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

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ABSTRACT: Literature data are reviewed relevant to the decision for a biowaiver of immediate release (IR) solid oral dosage forms containing metoclopramide hydrochloride. In addition, new solubility data, obtained under Biopharmaceutics Classification System (BCS) conditions are presented. Metoclopramide HCl is conservatively assigned to BCS Class III. Taken also into consideration excipient interactions reported in metoclopramide drug products, its pharmacokinetic properties and therapeutic use and therapeutic index, a biowaiver can be recommended when: (a) the test product contains only excipients present also in metoclopramide HCl containing IR solid oral drug products approved in ICH or associated countries, for instance as presented in this paper, (b) in amounts in normal use in IR solid oral dosage forms, and (c) the test product and the comparator both comply with the criteria for *very rapidly dissolving*. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3700–3708, 2008

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

INTRODUCTION

A biowaiver monograph of metoclopramide hydrochloride, based on literature data, together with additional, new experimental solubility data, is presented. The risks of basing a bioequivalence (BE) assessment on *in vitro* rather than *in vivo* study results for the approval of new immediate release (IR) solid oral dosage forms containing metoclopramide HCl ("biowaiving"), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. The purpose and scope of this series of monographs have been previously discussed.[1] Summarized in a few words, the aim is to evaluate all pertinent data

*A project of the International Pharmaceutical Federation FIP, Groupe BCS, www.fip.org/bcs.

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

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available from literature sources for a given active pharmaceutical ingredient (API) in the World Health Organization (WHO) List of Essential Medicines,[2] 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 risks. On the basis of these considerations, a recommendation is made as to whether a biowaiver is advisable or not. This systematic approach to recommend or advice against a biowaiver is referred to in the Annexes 7 and 8 of a recently published WHO report,[3,4] stating that these monographs provide detailed information which should be taken into account whenever available in the biowaiver consideration. It is pointed out that these monographs not simply apply this WHO Guideline, nor the FDA and/or EMEA Guidance, but also want to serve as a critical validation of these regulatory documents.

The details and progress of the project of writing these biowaiver monographs is available at www.fip.org/bcs. Biowaiver monographs have yet been published on acetaminophen (=INN: paracetamol),[5] amitriptyline,[6] atenolol,[1] chloroquine,[7] cimetidine,[8] ibuprofen,[9] isoniazide,[10] prednisone,[11] prednisolone,[12] propranolol,[1] ranitidine,[13] and verapamil.[1]

EXPERIMENTAL

Published information up to 01/2007 was obtained from PubMed, Medline, Embase, Biosis, Derwent Drugfile & SciSearch. Only literature written in English and German was included and the search was not limited to a certain time period. Keywords were: metoclopramide hydrochloride, pharmacokinetics, solubility, permeability, absorption, first pass metabolism, biowaiver, BCS, pharmacodynamics, interaction, therapeutic range, partition coefficient, and indication. Tertiary sources consulted were Martindale,[14] DrugDex,[15] Hager,[16] and the series of Florey.[17]

The solubility of metoclopramide hydrochloride monohydrate at 37°C was determined[1] in triplicate in 0.1 M HCl, corresponding to pH 1.02, and the USP buffers pH 4.5 and pH 6.8, shaken for 3 h by an overhead shaking device. The pH value was reassessed during testing and adjusted, if necessary. The obtained solutions were analyzed by HPLC. Also, the stability of metoclopramide HCl was determined in gastric fluid at pH 1.2 and in intestinal fluid pH 6.8. The investigations were performed at a temperature of 37°C over 1 h (gastric fluid) and 3 h (intestinal fluid). Recovery rates of 102% at pH 1.2 and 99% at pH 6.8, respectively, were observed, confirming metoclopramide to be stable throughout the whole GI pH range, in conformity with earlier reports.[17]

[1]Experiments performed at the laboratories of HEXAL AG, Holzkirchen, Germany.

