COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System (BCS) Literature Data: Verapamil Hydrochloride, Propranolol Hydrochloride, and Atenolol

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ABSTRACT: Literature data related to the Biopharmaceutics Classification System (BCS) are presented on verapamil hydrochloride, propranolol hydrochloride, and atenolol in the form of BCS-monographs. Data on the qualitative composition of immediate release (IR) tablets containing these active substances with a Marketing Authorization (MA) in the Netherlands (NL) are also provided; in view of these MA's the assumption was made that these tablets were bioequivalent to the innovator product. The development of a database with BCS-related data is announced by the International Pharmaceutical Federation (FIP). © 2004 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 93:1945–1956, 2004

Keywords: BCS; biowaiver; verapamil; propranolol; atenolol

INTRODUCTION

In recent years the necessity to provide a scientific basis for biowaivers for individual substances has met considerable interest. A biowaiver implies that bioequivalence (BE) assessment studies are waived for marketing authorizations (MA) by Health Authorities for a new tablet or capsule, or a new formulation of an existing immediate release (IR) dosage form, and hence the product is considered bioequivalent to its reference product, without carrying out a BE study. In this case the comparative *in vitro* study assures BE of the test product. The scientific basis for this work was

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

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developed by Amidon et al.[1] and is known as the Biopharmaceutics Classification System (BCS). The BCS states that three major factors govern the rate and extent of drug absorption of IR solid oral dosage forms: dissolution rate, solubility, and intestinal permeability. For IR dosage forms containing active pharmaceutical ingredients (APIs) showing high solubility, high intestinal permeability, and rapid dissolution a waiver from performing BE studies (biowaiver) can be scientifically justified.

In the regulatory domain this is adopted by both the FDA and the European CPMP in their Guidance for Industry: Waiver of *In Vivo* Bioavailability (BA) and BE Studies for Immediate-Release Solid Oral Dosage Forms Based on a BCS,[2] and the Note for Guidance on the Investigation of BA and BE,[3] respectively, together referred to as the Guidances. In particular the FDA document describes in detail the data that are necessary for a successful application for a biowaiver.

When a set of BCS-data for an API is established and could be made publicly available in the form of a monograph, this monograph could be referred to by subsequent applicants for biowaivers of other IR oral dosage forms with the same API without the need for reestablishing the data. Such a publicly available BCS-monograph is also of interest for Official Medicines Control Laboratories (OMCL's), which want to translate their dissolution test data into terms of the BA of the tested IR solid oral dosage forms.

To explore the scope and the possibilities of gathering BCS related data from scientific literature, and in order to set up such BCS-monographs, a literature search was carried out on verapamil hydrochloride, propranolol hydrochloride, and atenolol.

EXPERIMENTAL

Both chemical–pharmaceutical and pharmacokinetic BCS-related information on three substances, verapamil hydrochloride, propranolol hydrochloride, and atenolol, was obtained by means of a literature search. The following datafields were defined in order to standardize the dataset: indication, solubility, dissolution, polymorphism, partition coefficient, pK_a, available dose, permeability, stereospecificity, pharmacokinetic properties. In addition, the qualitative composition of IR tablets having an MA in the Netherlands (NL) was included.

The present article summarizes and discusses the main features obtained from the literature search.

RESULTS AND DISCUSSION

A literature search was performed in electronically available databases. The search performed included information from the Merck Index, the Dictionary of Substances and their Effects, the Hazardous Substances Data Bank, Medline, Toxline and Embase. Only literature published in the last 10 years and written in English or German was included. When searching for dissolution and solubility data, two problems occurred. The search resulted in a large number of hits so that a detailed study of all references on relevant data was considered to be too time consuming, and secondly almost all literature was related to modified release dosage forms. Therefore, the decision was made to use, in general, only data obtained form standard reference books like the United States Pharmacopeia (USP) and European Pharmacopoeia (EP).

For data on permeability the literature search was performed in the same way as described above, limiting the keywords to permeability and related to permeability, and the drug substance name. The outcome of the search was satisfactory and sufficient. Relevant literature on all three substances was obtained in this way.

It is known that dissolution and permeability of an API can be influenced by excipients in the solid oral dosage forms. In order to gather insight of possible excipient interactions tablet compositions of generic formulations registered in NL were examined. The qualitative composition of the IR tablets containing one of the three active substances was obtained from the publicly available Summary of Product Characteristics (SmPC). The SmPC's can be obtained from the website of the Medicines Evaluation Board in NL at www.cbg-meb.nl. Only the excipients used in the tablet cores were considered since we made the assumption that the tablet coating for an IR tablet will be of very limited influence on the dissolution properties of the tablet.

