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# DEVELOPMENT OF A NEW CONTROLLED RELEASE METOPROLOL PRODUCT

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## ABSTRACT

A new controlled-release preparation intended for once-daily dosage has been developed for the $\beta_1$-selective adrenoreceptor antagonist metoprolol. The scope of this presentation is to discuss biopharmaceutical and technical considerations in the development of the product.

Metoprolol is well absorbed from the entire gastro-intestinal tract. In-vitro/in-vivo correlation studies showed that a pH-independent and constant (zero-order) release during about 20 hours was suitable for the final preparation. A "multiple-unit" tablet consisting of several hundred coated metoprolol pellets was developed. Desired release properties were obtained by choosing a suitable salt (succinate), preparing compact pellets without soluble additives and coating the pellets with a pH-independent polymeric layer. The final preparation has shown good manufacturing reproducibility and produces uniform plasma concentration-time curves in vivo.

## INTRODUCTION

The ß1-selective adrenoceptor antagonist metoprolol has a relatively short elimination half-life of about 3-4 hours and is

consequently a candidate drug for an oral controlled-release (CR) preparation.

Different CR products based on the matrix principle, e.g. Betaloc® SA (Beloc®, Seloken® Durules®) and Lopressor® SR, have been developed and launched internationally. These preparations release about 80-100% of the dose within 8-10 hours. This means that absorption occurs only during the first half of the dosage interval when the products are administered once daily.

The purpose of this presentation is to discuss both biopharmaceutical and technical aspects of the development of a CR formulation of metoprolol giving continuous absorption over the main part of the dosage interval when given once daily.

## BASIC CONSIDERATIONS

### Absorption

A prerequisite for an acceptable systemic bioavailability of a CR preparation given once daily is that the entire gastrointestinal (GI) tract can be utilised for absorption of the drug. Metoprolol is completely absorbed from the proximal parts of the small intestine (1). In order to investigate distal absorption of metoprolol, the "positioned release" capsule technique (2, 3) was used to release a solution of 100 mg metoprolol tartrate in the colons of 9 healthy male subjects aged 24-35 years (4). The dose was released with a high frequency pulse (27 MHz). When activated the position of the capsule was the ascending colon in 6 cases, the transverse colon in 2 cases and the descending colon in 1 case, as determined by short-term x-ray controls. The time from administration until the drug was released varied between 3.2 and 3.6 (mean 3.4) hours. The approximate total GI transit time for the capsule was 9 hours in 1 subject, 24 hours in 7 subjects and about 32 hours in 1 subject. The same subjects were also given a conventional metoprolol tablet 100 mg (Betaloc®, Beloc®,

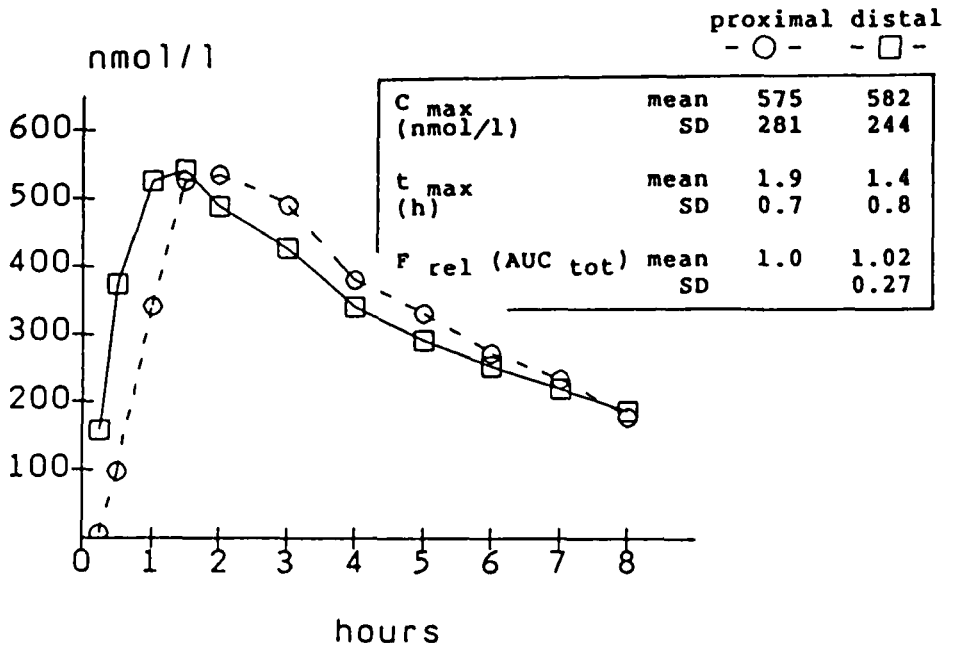


FIGURE 1

In-vivo results after proximal (oral tablet) and distal (positioned release capsule) administration of metoprolol 100 mg to 9 healthy males.

