In Vivo Validation of the Release Rate and Palatability of Remoxipride-Modified Release Suspension

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Remoxipride, a D2-dopamine receptor antagonist, is well tolerated and completely absorbed after oral administration. Because of its extremely bitter taste, an oral palatable suspension was developed by using a taste-masking microencapsulation. The bioavailability of remoxipride was investigated in two studies in healthy volunteers after administration of a 100-mg dose in suspension. The first study used a capsule as reference, and the second study a plain solution. Taste assessment was carried out in the second study. The extent of bioavailability was the same when comparing the oral suspension to a capsule and to a plain solution. However, the rate of absorption is delayed, and T_{max} was 3.0 hr after the suspension, 1.0 hr after the oral solution, and 1.6 hr after the capsule. The release rate *in vitro* from the suspension was determined by applying the USP-paddle method. By using numerical convolution and deconvolution, the release rates *in vivo* and *in vitro* were shown to be similar when using water with 0.5% sodium lauryl sulfate as dissolution liquid. The taste-masked oral suspension is suitable for full-scale production, with good control of the encapsulation process and of the preparation of a suspension.

KEY WORDS: remoxipride; modified release; suspension; bioavailability; convolution; deconvolution; dissolution.

INTRODUCTION

Remoxipride, a new antipsychotic drug, is a potent and selective dopamine D2 receptor antagonist. Thus, remoxipride has the potential to separate the benefits of control from the burden of side effects, such as extrapyramidal symptoms, and sedation, which is a problem for other neuroleptic drugs. Remoxipride has been administered to more than 1500 patients in controlled clinical studies in doses of 150 to 600 mg daily for 6 weeks or longer and has been shown to have antipsychotic activity and to be well tolerated (1–6).

The pharmacokinetics of remoxipride have been investigated in approximately 300 healthy volunteers after administration of single doses ranging from 0.5 to 140 mg and after repeated oral doses of 20, 70, and 140 mg three times a day. The drug is rapidly absorbed (7,8), with an oral bioavailability of above 90% compared to intravenous administration (9). It is well tolerated in single doses of 100 mg or less (10). Oral medication in tablet or capsule form can be a problem for those patients, particularly the elderly, who have difficulty in swallowing tablets. A solution or suspension formulation can facilitate drug-taking for such patients, thus increasing patient compliance. Because plain aqueous solution has an extremely bitter taste, a taste-masked formulation has been developed. A similar bad taste has been reported to be associated with most major neuroleptic liquid preparations (11). Taste-masking of drugs can be achieved by microencapsulation or related techniques (12–14), and it is required for improving patient compliance for certain groups of patients. The aim of the present study was to determine the rate and extent of bioavailability of microencapsulated remoxipride in suspensions with different *in vitro* characteristics and to establish specification limits of the *in vitro* release rate when considering the product manufactured both in small-scale and in large-scale production.

MATERIALS AND METHODS

Dosage Forms

Remoxipride Capsules, 100 mg. Remoxipride HCl monohydrate was mixed with lactose and granulated with polyvidone in water. The granulate was dried and lubricated with magnesium stearate before filling into hard gelatin capsules, No. 1.

Remoxipride Oral Solution, 50 mg/mL. Remoxipride HCl monohydrate was dissolved in water and no other additives were added.

Remoxipride Oral Suspension, 25 mg/mL. Remoxipride HCl monohydrate is freely soluble in water. In order to develop a palatable liquid formulation, a two-step manufacturing procedure has been developed. Step 1 is microencapsulation of remoxipride in wax and step 2 is preparation of the suspension. The microencapsulation procedure is performed in a spray-chilling apparatus where remoxipride is melted in wax at about 85°C. The melted substance is then applied through a tube connected to a rotating, vaned disk, forming droplets which, after solidification in cool air, are collected as microspheres in the bottom of the apparatus. The diameter of the microspheres is 150 μm (15).

