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Research paper

# Biopharmaceutical characterization of sotalol-containing oral immediate release drug products

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**Abstract**

The objective of this study was replacing an in vivo bioequivalence study by generating suitable in vitro data in order to get generic marketing authorisation. Solubility and permeability of sotalol hydrochloride were determined thereby achieving classification of this compound according to the biopharmaceutical classification system. In addition comparative investigation of in vitro dissolution properties of different Sota-saar® formulations and the reference product provided satisfying justification to waive in vivo bioavailability (BA)/bioequivalence (BE) studies. The investigations on solubility were performed considering the highest dose strength in aqueous media (250 ml) with pH conditions between pH 1.0 and 7.5. Permeability was studied using the human colorectal carcinoma cell line Caco-2. In vitro as well as in vivo data suggest high permeability of the drug compound through the intestinal membrane. Thus, evaluation of solubility and permeability allow sotalol hydrochloride to be classified as biopharmaceutics classification system class I drug. In vitro dissolution profiles demonstrate comparable rapid dissolution (more than 85% in 15 min) for test and reference products. Summarizing, relevant prerequisites are fulfilled to waive BA/BE studies.


*Keywords:* Sotalol HCl; Biopharmaceutics classification system; Dissolution; Solubility; Permeability; Caco-2

## 1. Introduction

The investigation of bioequivalence is an essential prerequisite to claim the same efficacy of a generic finished medicinal product as already proven and registered with the originator product or with regard to changes in the manufacturing process to show that the efficacy has not been altered. In addition, besides original clinical studies also toxicological original data can be replaced by an adequate demonstration of bioequivalence of the generic being essentially similar with the originator product in abridged applications for marketing authorisations. Therefore, bioequivalence data play a fundamental role within the administrative licensing process. In general, these investigations are associated with time-consuming and expensive phase I clinical studies.

Current US-FDA as well as European guidances describe definite prerequisites to waive in vivo bioequivalence studies considering basic principles of the Biopharmaceutics Classification System (BCS) [1–3]. Provided that also pharmacokinetic/pharmacodynamic prerequisites are fulfilled, the guidances allow to prove bioequivalence to the reference by means of sound, scientifically justified in vitro data. Accordingly, based on their solubility and permeability active ingredients are divided in four categories. For drug products containing active substances classified into BCS class 1 (high solubility and permeability) rapid dissolution ensures the absence of any limitation for the active to become systemically available after oral administration. This approach is in accordance to protect clinical trial subjects and reduce repetitive tests provided they are scientifically not necessary.

Sotalol was originally marketed as β-adrenoceptor antagonist, however, it belongs to the group of antiarrhythmic agents with combined class II and III properties. Though sotalol is the most hydrophilic compound of

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the homologous series of β-blocking agents it is reported to be almost completely absorbed with peak plasma concentrations occurring between 2 and 3 h after oral administration in humans [4].

In the present work it could be shown how to prove bioequivalence by means of appropriate in vitro experiments. The respective results had been submitted to the German regulatory authority (Bundesinstitut für Arzneimittel und Medizinprodukte-BfArM, Bonn) as a substitute for an in vivo bioequivalence study in order to get a marketing authorization for the generic product. It had been approved by BfArM on the basis of the modified CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) [2,3].

## 2. Experimental

### 2.1. Materials

The batches included in the comparative investigation of dissolution behaviour were: Sota-saar® 80 Chephasaar lot numbers 16709 and 17114 (product A); Sota-saar® 160 Chephasaar lot numbers 16718 and 17487 (product B); Sotalex® mite 80 Bristol-Myers Squibb lot numbers 1B03336 and 1C0341 (product C, innovator); Sotalex® 160 Bristol-Myers Squibb lot numbers 1B0104 and 1B0105 (product D, innovator).

All reagents used for dissolution experiments were of analytical grade and were purchased from Merck, Darmstadt. These experiments were performed at MiP International Pharma Research GmbH.

