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ORAL CONTROLLED DRUG DELIVERY SYSTEMS BASED ON MICROPOROUS POLYMERS

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ABSTRACT

Microporous polypropylene (PP) powder shows excellent properties for tabletting. Oral controlled release delivery systems were made by simply blending with drug and compressing to make both matrix and coated tablets. To prevent wetting problems and food interactions, sodium lauryl sulphate (SLS) was adsorbed prior to tabletting on the surface of the microporous PP. In order to reveal possible dosage form-food interactions a new and simple food interaction model (slight modification of the USP XX paddle method) is proposed to standardize both in vitro and in vivo testing procedures. The PP coated oxprenolol tablets show no food interactions when tested in vitro in the food simulation mixture. The same liquid food was used in the in vivo study. The PP coated oxprenolol tablets were given to six male volunteers with and without the food. The absorption profiles, which were calculated by numerical deconvolution, showed hardly any food interactions in vivo. The absolute bioavailability at 12 hours was 38±19% on an empty stomach and 37±20 for the food experiment. The developed coated tablets are able to control the release of oxprenolol at least 12 hours both with and without concomitant food intake. Their bioavailability is comparable to different OROS formulations of oxprenolol controlled release systems based on microporous PP are not only highly effective ones but also low cost formulation products.

INTRODUCTION

Microporous polymers show some exellent galenical properties which make them suitable as new excipients in tabletting technology.

Our objectives to develop oral controlled drug delivery systems using microporous polymers were the following (1):
To make oral tablets that showed controlled-release, were cheap and easy to produce without wetting or granulation, that showed release of drug over the whole surface of the tablet and which would show no ageing effect like e.g. seen with coatings of methacrylic esters. To accomplish this we tried to develop coatings of microporous polymeric powders by simple compression to achieve diffusion controlled release of drug. The systems made were matrix tablets, coated tablets and combinations of both. The last was done to prevent dose dumping caused by damage to the coat, e.g. by chewing. The matrix tablets were made by simply blending the drug and the microporous polymer and by using direct compression. The coated tablets were made by tabletting a blend of the microporous polymer and additives around a core of drug and the combination of both was made by compressing a blend of microporous polymer and additives around a matrix tablet which contained the drug.

MICROPOROUS POLYMERS

By microporous polymers (3,4) are meant porous structures that are made of thermoplastic polymers in such a way, that small cells and interconnecting pores are formed throughout their structure. This can be done as described in different patents (4,5) by using a phase separation technique. The polymer of choice is heated together with a compatible solvent to form a homogeneous mixture. At cooling phase separation occurs. This cooling must be done sufficiently fast so that the liquid-liquid phase separation does not occur under thermodynamic equilibrium conditions. Furthermore, the rate of cooling has a substantial effect upon the resultant microporous structure. It should take place in such a rate that the phase separation will result in the formation of a plurality of liquid drops of the same size at the same time. It is believed that as these nuclei start to grow, they become surrounded by a polymer-rich region, that will increase in thickness as it becomes depleted of liquid. As the polymer-rich region thickens, the diffusion of additional liquid towards the droplets decreases and finally stops.

The result of this whole process is a homogeneous three dimensional cellular microstructure with cells of 1-10 µm in diameter and connecting pores of 0.1-1 µm in diameter. The porous volume can be varied between 30 to 90% $^{V}/V$. The liquid can be removed from the pores and cells if necessary. Fig. 1 shows a picture of microporous polypropylene made by an electron microscope at a 10.000 fold enlargement. Clearly, its porous structure can be seen.

This technique has been described for e.g. polypropylene (PP). polyamide (PA), polystyreen (PS) and others, and can be used to prepare films, tubes, powder, granulate, etc. (trademark Accurel , ENKA AG, Obernburg FRG).

The microporous polypropylene (PP) particles produced in this way show the best qualities for tabletting compared with PA and PS. The flow characteristics of PP powder particles are good, they are easy to blend with drug and suitable additives and they show good coherence after compression, even at low compression.