In order to achieve a suspension of the remoxipride microspheres which prevents the drug from immediate dissolution, the microspheres are then suspended in a tasteless oily vehicle and thickened to give a proper viscosity. Sweetener and flavors are also added. The suspension had a viscosity of about 100 mPas, which maintains a homogeneous suspension for several days after shaking the bottle. The suspensions were produced at different scales (Table I). The bottles used for each volunteer in the bioavailability studies contained manually weighed microspheres and vehicle in order to get an exact dose of 100 mg remoxipride in 4 mL of suspension.

In Vitro Methods

Remoxipride Capsules, 100 mg. The *in vitro* dissolution of remoxipride from capsules was performed by using the paddle method (USP XXII, 500 mL water at 37°C, 50 rpm).

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Table I. Batch Sizes of Remoxipride Oral Suspension, 25 mg/mL, Manufactured

Formulation	Study	Production size: Microsphere	Production size: Suspension (kg)
Suspension A	1	300 g, 40% (w/w)[a]	3
Suspension B[b]	2	20 kg, 40% (w/w)	1200
Suspension C[b]	2	20 kg, 30% (w/w)	1200
Suspension D[c]	—	20 kg, 40% (w/w)	1200
Suspension E[c]	—	20 kg, 40% (w/w)	1200

[a] Payload of remoxipride in wax.
[b] Final filling in laboratory scale.
[c] Production.

Remoxipride Oral Suspension, 25 mg/mL. The same paddle method was used (USP XXII, 500 mL water, pH 7.1, phosphate buffer pH 4.1, or simulated gastric fluid without pepsin, pH 1.2, at 37°C and at 150 rpm). The suspension was added to the dissolution beaker after starting the paddle. Samples were withdrawn and analyzed by HPLC. The method had been optimized based on practical aspects, emulsifying capability, variability, and reproducibility. Accordingly the influence of agitation, volume of dissolution fluid, volume of added suspension, and surfactant have been studied. The following surfactants have been tested: sodium lauryl sulfate (SLS), cetrimide, DOSS, ethanol, Myrj 45, and Tween 80. Figure 1 describes the influence of the amount of surfactant added to the dissolution fluid. The *in vitro* dissolutions of the formulation studied are shown in Table II.

Design of the Studies

Two separate bioavailability studies were performed, one at the Department of Psychiatry at Huddinge University Hospital, Huddinge, Sweden (Study 1), and the other at the Royal Infirmary, Edinburgh, Scotland (Study 2). They were approved by the Ethics Committee at Huddinge Hospital and the Lothian Health Board Ethics Committee, respectively. All participants were fully informed both in writing and verbally about the purpose, investigational events, and possible risks involved with the studies. The volunteers were of both sexes and were healthy according to medical history, physical examination, blood and urine analysis, and ECG.

The studies were comparative, randomized, and crossover. Each volunteer was given a single dose of 100 mg remoxipride as one of three formulations. A washout period of at least 1 week elapsed between each treatment. After an overnight fast of minimum 8 hr and 150 mL tap water, given at least 1 hr prior to drug administration, the volunteers were given one of the formulations in the morning with 150 mL water. They continued fasting for a further 3 hr. A standardized lunch was served after the 3-hr sample. Further, a small meal and dinner were served 7 and 10 hr after drug administration, respectively. Venous blood samples (5 mL) were obtained from a cannula inserted in an antecubital vein or by

