containing that Excipient with an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with an MA in the US (mg)
Acacia	ES(1)	5–156[a]
Acetylated monoglycerides	ES(2–4)	0.3–3.7
Alginic acid	ES(5) NL(6)	32–80
Aluminium hydroxide	DE(7,8)	15
Beeswax	ES(1) NL(6,9)	0.44–2
Calcium hydrogen phosphate	ES(10,11)	109–636
Carnauba wax	ES(1) NL(6,9) US (12,13)	0.15–58[a]
Castor oil hydrogenated	DE(14) FI(15)	0.93–37.6[a]
Cellulose	DE(14,16) ES(17–19) FR(20–23) NL(6,9,24–26) UK (27) US (12,13,28–38)	4.6–1385[a]
Croscarmellose sodium	DE(16) NL(9) US(12,13,28,30,31)	2–180
Crospovidone	DE(39) DK(40) ES(41) FR(20,22,23) NL(42)	4.4–792[a]
Dimethicone	FR(21) NL(25)	3.7
Ethylcellulose	US(38)	1.0–121[a]
Furcellaran	NL(25)	
Gelatin	DE(7,8,16,39,43) DK(40) ES(2,3,5,10,11,17–19,41) NL(42) UK(44) US(29,31,37)	1–756[a]
Hydroxypropylcellulose	NL(9)	4–132
Hypromellose	FR(21) NL(6,24,25) US(12,13,30,33,36,38)	0.8–537
Hypromellose phthalate	ES(2,3)	13–104
Lactose	DE(7,8,14,16,43) ES(1,5,10,11,18,19,45) FI(15) FR(21) NL(6,9) US(12,13,31–36)	23–1020[a]
Macrogol	DE(7,8,16,43) ES(18) FR (20,21,23) NL(24) US(12,13,30,33–35)	0.12–500[a]
Magnesium stearate	DE(7,8,14,16,43) ES(1,5,10,11,17–19,45) FI(15) FR(20–23) NL(6,9,24–26) UK(27,44) US(12,13,28–38)	0.15–401[a]
Magnesium trisilicate	ES(10,11)	20–77
Methylcellulose	NL(9) US(33,34)	2.8–184
Polydextrose	US(13)	3.8–8.1
Polysorbate 80	US(12,30)	2.2–418[a]
Poly(vinylalcohol)	US(35)	0.7–20
Povidone	ES(1–4) NL(6,9,25)	0.17–80
Propylene glycol	NL(6,9,25) US(38)	1.5–52
Shellac	ES(5) NL(9) UK(44)	4.4–25
Silica	DE(7,8,14,16,43) ES(17,18) FR(20,21) NL(6,24,25) US(28,29,33–35)	0.65–99
Sodium hydrogen carbonate	FI(15)	2–125
Sodium lauryl sulphate	ES(5) FR(20) NL(6) UK(44) US(29,30,37,38)	0.65–50
Sodium starch glycolate	DE(14) NL(24) US(33,34)	2–876[a]
Starch	DE(7,8,14,16,39) DK(40) ES(1–5,10,11,18,41) NL(6,9,42) UK(44)	0.44–1135[a]
Stearic acid	US (33,34)	0.9–72[a]
Sucrose	DE(39) DK(40) ES(1–4,41) NL(42)	12–900

(*Continued*)

Table 1. (*Continued*)

Excipient	Drug Products Containing that Excipient with an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with an MA in the US (mg)
Talc	DE(7,8,16,39) DK(40) ES(1–4,17,18,41,45) FR(20,23) NL(24,25,42) US(35,38)	0.25–220[a]
Triacetin	US(13,36)	1–15

