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Comparison of Drug Release From Metoprolol Modified Release Dosage Forms in Single Buffer versus a pH-Gradient Dissolution Test

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Introduction

Metoprolol is a cardioselective beta blocker that has been classified as a class I substance according to the Biopharmaceutics Classification Scheme BCS [1], meaning that it is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the whole intestinal tract [2-4] but is subject to extensive first-pass metabolism resulting in incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentrations occur after about 1-2 hours. The drug is eliminated within 3 to 4 hours, which, depending on therapeutic intention, makes it necessary to administer simple formulations of metoprolol up to 4 times daily [5]. Based on these properties and the well-defined relationship between the beta-blocking effect and plasma drug concentration [6], metoprolol lends itself to an extended-release (ER) formulation. Metoprolol ER formulations smooth out peaks and valleys in the plasma levels and enable less frequent dosing. Dosing intervals are typically reduced to once or twice a day.

Several types of metoprolol ER formulations are available internationally at the time of writing. "Conventional" ER formulations of metoprolol are single-unit, coated dosage forms (tablets) containing metoprolol tartrate, which is highly soluble. These formulations have been the standard medication for hypertension and angina pectoris in Germany for many years. In 1990 Belok-Zok®, a different type of ER formulation, was released by AstraZeneca. This formulation consists of a tablet that rapidly disintegrates, releasing micropellets with a diameter of ~0.5 mm that contain metoprolol succinate. Like the tartrate, metoprolol succinate is highly soluble. Each of the pellets is designed to act as a diffusion cell that delivers the drug at a relatively constant rate, essentially relatively independent of physiological variations within the GI tract [6].

In 2001 an alternative zero order kinetics (ZOK) formulation was approved for the German market. This consists of a matrix tablet in which metoprolol tartrate is embedded. Hence, to date, there are basically three different types of ER metoprolol formulations available that are registered for equal therapeutic objectives on the German market.

Within the last years, especially in Germany, substitution of innovator products coming off patent by generics has become common practice. However, if substitution is only based on dosage strength without recognizing differences in formulation that could affect rate and/or extent of release, this could place the patient at unnecessary risk.

Based on these considerations, the present study was undertaken to assess the interchangeability of the various ER metoprolol tartrate and succinate dosage forms on the basis of their in vitro dissolution characteristics.

Recent pharmacopoeial test methods for metoprolol ER formulations prescribe the use of USP Apparatus 1 or 2 and simple dissolution media like SGFsp pH 1.2 or phosphate buffer pH 6.8 [7]. Such methods may be useful for quality control purposes in terms of batch-to-batch conformity. However, they do not comprehensively reflect conditions to which a dosage form moving through the human GI tract will be exposed and therefore cannot be used to predict drug release during the course of GI passage. In view of the properties of metoprolol and the release mechanisms of the various formulations on the market, it was deemed both necessary and sufficient to establish a simple pH-gradient method with elements of standard methods such as these described in the USP, but additionally reflecting the changing pH conditions as the dosage form proceeds through the human GI tract, in order to predict any differences in in vivo performance.

Materials and methods

Materials

Metoprolol tartrate salt (lot # 41K1098) standard substance was purchased from SIGMA-Aldrich GmbH, Steinheim, Germany. All other compounds were purchased commercially. The different drug formulations were kindly donated by their manufacturers or purchased commercially. The formulations that were studied are listed in Table 1.

At first glance, it appears that the two categories of "novel" ER formulations are not interchangeable as they contain different amounts of drug. However, these different amounts result from the different molecular weights of the two metoprolol salts (succinate and tartrate). Thus, 95 mg metoprolol succinate corresponds to 100 mg metoprolol tartrate, as both contain 78 mg metoprolol.