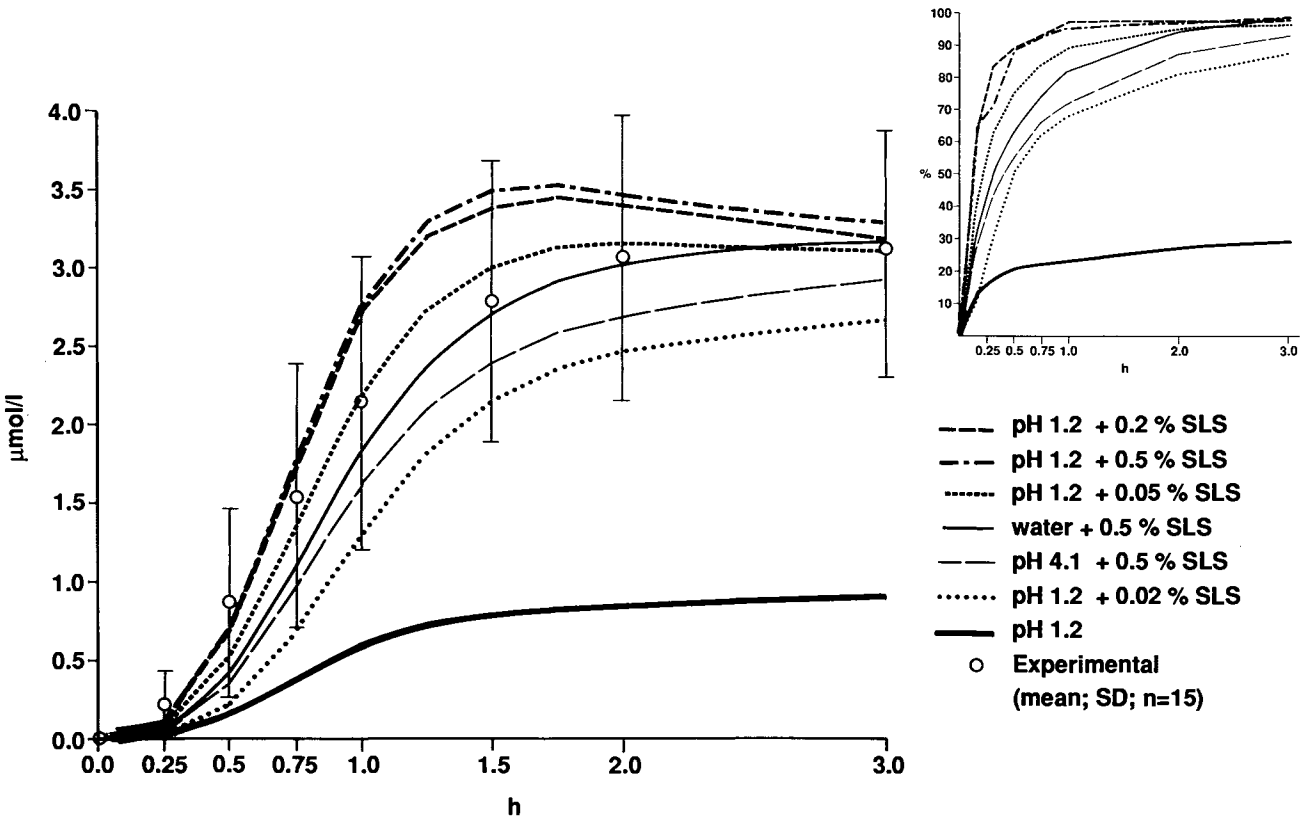

Fig. 1. Experimental plasma concentration of remoxipride versus time (mean; SD; $n = 15$) after 100 mg remoxipride in the modified release suspension A (Study 1). The curves are hypothetical levels derived by use of numerical convolution and the seven *in vitro* dissolution time functions, $I(t)$, shown in the inset.

Table II. *In Vitro* Dissolution of Remoxipride Capsules, 100 mg, and Remoxipride Oral Suspensions, 25 mg/mL: USP XXII Paddle Method, 500 mL, 37°C, and 150 rpm (50 rpm for Capsules)

Formulation	Study	Dissolution medium (a)	Percentage dissolved at time (min)						
			10	20	30	45	60	120	240
Capsules	1	Water	65	96	100	—	—	—	—
Suspension A	1	pH 1.2	46	72	83	92	95	101	—
		Water	32	42	—	53	65	80	91
Suspension B	2	pH 1.2	64	—	89	94	95	97	99
		Water	2		19	48	63	81	92
Suspension C	2	pH 1.2	40	—	68	76	80	87	93
		Water	2		13	31	43	63	79
Suspension D	—	Water	—	—	64	—	70	75	
Suspension E	—	Water	32	—	60	69	75	86	96

direct venipuncture and collected into heparinized Venoject tubes before and at scheduled times up to 30 hr after drug administration. The plasma was separated by centrifugation within 1 hr and transferred to polypropylene tubes. The samples were immediately frozen and stored at −20°C until assayed. Plasma concentrations of remoxipride were assayed by means of reversed-phase HPLC after a base extraction (16). The lower limit of determination was 0.02 μmol/L.