(1) DOXICICLINA NORMON 100 mg Grageas. (2) DOXIPIL 100 mg cápsulas duras. (3) MEDEDOXI 50 mg cápsulas duras. (4) PELEDOX 50. (5) VIBRACINA 100 mg cápsulas duras. (6) Doxycycline ratiopharm 100 mg, omhulde tabletten. (7) Aknefug® Doxy Filmtabletten (Mono). (8) Doxy-Wolff® 100/−200 Filmtabletten (Mono). (9) Doxycycline 100, omhulde tabletten 100 mg. (10) Dosil, cápsulas. (11) Dosil enzimático, cápsulas. (12) Doxycycline hyclate (doxycycline hyclate) tablet (100 mg), coated [Mutual Pharmaceutical Company, Inc.]. (13) Doxycycline hyclate (Doxycycline hyclate) tablet (20 mg), film coated [Mutual Pharmaceutical Company, Inc.]. (14) Doxycyclin AL 100 T/−200 T Tabletten (Mono). (15) Doximycin 100 mg/−150 mg tabletti. (16) Doxycyclin STADA® 100 mg/−200 mg Filmtabletten (Mono). (17) DOXITEN BIO, cápsulas. (18) DOXITEN ENZIMÁTICO, cápsulas. (19) RETENS® cápsulas. (20) DOXY 100 mg cp pellic. (21) DOXYCYCLINE ARROW 100 mg cp pellic. (22) DOXYCYCLINE BIOGARAN 100 mg cp pellic séc. (23) SPANOR 100 mg cp pellic séc. (24) Doxycycline 100 PCH, omhulde tabletten 100 mg. (25) Doxycycline Lagap, tabletten 100 mg. (26) Periostat 20 mg filmomhulde tabletten, filmomhulde tabletten. (27) PERIOSTAT® 20 mg film-coated tablets. (28) Doxycycline (doxycycline hyclate) tablet (100 mg), coated [West-Ward Pharmaceutical Corp.]. (29) Doxycycline hyclate (doxycycline hyclate) capsule (50/100 mg) [Watson Laboratories, Inc.]. (30) Doxycycline hyclate (doxycycline hyclate) tablet (100 mg) [Watson Laboratories, Inc.]. (31) Doxycycline hyclate (doxycycline hyclate) capsule (50/100 mg) [Mutual Pharmaceutical Company, Inc.]. (32) Doxycycline hyclate (doxycycline hyclate) capsule (50/100 mg) [West-ward Pharmaceutical Corp.]. (33) Doxycycline hyclate (doxycycline hyclate) tablet (100 mg), film coated [IVAX Pharmaceuticals, Inc.]. (34) Doxycycline hyclate (doxycycline hyclate) capsule (50/100 mg) [IVAX Pharmaceuticals, Inc.]. (35) Doxycycline hyclate (doxycycline hyclate) tablet (20 mg), film coated [Lannett Company, Inc.]. (36) Periostat (doxycycline hyclate) tablet (20 mg) [CollaGenex Pharmaceuticals, Inc.]. (37) Vibramycin hyclate (doxycycline hyclate) capsule (50/100 mg) [Pfizer Labs]. (38) Vibra-tabs (doxycycline hyclate) tablet (100 mg), film coated [Pfizer Labs]. (39) Antodox® 100 mg/−200 mg Hartkapseln (Mono). (40) Doxycycline "Ethypharm," kapsler, hårde. (41) PRODERMA 50 mg/−100 mg cápsulas duras. (42) Ethypharm doxycycline 50 mg/−100 mg/−200 mg, capsules. (43) Doxy 200 mg Kapseln (Mono). (44) Doxycycline capsules 50, 100 mg (Actavis UK, Ltd). (45) DOXICICLINA VALOMED.

*Colorants, flavors, and ingredients present in the printing ink are not included. Coating substances are excluded if in the SmPC the constituents of core and coating are stated separately.

**Excluded are: soft gelatin capsules filled with a solution and oral suspensions.

***Sources of data: see text, Dosage Form Strengths Section.

FDA's Inactive Ingredient Database, http://www.fda.gov/cder/iig/iigfaqWEB.htm #purpose (version date 11-01-2009).

