

COMMENTARIES

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Quinidine Sulfate

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ABSTRACT: Literature data are reviewed 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 quinidine sulfate. Quinidine sulfate's solubility and permeability, its therapeutic use and index, pharmacokinetics, excipient interactions and reported BE/bioavailability (BA) problems were taken into consideration. The available data are not fully conclusive, but do suggest that quinidine sulfate is highly soluble and moderately to highly permeable and would likely be assigned to BCS Class I (or at worst BCS III). In view of the inconclusiveness of the data and, more important, quinidine's narrow therapeutic window and critical indication, a biowaiver based approval of quinidine containing dosage forms cannot be recommended for either new multisource drug products or for major postapproval changes (variations) to existing drug products. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 98:2238–2251, 2009

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

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INTRODUCTION

A biowaiver monograph of quinidine sulfate based on literature data is presented. The risks of basing a BE assessment on *in vitro* rather than *in vivo* study results for the approval of new IR solid oral dosage forms containing quinidine sulfate ("biowaiving"), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing quinidine sulfate as the only Active Pharmaceutical Ingredient (API) and not to combination drug products.

The purpose and scope of this series of monographs have been previously discussed.¹ Summarized in few words, the aim 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 It is to be understood that these monographs do not simply apply the WHO,² FDA,³ and EMEA Guidances,⁴ but also aim to serve as a critical validation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),⁵ acetazolamide,⁶ aciclovir,⁷ amitriptyline,⁸ atenolol,¹ chloroquine,⁹ cimetidine,¹⁰ diclofenac,¹¹ ethambutol,¹² ibuprofen,¹³ isoniazid,¹⁴ metoclopramide,¹⁵ prednisolone,¹⁶ prednisone,¹⁷ pyrazinamide,¹⁸ propranolol,¹ ranitidine,¹⁹ and verapamil.¹ They are also available on-line at www.fip.org/bcs.

EXPERIMENTAL

A literature search was carried out. Electronically available databases searched included International Pharmaceutical Abstracts, Medline, the Merck Index, Toxline, the Hazardous Substances Data Bank and Embase. Databases were accessed throughout the years 2006 to April 2008. In addition, the qualitative composition of IR tablets from drug products having a Marketing Author-

ization (MA), that is, a registration, in various countries was included. Most of this information was taken from the Summary of Product Characteristics of these drug products, which are publicly available from several electronic databases.

GENERAL CHARACTERISTICS

Name

The chemical name of quinidine sulfate is cinchonan-9-ol, 6'-methoxy-, (9S)-, sulfate (2:1) and the IUPAC name is (S)-[(5S/7R)-5-ethenyl-1-azabicyclo[2.2.2]octan-7-yl]-(6-methoxyquinolin-4-yl)methanol; sulfuric acid dihydrate. The molecular formula is $C_{40}H_{48}N_4O_4 \times H_2SO_4 \times 2H_2O$ and the molecular weight of anhydrous quinidine sulfate is 782.96 of which 82.9% is quinidine base. Its structure is shown in Figure 1.

Quinidine is a diastereomer of quinine. According to the USP 31/NF 26 and Ph.Eur 6.2/JP/Ph.Int, quinidine sulfate may contain up to 20% and 15%, respectively, dihydroquinidine.²⁰⁻²³ Considerable differences in the amount of dihydroquinidine in commercial bulk quinidine (6-23%) were reported.²⁴

Therapeutic Indications, Therapeutic Index, and Toxicity

Quinidine is indicated in the treatment of atrial fibrillation and flutter and ventricular arrhythmias and treatment of malaria.^{25,26} The usual dose is 200-400 mg every 4-6 h. However, as long as no adverse effects are observed dose may be cautiously increased for achievement of therapeutic effects.²⁵ The relationship between quinidine plasma levels and effect or toxicity is difficult to define due to differences in the specificity of the applied assays and due to the presence of active metabolites and dihydroquinidine as a product

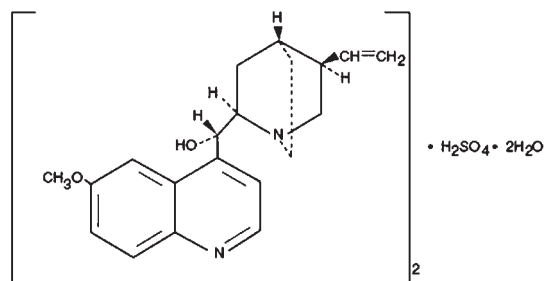


Figure 1. Structure of quinidine sulfate dihydrate.