Seloken®) orally in another experiment. The mean plasma concentration-time curves and the pharmacokinetic variables were very similar for the two administrations (figure 1), showing that metoprolol is also well absorbed in the distal regions of the GI-tract.

Release Rate In-Vitro and In-Vivo

A very important step in the development of a CR preparation is to define the in-vitro dissolution profile which corresponds to a desired response in-vivo. Since there is a well-defined relationship between the concentration of metoprolol in plasma and the ß-adrenoceptor blockade achieved (5, 6), the objective was to design a CR preparation that delivered the drug so as to

give a uniform plasma concentration-time profile over the dosage interval. In order to investigate the in-vitro/in-vivo relationship, four different CR formulations (A, B, C, D), were investigated in a cross-over study in six healthy males aged 22-26 years. After an overnight fast, each subject received a single dose of the four test formulations and a reference preparation (Betaloc® SA). The test formulations consisted of pellets of metoprolol tartrate coated with different polymeric membranes to yield different in-vitro dissolution profiles. The dose used in the study was 200 mg for all administrations.

The results are shown in figure 2 and in table 1 below. The figures illustrate the in vitro dissolution profiles for the test formulations in simulated gastric juice (pH 1.2) and in a phosphate buffer (pH 6.5) and the cumulative absorption of metoprolol after administration, calculated with the Wagner - Nelson equation (7). The elimination rate constant used was derived from the post-absorption phase of the individual plasma concentrations obtained after administration of formulation A.

For formulation A, having the fastest rate of dissolution, absorption seemed to be completed within 8-10 hours after administration, whereas with formulations B, C and D, continuous drug absorption was achieved during most of the time interval. The rate of dissolution from D seemed too slow, however, as indicated by the about 34% reduction in bioavailability in relation to the reference preparation. Comparing formulations B and C, it should be noted that B, having a rather pH-dependent rate of drug release, gave somewhat greater interindividual variability in e.g. $C_{max}$. In addition, a good in-vitro/in-vivo correlation was obtained for formulation C, as can be seen from figure 2. It was thus concluded from the study that the development of the final preparation should aim at a pH-independent release during about 20 hours.