Experiments with USP Apparatus 2

In a first step, drug release was characterized using the paddle apparatus and 900 mL of SIFsp pH 6.8 as the test medium. A stirring speed of 100 rpm was used to detect

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Table 1: Formulations studied

Brand Name	Manufacturer	Batch	Unit dose (mg)
"Conventional" formulations: coated single unit dosage forms			
Azumetop® retard 200 mg	Azupharma	# 93032	200
Meprolol® 200 mg Retard	TAD Pharma	# 2010175	200
Metoprolol AL 200 retard	Aliud® Pharma	# 94803	200
Metroprolol-retard ratiopharm® 200	Ratiopharm	# B 00067	200
Meto-Tablinen® retard	Pharmaceutica	# 54000037	200
metodura® retard	MerckDura	# 72595 A	200
"Novel" formulations: multiparticulates			
Beloc-Zok® mite	AstraZeneca	# CM88331A4	47.5
Beloc-Zok®	AstraZeneca	# CM9298A3	95
Beloc-Zok® forte	AstraZeneca	# CM1044A1	190
"Novel" formulations: matrix tablets			
metodra® Z 50 mg retard	MerckDura	# 7322A	50
metodra® Z 100 mg retard	MerckDura	# 73216A	100
metodra® Z 200 mg retard	MerckDura	# 73220A	200
Metoprolol-ratiopharm® O.K. 100	Ratiopharm	# A06404	100
Metoprolol-ZK AL 100 retard	Aliud® Pharma	# 15001	100

Table 2: Media and residence times used to simulate gastrointestinal passage in the fasted state

GI section	Passage time	Medium	pH
Stomach	60 min	SGFsp USP 24	1.8
Proximal jejunum	15 min	Phosphate buffer Ph. Eur. 1997	6.5
Distal jejunum	15 min	SIFsp USP 24	6.8
Proximal ileum	30 min	Phosphate buffer Ph. Eur. 1997	7.2
Distal ileum	120 min	SIFsp USP 23	7.5
Proximal colon	600 (240+360) min	Phosphate buffer	6.5
Distal colon	600 (360+240) min	SIFsp USP 24	6.8

erosion-derived changes in drug release rates that may possibly occur at higher shear rates. Samples (5 mL) were periodically withdrawn up to 24 hours using a glass syringe. The samples were immediately filtered through a 0.45-µm Teflon filter, and the drug concentration was measured with the UV spectrophotometer using a wavelength of 273 nm. All studies were performed in triplicate.

Experiments with USP Apparatus 3

The first step was to assess apparatus effects on release profiles. The paddle system was compared to USP Apparatus 3 (BioDis®) by testing release from the dosage forms in SIFsp pH 6.8. Based on observations made during paddle experiments, none of the metoprolol ER formulations included in the present study exhibited a pure erosion-

controlled drug release. Hence, the instrument parameters were selected on the basis of two series of tests by Rohrs et al. [8] and Klein [9], who described adequate instrument parameters in terms of creating a comparative test system for the in vivo behavior of erosion-diffusion- and diffusion-controlled MR dosage forms.

Based on the data presented by Rohrs et al. [8] and Klein [9], an agitation rate of 10 dips per minute (10 dpm) was assumed to be capable generating dissolution profiles similar to those obtained with the paddle apparatus at 100 rpm. Both the top and bottom of the glass cylinder were fitted with 420-µm mesh screens, and a volume of 220 mL of test medium was used for all experiments. The test duration was 24 hours in all cases.

In the next step, release profiles were examined using the same instrumental settings but with varying pH conditions, to check whether drug release might be influenced by changing pH as the dosage form passes through the GI tract. To simulate GI passage, different compendial media were used (see Table 2). To simulate residence times in the fasted state at different regions of the GI tract, mean transit times for single unit dosage forms from various gamma scintigraphy studies [10] were used. For colon simulations, in vitro conditions were streamlined to the use of phosphate buffers at pH 6.5 to simulate pH conditions in the proximal colon and pH 6.8 to simulate more distal sections. Samples (3 mL) were periodically withdrawn using a plastic syringe. As described for USP 2 experiments, the samples were immediately filtered and analyzed by UV spectrophotometry. All studies were performed in triplicate.

In vitro dissolution profile comparison

Difference factor f_1 and similarity factor f_2 [11, 12] were calculated for selected profiles to determine whether a paddle speed of 100 rpm corresponds to a reciprocating rate of 10 dpm for both conventional and novel metoprolol ER formulations. Similarity factor f_2 was calculated for various dissolution profiles to determine whether:

- dissolution profiles of 6 randomized conventional metoprolol ER formulations are similar in a buffer gradient simulating fasted GI conditions.
- the dissolution profiles of the "zero-order" multiparticulates of Belok-Zok® are similar to those of the "zero-order" matrices, e.g. metodura® Z.
- the dissolution profiles of conventional metoprolol ER formulations are similar to those of "zero-order" ER formulations, which would indicate that the products are interchangeable in terms of generic substitution.