impurity.²⁷ Therapeutic serum levels have been cited as 2–6 $\mu\text{g/mL}$ (6.2–18.5 $\mu\text{mol/L}$) but optimal plasma or serum levels may be outside this range for some individuals.^{28–31} In terms of unbound quinidine, lower concentrations may suffice for pharmacological action.²⁶ Toxicity may occur at concentrations higher than 5–8 $\mu\text{g/mL}$.^{32,33}

Death of a toddler after ingestion of a 5 g dose of quinidine has been described, while an adolescent survived ingestion of a 8 g dose.³⁴ Overdosing of quinidine is associated with occurrence of ventricular arrhythmias, cinchonism, and hypotension.^{26,34} The FDA listed quinidine sulfate capsules, tablets and extended release tablets as narrow therapeutic range drug products.³⁵

PHYSICOCHEMICAL PROPERTIES

Salt, Esters, Polymorphs, Hydrates

Quindine sulfate as referred to in this monograph is the dihydrate of a 2:1 salt of quinidine and sulfate as shown in Figure 1. Quinidine hydrogen sulfate tetrahydrate, also known as quinidine bisulfate, gluconate and polygalacturonate are known and have been used for parenteral or sustained release dosage forms,³⁰ but fall outside the scope of this monograph, being restricted to solid IR dosage forms of quinidine sulfate. No references towards polymorphic forms were identified.

Solubility

Quinidine sulfate was reported to be soluble 1 g in 90 mL of water, without stating the temperature.³⁶

Partition Coefficient

Experimentally $\log P$ and $C \log P$ for quinidine were determined to be 2.36 and 2.79, respectively.³⁷ Distribution into organic media such as octanol occurs to a considerable degree in the relevant pH range of pH 5–7, see Table 1.²⁴ Another source reports $\log D$ values for quinidine to show exponential increase between pH 4.5 and pH 8.0.³⁸ In the same study, $\log D_{(\text{pH}6.5)}$ was determined to be about 1.0–1.1.³⁸ These data confirm the data of Table 1.

pK_a

Quinidine contains two basic nitrogen atoms with pK_a values of 4.2 and (7.9–)8.8 (25°C).^{38,39}

Table 1. Distribution Coefficients (D) of Quinidine in Octanol/Aqueous Buffers at Different pH Values at $37.0 \pm 0.1^\circ\text{C}$

pH	D (Approximate Values)
4	0.4
5	2
6	13
7	29
8	30
9	30.5

Values were read from a diagram in Huynh-Ngoc and Sirois.²⁴

Although pK_a values in the literature do vary to a certain degree, the predominant form at pH 6.8 is the monocation.

Dose and Dosage Forms Strengths

Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are more commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).⁴⁰ Quinidine sulfate is listed in the WHO Model list of medicine as antiarrhythmic medicine as 200 mg tablet,⁴¹ most probably meant to be: 200 mg anhydrous quinidine sulfate. Quinidine sulfate in IR dosage forms is available in strengths of 100, 200, and 300 mg quinidine sulfate, see Table 2.

Stability

Quinidine sulfate was reported to be stable for up to 60 days in oral liquid formulations prepared extemporaneously.⁴² No reference towards instability in the gastrointestinal (GI) tract was found in the literature.

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

Permeability of quinidine is pH- and concentration-dependent. Apparent permeabilities determined with Caco-2 cells in apical to basolateral (a \rightarrow b) direction were approximately 1×10^{-6} cm/s at an apical pH of 5 and rose to about 60×10^{-6} cm/s