Investigation of solubility and permeability including Caco-2 cell culturing were performed based on valid standard operation procedures at the facilities of the Zentrallaboratorium Deutscher Apotheker with sotalol hydrochloride provided by Chephasaar, St Ingbert. All buffer constituents (NaCl, NaOH, $CH_3COOH$, HCl, *o*-$H_3PO4$, $NaH_2PO_4 \times 2H_2O$) used for solubility experiments were of analytical grade and were purchased from Merck, Darmstadt.

Regarding Caco-2 routine culturing, mycoplasma free, certified cells were obtained from ATCC (American Type Culture Collection) and were cultivated at 37 °C with 10% $CO_2$ in a humidified atmosphere. The culture medium consisted of DMEM (high glucose 4.5 g/l), supplemented with 1% non-essential amino acids (MEM), 50 mg/l gentamycin and 10% fetal calf serum. Items were purchased from Biochrom, Berlin. The medium was to be replaced on a regular schedule three times a week. Cells were passaged by trypsinization once a week definitely before reaching 90% confluency. For cell maintenance the cells were transferred into new culture flasks (approximately $0.1–1 \times 10^6$ cells per 75 $cm^2$ flask) after trypsinization. Cells were to be plated in 12 well Transwell® plates on polycarbonate filters (1.13 $cm^2$ area, 0.4 μm pore size, Corning Costar™) at a density of approximately $6 \times 10^4$ cells/$cm^2$. The medium volume was 0.5 and 1.5 ml in the apical and the basolateral compartment, respectively. Passage numbers of the Caco-2 cells used for the experiments were between 45 and 67.

### 2.2. Methods

#### 2.2.1. Solubility determination

Solubility of sotalol hydrochloride in media of different pH (pH 1.0, 4.5, 6.8 and 7.5) was investigated solubilizing the highest single unit dose strength (160 mg) in 250 ml at an experimental temperature of 37 °C. Three hours after incubation the drug concentration in solutions were determined by means of HPLC.

#### 2.2.2. Permeability of sotalol

The transwell plates were agitated on a plate shaker at 37 °C throughout transport experiments. Solutions of the drug compound were prewarmed to 37 °C for the transport studies. The pH of the drug solutions and transport buffer (HBSS = Hank's balanced salt solution) was to be adjusted to 6.5 and 7.4, respectively, using either 0.1 N NaOH or 0.1 N HCl if necessary. The drug concentration was 1.0 and 2.0 mM considering single doses of 80 and 160 mg, respectively, dissolved in a total volume of 250 ml.

After rinsing the monolayers with transport buffer, TEER (transepithelial electrical resistance) was determined during pre-incubation of the cells in order to verify the integrity of the monolayer. The pre-incubation buffer was to be replaced by the (clear) drug solution and pure buffer in the apical and basolateral compartment, respectively, or vice versa depending on the intended transport direction. Relating to physiological conditions the pH of the apical chamber was proven to be 6.5 and that of the basolateral chamber (representing the luminal side) was 7.4. After sampling the total volume of the chamber was replaced by drug solution. Samples of 0.5–1 ml were to be taken every 15 min for not more than 45 min, TEER measurements were to be done in blank buffer immediately after drug transport investigations. The total duration of the permeability experiments was less than 2 h, TEER values had to reach 250 $cm^2$ as a minimum. Samples were analysed employing a validated HPLC method.

Apparent permeability coefficients ($P_{app}$[cm/s $\times 10^{-6}$]) were calculated according to the following equation:

$$P_{app} = V/(A \times \mathrm{Co})\mathrm{d}C/\mathrm{d}t$$

$V$ = volume in the receiver chamber
$A$ = filter surface area
Co = initial concentration
D$C$/d$t$ = initial slope of the concentration vs. time curve

Permeability results were evaluated considering in-house permeability results used as 'internal standards' according to Ref. [1] (data not shown), as well as considering correlations published in literature.