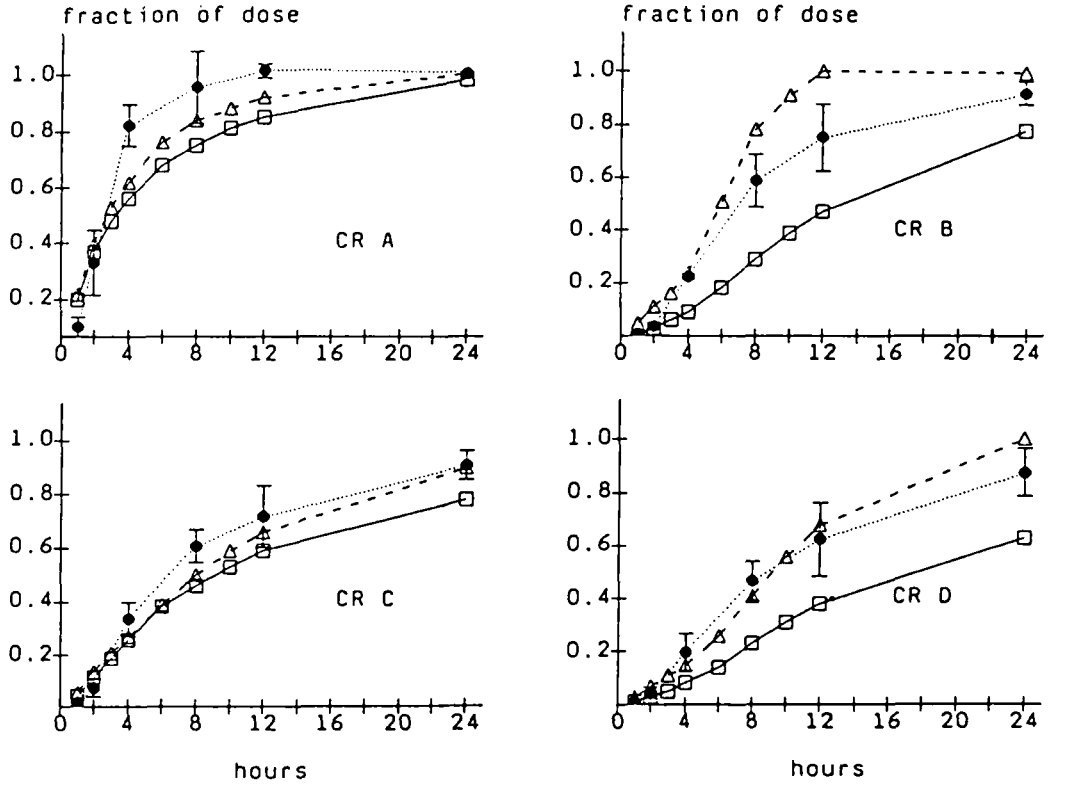


FIGURE 2

Fraction of the dose released in-vitro (USP method II, 100 rpm) or absorbed in-vivo in a cross-over study in 6 male volunteers. □, In-vitro pH 1.2; △, In-vitro pH 6.5; ●, In-vivo (mean ±SD).

TABLE 1
Pharmacokinetic Variables Determined from Individual Data (n=6)

| Variable | | Formulation A | B | C | D | Reference |
|---|---|---|---|---|---|---|
| $C_{max}$ (nmol/l) | mean | 377 | 196 | 188 | 121 | 322 |
| | SD | 171 | 223 | 61 | 73 | 132 |
| $t_{max}$ (h) | mean | 4.5 | 8.0 | 7.3 | 8.7 | 3.3 |
| | SD | 0.7 | 1.2 | 1.7 | 2.0 | 1.2 |
| $F_{rel}$ ($AUC_{tot}$) | mean | 1.03 | 0.90 | 0.94 | 0.66 | 1.0 |
| | SD | 0.22 | 0.24 | 0.20 | 0.15 | |

## Design of the Dosage Form

Having defined the biopharmaceutical properties, the next step in the development was to design a suitable and convenient dosage form. Apart from differences in the drug release mechanism, two major categories of CR preparations can be distinguished. The dose may either be contained in a single unit, e.g. a tablet coated to give an osmotic pump system (8), or may be divided into several small units such as coated pellets (multiple unit system). For many drugs, it is possible to obtain a suitable drug release profile with both these principles. However, the multiple unit system offers obvious advantages over a single-unit preparation. It gives greater flexibility as different dosage forms, e.g. capsules, tablets and sachets, with the same release properties can be produced. Furthermore, the dose is spread over a larger area of the GI-tract, thus avoiding exposure of the mucosa to high concentrations of drug. The risk of "dose-dumping", i.e. prompt release of the total dose due to defective coating or a mishandled preparation, should also be considerably lower than with a single unit tablet. Since tablets are well accepted by patients and allow division of the dose, it was decided to develop a disintegrating and divisible tablet containing several hundred coated metoprolol pellets. The basic considerations discussed in this section can be compared with recent reports describing the development of a single unit osmotic delivery system of metoprolol (9-14).

# FORMULATION CONSIDERATIONS DURING DEVELOPMENT

## Design of Pellets

To be able to construct a pellet of metoprolol having a constant (zero-order) and pH-independent rate of release, several considerations had to be met. A nondisintegrating barrier coating was considered to be the most promising way to obtain the desired properties. By coating pellets with a pH-independent polymer,

each of the coated pellets can be made to act as a diffusion cell releasing the drug according to the following equation;

$$dM/dt = A * D * K * \Delta C / L$$

Where dM/dt is the drug release rate, A is the area, D is the diffusion coefficient in the membrane or in water if the diffusion occurs via pores, and K is the partition coefficient of the drug between the membrane and an aqueous solution. In the case of pore diffusion, K represents a porosity factor, $\Delta C$ is the concentration difference over the membrane, and L is the thickness of the coat.

The equation is somewhat simplified as it does not take into account the possible influence of osmotic pressure. Nevertheless, it illustrates quite well the effect of the solubility of the drug, for example. A constant release rate should be obtained only as long as all the terms on the right hand side of the equation are constant. The concentration difference will decrease when the drug solution within the pellets is no longer saturated, i.e. when all drug has been dissolved. Obviously, the solubility of the drug and the available volume inside the membrane will strongly influence the time during which a constant release can be achieved.