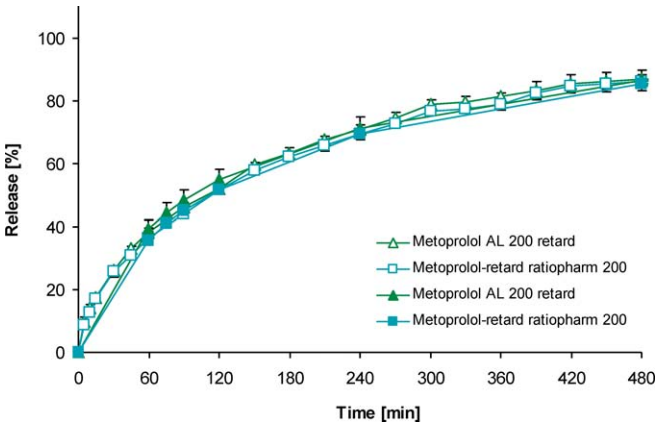

Figure 1. Dissolution profiles of Metoprolol AL 200 retard and Metoprolol-retard ratiopharm 200 generated with USP Apparatus 2 (open symbols) and USP Apparatus 3 (closed symbols)

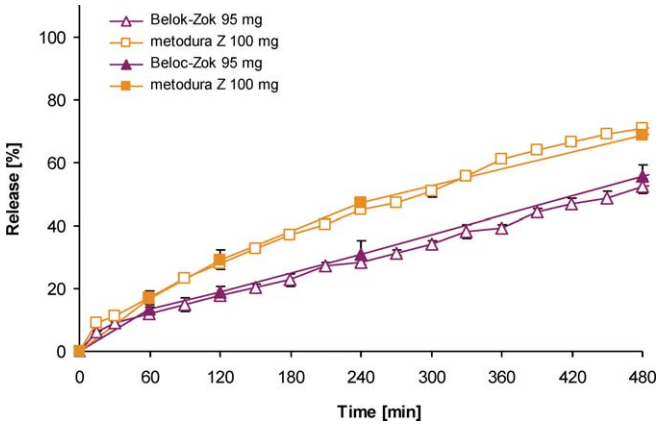

Figure 2. Dissolution profiles of Beloc-Zok 95 mg and metodura Z 100 mg generated with USP Apparatus 2 (open symbols) and USP Apparatus 3 (closed symbols)

Results and discussion

Comparison of dissolution profiles of USP Apparatus 2 and 3

Figure 1 illustrates the first 8 hours of the dissolution profiles of two so called "conventional" ER formulations

Table 3: f_1 and f_2 values from agitation speed comparison

	f_1 100 rpm vs. 10 dpm	f_2 100 rpm vs. 10 dpm
Beloc-Zok®	6,12 %	76, 27
metodura® Z 100 mg retard	2,63 %	88,61
Metoprolol AL 200 retard	1,45 %	89,27
Metoprolol-retard ratiopharm® 200	7,88 %	53,39

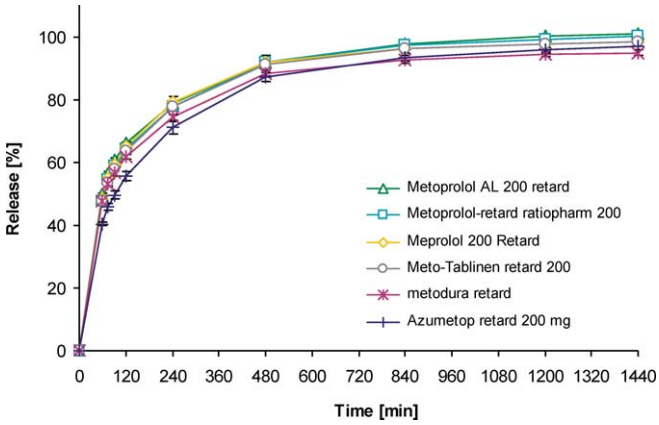

Figure 3. Dissolution profiles of various "conventional" ER formulations of metoprolol using a pH-gradient method