Study 1. Fifteen volunteers participated (seven men and eight women). Their mean characteristics were as follows: age, 27 years (range, 19–37 years); height, 176 cm (164–187 cm); and body weight, 68 kg (57–80 kg). An immediate-release capsule and a modified-release suspension (A) were compared.

Study 2. Fifteen volunteers were included. Two of them withdrew, one after contracting gastroenteritis secondary to food poisoning and one due to difficulty in the insertion of the sampling cannula. The mean characteristics of the remaining 13 (7 men and 6 women) were as follows: age, 26 years (range, 19–37 years); height, 168 cm (152–183 cm); and body weight, 67 kg (52–84 kg). A plain aqueous solution (reference formulation, A) and two modified release suspensions (test formulations, B and C), with different release rates *in vitro,* were compared.

Taste Evaluation. In Study 2 the subjects were requested to record their opinion of the taste of each formulation immediately after administration of the dose, using a 10-cm visual analogue scale, the extremes of which were marked "delicious—awful." Production batches were taste-tested by a taste panel from the laboratory, where 15 volunteers tasted the product in a standardized manner without swallowing. They recorded their judgment as 1 = awful, 2 = bad, 3 neither bad nor good, 4 = good, and 5 = delicious.

Data Analysis

Numerical Convolution and Deconvolution. A dose of an immediate-release capsule of remoxipride was considered a unit impulse to the gastrointestinal tract in Study 1, while a plain aqueous solution was used in Study 2. The plasma concentration–time course thus obtained was defined as the weighting function of the system [$W(t)$]. Predicted plasma response data [$R(t)$] for each suspension composition was obtained by weighting the *in vitro* release rates of the suspensions with the observed plasma concentration–time function of the solution by applying the convolution algorithm (17) in a computer program. The predicted plasma curves were compared with the experimentally found concentrations. The *in vivo* dissolution time functions [$I(t)$] were calculated by combining the observed plasma concentration–time function of the solution and the suspensions respectively, by means of deconvolution. The predicted *in vivo* release rates were compared to the experimentally found release *in vitro* expressed as a percentage.

The raw data in the algorithms were generated by the point-area method. Time intervals of 0.25–1.0 hr were selected and tested with linear interpolation of the functions involved.

Pharmacokinetics

Maximum plasma concentrations, C_{max}, and the time to reach C_{max} (T_{max}) were determined by each volunteer. The area under the plasma concentrations versus time curves, AUC (0–30 hr), was calculated using the trapezoidal rule. The log trapezoidal method was applied during the log-linear portion of the curve. The total area was estimated by adding the quotient of the last determinable plasma concentration and the overall elimination rate constant, β. The relative extent of bioavailability of the suspensions was found by comparing the total area obtained with the corresponding total area after administration of the solution.

Statistical Evaluation

Nonparametric methods were used because they are free of the assumption that the population distribution follows a specific parametric distribution. In order to study bioequivalence with respect to the relative bioavailability and the C_{max} ratio, and to estimate the difference in T_{max} between the different formulations, point estimates (Hodges–Lehmanns) (18) and 90 and 95% confidence intervals, respectively, were calculated by using the Wilcoxon sign rank statistic. For AUC and C_{max}, a complementary parametric analysis using the geometric mean and 90% confidence intervals based on the t distribution was also performed. The calculations of the AUC and C_{max} ratios were made in the natural logarithmic scale, but the point estimates and the lower and the upper confidence limits have been backtransformed.