The International Pharmaceutical Federation (FIP) will post these monographs on its website at www.fip.org. Additional information will be published and discussed in the form of Addenda to these monographs. The corresponding author of this article can be contacted for any contribution.

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The BCS-monographs of each of the three substances are presented and discussed separately.

VERAPAMIL HYDROCHLORIDE

Indication

Verapamil hydrochloride is a well-known calcium antagonist. It is used in the treatment of angina pectoris, supraventricular arrhythmia's, and hypertension.[4]

Solubility

Soluble (1 g dissolves in 10–30 mL).[5]
Water 7 g/100 g (21°C, pH = 4.24).[6]

The Analytical profiles of drug substances, (Volume 17)[7] contain a profile for verapamil hydrochloride. The solubility of verapamil hydrochloride as a function of the pH is shown in Table 1.

Polymorphism

No reference to polymorphic forms was found.

Partition Coefficient

Kasim et al.[8] calculated *n*-octanol/water partition coefficients using different fragmentation methods that were based on atomic contributions to lipophilicity; for uncharged verapamil, log *p* values of 4.47 and 5.69 were reported.

Table 1. Solubility of Verapamil Hydrochloride

Solvent[a]	Solubility (mg/mL)
Water, pH 2.32	82
Water, pH 3.05	78
Water, pH 4.65	89
Water, pH 4.86	82
Water, pH 5.59	76
Water, pH 6.35	83
Water, pH 6.54	46
Water, pH 6.59	29
Water, pH 6.76	11
Water, pH 7.32	0.44
Water, pH 8.09	0.17
Water, pH 8.87	0.062
0.1 N NaOH, pH 12.6	0.025

[a]A 0.1 N NaOH solution and a 0.1 N HCl solution were used for adjustment of the pH.

pK_a

A pK_a of 8.6,[8] and a range 8.6–8.9, respectively, were reported.[9]

Available Dose/Tablet

Strengths currently having an MA in NL: 40, 80, and 120 mg.

Permeability

The permeability data found for verapamil are summarized in Table 2.

Stereospecificy

After oral administration of a mixture of R- and S-verapamil, plasma concentrations of the R-isomer were substantially higher than those of the S-isomer, suggesting stereospecific first-pass metabolism.[4,15]

Pharmacokinetic Properties

Absorption

Oral absorption of labeled ^{14}C-verapamil in man averaged over 90%. The absolute BA is 10–20%, indicating extensive first-pass metabolism.[4,16] Peak plasma concentrations are reached within 1–2 h after administration of a single dose.[17,18] Pharmacokinetics shows a large inter-individual variability.[19]

Food intake prolonged the time to peak concentration, but no effect was observed on C_{max} and area under the curve (AUC) of both isomers.[20]

Distribution

The apparent volume of distribution of verapamil is about 2.5 L/kg. Protein binding is moderate (90%),[4] not concentration dependent over the range of 10–2000 ng/mL[16] and similar for both enantiomers.[21] Verapamil binding to red blood cells is low.[22]

Metabolism and Excretion

Verapamil is extensively metabolized in the liver, primarily by *N*-dealkylation and *O*-demethylation. Nor-verapamil is the only active metabolite formed. Further metabolism results in the forming of several metabolites that are excreted as inactive conjugates. There is a wide interpatient variation in verapamil metabolism consistent

Table 2. Permeability of Verapamil

Substance	P_{eff} ($\times 10^{-6}$ cm/s)	Method Used	Reference
Verapamil	519	Caco-2	10
R-verapamil 4 mg/mL	271 (200–341)[a]		
R-verapamil 40 mg/mL	474 (334–613)[a]		
S-verapamil 4 mg/mL	225 (171–279)[a]	Intestinal perfusion technique	11
S-verapamil 40 mg/mL	469 (311–627)[a]		
Verapamil	670 ± 290	Intestinal perfusion technique	12
R-verapamil 120 mg/mL	556 ± 197	Intestinal perfusion technique	13
S-verapamil 120 mg/mL	562 ± 205		
R-verapamil 400 mg/mL	500	Intestinal perfusion technique	14
S-verapamil 400 mg/mL	500		

[a]95% confidence interval; concentrations are concentrations of the racemate.

with the fact that verapamil undergoes extensive first-pass extraction. Urinary and fecal excretion account for about 70 and 15%, respectively, of verapamil over 5 days. An average of 3% of the parent drug is recovered unchanged in the urine. The elimination half-life is about 4–5 h, and is similar for the R- and S-isomer.[23]

Excipients

A number of different excipients are used in the manufacturing of IR verapamil hydrochloride tablets. The excipients used in the formulation of the core of the IR tablets having an MA in NL are summarized in Table 3.