GENERAL CHARACTERISTICS

Name

INN, metoclopramide; INNM, metoclopramide hydrochloride. The structure is shown in Figure 1.

Salt, Esters, Stereoisomers, Polymorphy

Metoclopramide exists as base, as monohydrochloride as well as dihydrochloride.[16] Only the monhydrochloride monohydrate is subject of this monograph. The Ph.Eur.[18] and the USP[19] both have monographs on the monohydrochloride monohydrate and both pharmacopoeias use the name metoclopramide hydrochloride for the monohydrochloride monohydrate. In this monograph we use the same terminology unless otherwise indicated.

Metoclopramide shows no stereochemistry. According to one source, metoclopramide hydrochloride exhibits polymorphism, one form being stable and the other form metastable.[20] No information was found concerning differences in bioavailability (BA) of different polymorphic forms and different crystalline structures.

Therapeutic Indication and Therapeutic Index

Metoclopramide is a centrally acting anti-emetic, stimulating the motility of the upper gastrointestinal (GI) tract and possessing parasympathomimetic activity. Therapeutic indications are

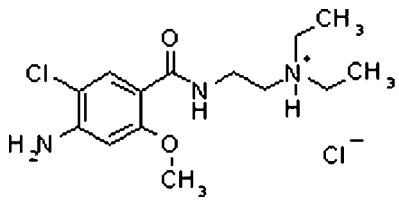

Figure 1. Structure of metoclopramide hydrochloride, M_w 336.3.

gastroparesis or ileus, gastro-oesophageal reflux disease, dyspepsia, nausea and vomiting during migraine or cancer therapy.[14] Its therapeutic range is from 1 mg for pediatric use to 40 mg for adults.[14] The total daily dosage should not exceed 500 μg/kg.[14] A tenfold accidental overdose induced methemoglobulinemia in infants.[21] Dosages of 10 and 4 mg/kg administered to children caused extrapyramidal reactions, supraventricular tachycardia, and atrioventricular block.[22,23] The LD_{50} for rats and mice is 86 and 71 mg/kg i.v., respectively.[17]

PHYSICOCHEMICAL PROPERTIES

Solubility

Metoclopramide hydrochloride is reported to be "highly soluble" in water with no indication of the temperature; presumably, room temperature was used.[14,19,24,25] The series of Florey[17] reports a solubility in water at 25°C, but without reporting the amount dissolvable. As these data do not conform to the conditions defined for BCS applications,[3,4,26,27] new experiments were carried out. The results are reported in Table 1.

Partition Coefficient

The series of Florey[17] reports at 20°C an experimental log*P* of 2.667 and a calculated log*P* of 2.76 in octanol/water. Another tertiary source reports values of log*P* octanol/water of 2.618 and 2.667 and a log*D* octanol/water pH 7.4 of 0.46.[28] Kasim et al.[24] calculated log*P* by different *in silico* methods and reported values of 1.48 (log*P*) and 2.23 (Clog*P*®).

pK_a

Metoclopramide HCl shows two ionization constants. For the primary aromatic amine a pK_a value of 0.42[17,28] is reported, for the tertiary aliphatic amine pK_a values of 9.71[17,28] and 9.36 are reported.[28]

Strength of Marketed Drug Products

The expression of the drug content in marketed drug product is confusing. The labeled strength of metoclopramide hydrochloride monohydrate containing drug products is usually expressed in the equivalents of anhydrous hydrochloride, but in the USA the strength is usually expressed in terms of the base.[14,29] In some countries both expressions are in use. For instance, in Germany (DE), MCP Sandoz® 10 mg tablets contain 10.53 mg metoclopramide hydrochloride monohydrate, that is, the equivalent of 10 mg metoclopramide hydrochloride anhydrous,[30] whereas MCP-ratiopharm® 10 tablets contain 11.82 mg metoclopramide hydrochloride monohydrate, that is, the equivalent of 10 mg metoclopramide base.[31] So, these two drug products, both with figure "10" in their brand name, suggesting the same strength, actually contain different amounts of the active principle. The current USP requires metoclopramide tablets to contain an amount of metoclopramide hydrochloride monohydrate equivalent to 90.0–110.0% of the labeled amount of metoclopramide base.[32] The