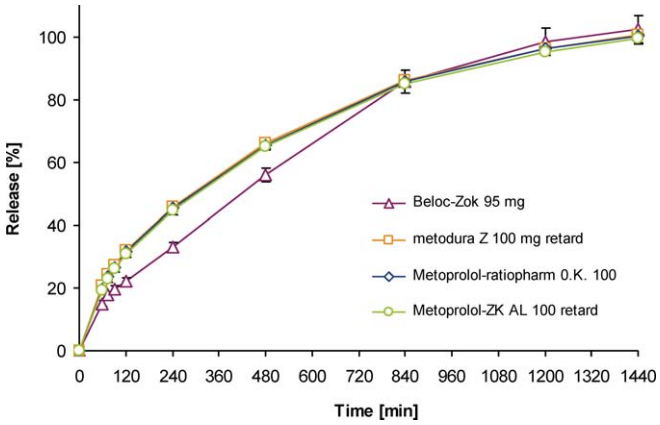

Figure 4. Dissolution profiles of "novel" ER formulations of metoprolol using a pH-gradient method

(Metoprolol AL retard and Metoprolol-retard ratiopharm®) that were generated with both apparatus (Paddle and BioDis®) using SIFsp pH 6.8 as test medium, and Figure 2 shows those of two "zero order" ER formulations (Belok-Zok® and metodura®).

Using USP Apparatus 3 with a reciprocating rate of 10 dips per minute (dpm) and 420-µm mesh screens at top and bottom of the glass cylinders resulted in dissolution profiles that are very similar to those obtained with the paddle apparatus at 100 rpm. This observation was confirmed by calculating f_1 and f_2 values. For calculation of both f_1 and f_2, mean cumulative percentages released after 60, 120, 240, 480, and 1440 min were used. Resulting values are given in Table 3.

For all dosage forms tested, f_1 was less than 10% and f_2 was between 50 and 100. Hence, the use of the BioDis® method at 10 dpm / 420 µm / 420 µm / 220 mL to investigate pH dependency of the formulations using "standard" test conditions could be justified.

Because of the numerous "conventional" Metoprolol ER formulations available on the German/European market, six products from this group were chosen at random and tested using the pH-gradient method (see Figure 3).

All dosage forms showed a drug release that follows first-order kinetics. The test results show that "conventional" metoprolol ER products exhibit virtually identical dissolution behavior that is independent of pH and suggest that they are interchangeable. This assumption was supported by a series of tests using SIFsp USP pH 6.8 as the single dissolution medium (data not shown here). To prove similarity of the profiles generated in the pH-gradient, they were compared among one another by f_2 calculation using dissolution time points at 60, 75, 90, 120, 240, and 480 min. These time points correspond to FDA criteria, i.e., not more than

Table 4: f_2 values from comparison of conventional metoprolol ER formulations

	Metoprolol AL 200 retard	Metoprolol-retard Ratiopharm® 200	Meprolol® 200 Retard	Meto-Tablinen® retard	metodura® retard	Azumetop® retard 200 mg
Metoprolol AL 200 retard		87.26	92.06	81.71	70.48	51.59
Metoprolol-retard ratiopharm® 200	87.26		95.82	95.81	77.72	55.23
Meprolol® 200 Retard	92.06	95.82		90.53	74.04	53.71
Meto-Tablinen® retard	81.71	95.81	90.53		81.28	56.94
metodura® retard	70.48	77.72	74.04	81.28		61.59
Azumetop® retard 200 mg	51.59	55.23	53.71	56.94	61.59	

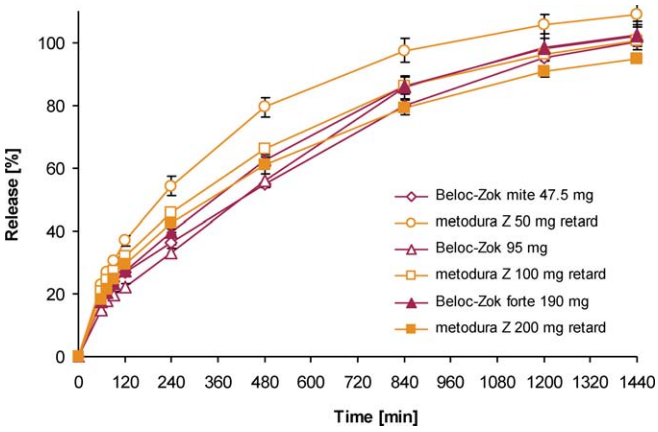

Figure 5: Dissolution profiles of different dosage strengths of "novel" ER formulations of metoprolol using a pH-gradient method

one measurement after 85% dissolution of the product was considered [13].