Dissolution

The USP 26 specification for verapamil hydrochloride tablets is not less than (NLT) 75% (Q) dissolved in 30 min in 900 mL 0.01 N HCl, using the paddle method operated at 50 rpm.[24]

Table 3. Excipients Used in Verapamil Hydrochloride Immediate Release (IR) Tablets in the Netherlands (NL)

Carboxymethylcellulose sodium
Cellulose (microcrystalline)
Colloidal anhydrous silica
Croscarmellose sodium
Furcelleran[a]
Gelatine
Lactose anhydrate/monohydrate
Magnesium stearate
Maize starch
Potato starch
Povidone
Pregelatinized (maize) starch
Sodium lauryl sulfate
Sodium starch glycollate
Talc

[a]Furcelleran is also known as Danish Agar or Danagar.

DISCUSSION

Solubility

The solubility values observed are critical at a pH at or above 6.76. When the current solubility criteria of the Guidances for the highest dose strength (120 mg) in 250 mL or less of aqueous media over the pH range of 1–7.5[2] or 8.0,[3] are strictly applied, verapamil hydrochloride fails to meet these criteria. At pH 7.32 the solubility is about equivalent to the minimally required solubility of 0.48 mg/mL (120 mg/250 mL). At higher pH values the solubility will be below the minimal limit of 0.48 mg/mL. However, since the major fraction of the drug substance will be absorbed in the upper part of the gastrointestinal (GI) tract where the pH value will normally be below 7.3 the limited solubility at high pH values is considered to be of no concern. This is also supported by a recent proposal to narrow the required pH range for sufficient solubility from pH 1.0–7.5 to pH 1.0–6.8.[25]

Dissolution

The requirements of the USP 26 differ from the stricter and more extensive requirements of the Guidances. They serve however a different purpose. The criteria defined by the Guidances aim to assure BE with a reference product, in the context of a regulatory decision, while the USP criteria define the attributes for an acceptable article. In the preface of the USP 24[26] the goal of the method was described, which was essentially: to set

standards for "clinically acceptable articles" by defining a dissolution method that is sufficiently discriminating so that both BA and quality control is covered. This paragraph was deleted starting with the USP 25, but it seems safe to assume that the USP 26 still aims at clinically sufficient BA, which is less strict than bioequivalent towards a reference product. For verapamil hydrochloride tablets the USP 26 prescribes 900 mL of 0.01 N HCl as dissolution medium. Given the limited solubility at higher pH values of this API, testing at a pH of 6.8–7.5 seems more discriminative. However, the solubility of this API will not be the limiting factor at this pH-range. The decisive factor for the BA of an IR solid dosage form with this API will be the dissolution rate. This parameter is suitably controlled by the USP 26 method, which makes it highly likely that an insufficient dissolution from the formulation will be detected. So, the practice to carry out the batch to batch dissolution testing according to USP 26 once a formulation has been shown to be bioequivalent to the reference formulation by a BE study or by comparative dissolution studies is supported by the BCS-characteristics of this API.

Intestinal Permeability

In the Guidances the term "highly permeable" is used for substances whose absorption in humans from an orally administered dose is 90% or more. The work of Amidon et al.[1] has demonstrated that the limit for absorption of >90% corresponded with a permeability $>2.10^{-4}$ cm/s (Attachment A of the Guidance for Industry[2]).

On the basis of the data presented in Table 2 verapamil can be considered as a highly permeable drug substance.

Verapamil is passively transported and is a substrate for P-gp. The effect of P-gp on verapamil absorption is low, due to the high permeability of the drug. At high doses the efflux-mediated mechanism by P-gp becomes saturated and therefore effective permeability (P_{eff}) increases.[11] No difference in P_{eff} is observed between R- and S-verapamil.