Table 1. Solubility of Metoclopramide Hydrochloride at 37°C and the Corresponding Dose/Solubility (D/S) Ratios for Different Tablet Strengths

		D/S Ratio (mL)			
		5 mg Tablet		10 mg Tablet[b]	
Medium	Solubility (mg/mL)[a]	Tablet Strength Expressed in mg HCl anh	Tablet Strength Expressed in mg base	Tablet Strength Expressed in mg HCl anh	Tablet Strength Expressed in mg base
0.1 M HCl	0.0483	104	116	207	232
Buffer pH 4.5	0.0473	106	119	211	237
Buffer pH 6.8	0.0423	118	133	236	265[c]

[a]The experiments were carried out with metoclopramide monohydrochloride monohydrate, but the results under solubility are expressed in mg HCl anh.
[b]Dose recommended by WHO.[2]
[c]Above the critical limit of 250 mL.[3,4,27,28]

WHO recommends for oral administration: "tablet, 10 mg (hydrochloride)",[2] most probably meant as: anhydrous hydrochloride.[2] Single API dosage forms with a MA in DE,[33] Denmark (DK),[34] Finland (FI),[35] France (FR),[36] The Netherlands (NL),[37] Norway (NO),[38] and Sweden (SE)[39] also all contain 10 mg. In DE, there are MAs existing for 10 mg IR oral formulations.[33] In the USA, single API dosage forms of 5 and 10 mg exist, mainly expressed in terms of the base, but in some cases the hydrochloride dose equivalent is used.[29]

PHARMACOKINETIC PROPERTIES

Absorption and Permeability

Peak plasma concentrations of metoclopramide occur about 1–2 h after an oral dose.[14] Oral BA values in the range 60–90% are reported.[28] Another source reports the BA of oral metoclopramide to be about 75%, but varying between approx 30% and 100%.[14] Other sources report values of 51% (standard deviation: 31%),[40] 32–97%,[41] 77%,[42] and 68% (standard deviation: 13%).[43] This wide range in BA has been attributed to the interindividual variable first-pass effect.[42,44–46] No data on fraction of dose absorbed, that is, before the first-pass elimination, could be identified. Metoclopramide shows linear kinetics over oral doses ranging from 5 to 20 mg.[47] Studies with ^{14}C-labelled metoclopramide in rats and dogs and humans show that the drug is distributed within a few min after oral administration and is eliminated mainly in the urine of the first 24 h.[15] After oral administration metoclopramide is rapidly absorbed.[44] Maximum peak plasma concentration are reached after approximately 1 h.[44] Metabolism occurs rapidly after administration, indicating a high first-pass-effect.[42,44–46] About 5% of a dose is excreted in faces via the bile, indicating a high permeability of the administered drug substance; the main proportion of the dose is excreted in the urine, of which 20–30% is unchanged.[14] Metoclopramide is conjugated with sulfuronic- and/or glucuronic acid, however, the major urinary metabolite is metoclopramide-*N*-4-sulfate.[41,45,46] According to Rao et al.[48] pharmacokinetic parameters are significantly different between males and females. No results of *in vitro* transport studies in Caco-2 or other cell culture systems could be identified and no information about the intestinal absorption mechanism of the drug substance was found.

[2]When in the WHO Essential Medicines List the strength of a medicine is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as" (Kopp S, personal communication).