A potential problem is, however, the occurence of food interactions as has been demonstrated for theophylline both in vitro and in vivo (1). The reason for this effect may be the hydrophobic nature of the PP material which gives lipophilic components of food mixtures the opportunity to interact with the polymer. To prevent a possible food interaction it seems reasonable to hydrophilize the polypropylene surface by adsorption of suitable surfactants. To improve the wettability this technique

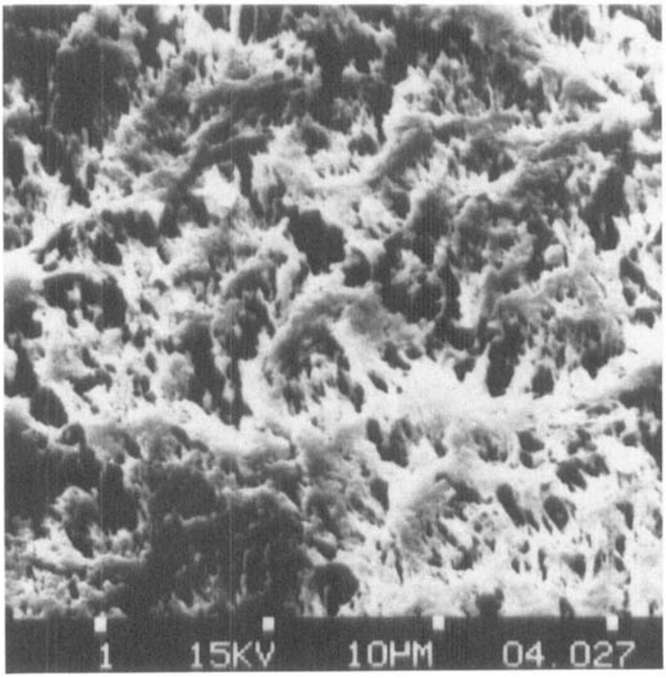

FIGURE 1
The internal structure of microporous PP powder (SEM, black bar corresponds 10μm).

has been widely exploited for hydrophobic drugs with Sodium Lauryl Sulphate (SLS) (6-8). With the absorption of SLS on the surface of the microporous PP it was aimed not only to improve the wetting properties but also to prevent possiblefood interactions (9).

METHODS AND MATERIALS

The formulation of an oral controlled release tablet is given in table I. All other data on methods and materials are given elsewhere (9,10).

TABLE I

Specifications of the newly designed oral controlled-release tablet of oxprenolol % m/m

Matrix core	: Oxprenolol HCl	60	%
	Polypropylene powder (PP)	34	%
	PEG-6000	5	%
	Mg-stearate	0.5	%
	Aerosil 200	0.5	%
Coat	: Polypropylene powder (PP) treated with 2.4 % m/m Sodium Lauryl Sulphate (SLS)	90	%
	Oxprenolol HCl	10	%

average weight: 332.7 + 0.9 mg (n=10)
average dose : 137.0 ± 1.5 mg
diameter : 12 mm
shape : convex

RESULTS

SLS Adsorption on Microporous PP

The total surface of the microporous PP powder (voidspace 70 % ^{v}/v) used in the experiments was 50.3 ± 0,2 m^2/g (T=20°C) and was determined by nitrogen adsorption. For SLS a CMC of 7,62 x 10 exp (-3) Mol/l (T=20°C) was found by a stalagmometer method. The adsorption curve (figure 2) shows a maximum at a concentration of 3.43 % m/m. A surface area of 0.68 nm^2 per SLS molecule can be calculated under the assumption of a monolayer adsorption. This value is in reasonable agreement with results of SLS adsorption on Graphon (0.45 - 0.59 nm^2 (11)) and on polystyrene (0.46 nm^2 (12)).