Permeability values obtained *in vivo* by the intestinal perfusion technique were comparable with the P_{eff} obtained by Caco-2 cell line studies. Permeability values of verapamil, obtained from a correlation of partition coefficients versus intestinal permeability, also suggest a high permability of verapamil.[8]

The observed high permeability of verapamil is in line with the reported oral absorption of about 90%. The presence of an absorption window cannot be ruled out from the literature data reviewed here but the postulated mechanism of the permeability of verapamil, being passive transport, makes such an absorption window unlikely.

In the IR verapamil hydrochloride tables which have an MA in NL, and hence are assumed to be bioequivalent to the innovator's product, a wide range of excipients are used (see Table 3). This provides evidence that for the usual pharmaceutical excipients no effect on the extent (and rate) of absorption is to be expected. However, it should be kept in mind that this holds only for excipient amounts which are normally used in IR tablet formulations. In addition, for highly soluble and highly permeable drug substances, formulated into IR tablets with known excipients, it has been reported that no excipient interaction in the rate and extent of absorption is to be expected.[2]

In conclusion, when the criteria of the Guidances are strictly applied, verapamil hydrochloride is a BCS Class II substance and this API can not be considered a candidate for granting a biowaiver. However, this API is clearly on the borderline, the only problematic area is the insufficient solubility between pH 7.3 and 8.0. *In vivo* the limited solubility in this pH interval will not be problematic. This means that the solubility boundaries for this API should be redefined to for instance 1.0–6.8, as is recently suggested in general.[25] In a provisional classification of the WHO Essential Drugs, verapamil was classified to be BCS Class I.[8] So, from a scientific point of view, verapamil hydrochloride is a candidate for granting a biowaiver when the IR tablets are formulated with well-known excipients, show rapid *in vitro* dissolution, and meet the dissolution profile comparison criteria as defined in the Guidances, but with a redefined upper boundary for the pH of 6.8. The USP 26 criteria and method are suitable to assure batch to batch consistency.

PROPRANOLOL HYDROCHLORIDE

Indication

Propranolol hydrochloride is a well-known nonselective β-blocker, which is used in the management of angina pectoris, hypertension myocardial infarction, phaeochromocytoma, and cardiac arrhythmia's.[4]

Solubility

Soluble (1 g dissolves in 10–30 mL) in water.[5,6]

Polymorphism

Propranolol hydrochloride is known to have two polymorphic forms.[9]

Partition Coefficient

Kasim et al.[8] calculated *n*-octanol/water partition coefficients using different fragmentation methods that were based on atomic contributions to lipophilicity; for uncharged propranolol, log *p* values of 2.75 and 2.65 were reported.

pK_a

A pK_a range of 9.03–9.09 was reported.[9]

Available Dose/Tablet

Strengths currently having a MA in NL: 10, 40, and 80 mg.

Permeability

The permeability data found for propranolol are summarized in Table 4.

Pharmacokinetic Properties

Absorption

Propranolol is almost completely absorbed after oral administration (>90%). Peak plasma concentrations are reached within 1–2 h after administration of a single dose. The absolute BA varies between 5 and 50%, due to a high pre-systemic metabolism. As a result, the BA and plasma levels show a large inter-individual variability.[36–38]

The presence of an absorption window cannot be ruled out from the data reviewed here but the postulated mechanism of the permeability of propranolol: passive transport driven by the strong lipophilic nature of the substance, makes the existence of such an absorption window unlikely.

Distribution

Propranolol is rather rapidly distributed over tissues. It is highly lipophilic and moderately bound to plasma proteins (80–95%), mainly to α-1 acid glycoprotein. The distribution volume is about 4 L/kg. Studies in animals showed that propranolol is distributed into the lungs, liver, kidneys, brain, and the heart.[37–39]

Metabolism and Excretion

Propranolol is almost completely metabolized in the liver. Only a small portion of the administered dose is excreted unchanged in urine and feces (1–4%). The main metabolites are naphtoxyl acetic acid (42%), 4-hydroxypropranolol (41%), and propranolol-*O*-glucuronide (17%). 4-hydroxy-propranolol is pharmacologically active and is equipotent to the parent drug. However, due to rapid conjugation, the contribution to the pharmacological effect is low. The main metabolites are metabolized by cytochrome P450. Propranolol and its metabolites are mainly excreted in urine (>90%). The elimination half-life is about 4 h.[36–40]

Excipients

The excipients used in the formulation of the core of the IR tablets having an MA in NL are summarized in Table 5.