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

since the absorption of doxycycline may be impaired.[69]

Permeability

An apparent permeability coefficient (P_{app}) of doxycycline of 17.5×10^{-6} cm/sec using the Caco-2 monolayer system was reported.[70] In the same study a high permeability internal standard suggested by the US FDA,[3] antipyrine, demonstrated a P_{app} of 45.3×10^{-6} cm/sec.[70] By comparing the drug permeability between Caco-2 and PAMPA assay, it was demonstrated that transcellular but not paracellular permeation is the main transport pathway of doxycycline.[70]

Distribution

The volume of distribution of doxycycline at steady-state ($V_{d_{ss}}$) varies between approximately 53 and 134 L and the volume of the central compartment (V_c) is 22 L.[40] These values can vary slightly according to the doxycycline salt.[65] In the elderly, the volume of distribution is higher than in young patients.[71] Doxycycline distributes effectively into the body tissues especially liver, kidneys, and digestive tract.[26,40] Doxycycline as well as other tetracycline antibiotics can be retained at the sites of new bone formation and impair calcification in developing teeth, and in some injured soft tissues.[26] The plasma protein binding of doxycycline is the highest among tetracycline antibiotics, between 80% and 95% at usual therapeutic concentrations.[26,40,42]

Metabolism and Excretion

No problems with instability of doxycycline in the GI tract have been reported.

Although it has been demonstrated that no metabolites of doxycycline are found in blood, urine, or feces,[40] some reference sources indicate that some metabolism does occur.[42,71,72] Additionally, a decrease in the area under the plasma

concentration–time curve (AUC) of doxycycline was observed during concomitant treatment with drugs that induce hepatic enzymes, for instance, alcohol (chronic use), rifampicin, carbamazepine, phenobarbital, phenytoin, and primidone, owing to the increased metabolism of doxycycline.[26,73]

Doxycycline is slowly eliminated *via* the kidneys to an extent of approximately 30–40% in patients with normal renal function.[26,40] A renal clearance of 1.8–2.1 L/h was reported.[40] The rest of the dose is eliminated through the digestive tract and excreted in the feces, probably due to partial biliary elimination in addition to diffusion through the intestinal wall and subsequent chelation with the metal ions, for example, Ca^{2+}, Mg^{2+} present in the small intestine.[26,40] The nonchelated doxycycline is reabsorbed and undergoes enterohepatic cycling.[26,40] The elimination half-life ($t_{1/2\beta}$) of doxycycline varies from about 12 to 25 h [26,40,42,74,75] after single dosing and between 17 and 24 h after multiple dosing.[76] These values do not change in the elderly patients although the serum and tissue concentrations are higher than those observed in young adults.[40] In renal failure patients, the $t_{1/2\beta}$ and AUC remain unchanged and no accumulation is observed even after repeated doses in anuric patients.[40] At first glance, these results appear to be inconsistent with renal elimination as the major route of doxycycline elimination. However, a decrease in the fraction of doxycycline bound to plasma proteins in renal failure patients appears to result in an increase in nonrenal clearance, which then compensates for the decrease in renal clearance.[77]

DOSAGE FORM PERFORMANCE

Bioavailability and Bioequivalence

Several reports in the literature have demonstrated BE of doxycycline products.[37,65,67,74,75,78–87] The study details, BE criteria, and results of the pharmacokinetic studies conducted from 1975 to 2007 are summarized in Table 2. All studies reported the pharmacokinetic parameters between doxycycline hyclate products, various doxycycline salt forms and different dosage forms of doxycycline to be "bioequivalent" or "not significantly different." It should be noted that doxycycline can be regarded as a borderline "highly variable drug" based on the data from Kitzes-Cohen et al.[86] Indeed, the Central Labora-

tory of German Pharmacists proposed using a 95% confidence interval (CI) and an acceptance range of 70–130% to assess BE.[88] Nevertheless, most studies showed that the 90% CI of the AUC and C_{max} of the multisource products lay within the 80–125% range of those of the comparator.

Excipients

Table 1 shows the excipients present in IR doxycycline hyclate products with an MA in a large number of countries. In view of their MAs, it may be supposed that most of these drug products successfully had passed an *in vivo* BE study. In this respect, the regulatory authorities of DE classified doxycycline an API for which *in vivo* BE testing is required,[89] but in NL doxycycline was, and still is, exempted from *in vivo* BE studies for national MAs.[90] For other countries no such information was available and hence it is not possible to judge which products had actually passed an *in vivo* BE study. However, due to their MAs, and hence use in clinical practice, it is concluded that the risk of excipients listed in Table 1 exerting a significant effect on the extent and rate of absorption of doxycycline is probably small.