All f_2 factors calculated are in the range of 50 to 100 (see Table 4). Therefore, it can be assumed that the conventional ER dosage forms of metoprolol are interchangeable when administered in the fasted state.

In the second step, the dissolution behavior of the "zero-order" ER formulations was examined (see Figure 4).

Figure 4 shows the release behavior of Beloc-Zok®, a once daily tablet consisting of ethylcellulose-coated metoprolol succinate micropellets, and three randomized products of "novel" swellable matrix-type tablets containing metoprolol tartrate. According to the specifications, all four dosage forms should exhibit zero-order drug release. This requirement was not fulfilled under the pH-gradient test conditions. However, it was obvious that the release profiles of the three matrix formulations were superimposable. As all tested matrix formulations consist of the same excipients, have the same shape, and exhibit superimposable dissolution profiles, it was concluded that they are likely from the same manufacturer even though they appear on the market under different brand names.

As for the "conventional" metoprolol ER formulations, drug release from "novel" ER formulations was independent of pH. A series of tests using SIFsp USP pH 6.8 as dissolution medium (data not shown here) resulted in dissolution profiles comparable to those with the pH-gradient method.

Whereas "conventional" ER formulations are available only in a strength of 200 mg metoprolol tartrate per tablet, three different strengths exist for both types of "novel" formulations. The objective of the third and final step of this series of tests was to examine whether there are dose-dependent changes in the dissolution profile of the "novel" formulations. Additional experiments were performed using the pH-gradient method. Six different dosage forms were included in this study: Belok-Zok® multiparticulates at three strengths (47.5, 95, 190 mg) and the corresponding strengths of metodura® Z (50, 100, 200 mg) tablets (see Figure 5).

In previous experiments (data not shown here), it was shown that drug release is not pH-dependent from conventional products containing 200 mg or from novel products containing 100 mg metoprolol salt. Percentage release vs. time profiles from the Beloc-Zok® proved to be almost independent of strength of the dosage from. This observation was confirmed by calculating f_2 values for the complete dissolution profile (60–1440 min). Values of f_2 are given in Table 5.

Table 5: f_2 values from comparison of different strengths of Beloc-Zok®

			f_2
Belok-Zok® mite 47.5 mg	versus	Belok-Zok® mite 95 mg	70.17
Belok-Zok® mite 47.5 mg	versus	Belok-Zok® forte 190 mg	70.65
Belok-Zok® mite 95 mg	versus	Belok-Zok® forte 190 mg	69.77

Table 6: f_2 values from comparison of different strengths of metoduara® Z

			f_2
metodura® Z 50 mg retard	versus	metodura® Z 100 mg retard	54.50
metodura® Z 50 mg retard	versus	metodura® Z 200 mg retard	45.28
metodura® Z 100 mg retard	versus	metodura® Z 200 mg retard	67.10

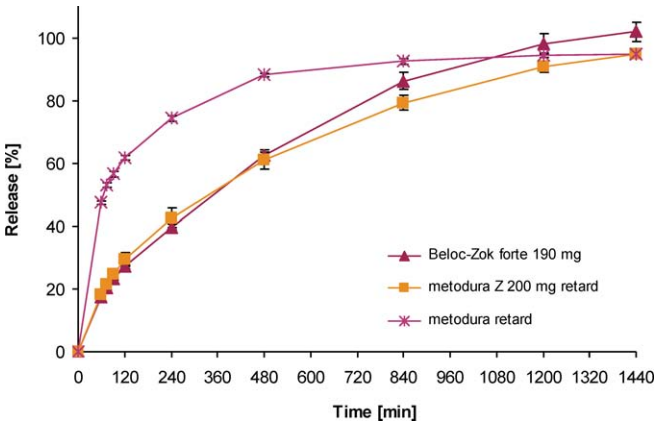

Figure 6: Comparison of drug release from different types of metoprolol ER formulations