Table 4. Permeability of Propranolol

P_{eff} ($\times 10^{-6}$ cm/s)	Method Used	Reference
43.0 ± 3.6	Caco-2	27
41.9 ± 4.3	Caco-2	28
41.9	Caco-2	29
11.2 ± 0.5	Caco-2	30
30.1 ± 1.2	Caco-2 (pH 7.2)	31
5.45 ± 0.08	Caco-2 (pH 5.4)	31
34.4 ± 2.3	Caco-2	32
34.7 ± 3.0	TC-7	32
35.3 ± 9.7	Caco-2	33
280 ± 130	Intestinal perfusion technique	34
667 ± 342	Intestinal perfusion technique	35
290 ± 220	Intestinal perfusion technique	33

Table 5. Excipients Used in Propranolol Hydrochloride IR Tablets in NL

Calcium carbonate
Carboxymethylcellulose sodium
Cellulose (microcrystalline)
Colloidal anhydrous silica
Croscarmellose sodium
Gelatine
Lactose anhydrate/monohydrate
Magnesium stearate
Maize starch
Potato starch
Povidone
Pregelatinized (maize) starch
Sodium carboxyamylopectin
Sodium starch glycollate
Soluble starch
Stearic acid
Talc

Dissolution

The USP 26 specification for dissolution of propranolol hydrochloride tablets is NLT 75% (Q) dissolved in 30 min in 1000 mL of dilute HCl using the basket method operated at 100 rpm.

DISCUSSION

Solubility

The pK_a value of propranolol is about 9.05. At a pH of 7.2, it is reported that propranolol is highly soluble. Therefore, solubility will not be the rate-limiting step in the absorption process of propranolol from the GI tract.

Dissolution

The differences in purpose between the dissolution tests of the Guidances and the USP were discussed under "verapamil hydrochloride." For propranolol hydrochloride solubility within the physiological pH is not critical, so the dissolution rate of the formulation will be the decisive factor for BA of this API. The USP 26 dissolution method, using dilute HCl as dissolution medium, can be expected to control insufficient dissolution from the formulation. So, the practice to carry out the batch to batch dissolution testing according to USP 26 once a formulation has been shown to be bioequivalent to the reference formulation by a BE study or by comparative dissolution studies is supported by the BCS-characteristics of this API.

Intestinal Permeability

Using the Caco-2 cell lines, comparable permeability values were found (see Table 4). At a pH of 5.4 permeability decreases at the apical (i.e., the luminal) site,[41] but still takes place although the unionized fraction is very small (this is also the case at a pH of 7.2). This is probably due to the fact that the paracellular route represents a relatively small fraction of accessible area of the cell monolayer. Beside this, propranolol is lipophilic enough to take advantage of the large surface area for transcellular permeation.[31] Using a different cell line, TC-7 (which is a clone of Caco-2, displaying increased tauro-cholic acid transport) similar P_{eff} values were obtained.[32]

Adding plasma to the basolateral chamber does not influence the P_{eff} of propranolol, due to its high lipophilicity. However, propranolol is avidly bound to plasma protein, and this resulted in a significant decrease of the exsorption (from basolateral to apical) of propranolol.[33]

Permeability values obtained *in vivo* by the intestinal perfusion technique were about 10–20-fold higher than obtained by Caco-2. This difference is less than observed for atenolol (see further, up to 500-fold). As propranolol is a highly lipophilic drug, and transported transcellularly, factors influencing permeability *in vitro* versus *in vivo* will be less pronounced or even lacking.

The high permeability of propranolol is in line with the reported high oral absorption of more than 90%.

Given the high permeability of propranolol, it is considered unlikely that excipients should have an effect on the permeability and hence have an influence on the rate and extent of absorption, provided that rapid and complete dissolution over the physiological pH-range has been demonstrated. This is substantiated for the excipients of the IR tablets which have an MA in NL as listed in Table 5.

In conclusion, according to the criteria of the Guidances, propranolol hydrochloride is a BCS Class I substance. In a provisional classification of the WHO Essential Drugs, this API was also classified to be BCS Class I.[8] So, from a scientific point of view this API is a candidate for granting a biowaiver when the IR tablets are formulated with well-known excipients, show rapid *in vitro* dissolution, and meet the dissolution profile comparison criteria as defined in the Guidances. The USP 26 criteria and method are suitable to assure batch to batch consistency.