No study directly investigating the influence of excipients on the absorption of doxycycline has been reported in the literature. However, studies on the effects of antacids and drugs that can modify the GI environment on doxycycline absorption have been reported.[91] These results can indirectly be applied to the excipients having similar characteristics, since the same influence on doxycycline absorption can be anticipated.

A randomized, crossover study conducted by Deppermann et al.[91] investigated the influence of antacids on the BA of doxycycline. The antacid studied contained 900 mg of aluminum hydroxide ($Al(OH)_3$) and 600 mg of magnesium hydroxide ($Mg(OH)_2$) per dose. The results of this study indicated that antacids, such as a mixture of $Al(OH)_3$ and $Mg(OH)_2$, lead to subtherapeutic serum levels of doxycycline. Administration of doxycycline after antacid treatment resulted in approximately 85% reduction in absorption, leading to a relative BA of only 15%. The ability of doxycyline to form chelates with metal ions such as Fe^{2+}, Al^{3+}, Ca^{2+}, Zn^{2+}, and Mn^{2+} was used to explain the results. The second part of the same study was a randomized, double-blind study

Table 2. Summary of the Bioequivalence Studies of Doxycycline Products

Refs.	Formulations Studied	Composition	Subjects	Prandial	Study Design	Pharmacokinetic Parameters	Bioequivalence Criteria, Statistics	Results	In Vitro Tests
Antal et al. (1975)[78]	200 mg doxycycline hyclate capsules, and oral solution except for suspension which contained doxycycline base	An oral solution contained 480 mg ascorbic acid	6 male volunteers (21–30 yo)	Fasted (meal after 3 h)	Randomized, five-way, crossover/washout 1 week	AUC, C_{max}, T_{max}	ANOVA, then Tukey's or Student's t-test	Three capsules—bioequivalent to each other and to the oral solution	Basket, 25 rpm, 0.1 N HCl. Rank-order for 50% dissolution
Welling et al. (1977)[67]	200 mg doxycycline hyclate capsules and oral solution (dissolved capsules)	Not reported	4 male and 2 female volunteers (19–36 yo)	Fasted (meal after 4 h) versus fed	Six-way, single dose, crossover/washout 2 weeks	Serum level comparison, paired t-test	Not specified but comparing the mean serum level	Not significantly different in terms of clinical effects	No
Saux et al. (1981)[65]	200 mg doxycycline polyphosphate, hyclate, and base capsules	Not reported	2 male and 4 female volunteers (20–28 yo)	Fasted (meal after 5 h)	Single dose, subjects received two of three products/washout 2 weeks	AUC, C_{max}, T_{max}	Not specified	Not significantly different	No
Malmborg et al. (1984)[37]	100 mg doxycycline monohydrate and hydrochloride tablets	Not reported	10 male and 2 female volunteers (24–36 yo)	Fed (breakfast)	Two-way, single dose, crossover/washout 1 week	AUC, C_{max}	Student's t-test (no significance level specified)	Not significantly different	No
Campistron et al. (1986)[80]	200 mg doxycycline hyclate solutions, capsules, and tablets	Not reported	10 male and 2 female volunteers (23–32 yo)	Fasted (meal after 4 h)	Randomized, three-way, single dose, crossover/washout 1 week	AUC, C_{max}, T_{max}	ANOVA (Westlake CI)	Not significantly different	No
Linberg et al. (1989)[81]	200 mg doxycycline hyclate tablets and capsules	Not reported	8 male yersiniosis patients (20–30 yo)	Not specified	Oral administration in 6 patients, i.v. for 2 patients	Absorption rate constant, serum level comparison	Not specified	Not significantly different	No
Kees et al. (1990)[75]	2 brands, 100 mg doxycycline hyclate tablets	Not reported	16 male volunteers (22–27 yo)	Fasted (meal after 4 h)	Randomized, two-way, single dose, crossover/washout 2 weeks	AUC, C_{max}, T_{max}, $t_{1/2}$	95% CI	Bioequivalent	No
Saano et al. (1990)[83]	150 mg doxycycline hydrochloride tablets, dissolved hydrochloride tablets, and dissolved monohydrate tablets	Not reported	8 male and 7 female volunteers (21–25 yo)	Standard low-fat breakfast was given after 30 min of drug administration	Randomized, three-way, single dose, crossover/washout 1 week	AUC, C_{max}, T_{max}	ANOVA	Not significantly different	No