DOSAGE FORM PERFORMANCE

Excipients and Manufacturing Variations: Interactions on Bioavailability

El-Sayed et al.[49] demonstrated *in vivo* BE of a tablet formulation versus Plasil®. The study was carried out in 18 healthy male volunteers using a randomized balanced 2-way crossover design. Pharmacokinetic parameters estimated were C_{max}, AUC $_{\text{up to the last measurable concentration}}$ and $AUC_{0\rightarrow\infty}$. The 90% confidence intervals of the mean values of each of these three pharmacokinetic parameters were all within the range of 0.8–1.25 and the relative AUC of the new formulation was 104% with respect to the reference product. Neither the composition of the two drug products nor dissolution results were reported. The two preparations were considered bioequivalent and hence interchangeable.[49]

Honkanen et al.[50] compared hydroxypropylmethylcellulose (HPMC) and classic hard gelatin capsules, both containing metoclopramide HCl mixed with lactose. After oral administration, the absorption in terms of AUC and C_{max} of metoclopramide was quite similar and no statistically significant differences could be detected. The time to peak absorption (t_{max}) was significantly shorter for the HPMC capsules compared to the gelatin ones, the difference being about 23 min. In contrast, the *in vitro* dissolution of the gelatin capsules was faster than the *in vitro* dissolution of the HPMC capsules. As t_{max} is not considered a BE criterion, the authors concluded that the two capsules investigated can be regarded as interchangeable.

Table 2 shows the excipients used in IR metoclopramide HCl tablets having a MA in DE, DK, FI, FR, NL, NO, and SE. In view of these MAs, it is reasonable to expect that these formulations successfully passed an *in vivo* BE study, and hence these excipients do not exert an influence on the BA when present in amounts in normal use in solid oral dosage forms. However, in DE, drug products containing metoclopramide were exempted for some years from *in vivo* BE studies;[51,52] this exemption ended in 2003.[53] In

Table 2. Excipients[a] Present in Metoclopramide Hydrochloride IR Solid Oral Drug Products with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO) and Sweden (SE), and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a MA in the USA[b]

Excipient	Drug Products Containing that Excipient with a MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with a MA in the USA (mg)
Calcium hydrogen phosphate	DE (1)	104–850
Cellulose	DE (2-7) DK (8,9) FI (10,11) FR (12-14) NL (15,16) NO (17,18) SE (19)	4.6–1385[c]
Copovidone	DE (20)	357–854
Croscarmellose sodium	NL (21)	2–180
Gelatin	DE (2,22)	1–756[c]
Lactose	DE (1-4,6,7,20,22) DK (9) FI (11) FR (12-14) NL (15,21,23) NO (18) SE (19)	23–1020[c]
Magnesium stearate	DE (1,3-7,20,22,24) DK (8,9) FI (11) FR (12-14) NL (15,16,21,23) NO (17,18) SE (19)	0.15–401[c]
Mannitol	NL (16) NO (17)	10–454
Methylcellulose	DE (24)	2.8–184
Povidone	NL (16)	0.17–75
Silica	DE (1,2,5,22) DK (8,9) FI (11) FR (12-14) NL (15,16,23) NO (18) SE (19)	0.65–99
Sodium lauryl sulfate	DE (3,4,6,7)	0.65–50
Sodium starch glycolate	DE (1)	2–876[c]
Sodium stearyl fumarate	FI (10)	1.2–24
Starch	DE (1,3-7,20,22,24) DK (8,9) FI (11) FR (12-14) NL (15,23) NO (17,18) SE (19)	0.44–1135[c]
Starch, pregelatinized	NL (23)	6.6–600
Talc	DE (2) DK (8) NO (17)	0.26–220[c]