Consequently, it should be preferable to;
- use a salt of the drug with sufficiently low solubility,
- avoid soluble additives in the composition and
- construct pellets with low porosity.

The tartrate salt of metoprolol is very soluble (> 700 mg/ml) in water and is therefore unsuitable according to the discussion above. Several other salts of metoprolol with lower solubility were tested. Metoprolol succinate, having an appropriate solubility of about 200 mg/ml in water, was selected. Figure 3 shows that a large part of the total dose is released at a practically

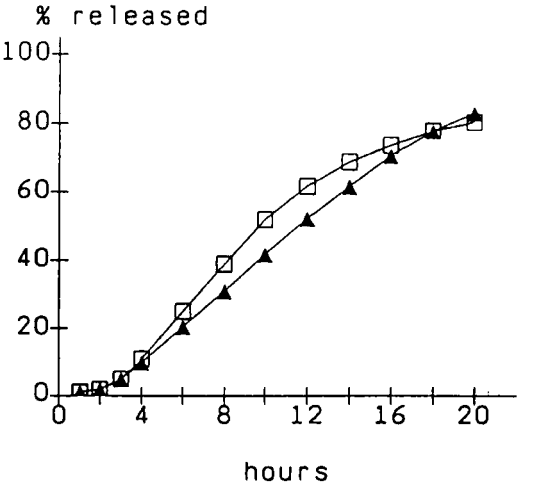


FIGURE 3

In-vitro release from coated pellets of metoprolol salts. ▲, succinate; □, fumarate. Phosphate buffer 500 ml, pH 6.8, 37°C, USP paddle at 100 rpm. Mean values of duplicate trials.

constant rate when the succinate salt is used in coated pellets. With metoprolol fumarate, an alternative salt with about 2.5 times higher solubility, a less favourable result was obtained. The same ethylcellulose-based coating solution was used in both cases although the amount was adjusted to give pellets that released about the same amount of metoprolol in 20 hours. The effect of using soluble additives in the composition is illustrated in Figure 4. The larger volume inside the membrane gives a shorter time interval during which a saturated solution can be maintained and the release profile is significantly affected.

A high porosity not only means a larger volume inside the membrane, but may also make the pellets more fragile during tabletting.

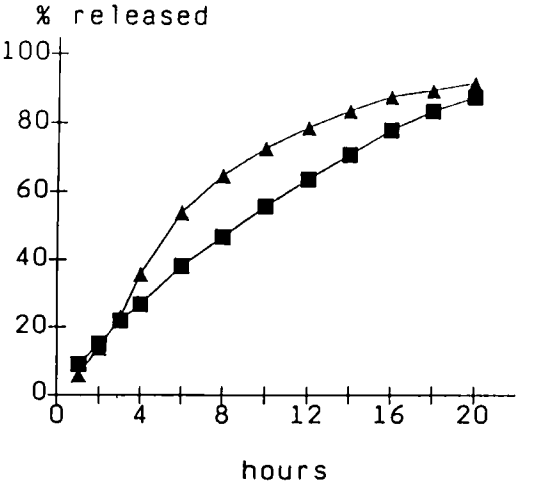


FIGURE 4

In-vitro release from coated metoprolol succinate pellets with soluble (▲) and insoluble additives (■). About 20% of the uncoated pellets consisted of additives. Mean values of 4 samples (Test conditions as in Fig 3.)



Tabletting

The stress induced when compressing coated pellets into tablets may rupture the polymeric membrane, resulting in a much faster drug release than desired. As illustrated in figure 5, an increase in the particle size of the pellets tends to give more rupture during tabletting, resulting in a large difference in the release from the pellets before and after tabletting. In the present case, the same coating solution was used for all three sizes of pellets although adjustments were made to obtain coated pellets that released 80-90% of the metoprolol content within 20 hours.