Reference	Product		Subjects	Condition	Design	Parameters	Statistics	Result	Additional
Balogh et al. (1991)[84]	2 brands, 100 mg doxycycline hyclate capsules	Not reported	19 male and 1 female volunteers (21–26 yo)	Fasted (meal after 4 h)	Randomized, two-way, single dose, crossover/washout 1 week	AUC, C_{max}	95% CI, 70–130%	Bioequivalent	No
Saket et al. (1993)[85]	2 brands, 100 mg doxycycline hyclate capsules	Not reported	18 male volunteers (19–26 yo)	Fasted (meal after 5 h)	Randomized, two-way, single dose, crossover/washout 1 week	AUC, C_{max}, T_{max}	Student's t-test	Not significantly different	Disintegration tests—both disintegrated within 15 min
Kitzes-Cohen et al. (1998)[86]	100 mg doxycycline monohydrate and hydrochloride tablets	Not reported	22 male volunteers (18–32 yo)	Fasted (meal after 4 h)	Randomized, two-way, single dose, crossover/washout 2 weeks	AUC, C_{max}, T_{max}, $t_{1/2}$, MRT	90% CI	Bioequivalent	No
Alsarra et al. (2004)[87]	2 brands, 100 mg doxycycline hyclate capsules	Not reported	24 male volunteers (24–43 yo)	Fasted (meal after 4 h)	Randomized, two-way, single dose, crossover/washout 2 weeks	AUC, C_{max}, T_{max}	ANOVA, 90% CI, 80–125%	Bioequivalent	No
Gschwend et al. (2007)[74]	2 brands, 100 mg doxycycline hyclate capsules	Not reported	24 male volunteers (18–43 yo)	Fasted (meal after 4 h)	Randomized, two-way, single dose, crossover/washout 16 days	AUC, C_{max}, T_{max}, $t_{1/2}$	90% CI, 80–125%	Bioequivalent	No

yo, years old.

which investigated the possible influence of pirenzepine, an antimuscarinic drug, and ranitidine, an H_2-receptor antagonist, on the BA of doxycycline. These two drugs modified the GI tract conditions, with pirenzepine changing the motility and ranitidine increasing the upper GI pH. No changes in C_{max} and AUC were observed either with pirenzepine or ranitidine coadministrations, although the T_{max} was prolonged in both cases. It was concluded that physical interactions *via* chelation rather than changes in the GI environment are responsible for the decrease in the BA of doxycycline when administered with antacids.

Dissolution

According to the USP 32,[43] the same dissolution test conditions are used for doxycycline hyclate capsules and doxycycline hyclate tablets: USP Apparatus 2 (paddle method), rotational speed 75 rpm, 900 mL water as a dissolution medium, temperature 37°C. The dissolution specification for the capsules is "not less than 80% (Q) dissolves within 30 min" and for the tablets is "not less than 80% (Q) dissolves within 90 min."[43] The Ph.Int. 4th ed. describes the dissolution test conditions for doxycycline capsules and doxycycline tablets as: paddle method, rotational speed 75 rpm, 500 mL pH 6.8 buffer as a dissolution medium, temperature 37°C.[48] The dissolution specification for both tablets and capsules is "not less than 80% (Q) dissolves within 30 min."[48]

Recently, dissolution of five marketed doxycycline hyclate IR products in DE was tested using both the WHO and the US FDA "BCS-conform" methods.[50] The dissolution test conditions consisted of the paddle method, medium volume 500 mL, rotational speed 75 rpm (WHO)[2] or 50 rpm (US FDA),[3] and temperature 37°C. The products were tested in three different dissolution media: SGF$_{sp}$—pH 1.2; acetate buffer—pH 4.5; and SIF$_{sp}$—pH 6.8. The results indicated that *in vitro* BE evaluation based on the WHO test procedure is more appropriate than the US FDA[3] testing method and that *in vitro* BE evaluation based on comparative dissolution testing tends to be over-discriminating compared to *in vivo* evaluation, as some products that had successfully passed an *in vivo* BE evaluation failed to pass the *in vitro* BE evaluation.