(1) MCP HEXAL® 10 Tabletten (Mono).
(2) Gastronerton® Kapseln (Mono).
(3) MCP 10 von ct Tabletten (Mono).
(4) MCP AL 10 Tabletten (Mono).
(5) MCP-ratiopharm® 10 Tabletten (Mono).
(6) MCP Sandoz® 10 mg Tabletten (Mono).
(7) MCP STADA® Tabletten (Mono).
(8) Emperal, tabletter 10 mg.
(9) Primperan, tabletter 10 mg.
(10) METOPRAM® 10 mg-tabletti.
(11) Primperan 10 mg tabletti.
(12) METOCLOPRAMIDE MERCK 10 mg cp séc.
(13) METOCLOPRAMIDE SANDOZ 10 mg Cpr séc.
(14) PRIMPERAN 10 mg cp séc.
(15) Primperan tabletten, tabletten 10 mg.
(16) Metoclopramide HCl 10 PCH, tabletten 10 mg.
(17) Afipran.
(18) Primperan 10 mg tabletter.
(19) Primperan 10 mg tabletter.
(20) Gastronerton® Tabletten (Mono).
(21) Metoclopramide HCl CF 10 mg, tabletten.
(22) Cerucal® Tabletten (Mono).
(23) Metoclopramidemonohydrochloride 10 mg, tabletten.
(24) Paspertin® Filmtabletten (Mono).

[a]Colorants, flavors and ingredients present in the coating and/or the printing ink are not included.

[b]Sources of data: DE, www.rote-liste.de (assessed 27-10-2006); DK, www.dkma.dk (assessed 27-10-2006); FI, www.nam.fi (assessed 27-10-2006); FR, www.vidal.fr (assessed 27-10-2006); NL, www.cbg-meb.nl (assessed 27-10-2006); NO, www.legemiddelverket.no (assessed 27-10-2006); SE, www.lakemedelsverket.se (assessed 27-10-2006); USA, http://www.fda.gov/cder/iig/iigfaqweb.htm#purpose (version date 03-10-2006).

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

NL, such a list still exists for national MA applications;[54] but in NL metoclopramide was and is not exempted from *in vivo* BE.

Dissolution

The current USP specification for *in vitro* dissolution requires not less than 75% (Q) of metoclopramide being dissolved within 30 min in 900 mL purified water at 50 rpm using the basket apparatus.[32]

DISCUSSION

Solubility

According to the FDA Guidance,[26] an API is *highly soluble* when at 37°C the highest tablet strength is soluble in less than 250 mL over the pH range of 1–7.5, whereas the EU[27] and the WHO[3,4] define a pH range of 1–6.8. Metoclopramide hydrochloride meets the criteria of the two latter, more recent Guidances. When the highest tablet strength is expressed in mg base, the D/S quotient marginally passes the critical limit of 250 mL, but when the highest tablet strength is expressed as metoclopramide hydrochloride anhydrous it falls slightly above the limit, see Table 1. Since the critical volume of 250 mL is considered conservative[55] and it has been suggested to increase the volume for solubility classification to 500 mL,[56] we believe it is reasonable to regard metoclopramide HCl as *highly soluble*.

Absorption and Permeability

According to the FDA Guidance, an API is *highly permeable* when the extent of absorption is 90% or more.[26] The EU Guidance only states that linear and complete absorption indicate high permeability,[27] whereas the recent WHO Proposal to waive *in vivo* BE requirements considers an API to be *highly permeable* when that API is absorbed to an extent of 85% or more.[3,4] Taking a conservative approach, we conclude that there is insufficient evidence to classify this API as *highly permeable*.

BCS Classification

Lindenberg et al.[25] used literature sources for their permeability classification based on BA data but found these data to be inconclusive and consequently classified metoclopramide as BCS Class I/III. Using an *in-silico* approach, Kasim et al.[24] classified metoclopramide using two different estimated lipophilicity values comparable to metoprolol. Using the log*P* approach, metoclopramide was classified as BCS Class III, whereas the Clog*P*® approach classified metoclopramide as BCS Class I.

A slightly modified classification system was proposed by Wu and Benet,[57] in their Biopharmaceutics Drug Disposition Classification System (BDDCS), a system using the disposition characteristics of an API as estimate for its GI permeability. As criteria for a waiver of *in vivo* BE under BDDCS were proposed, in addition to the solubility criterion: $\geq$70% metabolism, or, alternatively, $\geq$50% metabolism. Using the latter criterion, metoclopramide was classified as BDDCS Class III.[57]

We provisionally classify metoclopramide hydrochloride as BCS Class III.