Table III. Pharmocokinetic Parameters from Study 1 and Study 2 of Remoxipride Suspension, 100-mg Dose in Healthy Volunteers (Numbers in Parentheses Are Standard Deviations)

Formulation	C_{max} (μmol/L)	T_{max} (hr)	AUC (μmol/L hr)	β (L/hr)	$t_{1/2}$ (hr)	MRT (hr)	F (%)
Study 1 (n = 15)[a]							
Caps.	3.67 (1.15)	1.60 (0.82)	28.0 (9.4)	0.17 (0.03)	4.3 (0.8)	7.2 (1.3)	100
Suspension A	3.36 (0.81)	2.77 (1.03)	31.0 (9.5)	0.16 (0.03)	4.4 (0.8)	7.9 (1.4)	113 (20)
Study 2 (n = 12)[b]							
Solution	4.80 (1.14)	1.02 (0.94)	36.2 (9.6)	0.14 (0.02)	5.3 (1.08)	7.7 (1.48)	100
Suspension B	3.97 (0.84)	3.04 (1.53)	39.2 (13.4)	0.12 (0.03)	5.9 (1.22)	9.7 (1.89)	107 (16)
Suspension C	3.69 (1.07)	3.04 (0.96)	39.6 (14.3)	0.13 (0.02)	5.7 (1.35)	9.9 (2.27)	110 (27)

[a] No missing data.
[b] Three volunteers were excluded from the calculations.

The taste evaluation was analyzed by using the two-side Wilcoxon signed-rank test for paired comparisons in each volunteer. A P value less than or equal to 0.05 was considered significant. The data were analyzed by the release version 5.15 of SAS system under VMS.

RESULTS AND DISCUSSION

Relative Bioavailability

The mean pharmacokinetic parameters observed (C_{max}, T_{max}) and calculated (β, $t_{1/2}$, MRT, AUC, F) after administration of the different dosage forms in the two studies are given in Table III. The statistical evaluations are given in Tables IV and V. The results in Study 1 show that the suspension causes a prolonged MRT of 40 min, which indicates a delayed release from the dosage form in the gastrointestinal tract. A corresponding statistically significant formulation effect was observed in the T_{max} value. Mean maximum plasma concentrations of 3.7 and 3.4 μmol/L are reached within 1.6 and 2.8 hr after administration of the standard capsule and the modified release suspension (A), respectively. Since the calculated 90% confidence intervals for the relative extent of bioavailability and the C_{max} ratio lie within (0.8, 1.25) the suspension and the capsule, those are assumed to be bioequivalent. An overall elimination half-life of remoxipride of 4.2 hr (range, 3.1–6.1 hr) is obtained.

In Study 2 a mean maximum plasma concentration of 4.8 μmol/L is reached within 1 hr after administration of a plain aqueous solution. Significantly decreased concentrations of 4.0 and 3.7 μmol/L are attained 2 hr later after the two modified release suspensions B and C, respectively. A similar mean delayed release of 2 hr was calculated based on the MRT difference between the solution and each separate suspension. Measurable plasma concentrations were attained within 15 min in 12 of the 13 volunteers after intake of the solution, while the corresponding numbers are 5 and 3 after suspensions B and C, respectively. The three formulations are assumed to be bioequivalent according to the relative extent of bioavailability and the two suspensions are also bioequivalent with respect to C_{max}. There was no statistically significant difference in T_{max} between B and C. However, statistically significant differences in T_{max} were found in the comparisons of the suspensions with the solution. The overall elimination rate corresponds to an average half-life of 5.6 hr (range, 3.8–8.4 hr).