Table 2. Excipients* Present in Quinidine Sulfate IR Solid Oral Drug Products with a Marketing Authorization (MA) in The Netherlands (NL) and the United States (US)**, and the Minimal and Maximal Amount of that Excipient Present Pro 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)
Basic butylated methacrylate copolymer	NL (1)	
Calcium carbonate	NL (1)	8.6–350
Calcium stearate	US (2,3)	0.7–43 ^a
Carnauba wax	NL (1)	0.15–58 ^a
Cellulose	NL (1); US (2,3)	4.6–1385 ^a
Lactose	NL (1)	23–1020 ^a
Macrogol	NL (1)	0.12–500 ^a
Magnesium stearate	NL (1)	0.15–401 ^a
Polysorbate 80	NL (1)	2.2–418 ^a
Potato starch (oxidized and acetylated)	NL (1)	
Povidone	NL (1)	0.17–75
Silica	US (2)	0.65–99
Sodium starch glycolate	NL (1); US (2,3)	2–876 ^a
Starch	US (3)	0.44–1135 ^a
Starch, pregelatinised	NL (1); US (2)	6.6–600
Sucrose	NL (1)	12–900
Talc	NL (1)	0.25–220 ^a

(1) Kinidinesulfaat 200 PCH, dragees 200 mg; (2) Quinidine sulfate 100/200/300 mg tablet [Mutual Pharmaceutical Co., Inc.]; (3) Quinidine sulfate 200/300 mg tablet [Watson Laboratories, Inc., Corona, CA].

*Colourants are not included.

**Sources of data: NL, www.cbg-meb.nl (assessed 29-05-2008); US, www.dailymed.nlm.nih.gov (assessed 29-05-2008).

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

^aThe upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

at a pH of 8 (see Tab. 3 for details) with $b \rightarrow a$ transport always exceeding $a \rightarrow b$ transport.⁴³ In the rat jejunum permeabilities for quinidine ranged from about 15×10^{-6} cm/s at pH 4.5– 30×10^{-6} cm/s at pH 7.4 at the highest quinidine concentration of 300 μ M and from 3 to 6×10^{-6} cm/s for the lowest concentration (3 μ M) tested, see Table 3.³⁸ An increase in permeability is expected at higher pH according to the pH-partition hypothesis, since the equilibrium is shifted towards the deprotonized and more lipophilic moiety. Since quinidine is a P-glycoprotein (P-gp) substrate, also one of the substrates recommended for studying P-gp mediated drug interactions by the FDA,⁴⁴ concentration dependent absorption can be ascribed to saturation of P-gp efflux. At a 300 μ M quinidine concentration, P-gp mediated transport was almost completely saturated as estimated by inhibition with verapamil in rat jejunum.³⁸ Both in Caco-2 cells and rat jejunum, permeability of quinidine at any one pH was lower than that of the high permeable

Table 3. Quinidine Rat and Caco-2 Permeability Data

pH	Rat Tissue/ Cell Culture Model	Initial Concentration (μ M)	Permeability (Approximated) ($\times 10^{-6}$ cm/s)
4.5	Jejunum	10	3.5
5.5	Jejunum	10	7.5
6.5	Jejunum	10	9.0
7.4	Jejunum	10	14
8.0	Jejunum	10	19
4.5	Ileum	10	13
7.4	Ileum	10	26
4.5	Jejunum	3	3.0
4.5	Jejunum	300	15
7.4	Jejunum	3	6.0
7.4	Jejunum	300	30
5.0	Caco-2	50	1.0
6.5	Caco-2	50	10
7.4	Caco-2	50	30
8	Caco-2	50	63

Varma and Panchagnula³⁸ and Neuhoff et al.⁴³

reference substance metoprolol or propranolol, respectively. For low concentrations (3–10 μM) quinidine permeability was in the range of the low permeable reference substances (furosemide, hydrochlorothiazide), while for high concentration and neutral pH its permeability was much closer to the high permeability reference substance propranolol.

Mori et al. investigated quinidine absorption in rats by determining recovery of quinidine in different regions of the GI tract at different time points and concluded that quinidine was rapidly absorbed from the proximal intestine after release from the stomach and only smaller amounts reached the distal intestine.⁴⁵

In the scientific literature it seems to be agreed that quinidine is almost completely absorbed from the intestine after oral delivery (less than 5% quinidine recovered in the feces after oral delivery).^{46–48} Furthermore, absorption of quinidine from solution occurs rapidly with quinidine appearing in the systemic circulation usually within 5–15 min after administration and reaching peak levels at about 45 min. Absorption from different tablets occurred with a lag time of about 10–20 min and peak concentrations around 80–90 min.⁴⁹ Mean oral absolute BA has been reported as about 70–80% but shows a large intraindividual (50–80%) and interindividual (50–100%)^{50,51} range. The 20–30% reduction in BA after oral administration as compared to i.v. can probably be ascribed to first-pass metabolism in most patients.^{46,51} Interestingly, the majority of data generated by the studies of Guentert et al.⁵⁰ after oral administration was best fitted with a model assuming zero-order absorption from the intestine.