The effect of the pellet size is of course dependent on the choice of coating material, i.e. the thickness and mechanical strength of the polymeric film, as well as the amount and properties of the pellets and the excipients forming the inert part of

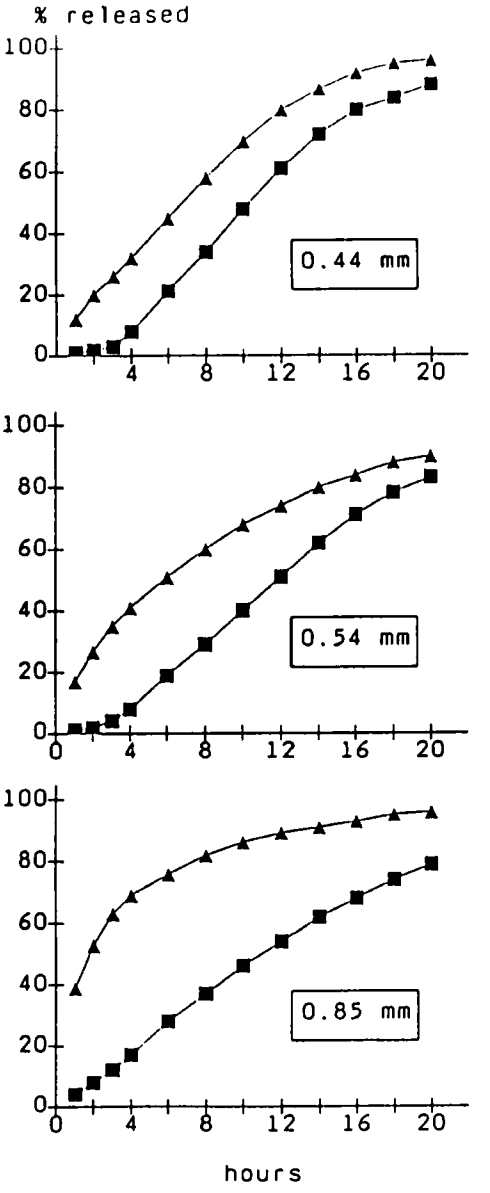


FIGURE 5

The influence of tabletting on the release rate from coated metoprolol pellets of different sizes. ■, coated pellets; ▲, tablets , 10 mm biconvex, compression force 8 - 9 kN. Mean particle size of the pellets as indicated in the figure. (Test conditions as in Fig 3.)

TABLE 2
In-Vitro Release of Metoprolol Succinate from Biconvex Circular Tablets with a Diameter of 10 mm Compressed at Different Force Levels in a Production Scale Trial. (Test conditions as in Fig 3).

| Compaction force, kN | Cumulative % released within 1 h | 4 h | 8 h | 20 h |
|---|---|---|---|---|
| 13 | 14 | 29 | 47 | 85 |
| 15 | 16 | 32 | 50 | 89 |
| 20 | 15 | 32 | 49 | 85 |

the tablet mass. When these factors were considered, it was possible to produce mixtures of coated pellets and tablet-forming excipients that could resist high pressures without excessive damage to the coating layer. The release rate of metoprolol will thus be virtually independent of the compaction force within a broad force range, which should mean a high reproducibility during manufacture (Table 2).

## PROPERTIES OF THE FINAL PREPARATION

When selecting the test method for the in-vitro dissolution of the product, several techniques were evaluated and most seemed appropriate as regards reproducibility, sensitivity and correlation to in-vivo data. The paddle method of the USP XXI was chosen because it is a well-known standard method which can easily be automated. The drug dissolution from the final preparation is rather independent of changes of the test conditions, e.g. agitation and pH of the medium, as is shown in table 3.

The mean steady-state plasma concentrations of metoprolol on day 5 after once-daily administration of the final CR preparation (100 mg) to 12 healthy males, aged 21-34 years, are shown in

TABLE 3
Mean (n=6) In-Vitro Dissolution when Testing the Final Preparation in the USP II Apparatus Under Various Test Conditions. 500 ml Dissolution Medium with a Temperature of 37°C was used in all Experiments.

| pH * | | 1.2 | 2.0 | 3.0 | 4.0 | 5.0 | 6.0 | 6.8 | 7.5 | 6.8 | 6.8 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| paddle speed (rpm) | | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 50 | 150 |
| % released | | | | | | | | | | | |
| at 4 h | mean | 34 | 32 | 30 | 30 | 30 | 30 | 32 | 32 | 29 | 32 |
| | SD | 1.4 | 1.1 | 0.8 | 1.6 | 1.0 | 1.2 | 1.9 | 0.8 | 1.4 | 1.7 |
| 8 h | mean | 47 | 43 | 45 | 46 | 45 | 45 | 50 | 48 | 47 | 48 |
| | SD | 1.2 | 1.1 | 0.8 | 1.5 | 1.5 | 1.6 | 1.8 | 1.6 | 1.3 | 2.5 |
| 20 h | mean | 83 | 77 | 81 | 84 | 82 | 83 | 89 | 85 | 87 | 86 |
| | SD | 1.3 | 1.5 | 0.5 | 2.1 | 2.1 | 1.4 | 2.5 | 2.9 | 1.0 | 3.1 |