*2.2.3. In vitro dissolution of the active agent*

Based on the paddle method the dissolution behaviour of the sotalol-containing film-coated tablets was studied in three different aqueous dissolution media. The media 0.1 N HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8 were prepared as described in the European Pharmacopoeia [5].

*2.2.3.1. Test conditions*. Apparatus: Pharma Test PTW S with six measuring sites and microprocessor control (Pharma Test GmbH, Germany). Rotation speed: 75 rpm. Temperature: 37 ± 1 °C. Dissolution medium volume: 500 ml. Sampling time: 2, 5, 8, 12, 15 and 20 min. Sample volume: 2 ml (replaced by blank buffer).

Measurement: by HPLC with UV detection at 228 nm. Column: LiChrospher® 100 RP18 (Merck KGaA Darmstadt, Germany). Eluent: 79 volumes of aqueous Sodium octanesulfonate solution (2 g/l) and 21 volumes of acetonitrile (pH 3.0 adjusted with $H_3PO_4$). Flow: 1.5 ml/min. Column temperature: 35 °C.

The analytical method inclusive of the stability of sotalol in test solutions was validated considering ICH recommendations for the validation of analytical methods [6].

From the assay data, the amounts of sotalol dissolved were calculated. The results are presented as the average of 12 individual tablets in percent of the declared sotalol content of the tablets.

## 3. Results and discussion

### *3.1. Solubility*

Solubility of sotalol was investigated considering the main aspects of the BCS concept outlined in current guideline recommendations [1–3]. Accordingly, solubility of the highest dose strength (160 mg) is ensured in 250 ml aqueous buffer solution at pH 1, 4.5, 6.8, and 7.5.

### *3.2. Permeability through the Caco-2 monolayers*

Permeability of sotalol has been investigated by means of the Caco-2 cell culture under different conditions in order to get various information regarding the transport properties of the compound. Results are outlined in Table 1.

The experimental concentrations of 1.0 and 2.0 mM were chosen considering single unit doses of 80 and 160 mg sotalol, respectively, administered as immediate oral dosage forms with 250 ml liquid volume. The influence of pH conditions was investigated during screening by transport experiments using pH 6.5 and 7.4 in the apical chamber, respectively. There was almost no impact of pH on permeability of the compound (data not shown), however, all transport experiments were performed considering the physiological pH of 6.5 in the apical chamber that represents the luminal (absorptive) site.

Considering the correlation established by Yee [7] results of the apical to basolateral transport of sotalol at physiological temperature suggest intermediate permeability of the compound. However, sotalol is known to be hydrophilic which is characterized by a partition coefficient (calc. log *P*) of 0.37 [4]. Hydrophilic compounds usually use the paracellular rather than the transcellular pathway through intestinal membranes as they lack lipophilic properties necessary to penetrate the cell membrane [8,9]. The paracellular pathway of the Caco-2 monolayer was shown to be much more restrictive than rat or human small intestine which is expressed by higher TEER and low permeability of hydrophilic marker compounds [8–13]. As a consequence, opening of the tight junctions that are controlling the paracellular pathway would lead to higher permeability coefficients. Accordingly, high permeability ($P_{app}$ : $10.6 \times 10^{-6}$ cm/s) was determined after 30 min pre-incubation with verapamil [14]. In addition, the concomitant transport of sotalol with taurocholate resulted in higher permeability coefficients. In contrast, $P_{app}$ of propanolol employed as a lipophilic marker