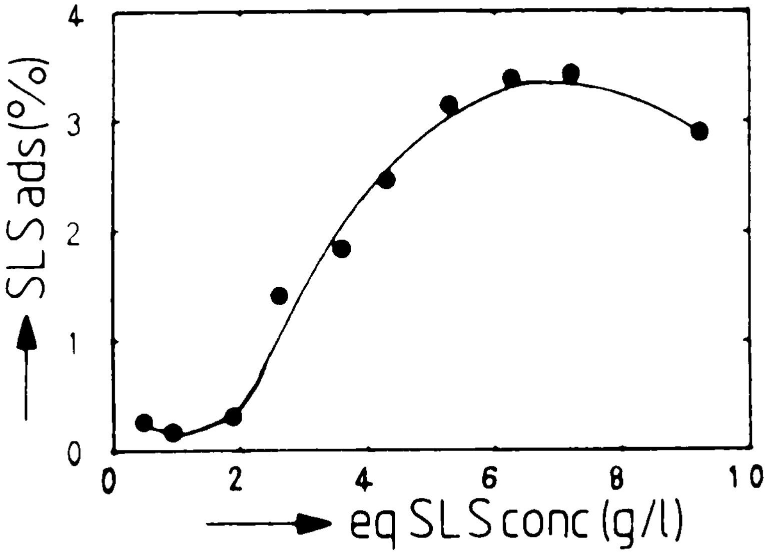

FIGURE 2
The amount of Sodium Lauryl Sulphate (SLS) being adsorbed on the surface of the microporous polypropylene, depending on the concentration of SLS in the solution. The analysis was performed by desorption experiments. The maximum amount adsorbed on the microporous PP is 3.43 % m/m. Each data point of the curve represents a single adsorption experiment, whereas the titration was performed in triple (differences within a 1 % limit).

Figure 3 shows the effect of the SLS amount adsorbed on the rate of release in vitro from coated tablets. An enormous effect on the rate of drug release can be found on SLS amounts adsorbed above a concentration of about 1,40 % (m/m). Higher adsorbed concentrations than 2,50 % (m/m) do not result in a much further increase in the rate of drug release. Figure 3 also shows that there is a lag time for drug release especially at low SLS amounts adsorbed. A complexation between the anionic surfactant and the diffusing cationic oxprenolol may be the explanation for this phenomenon. Desorption of highly coated powders by washing

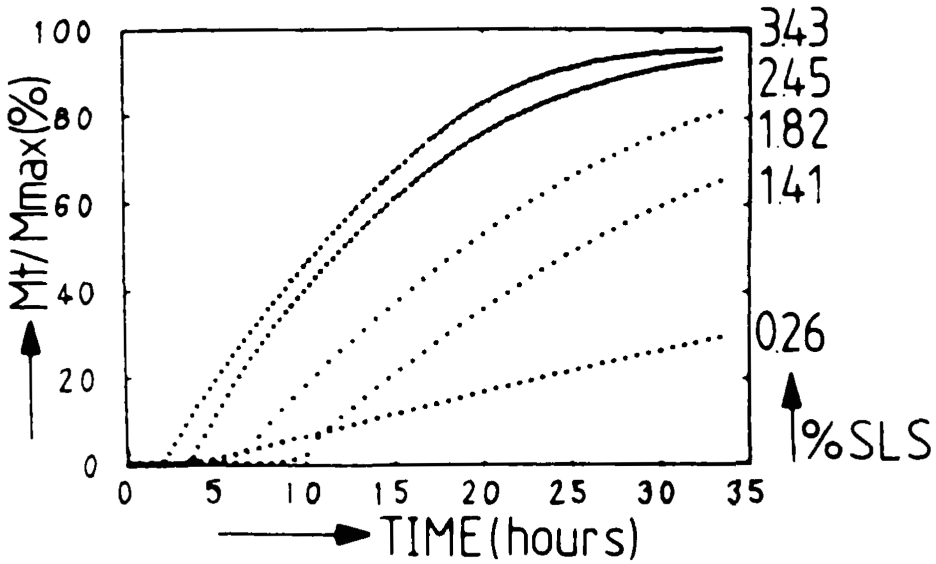

FIGURE 3
The release kinetics of oxprenolol from coated tablets in vitro. The microporous polypropylene used as the coating material was pre-treated with increasing amounts of sodium lauryl sulphate (SLS). The initial increase in lag time is probably due to the "ion-exchange" effect of the adsorbed SLS. Each curve represents an average of 6 dissolution experiments. The standard deviations were all within a 2 % limit.

with water showed no reducing effect on the release rate of oxprenolol indicating a rather stable adsorption complex between SLS and PP with sufficient hydrophilization properties.

In Vitro Dissolution Testing

The results of the in vitro dissolution testing (performance according to the USP XX paddle method) are shown in figure 4. The tablets show a 100 % release of drug during a 24 hour interval, although there is a difference in the Mean Dissolution Time of about a factor 2 between the release experiments in phosphate buffer and the hydrochloric acid medium. When using antipyrin as