Using the static pellet method to assess the dissolution performance of the hyclate and other salt forms of doxycycline in various media at 25°C it was found that the hyclate form is less sensitive to the common ion effect than the other salts.[92] Insensitivity to the common ion effect of doxycycline hyclate in terms of dissolution is important, especially for *in vivo* dissolution in the GI tract, due to the high chloride level in the human gastric juice, and thus justifies the widespread use of this salt form in doxycycline oral dosage forms.

DISCUSSION

Solubility

Doxycycline hyclate is "highly soluble" according to all BCS criteria[2,3] and no solubility problems in the upper GI milieu are expected.

Permeability and Absorption

Doxycycline hyclate is "highly permeable" according to all BCS criteria[2,3] since the BA of doxycycline is nearly complete following oral administration.[40] Caco-2 studies support this classification.[70]

Risks Associated with Biowaiving

With any positive biowaiver decision there is, statistically speaking, a risk that the decision reached is incorrect. Therefore the risk of reaching such an incorrect decision needs to be assessed. Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.[93] Therefore, the overall risk of a positive biowaiver decision can be defined as the probability that the test product, after passing the surrogate BE testing, is actually bio*in*equivalent and the therapeutic consequences for the patient, if such a situation should occur. Each of these possibilities is discussed below.

Probability of Occurrence of Bio*in*equivalence

One report has identified an effect of antacids on the BA of doxycycline.[91] Seemingly contradictory to this finding, two doxycycline hyclate products with an MA in DE contain Al(OH)$_3$, see Table 1, however, the amount of Al(OH)$_3$ present in these drug products is likely far lower than used in the study cited. No other reports of BE problems were identified and hence it can be concluded that

doxycycline hyclate, formulated in solid IR dosage forms, appears to exhibit very little risk in terms of bio*in*equivalence. This is in line with its BCS Class I classification.

Probability of False Positives of Surrogate BE Testing

Comparative dissolution[b] testing, especially based on the WHO method,[2] appears to assure detection of bio*in*equivalence caused by poor *in vivo* disintegration and *in vivo* dissolution, should such an unlikely situation arise.

Although comparative dissolution testing will not elucidate excipients and formulation effects on the absorption of doxycycline, the "highly permeable" characteristic of doxycycline hyclate combined with lack of excipient effects on BE would indicate that excipient effects on permeability are unlikely. By using only excipients which are listed in Table 1 in the formulation, the probability of occurrence of an excipient effects on permeability is further reduced.

Patient's Risks Associated with Bio*in*equivalence

Doxycycline hyclate has a wide therapeutic index and is mainly used as an antibacterial and for prophylaxis of malaria.[31] Moreover, according to the draft "Science-based criteria for BE *in vivo* and *in vitro*, biowaivers, and strategic framework for implementation" of the Pan American Health Organization,[94] doxycycline is classified as having "Intermediate Health Risk," which basically means that when the plasma concentrations of doxycycline are outside the therapeutic window, adverse (but not necessary serious) reactions may occur.[94]

However, the risk that a bio*in*equivalent drug product could be formulated, and the further risk that this product would pass all the criteria for accepting BE on the basis of *in vitro* data, and yet give rise to supra- or subtherapeutic plasma levels, or a C_{max} different from the comparator, is minimal.

CONCLUSION

A biowaiver for IR solid oral dosage forms containing doxycycline hyclate is scientifically justified, provided that the test product contains only excipients present in a number of doxycycline hyclate IR solid oral drug products approved in ICH or associated countries, for instance as presented in Table 1; and that both the test and comparator products either (a) are both "very rapidly dissolving," or (b) are both "rapidly dissolving" with similarity of the dissolution profiles demonstrated at pH 1.2, 4.5, and 6.8, as described in the WHO test procedure.[2] When not all of these conditions can be fulfilled, BE should be established on the basis of *in vivo* pharmacokinetic study.

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[b]False positives defined as: a bioinequivalent drug product being declared bioequivalent.

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