Linearity

It is assumed in the literature that quinidine shows linear pharmacokinetics.⁵² However, in some individuals nonlinear pharmacokinetics seem to occur, probably due to differences in oxidative metabolism,^{53,54} see the section Metabolism and excretion.

Distribution

Quinidine disposition can be described by a two-compartment open model. Despite a plasma protein binding of 80–90%,^{55–58} the steady-state volume of distribution ($V_{d_{ss}}$: 3.03 ± 0.25 L/kg)⁵⁹

and the volume of central compartment (V_c : 0.398–0.908 L/kg)^{50,59,60} suggest a distribution to extravascular tissues.^{58,59} Furthermore, quinidine is also distributed into erythrocytes.^{61–63}

Metabolism and Excretion

Quinidine is mainly metabolized in the liver by cytochrome P450 under participation of CYP3A4.⁶⁴ The major metabolites are 3-hydroxyquinidine,^{50,65,66} 2'-quinidinone,^{50,65,66} and quinidine-N-oxide.⁶⁶ Some of these metabolites are pharmacologically active.⁵¹

Elimination occurs both by hepatic metabolism (60–85% of total clearance) and renal excretion of the remaining intact drug (15–40%).⁵¹

Food Effect

Food does not seem to affect the extent of absorption as measured by AUC.^{67,68} However, a 44% increase in t_{max} has been observed after administration of quinidine with food.⁶⁷ Woo et al. found a decreased t_{max} and C_{max} when only unbound serum quinidine was measured, while when measuring total serum quinidine no significant differences in C_{max} and t_{max} were observed.⁶⁸ It was suggested that higher postprandial serum protein would reduce the fraction of unbound quinidine. Intake of dietary salts may increase hepatic first-pass metabolism of quinidine.⁶⁹ Furthermore, concomitant intake of grapefruit juice may alter quinidine pharmacokinetics.^{70–73} Food may have differing effects on modified release dosage forms,⁷¹ however, this monograph is not concerned with modified release formulations.

DOSAGE FORM PERFORMANCE

Bioequivalence of Different Formulations

Several *in vivo* BE studies of quinidine sulfate drug products have been identified,^{49,74–76} see Table 4. McGilveray et al.⁷⁵ tested 11 different formulations containing quinidine sulfate, gluconate, or polygalacturonate. All formulations containing quinidine sulfate were bioequivalent with respect to AUC and C_{max} using the common acceptance intervals of 0.8–1.25 for AUC and C_{max} (log-transformed), with only one formulation

Table 4. Bioequivalence Studies with Quinidine Formulations

References	Composition of Test Formulations	Number of Subjects	Pharmacokinetic Parameters	Result
Strum et al. ⁷⁶	200 mg quinidine sulfate tablets; different manufacturers	11	C_{\max} $AUC_{0-\infty}$ T_{\max} k_{el} k_{ab}	Test formulation bioequivalent with respect to C_{\max} and AUC
McGilveray et al. ⁷⁵	200 mg quinidine sulfate or 325 mg quinidine gluconate or 275 mg polygalacturonate	12	C_{\max} AUC_{0-30h} $AUC_{0-\infty}$ T_{\max} $T_{1/2(abs)}$	Test formulation bioequivalent with respect to C_{\max} and AUC except for one quinidine gluconate formulation
Guentert et al. ⁴⁹	200 mg quinidine sulfate tablets, different manufacturers; quinidine sulfate solution; quinidine gluconate solution	12	C_{\max} $AUC_{0-\infty}$ T_{\max} T_{lag}	Tablets bioequivalent with respect to C_{\max} , $AUC_{0-\infty}$, T_{\max} , T_{lag}
Mason et al. ⁷⁴	Quinidine sulfate injection, solution, capsule, tablet.	13	C_{\max} AUC_{0-24h} $AUC_{0-\infty}$ T_{\max}	Solution, capsule and tablet bioequivalent with respect to C_{\max} , AUC_{0-24h} , $AUC_{0-\infty}$, T_{\max}

showing a significant but small difference in t_{\max} . One of the two tested quinidine gluconate formulations was found to be nonequivalent¹ compared to the quinidine sulfate reference, however, that formulation may have been designed as slow-dissolving.