ATENOLOL

Indication

Atenolol is a cardio selective β-blocker, widely used in the management of hypertension, angina pectoris, cardiac arrhythmia's, and myocardial infarction.[4]

Solubility

Sparingly[5] (1 g dissolves in 3–100 mL) to slightly[6,42] (1 g dissolves in 100–1000 mL) soluble in water.

3.13 g/100 mL in 0.2 M NaCl/0.2 M HCl at pH = 1.2[43] and 2.48 g/100 mL in 0.2 M KH_2PO_4/0.2 M NaOH at pH = 7.4.[43]

Polymorphism

No reference to polymorphic forms was found.

Partition Coefficient

Partition coefficients of 0.008 at pH 7.0 and 0.052 at pH 8.0 (*n*-octanol/phosphate buffer (0.16 M)) were reported.[6,42] Kasim et al.[8] calculated *n*-octanol/water partition coefficients using different fragmentation methods that were based on atomic contributions to lipophilicity; log *p* values of −0.11 and 0.50 were reported.

pK_a

A pK_a value of 9.6 was reported.[6,8,42]

Available Dose/Tablet

Strengths currently having an MA in NL: 25, 50, and 100 mg.

Permeability

The permeability data found for atenolol are summarized in Table 6.

Pharmacokinetic Properties

Absorption

Following oral administration about 46–62% of a radio-labeled dose is absorbed.[4] Peak plasma concentrations are reached within 2–4 h after administration of a single dose.[4] Atenolol plasma concentrations increase proportionally to the dose. In BA studies in healthy subjects in which the AUC after orally and intravenously administration of atenolol was compared, an absolute BA of 40–60% was reported. Since only 10% of an intravenous dose, but about 50% of an oral dose is excreted in the feces, biliary excretion appears to be minimal and the limited BA is thus probably due to incomplete absorption.[51–54] Stereoselective oral BA has been indicated, as it has been observed that the amount excreted unchanged in the urine, the AUC and the peak concentrations differed between the enantiomers.[55] Food intake significantly shortened the time to peak concentration and also caused a significant reduction in the AUC values (about 20%), while the elimination half-life remained essentially unaffected.[56]

Distribution

Atenolol is relatively widely distributed, with an apparent volume of distribution of 50–75 L. Protein binding is low and in the range of 6–16%.[54]

Metabolism and Excretion

Atenolol is mainly excreted unchanged in urine in man.[4] Small amounts of the glucuronide metabo-

Table 6. Permeability Data of Atenolol

P_{eff} ($\times 10^{-6}$ cm/s)	Method Used	Reference
0.051 ± 0.012	Caco-2	44
0.13 ± 0.012	Caco-2	30
0.13 ± 0.01	Caco-2	45
0.19 ± 0.02	Caco-2	45
0.20 ± 0.01	Caco-2	27
0.20 ± 0.004	Caco-2	28
0.47	Caco-2	46
0.57	Caco-2	10
3.7 ± 1.3	Caco-2	47
14 ± 18 (range 0.00–50.0)	Intestinal perfusion technique	48
15	Intestinal perfusion technique	49
27 ± 20	Intestinal perfusion technique	50

Table 7. Excipients Used in Atenolol IR Tablets in NL

Calcium hydrogen phosphate dihydrate
Cellulose (microcrystalline)
Colloidal anhydrous silica
Croscarmellose sodium
Crospovidone
Gelatine
Hydroxypropylcellulose
Hypromellose
Lactose anhydrate/monohydrate
Magnesium carbonate light and/or heavy
Magnesium stearate
Maize starch
Povidone
Pregelatinized (maize) starch
Sodium lauryl sulfate
Sodium starch glycollate
Talc
Vegetable oil hydrogenated

lite (*ca*. 2%) and of the non-conjugated hydroxylated metabolite (2–3% of the ^{14}C-labeled dose after oral administration and 5.8% after i.v. administration) have been reported in the urine of healthy subjects.

Excretion is essentially complete after 48 h after administration of a single dose.[56] The total body clearance of atenolol is about 100 mL/min/1.73 m^2 and the elimination half-life is 6–9 h.[57]

Excipients

The excipients used in the formulation of the core of generic IR atenolol tablets marketed in NL are summarized in Table 7.