* pH 1.2 = simulated gastric juice, ionic strength 0.1
pH 2.0 - 7.5 = phosphate buffer solutions, ionic strength 0.1

figure 6. The extended absorption process resulted in a uniform plasma concentration curve without marked peaks and troughs, as indicated by a $C_{max}/C_{min}$ ratio of 1.8±1.3 (mean±SD). The corresponding ratio was 8.4±6.2 when the same daily dose was given to the subjects as conventional tablets (Betaloc®, Beloc®, Seloken®) every 12 hours (15).

As the rate and extent of the bioavailability of a CR preparation are strongly influenced by the release from the dosage form, it is of utmost importance that the manufacturing process is reproducible and that it can be adequately controlled. Tests on several batches of the final composition in full scale production (batch sizes 0.3-0.8 million tablets) have shown very good reproducibility, both regarding the in-vitro release properties and with respect to the content uniformity of the tablets (table 4).

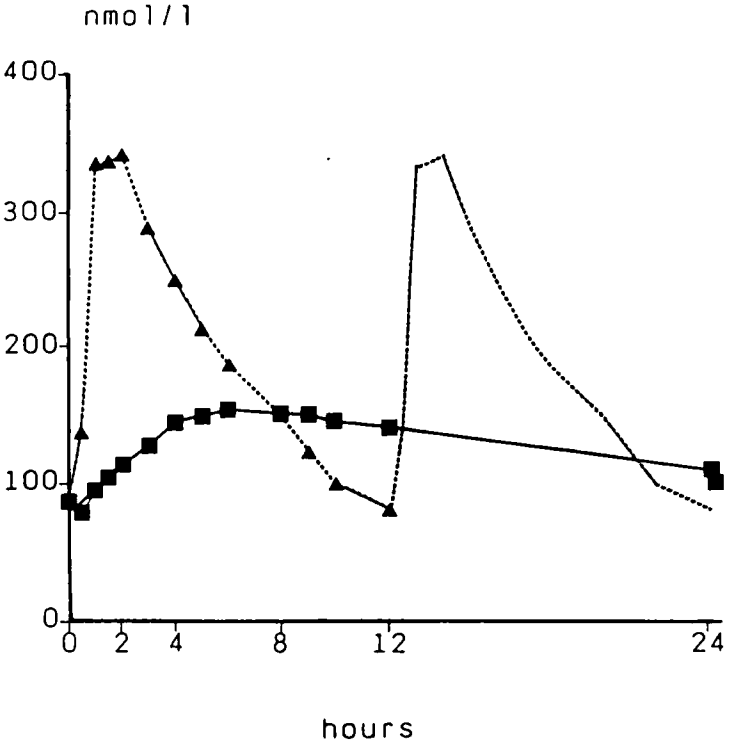


FIGURE 6

Mean (n=12) plasma concentrations of metoprolol at steady-state. ■, CR tablets 100 mg once daily; ▲, conventional tablets 50 mg b.i.d.

TABLE 4
In-Vitro Release (Range of 6 Tablets) and Content Uniformity (10 Tablets) of Seven Consecutive Production Batches.

| Batch | Cumulative % released within | | | | Relative standard deviation of the Metoprolol succinate content, % |
|---|---|---|---|---|---|
| | 1 h | 4 h | 8 h | 20 h | |
| 1 | 14-17 | 30-35 | 46-52 | 84-91 | 2.8 |
| 2 | 11-14 | 26-33 | 41-48 | 80-87 | 2.4 |
| 3 | 11-15 | 27-36 | 44-53 | 81-89 | 2.9 |
| 4 | 15-19 | 31-35 | 47-52 | 80-86 | 4.9 |
| 5 | 15-18 | 33-39 | 48-55 | 85-93 | 3.7 |
| 6 | 14-17 | 31-36 | 48-54 | 85-89 | 3.3 |
| 7 | 16-18 | 37-38 | 52-55 | 86-89 | 3.0 |

## CONCLUSIONS

To obtain adequate control over drug delivery from an oral CR preparation, an understanding of both the absorption properties of the drug and the effect of its physicochemical characteristics on the formulation is required. By applying such knowledge and integrating the biopharmaceutical and technical development, it was possible to produce a reproducible and effective controlled release preparation of metoprolol.

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