Table 1
Permeability of sotalol through the Caco-2 monolayer

| Transport conditions | Mean apparent coefficient of permeability $P_{app}$ ($10^{-6}$ cm/s) | | |
|---|---|---|---|
| | Low (0 − 1) | Intermediate[a] (1–10), high (>1[b]) | High (>10) |
| 0.5 mM, 37 °C (apical → basolateral) | | 2.61 ($n = 3$) | |
| 1.0 mM, 37 °C (apical → basolateral) | | 2.86 ($n = 4$), 2.81 ($n = 6$) | |
| 2.0 mM, 37 °C (apical → basolateral) | | 2.91 ($n = 3$) | |
| 1.0 mM, 4 °C (apical → basolateral) | | 1.92 ($n = 4$) | |
| 1.0 mM, 37 °C (basolateral → apical) | | 3.85 ($n = 3$) | |
| 1.0 mM, 37 °C after verapamil pre-incubation (apical → basolateral) | | | 10.5 ($n = 3$) |
| 1.0 mM, 37 °C +4% albumin (apical → basolateral) | | 3.4 ($n = 4$) | |
| 1.0 mM, 37 °C + 1 mM verapamil (apical → basolateral) | | 2.82 ($n = 4$) | |
| 1.0 mM, 37 °C + 10 mM taurocholate (apical → basolateral) | | | 21.38 ($n = 4$) |

[a] Experimental definition.
[b] Correlation according to Artursson [8].

for the transcellular pathway was markedly reduced when concomitantly transported with taurocholate (data not shown) [15]. Hence, high permeability of the drug compound is concluded from the present findings which corresponds to literature information about almost complete absorption of sotalol in humans after oral administration [16–19].

Additional experiments were performed in order to characterize transport characteristics of the drug substance. Transport experiments with different drug concentrations resulted in essentially similar $P_{app}$ values (2.61 (0.5 mM), 2.86 (1 mM) [$10^{-6}$ cm/s]) indicating the absence of any saturable mechanism during the absorption process. Permeability coefficient derived from the transport at 4 °C was almost unchanged suggesting no contribution of any active transport mechanism in the present model.

The result of the concomitant transport of sotalol with albumin in the secretive direction (b → a) indicates plasma binding of the drug compound to be irrelevant [19] which also reflects literature data stating that sotalol is not bound to plasma proteins [16].

Verapamil is known to act as a substrate and inhibitor for the *p*-glycoprotein efflux pump. Hence, permeability of sotalol was investigated using the drug compound concomitantly with verapamil in order to evaluate whether the efflux mechanism might contribute to sotalol transport properties. The resulting $P_{app}$ of $2.8 \times 10^{-6}$ cm/s as well as the similar results of the apical to basolateral transport and the vice versa permeation indicate *p*-glycoprotein certainly not being involved in the permeation process of sotalol through the Caco-2 monolayer.

Summarizing, the Caco-2 cell culture is an appropriate model for permeability investigations of the compound revealing rather good permeation through the cell monolayer.

### *3.3. Classification of sotalol based on solubility and permeability according to the BCS concept*

Lipophilicity is regarded as probably determining for many pharmacokinetic properties of β-blocking drugs [20,21]. Sotalol may be considered the most hydrophilic compound belonging to the homologous group of β-blocking agents as opposed to propranolol which is generally known as highly lipophilic β-blocking drug [20,21]. Though high lipophilicity is often related to high absorption in vivo, the small and hydrophilic sotalol molecule (MW 272) was proven to be also rapidly absorbed through the gastrointestinal membrane leading to absolute bioavailability of >90% in humans [16–18].

Experiments on permeability by means of the Caco-2 model indicate major contribution of passive paracellular transport for sotalol unlike the lipophilic compound propranolol which is predominantly subject to transcellular transport through the gastrointestinal membrane. In addition, in humans neither binding of sotalol to plasma proteins nor metabolism related non-linearity (absence of any first pass metabolism) is evident with pharmacokinetic properties of the compound [22]. Sotalol does not accumulate in lipophilic tissue and is primarily eliminated unchanged via the renal route [23].