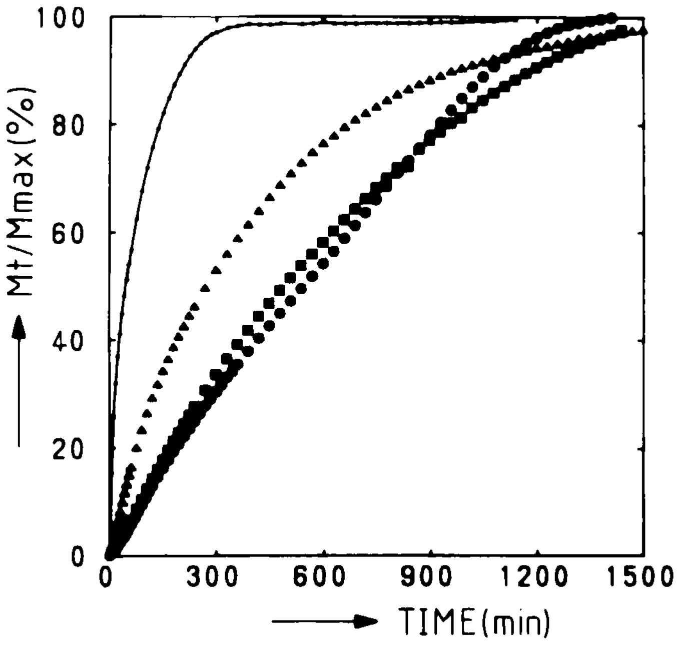

FIGURE 4
The dissolution profiles of the coated tablet (see table I) in different dissolution media:
(▲) 0.1 n HCL, (●) phosphate buffer pH 6.8, (■) demineralized water.
The upper curve shows the release of oxprenolol from the core tablet (•). Each curve represents the average of 6 dissolution experiments, each having a standard deviation within a 1.5 % limit.

a neutral compound this effect did not occur. There is evidence that at the strongly acidic pH the SLS will be mostly unionized, showing no ion exchange effect whereas with increasing pH values these effects become dominant resulting in an almost zero order release profile.

The advantage of a 24 hour dosing interval is the possibility to evaluate the behaviour of the dosage form design in the gastro-intestinal tract and to monitor the kinetics of oxprenolol in vivo. The dissolution experiments (9,10) using the food-

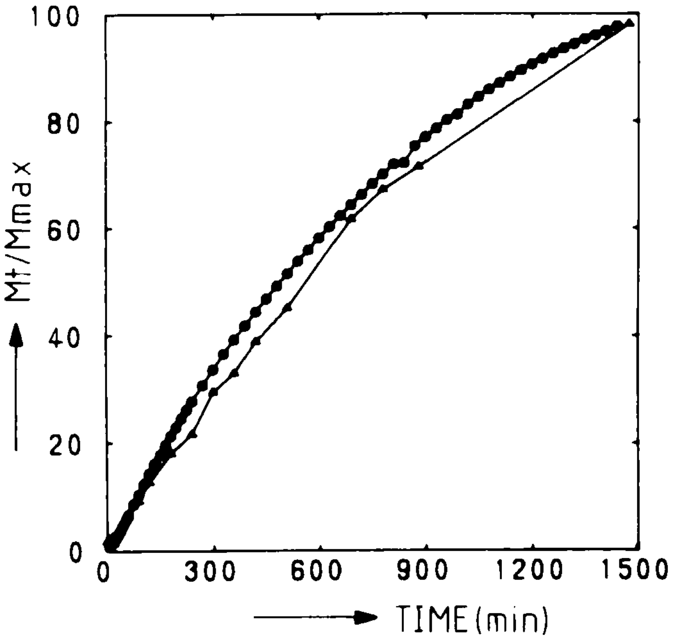

FIGURE 5
The data represent the results of the in vitro food simulation test. The food mixture consisted of 200 ml Nutridrink, 50 ml 0.5 M phosphate buffer (pH 6.8) and 250 ml of demineralized water.
The (●) represent the dissolution data in regular pH 6.8 dissolution medium and the (▲) the food mixture data.
Each curve represents the average of 6 dissolution experiments. The standard deviation for the (●) curve was within a 1.5 % limit, the standard deviation of the food simulation curve (▲) within an approximately 4 % limit.

simulation mixture (composed of 200 ml Nutridrink (Nutricia, Zoetermeer, The Netherlands), 50 ml 0,5 M phosphate buffer (pH 6.8) and 250 ml of water) do not show any interfering effects of the food components on the release profiles of oxprenolol from the optimized SLS-treated coated tablet. (figure 5).