Dissolution

The USP 26 specification for dissolution of atenolol tablets is NLT 80% (Q) dissolved in 30 min in 900 mL acetate buffer pH 4.6, using the paddle method operated at 50 rpm.[24]

DISCUSSION

Solubility

Atenolol with a pK_a value of 9.6 is expected to be sufficiently soluble under physiological conditions. The highest tablet strength dissolves in about 25 mL of water at pH 7.4. "Highly soluble" according to the Guidance for Industry[2] is defined as the highest dose dissolvable in 250 mL or less. Based on the limited information available with regard to atenolol solubility at different pH's, the solubility of atenolol is not expected to be the rate-limiting step in the absorption of atenolol from the GI tract.

Dissolution

The differences in purpose between the dissolution tests of the Guidances and the USP were discussed under "verapamil hydrochloride." For atenolol solubility within the physiological pH range is not critical, so the dissolution rate of the formulation will be the decisive factor for BA of this API. The USP 26 dissolution method, using 900 mL acetate buffer pH 4.6 as dissolution medium, can be expected control insufficient dissolution from the formulation. So, the practice to carry out the batch to batch dissolution testing according to USP 26 once a formulation has been shown to be bioequivalent to the reference formulation by a BE study or by comparative dissolution studies is supported by the BCS-characteristics of this API.

Intestinal Permeability

On the basis of the data in Table 6, in accordance with the definition of permeability in the Guidances, atenolol can be considered as a low permeable drug substance.

The Caco-2 cell drug transport studies showed comparable permeability values. A value of about 3.7×10^{-6} cm/s was found by Rubas et al.[47] that was significantly higher than those values reported by the other groups. The cause of this high permeability value is not clear from the report.

Permeability values obtained *in vivo* by the intestinal perfusion technique were up to 500-fold higher than those obtained by Caco-2. Factors that may explain the observed difference are: firstly, atenolol is a hydrophilic drug that is transported via the paracellular route through tight junctions. A higher permeability observed in the intestinal perfusion technique may be due to a lower paracellular transport and/or a larger area available for absorption *in vivo* in humans, as it is assumed that the absorption of hydrophilic compounds is so slow that a larger surface area of the intervillous space is exposed.[48,49] Secondly, the intestine has mucus producing goblet cells, which influence the tight junctions. When Caco-2 cells

are mixed with mucus producing cells (HT29-MTX), permeability of atenolol increased.[30] When mucus-producing cells were used instead of Caco-2, permeability increased up to 30-fold.[45] Thirdly, differences in extracellular Ca^{++}-concentrations can lead to a change in the integrity of the cell structures, thereby causing a change in the paracellular permeability of atenolol. It has been reported that by lowering the (free) extracellular Ca^{++}-concentration, the permeability of atenolol increased about 7-fold.[27] Finally, cell tissue of intestine has a transepithelial electrical resistance (TEER) of 50–100 $\Omega \cdot cm^2$.[46] Caco-2 cell lines have a TEER of >200–300 $\Omega \cdot cm^2$. Atenolol, having a low permeability and being paracellularly transported, the higher TEER of Caco-2 cells may contribute to the lower permeability when compared to intestinal cell tissue.

The data obtained with the intestinal perfusion technique are in reasonable agreement. On the average, a value of 2.10^{-5} cm/s is found, demonstrating that the permeability of atenolol is low.

The low permeability of atenolol is in line with the reported moderate oral absorption of about 50%.

In the IR atenolol tables which have an MA in NL, and hence are bioequivalent to the innovator's product, a wide range of excipients is used (see Table 7). This provides evidence that for the usual pharmaceutical excipients no effect on the extent (and rate) of absorption is to be expected. However, it should be kept in mind that this holds only for excipient amounts which are normally used in IR tablet formulations. Probably for atenolol the low permeability is not so critical with regard to excipient interaction.

In conclusion, the Guidances only describe the possibility of a biowaiver for Class I substances. From the data obtained, atenolol is indicated as a BCS Class III substance. In a provisional classification of the WHO Essential Drugs, this API was also classified to be BCS Class III.[8] However, we conclude that atenolol might be a candidate for a biowaiver, as excipient interaction appeared not to be critical with regard to the absorption of atenolol, provided that tablets are formulated with well-known excipients as listed in Table 7, show rapid *in vitro* dissolution, and meet the dissolution profile comparison criteria as defined in the Guidances. Class III substances have also been reported as candidates for biowaivers by other authors.[25,58] The USP 26 criteria and method can be used to assure batch to batch consistency.

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