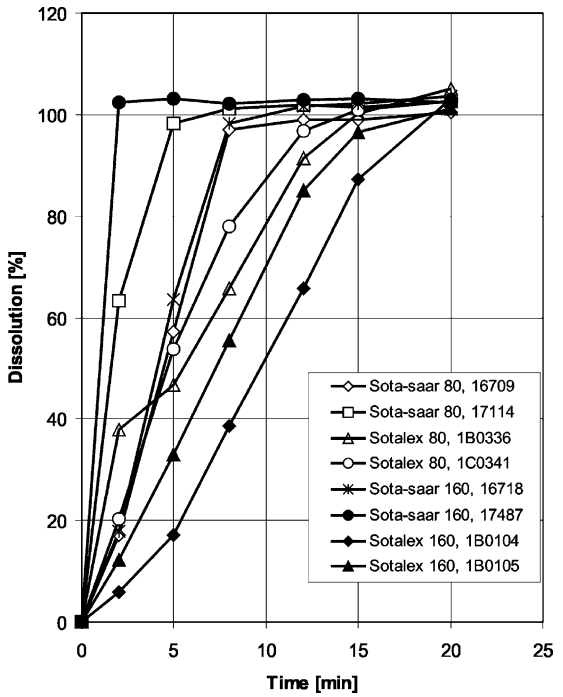


Fig. 1. Dissolution profiles of different batches of the finished products in dissolution media at pH 1.0 (mean values of 12 tablets each).

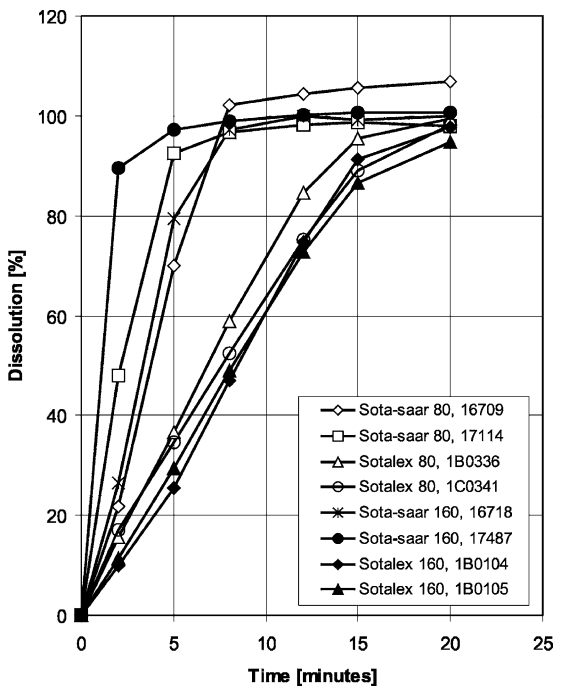


Fig. 2. Dissolution profiles of different batches of the finished products in dissolution media at pH 4.5 (mean values of 12 tablets each).

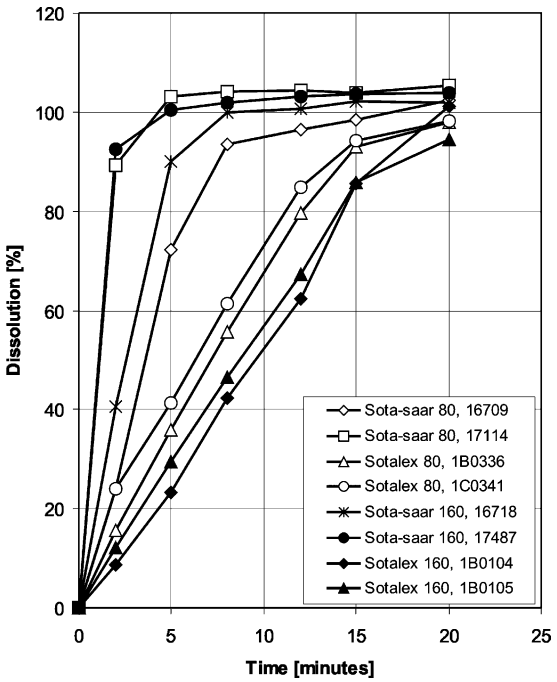


Fig. 3. Dissolution profiles of different batches of the finished products in dissolution media at pH 6.8 (mean values of 12 tablets each).