Strum et al.⁷⁶ tested four different formulation of quinidine sulfate tablets (Quinidine sulfate tablets USP, Eli Lilly & Co., Indianapolis, IN; Quinidine sulfate tablets USP, Phillips Roxane Laboratories, Columbus, OH; Quinidine sulfate tablets USP, Stanlabs, Portland, OR; Quinora tablets, Lakeside Laboratories, Milwaukee, WI) and analyzed AUC, C_{\max} , and t_{\max} . Significant differences were only found for t_{\max} . Guentert et al.⁴⁹ performed a comparative investigation of the absorption of quinidine from solutions and commercial tablets. Relative BAs of the tablets and the solution were not significantly different with respect to AUC and peak concentration, and

¹The authors report *bioinequivalence*. However, in many situations, it is not clear if *bioinequivalence* was present, or not meeting BE criteria. *Bioinequivalence* implies that the whole 90% confidence interval of one, or more, BE attributes (AUC, C_{\max} , t_{\max}) falls outside of their acceptance range, whereas not meeting BE criteria implies that the 90% confidence interval of one, or more, BE attributes not fully fall inside their acceptance range. In this article, we will use throughout the expressions nonequivalence and nonequivalent, meaning: *bioinequivalence* and/or not meeting BE criteria.

BAs of the tested quinidine sulfate tablets were not significantly different with respect to AUC, C_{\max} , and t_{\max} and thus bioequivalent. Thus, IR dosage forms containing quinidine sulfate were usually bioequivalent. As stated before USP and Ph.Eur/JP/Ph.Int allow a dihydroquinidine content of 20% or 15% of quindine, respectively. The cited BE studies determined dihydroquinidine content to be relatively low (4–7%) or at least of similar concentration.

Excipient Interactions

We carried out a search in databases providing the qualitative composition of IR solid oral drug products containing quinidine sulfate as sole API having a MA. Databases searched were: Rote Liste[®]—Arzneimittelinformationen für Deutschland;⁷⁷ Danish Medicines Agency;⁷⁸ Agencia española de medicamentos y productos sanitarios;⁷⁹ National Agency for Medicines,⁸⁰ Vidal—l'Information de référence sur les produits de santé;⁸¹ Medicines Evaluation Board,⁸² Norwegian Medicines Agency;⁸³ Medical Products Agency;⁸⁴ Datapharm Communications Ltd.;⁸⁵ DailyMed—Current Medication Information.⁸⁶

Table 2 shows the results. Only in The Netherlands (NL) and the United States (US), MA

existed for IR solid oral drug products containing quinidine sulfate as sole API. It can be inferred that the drug products having an MA in these countries successfully passed an *in vivo* BE study and hence these excipients do not modify the permeability of quinidine. However, quinidine is a P-glycoprotein substrate. Thus, excipients known to modulate P-glycoprotein activity, for example, tocopheryl polyethylene glycol succinate,^{87,88} may affect quinidine absorption. The same is true for excipients known or suspected to alter epithelial permeability, for example, sodium dodecyl sulfate^{89,90} or chitosan.^{91,92}

Dissolution

Marketed dosage forms are usually designed to comply with the USP specifications.

The USP specification for quinidine sulfate tablets and capsules is not less than 85% (Q) of quinidine sulfate dissolved in 30 min in 900 mL 0.1 N HCl, using the basket method operated at 100 rpm.²²

A study by McGilveray et al.⁷⁵ investigated release of quinidine from 10 different formulations containing quinidine sulfate and quinidine gluconate applying different *in vitro* dissolution methodologies. No significant differences were found in the percentage dissolved or t_{60} between the reference product, of which the identity was not stated and the other quinidine sulfate formulations (formulations A–G in Tab. 5). Dissolution in distilled water was slower than in 0.1 N HCl. A significantly slower dissolution in

0.1 N HCl was found for one quinidine gluconate (formulation H in Tab. 5) formulation, the latter showing dissolution properties of a sustained release product.⁷⁵ The authors could not find any meaningful correlation between dissolution and BA of the quinidine sulfate formulation, while the quinidine gluconate product with the significantly lower dissolution was found to be nonequivalent as compared to the reference. The authors mention, that this product may have been conceived as slow-dissolving.