Risks with Respect to Excipients and/or Manufacturing Variations

Not a single *in vivo* study was identified reporting bio*in*equivalence of drug products tested. So, the risk of bio*in*equivalence of metoclopramide HCl IR dosage forms seems low. Moreover, when a test product is formulated with only excipients present in metoclopramide HCl IR solid oral drug products approved in ICH or associated countries, for instance as shown in Table 2, the risk of bio*in*equivalence due to an excipient interaction is further reduced. Moreover, a recent survey showed that most commonly used excipients in solid dosage forms have no significant effect on absorption and hence there is no reason to believe that drug products formulated with those excipients would not be bioequivalent.[56] Some experts consider BCS Class III APIs even more suitable for biowaiving than APIs BCS Class I.[58,59]

Surrogate Techniques for *In Vivo* Bioequivalence Testing

Bio*in*equivalence of formulations caused by differences in disintegration and/or dissolution *in vivo* are unlikely for this *highly soluble* API. Requiring that the test and comparator drug product both are *very rapidly dissolving*, that is, dissolve not less than 85% of the labeled amount in 15 min, using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of

900 mL in the three BCS media,[3,4] will further reduce the risks of bio*in*equivalence.

Up to now, there exists no *in vitro* test to detect bio*in*equivalence caused by differences in permeability and/or GI transit time. Such causes of bio*in*equivalence must be excluded by considerations with respect to the excipients present in the test product.

Patient's Risks Associated with Bio*in*equivalence

The risk of bio*in*equivalence of metoclopramide HCl IR solid oral dosage forms in general seems to be low. Moreover, if the test product is formulated only with excipients also present in metoclopramide HCl containing IR solid oral drug products approved in ICH or associated countries, shown in Table 2, the risk of bio*in*equivalence is further reduced. The risk to accept a bio*in*equivalent drug product is further decreased if the test product and the comparator drug product both comply with the criteria for *very rapidly dissolving*.[3,4]

But in the very unlikely case that a bio*in*equivalent drug product, fulfilling all criteria mentioned above, would pass, then the consequences for the patient need to be considered. Rapid onset of action will not be essential, so, bio*in*equivalence with respect to C_{max} will likely be without serious consequences for the patient. This also holds for bio*in*equivalence with respect to AUC, as registered drug products containing 10.53 and 11.82 mg metoclopramide HCl monohydrate apparently are considered therapeutically equivalent, see the Strength of Marketed Drug Products Section. Hence the metoclopramide dose–response curve is not steep. Indeed, metoclopramide is not considered a narrow therapeutic index drug and is not used for life threatening indications.

Metoclopramide stimulates the motility in the upper GI tract and it could be questioned if that would have consequences for the biowaiver decision and/or the tolerance limits for dissolution testing in context of biowaivers. However, dissolution testing in context of biowaivers is an equivalence test; the test drug product and the comparator contain the same API. So, bio*in*equivalence can only be an effect of differences in the formulation and/or the physico-chemical properties of the API. It is not conceivable how the pharmacological effect of stimulation of the upper GI tract by metoclopramide could be subject to such effects. Also, when *in vivo* BE testing for metoclopramide drug products is used, not special equivalence limits are in use. So, there is no reason to do so when another methodology for BE testing, that is, *in vitro* BE testing, is used.

CONCLUSIONS

A biowaiver can be recommended for IR solid oral dosage provided that (a) the test product contains only excipients present in metoclopramide HCl IR solid oral drug products approved in ICH or associated countries, for instance as presented in Table 2, and (b) the excipients in the test product are present in amounts in normal use in IR solid oral dosage forms, for instance as presented in Table 2, and (c) the test product and the comparator drug product both comply with the criteria for *very rapidly dissolving* according to the WHO Guidance, that is, 85% or more dissolution of the labeled amount of the API within 15 min in standard media pH 1.2, 4.5, and 6.8, using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm.[3,4]

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