It is stated that D-sotalol and rac-sotalol exhibit similar pharmacokinetic properties [18]. Pharmacokinetic properties are not modified by longterm treatment [23].

Summarising, sotalol may be classified a BCS class I drug exhibiting high solubility and high permeability according to the BCS concept. Hence, bioequivalence of immediate release drug products containing sotalol may be sufficiently ensured by means of appropriate in vitro dissolution results generated under pH conditions relevant for the gastrointestinal tract, i.e. pH 1.0, 4.5, and 6.8.

### 3.4. In vitro dissolution

The results of the investigation of in vitro dissolution are shown in Figs. 1–3 in dependency of the pH values of the dissolution media. For each batch 12 tablets were investigated and the line of best fit was calculated from all individual values.

No significant differences occur between the different strengths of the respective products within the investigative period of 20 min. All Sota-saar® batches exhibit a dissolution rate exceeding 90% after 8 min in all investigative media. The two strengths of Sotalex® show a slightly slower dissolution behaviour though 85% of the declarated amount were released within 15 min. There was no pH related effect on dissolution rate.

Rapid dissolution was proven for all investigative products according to guidance recommendations [1,2] since 85% of the labelled amount of the active ingredient are released within 30 min. However, as dissolution rate exceeded 85% within 15 min in all cases no further statistical evaluation is necessary to prove similarity [1–3].

Rather slight differences between the originator and the generic are considered not relevant, since in the present case bioavailability is not controlled by dissolution. Due to the fact that gastric residence time is 15–20 min under fasting conditions slight dissolution differences within the first 15 min do not affect absorption of the active ingredient. In this case the rate limiting step of drug absorption is gastric emptying.

The excipients used in the tablets of the generic (Table 2) are well established in the manufacture of solid oral dosage forms of medicinal products. Within the formulation they were used in commonly used amounts [24] as filler, binder, disintegrant, lubricant and flow promoter. Considering the influence of these on the absorption of the active ingredient, special attention must be paid to the filler mannitol which amounts to about 50% of the total tablet weight. Mannitol accelerates the small intestine transit time at concentrations of above 0.755 g per 200 ml. Adkin et al. [25] concluded that small concentrations of mannitol included in a pharmaceutical formulation could therefore lead to reduced uptake of any drug exclusively absorbed from small intestine. In the investigated case the concentration of mannitol is below 1/3 of the above-mentioned concentration and it is not likely that mannitol affects the small intestine transit. Furthermore there was no evidence in literature that sotalol is absorbed only in the small intestine.

Table 2
Qualitative composition of the products

| Product A | Product B | Product C | Product D |
|---|---|---|---|
| Sotalol hydrochloride | Sotalol hydrochloride | Sotalol hydrochloride | Sotalol hydrochloride |
| Mannitol | Mannitol | Maize starch | Maize starch |
| Microcrystalline cellulose | Microcrystalline cellulose | Magnesium stearate | Magnesium stearate |
| Crospovidone | Crospovidone | Maize swelling starch | Maize swelling starch |
| Talc | Talc | Calcium hydrogene phosphate | Cellulose |
| Magnesium stearate | Magnesium stearate | Talc | Indigo carmine lake (E132) |

## 4. Conclusion

Sotalol hydrochloride was classified as BCS class I drug substances exhibiting high solubility and high permeability as defined in respective guidances [1–3]. Similarity of dissolution profiles of the originator and the generic drug product is demonstrated with in vitro dissolution of more than 85% within 15 min.

These results were reported together with additional information to the active ingredient and the finished medicinal product in the framework of an BCS-documentation as stipulated by Moeller [26] to the German regulatory authority (BfArM, Bonn) who—as far as to our knowledge—for the first time accepted and approved those data to substitute bioequivalence in vivo studies by in vitro data.

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