TABLE II

The intra-individual data of both the oral and iv experiments.

parameter	units	B	E	G	T	W	Z	average
<u>iv data</u>								
D	mg	10.14	10.17	10.14	8.16	10.13	10.18	-
Vd	l/kg	0.62	0.68	0.84	0.59	0.74	0.71	0.70 ± 0.09
Kel	l/min	14.18	11.8	9.8	7.2	6.7	8.4	9.8 ± 3.1
Cl	l/min	9.18	8.02	8.23	4.25	4.96	5.96	6.77 ± 1.99
<u>food</u>								
Ka	l/min	5.77	3.52	12.52	25.32	3.82	16.30	11.21 ± 8.60
Kel	l/min	5.71	2.90	1.02	0.96	3.07	0.22	2.31 ± 2.02
t(lag)	min	42.7	9.9	34.7	68.0	15.2	48.5	36.5 ± 21.6
t(max)	min	216.9	322.5	253.0	202.3	306.7	315.8	269.5 ± 52.7
c(max)	µg/l	183.7	161.8	72.9	303.4	377.0	116.7	207.1 ± 120.7
F	%	40.5	23.8	7.9	36.1	67.3	45.0	36.8 ± 20.0
<u>non-food</u>								
Ka	l/min	6.03	4.38	8.05	34.30	30.38	21.88	17.50 ±13.12
Kel	l/min	4.18	3.98	7.30	1.47	0.33	0.87	3.02 ± 2.64
t(lag)	min	50.9	77.0	80.1	88.4	67.5	88.9	75.5 ± 14.4
t(max)	min	248.9	316.7	210.4	184.3	218.1	254.4	237.3 ± 45.6
c(max)	µg/l	145.0	136.8	97.9	391.1	312.4	193.5	212.8 ± 114.6
F	%	47.8	31.2	10.0	36.5	66.8	37.2	38.3 ± 18.8
Θ	-	0.48	0.54	0.53	0.76	0.72	0.66	0.62 ± 0.11

D	Dose
Vd	Volume of distribution (β)
Kel	Elimination constant
Ka	Absorption constant
Cl	Clearance
F	Bioavailability
t(lag)	Lag time
t(max)	Time of the maximum in the plasma curve
c(max)	Maximum concentration in the plasma
Θ	Hepatic clearance

In Vivo Testing (9, 10)

The in vivo experiment was approved by the Medical Ethical Committee of the Leiden Univerity Hospital. 6 Healthy male volunteers (age 22-33, body weight 58-80 kg, all non-smokers except for subject G, no alcohol abuse) gave their informed written consent to participate in the following study design:
They were requested to withold all food and alcoholic beverages from 12 hours preceding the experiment. At the start of the experiment they received in a rando mized way either an oxprenolol tablet with 200 ml of water, an oxprenolol tablet with 200 ml of Nutridrink or an infusion of oxprenolol (10 mg in 100 ml, infusion time approximately 5 minutes). Blood samples were collected according to the following schedule: 15, 30, 45 minutes, 1, 1½, 2, 3, 4, 6, 8 and 12 hours. The volunteers took lunch at 4