Guentert et al.⁴⁹ performed a comparative investigation of the absorption of quinidine from solutions and commercial tablets. Dissolution of the different tablets was complete after 60–120 min in 900 mL of 0.07 N HCl. Relative BAs of the tablets and the solution were not significantly different with respect to AUC and peak concentration. Strum et al.⁹³ found a rank-order correlation between absorption rate or t_{max} and disintegration time or dissolution times ($t_{50\%}$, time to 50% release; dissolution conditions: 900 mL 0.1 N HCl at 37°C, rotating-basket at 25 rpm) of the respective formulations. Reasons other than reduced disintegration/dissolution as explanations for the reduced t_{max} could not be identified.

However, despite this correlation, the formulations were bioequivalent with respect to AUC and C_{max} , and at least two of the formulations, also with respect to t_{max} . Thus, slower dissolution may retard absorption but time for absorption in the intestine is still sufficient.

Therefore, in summary, *in vivo* dissolution in the GI tract should be essentially complete and does not affect BA in a way to create none-

Table 5. *In Vitro* Dissolution of Quinidine IR Solid Oral Drug Products

Formulation	0.1 N HCl		Water
	Release After 30 min (% ± SD)	Time for 60% Release (min ± SD)	Time for 60% Release (min) (% ± SD)
Reference	87 ± 9	15 ± 2.4	38 ± 7.2
A	95 ± 3	13 ± 1.6	89 ± 8.0
B	101 ± 4	12 ± 2.0	63 ± 20
C	106 ± 4	3 ± 0.1	8 ± 10 ^a
D	101 ± 4	7.3 ± 2.4	19 ± 1
E	103 ± 4	3.6 ± 1.2	4.3 ± 0.7
F	103 ± 3	10 ± 0.6	16 ± 1.0
G	103 ± 4	3 ± 0.2	4.8 ± 1.3
H	28 ± 0.3	127 ± 3.8	47 ± 1.9 ^b
K	98 ± 1	10 ± 2.2	14 ± 1.0

McGilveray et al.⁷⁵

^aPossibly an error in the original publication, since negative.

^bPercentage released after 120 min.

quivalence if the drug product dissolves not less than 85% in 0.1 N HCl within 30 min, using the basket method at 100 rpm.

DISCUSSION

Solubility

According to the FDA biowaiver guidance, a drug can be considered *highly soluble* if the highest dosage form strength is soluble in less than 250 mL aqueous media over the pH range of 1–7.5 at 37°C, whereas according to the WHO, an API is *highly soluble* if the highest oral dosage strength as given in the WHO Essential Medicines List dissolves in 250 mL or less over a pH range of 1–6.8 at 37°C. According to the EMEA, the highest tablet strength of an API should dissolve in 250 mL in each of three buffers over the pH range of 1–8, preferentially pH 1.0, 4.6, and 6.8.

The highest oral strength of quinidine sulfate listed in the WHO Essential Medicines List is 200 mg, the highest marketed strength 300 mg.

To meet the criterion for *highly soluble*, 1.2 mg/mL would have to be soluble over the pH range of pH 1–7.5 (FDA criterion) or 1–6.8 (EMEA and WHO criterion). The reported solubility of 1 g in 90 mL in water, corresponding with a solubility of 11 mg/mL, exceeds these criteria nearly ten times. However, the temperature at which that solubility was determined, was not reported. Also, no data covering the whole pH range were identified. So, the available data do not meet regulatory requirements. Nevertheless, solubility under *in vivo* conditions seems to be sufficient, as the release of quinidine sulfate from marketed dosage form was usually almost complete after 30 min, while gastric residence time is usually 15 min to several hours⁹⁴ and subsequent transit to the ileum takes about 85 min.^{95,96} Furthermore, as stated before, reduction in BA could be accounted for by first-pass extraction with some exceptions which would bring up the fraction absorbed to more than 0.9. This would not be achievable if the solubility of quinidine would be rate-determining.