Table 7: f_2 values from comparison of conventional and novel types of metoprolol ER formulations

			f_2
Belok-Zok® forte 190 mg	versus	metodura® Z 200 mg retard	67.47
Belok-Zok® forte 190 mg	versus	metodura® retard	28.97
metodura® Z 200 mg retard	versus	metodura® retard	29.68

By contrast, release from the matrix tablet seemed to be dependent on both the shape of the dosage form and the amount of drug dispersed in the matrix. By comparing dissolution profiles of three strengths of metodura® Z, a clear trend can be observed with drug release rate (expressed as % label strength) increasing from higher to lower strengths (see Figure 5). As the appearance of the 50-mg tablet differs from that of the 100- and 200-mg tablets and drug release rate is particularly high for this tablet, it seems that the geometry of the matrix formulation is likely to be the culprit. To check for similarity of the dissolution profiles of metodura® Z, f_2 was additionally calculated using all sampling time points of the dissolution profile (60–1440 min).

F_2 values in Table 6 clearly indicate that drug release rate from metodura® Z retard differs among the strengths. Dissolution profiles from the lowest and highest dose are different ($f_2 < 50$) so they cannot be considered interchangeable (i.e., 4 metodura® Z 50 mg retard would not have the same profile as 1 metodura® Z 200 mg retard).

In terms of assessing the interchangeability of the different types of metoprolol dosage forms, dissolution profiles of three formulations, representing the different types of formulations currently available on the market, were compared using dissolution data generated with the pH-gradient method (see Figure 6). A dosage strength of 190/200 mg had to be used for this comparison as "conventional" formulations are available only in this strength.

Overall, dissolution results indicate that "conventional" and "novel" ER formulations of metoprolol are not therapeutically interchangeable. F_2 was calculated using dissolution time points at 60, 75, 90, 120, 240, 480, 840, 1200, and 1440 min. The values are given in Table 7.

Table 8: f_2 values from comparison of "zero-order" multiparticulates and matrices of same strength

			f_2
Belock-Zok® mite 47.5 mg	versus	metodura® Z 50 mg retard	43.51
Belock-Zok® 95 mg	versus	metodura® Z 100 mg retard	56.05
Belock-Zok® forte 190 mg	versus	metodura® Z 200 mg retard	67.47

According to the specifications, both dosage forms Belok-Zok® and metodura® Z should exhibit zero-order drug release. This requirement was not fulfilled under the pH-gradient test conditions. Despite different release mechanisms and different salts within the formulations, no significant difference in the dissolution profiles was detected between the 190-mg and 200-mg "zero-order" dosage forms, but this observation cannot be generalized to other strengths (see Table 8).

It was confirmed by f_2 calculation (see Table 8) that the 95/100- and 190/200-mg dosage forms resulted in similar dissolution profiles. However, the 47.5-mg and 50-mg dosage forms show particularly large deviations, so that substitution of these two formulations for one another is questionable.

From these results, it is obvious that "conventional" and "novel" ER formulations cannot be considered therapeutically interchangeable. Substitution between these two product types should be avoided, since this could result in an increased risk of side effects on the one hand (ZOK Æ conventional) or a reduction of the therapeutic effect on the other hand (conventional Æ ZOK). Nevertheless, all but Belok-Zok® can be substituted for one another under the current German "*aut idem*" rule, even though switching between "conventional" and "zero-order" is expected to result in quite different release profiles in vivo.

Summary

Results of these studies indicate that the USP Apparatus 3 pH-gradient method is a convenient and discriminating method for comparing the drug release behavior of ER dosage forms during their passage through the GI tract. In the present study, it could be shown that it is possible to differentiate between individual release characteristics of metoprolol ER dosage forms. Specificity of drug release profiles during gastrointestinal passage as well as pH-dependency of drug release could be shown. The method used in the present study therefore represents a useful tool in estimating the interchangeability of seemingly similar dosage forms when administered in the fasted state.

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