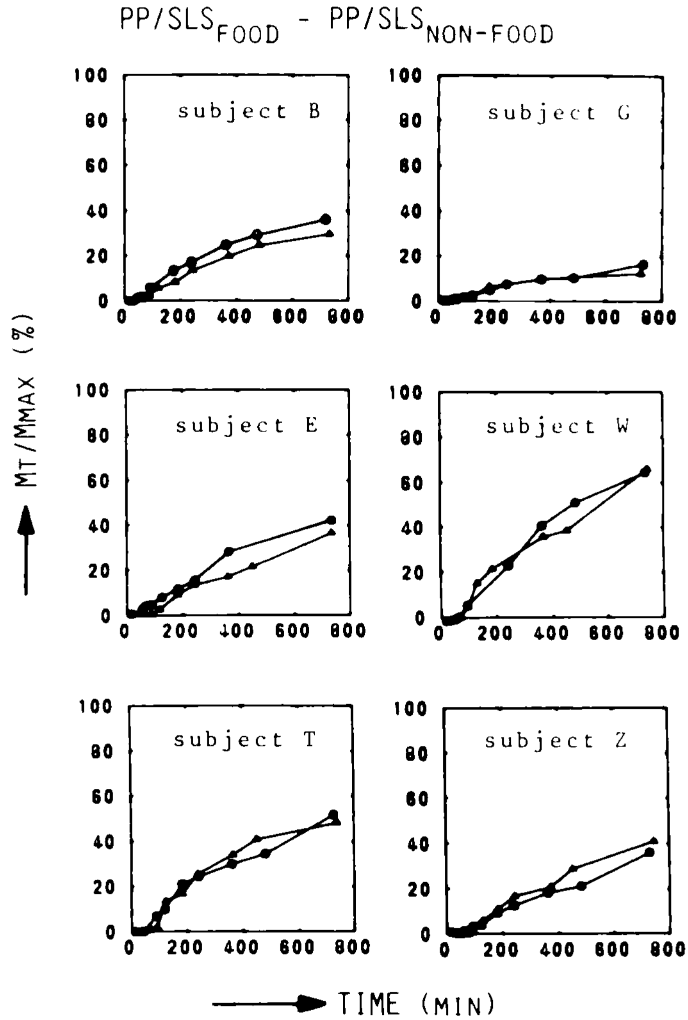

FIGURE 6
The figure shows the in vivo absorption curves for the individual volunteers:
(▲) food conditions and (●) non-food conditions.
The absorption curves were calculated by numerical deconvolution using the iv bolus injection as a reference.

hours after the start of the experiment. The GLC assay was performed according to Gyllenhaal et al (13).

The intra individual results of the in vivo experiments are given in table II. The calculated absorption plots for the six subjects (figure 6) strongly suggest the absence of interfering effects of food, prooving the success of the tablet formulation used. This was tested by analysis of variance showing no significant differences in absorption kinetics (subjects W, T, Z and G). For the other two subjects, although significant ($\alpha < 0.1$) these differences are small.

The average bioavailability after 12 hours was 37 ± 20 % when food was taken and 38 ± 19 % when the subjects took the tablet on an empty stomach. The peak plasma concentrations average 250 μg/l with only minimal intra-subject differences between the two oral experiments. The corresponding average time was approximately 4 hours. The absorption plots suggest a continuing absorption after 12 hours.

The interindividual absorption from the tablets is differing widely as can be expected for a drug having a large first-pass effect. In contrast, the intra-individual differences between food and non-food are minimal. This indicates that intra-subject variability between the two oral applications (in reference to the same iv. data set) is minimal, although there was a more than two week wash-out period between both experiments.

As a consequence it can be stated that the controlled release formulation is a succesful one for dosing oxprenolol during an interval of 12 hours or longer.

CONCLUSIONS

Microporous PP possesses favourable tabletting properties even at low compression forces without loosing its microporous strucure. Therefore, coated tablets with microporous PP show controlled drug release properties. The unfavourable interactions between microporous PP and food components can be neutralized by adsorbing SLS onto the surface of the particles. A sufficient strong adsorption complex between SLS and PP provides a good hydrophilization of this polymer material without loosing the excellent tabletting properties.

The developed in vitro food simulation model in order to detect possible food-dosage form interactions has been prooved to be useful in the optimization of dosage form concepts. Because this food simulation model is analoguous to the well known USP paddle method its applicability is versatile and can be used in all research laboratories to detect food-dosage form interactions in a very early stage in the development of controlled drug release dosage forms. In addition, the in vivo experiments can be performed under well standardized food conditions. Both data - from the in vivo and in vitro experiments - can then be compared as both use the same food mixture. To check the general applicability of the in vitro food interaction simulation model further investigations are necessary.

The developed coated tablet is able to control the release of oxprenolol at least 12 hours both with and without concomitant food intake. The bioavailability is comparable to an oxprenolol OROS-system containing 260 mg oxprenolol which should be released within 16 hours (14). The OROS formulation has been considered by many to be an ideal dosage form with an ideal dissolution profile. Given on an empty stomach Bradbrook et al. (14) found an absolute bioavailability of approximately 43 %. Their plasma concentrations peaked at approximately 220 µg/l after 5-6 hours. Langenbucher et al. (15) did evaluate the absorption profiles in vivo of two different OROS formulations of oxprenolol. They gave absolute bioavailabilities of resp. 42 ± 10 % and 43 ± 20 %. In our case we calculated a bioavailability (0-12 hours) of 38 ± 19 % on an empty stomach and 37 ± 20 % for the food experiment.

In comparison to other drug release systems, the coated oxprenolol tablet presented here will be a low cost formulation product. Unfortunately, toxicity studies about the chronical peroral use of microporous PP lack at this moment. Because of this handicap, an introduction of controlled drug release systems based on microporous PP is not possible at this moment.

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