Permeability

According to Kasim et al.⁹⁷ $\log P$ values can be correlated with human permeability for a large number of drugs and compounds. Their proposal was to classify drugs with $\log P$ higher than or equal to metoprolol as *highly permeable*, drugs with

a $\log P$ lower than metoprolol as *low-permeable*. $\log P$ and $\log D_{pH6.5}$ for quinidine are 2.37³⁷ and ~ 1.0 – 1.1 ,³⁸ respectively, and both higher than for metoprolol (1.72, -1.48 ⁹⁷). Thus, quinidine would be classified *highly permeable*. However, correlations of partition coefficients with permeability have limited predictability, especially for drug transporter substrates as quinidine. For instance, the correlation of $\log P$ with permeability reported by Kasim et al. resulted in eight false negatives out of 25 predictions.

Yee suggests that compounds with permeabilities higher than 10×10^{-6} cm/s, determined by Caco-2 permeability assay at pH 6.5 may be classified *highly permeable*.⁹⁸ Quinidine permeability data found in the literature fail to meet this criterion (see Tab. 3). However, comparability of these data may suffer from differences in cell culture conditions.

Results from rat permeability studies showed a pH and concentration dependent permeability of quinidine.³⁸ At any one pH and concentration quinidine permeability was lower than permeability of the reference substance propranolol. Metoprolol, the usual reference substance, was not used in this study, but also the use of propranolol would lead to classifying quinidine as moderately, but not *highly permeable*.

Overall, the usefulness of the *in vitro* permeability data from cell culture and rat permeability studies to predict *in vivo* permeability of quinidine or other drug transporter substrates is questionable for several reasons. Differences in the expression of drug transporter in Caco-2 and rat intestine on the one side and human intestine on the other side, may exist. The expression pattern of drug transporters along the human GI-tract is not adequately represented by Caco-2 permeability measurements. GI-intestinal fluid content (e.g., bile salts) may effect drug transporter functionality, which has not yet been sufficiently investigated.

There is indirect evidence for almost complete absorption of quinidine, that is, only 5% quinidine recovery in feces after oral administration^{47,48} and it has been reported that the reduction in BA of an oral solution could be accounted for by first-pass extraction with the exception of some individuals. This would imply a fraction absorbed of 0.9 or higher in most patients. Nevertheless, the few exceptions indicate that in some individuals either permeability or GI stability were much lower or intestinal metabolism much higher than in others.

Classification of quinidine's permeability strictly according to the FDA biowaiver guidance is not feasible on the basis of the present literature data. For the classification of an API to be *highly permeable*, in principal the guideline allows the use of mass-balance studies; absolute BA studies; and *in vivo/in vitro* animal/cell culture models.

With respect to mass-balance studies: quinidine is metabolized in the liver and excreted by the kidneys to a variable extent. Therefore, for a real mass-balance study, intact drug and all metabolites would have to be quantified. We could not find adequate mass-balance studies in the literature.

With respect to absolute BA studies: the absolute BA of oral quinidine sulfate is about 70%, showing however large inter- and intraindividual variability. In the absence of data showing GI stability, FDA requests a BA of greater than 90% to grant a biowaiver. However, we could not find data on the GI stability of quinidine sulfate. Therefore, the 70% BA of quinidine alone is insufficient to qualify for a biowaiver. On the other side, it seems quite likely that quinidine is rather stable in the GI tract and there seems a consensus in the literature that the reduced systemic availability is due to first-pass metabolism.

With respect to *in vivo/in vitro* animal/cell culture models: Caco-2 cells and rat intestinal perfusion showed a lower permeability of quinidine in comparison with metoprolol/propranolol, classifying quinidine moderately but not highly permeable. Furthermore, permeability was concentration dependent and therefore nonlinear.³⁸ However, nonhuman permeability test methods are reliable surrogate techniques only for the estimation of the permeability of passively transported API, that is, not for quinidine.

According to a recent WHO proposal,² "An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose." Despite this relaxed BA criteria no clear conclusion can be drawn for the same reasons as discussed earlier in this section.

The EMEA criteria are less precise, only stating that "Linear and complete absorption indicating high permeability reduces the possibility of an immediate release dosage form influencing the bioavailability." However, on the basis of the literature data complete absorption has not been unequivocally shown.

In summary, literature data is inconclusive. Most data from *in vitro* studies suggest moderate to high permeability, while some indirect evidence from *in vivo* studies would suggest almost complete absorption and thus high permeability and hence quinidine cannot be unequivocally classified as *highly permeable* according to the guidances due to lack of appropriate *in vivo* data.

BCS Classification

BCS classification according to the FDA, WHO, and EMEA guidances is inconclusive in part due to a lack of adequate data on solubility but mainly due to inadequate data in the case of permeability. However, on the basis of the presented data, quinidine sulfate is most likely BCS III close to BCS I, or BCS I. The WHO technical report also concludes that data on quinidine sulfate is inconclusive with respect to permeability and that therefore quinidine should be classified BCS I or BCS III.² Wu and Benet⁹⁹ list quinidine as BCS I substance and using the disposition characteristics of the API as an estimate for its permeability, they assigned quinidine to Class I in a Biopharmaceutics Drug Disposition Classification System (BDDCS).

Risk of Excipient and/or Manufacturing to Cause Nonequivalence

No bioinequivalent drug products were identified, based on the acceptance interval of 0.8–1.25 for AUC and C_{max} ratios of test to reference products, hence the risk of excipient and/or manufacturing causing nonequivalence is probably low. However, for drugs with a narrow therapeutic range, narrower acceptance intervals may be imposed.⁴

Surrogate Techniques for *In Vivo* Bioequivalence Testing

As no nonequivalent drug products are reported, no solid data are available to evaluate the predictive power of *in vitro* technique, such as the comparative *in vitro* dissolution testing in three media. But drug products which dissolved to more than 85% within 30 min in 0.1 N HCl were found to be bioequivalent.⁷⁵ A study by Strum et al.^{76,93} with quinidine, using dissolution in 0.1 N HCl and the basket method at 25 rpm, concluded that values greater than 27 min for

50% release and disintegration times greater than 7 min result in decreased absorption rates, however, do not affect AUC or C_{\max} . Hence, rapid dissolution in 0.1 N HCl seems to achieve BE. However, *in vitro* dissolution testing addresses only disintegration/dissolution *in vivo*, but not permeability.

Another problem is the potential of a large difference in the content of dihydroquinidine between test product and comparator product. Dihydroquinidine itself is pharmacologically active, but it is not obvious that an *in vitro* test method that only estimates the sum of quinidine plus dihydroquinidine, such as *in vitro* dissolution testing with UV detection, is an acceptable BE methodology.

Patient's Risks Associated with Bioinequivalence

The US Code of Federal Regulations (CFR, 2005)¹⁰⁰ defines narrow therapeutic index (NTI) as “less than a two-fold difference in minimum toxic concentrations and minimum effective concentrations in the blood; and safe and effective use of the drug products requires careful dosage titration and patient monitoring.” This definition certainly applies to quinidine, since the safety margin between supposed therapeutic serum levels (2–6 $\mu\text{g/mL}$) and toxic serum levels (5–8 $\mu\text{g/mL}$) may be less than twofold. Therefore, the patient's risk associated with bioinequivalence is rather high, not so much with respect to t_{\max} as a difference in t_{\max} will not be decisive for quinidine therapy. However, a difference in AUC or C_{\max} poses a serious patient's risk. Drug products with a lower BA may result in ineffective treatment, while even worse, suprabioavailable drug products with respect to AUC or C_{\max} may increase adverse reactions and toxicity.

CONCLUSION

The risk for the occurrence of nonequivalent drug products is probably low and could be further reduced if a test drug product is known to contain only excipients supposed not to modify the permeability of quinidine. However, the solubility data are incomplete and the data on permeability based on *in vitro* models are not fully adequate for assessing *in vivo* permeability of quinidine, leading to an inconclusive BCS classification. Moreover, APIs with a narrow therapeutic index

are ineligible for biowaivers, as explicitly stated in the Guidances, as the patient's risks associated with a nonequivalent drug product are considered unacceptable.

Taking all aspects into account, a biowaiver based approval of new multisource IR solid oral products containing quinidine sulfate appears unsuitable and therefore the BE should be established with an *in vivo* BE study. For variations (postapproval changes) to existing products, an *in vivo* BE study is required only for major changes, which are defined in the respective regulatory documents. Here, too, a waiver of *in vivo* BE studies is not recommended for quinidine sulfate containing drug products.

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