Taste Assessment

The results of the taste assessment from Study 2 are shown in Fig. 2. The two suspensions are significantly different from the aqueous solution (P = 0.0002), and the median score of the solution and suspensions B and C was 98, 35, and 47, respectively. The difference between the two

Table IV. Estimated Hodges–Lehmanns (H-L) and Confidence Intervals (c.i.) for the AUC, C_{max} ratios, and the Difference in T_{max}

	Comparison			
		Study 2 (n = 12)		
Variable	Study 1 (n = 15), Suspension A vs capsule	B vs solution	C vs solution	B vs C
F_{rel}				
H-L	1.08	1.07	1.07	1.01
90% c.i.	(1.03, 1.19)	(0.99, 1.15)	(0.92, 1.23)	(0.90, 1.11)
C_{max} ratio				
H-L	0.93	0.84	0.78	1.08
90% c.i.	(0.82, 1.06)	(0.75, 0.94)	(0.66, 0.89)	(1.01, 1.7)
T_{max} diff.				
H-L	1.19	1.73	2.00	0.00
95% c.i.	(0.38, 1.88)	(1.25, 2.54)	(1.23, 2.75)	(−1.00, 0.50)

Table V. Estimated Geometric Means and 90% Confidence Intervals (c.i.) for the AUC and C_{max} Ratios

Variable	Comparison			
	Study 1 (n = 15), Suspension A vs capsule	Study 2 (n = 12)		
		B vs solution	C vs solution	B vs C
F_{rel}				
Mean	1.11	1.06	1.07	0.99
90% c.i.	(1.04, 1.20)	(0.98, 1.15)	(0.95, 1.21)	(0.90, 1.09)
C_{max} ratio				
Mean	0.93	0.83	0.76	1.09
90% c.i.	(0.83, 1.06)	(0.75, 0.93)	(0.67, 0.87)	(0.99, 1.20)

suspensions was not statistically significant. The solution was ranked as awful by all volunteers, while the suspensions were considered between delicious and awful. Thus, the taste performance of the two suspensions is improved significantly compared to a plain solution of remoxipride. However, the difference in *in vitro* release rate is not large enough to distinguish between the taste of the two suspensions. The means of the individual taste scores given to two production batches were 4.0 in both cases, which corresponds to good.

Choice of Dissolution Method

The plasma concentrations of remoxipride after administration of the suspensions are shown in Figs. 1 and 3, achieved both experimentally and by using numerical convolution, $R(t)$, which facilitates the translation of *in vitro* dissolution data to an adequate *in vivo* response. Different hypothetical absorption profiles are thus obtained, depending on which *in vitro* data are used in the $I(t)$ function. It appears necessary to use a surfactant in the release liquid, and a good agreement is obtained in Study 1 between experimental plasma concentration values and hypothetically derived levels when using sodium lauryl sulfate in both artificial gastric juice and water. The concentrations during the initial 60 min of the absorption seem to be best described by using acid with 0.05% or more of the surfactant.

The plasma concentrations predicted in Study 2 corresponded best with the experimental values for the two suspensions obtained with water and surfactant as *in vitro* dissolution medium. From the results it is apparent that acid with the same concentration of surfactant predicts plasma curves with large deviations from the actual values found, especially during the initial hour.

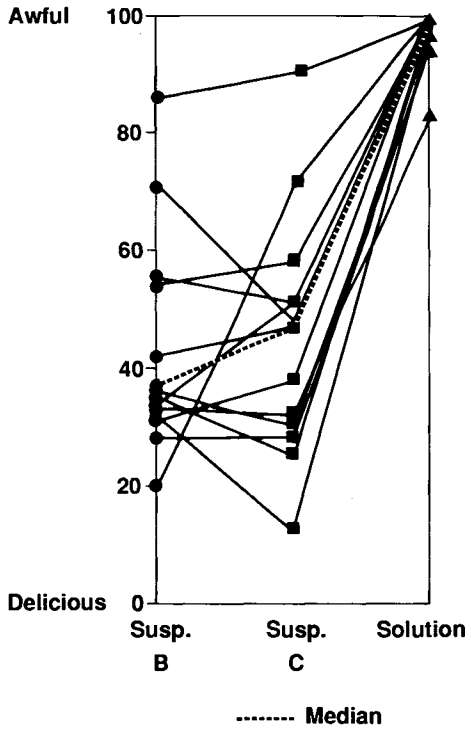

Fig. 2. Individual and median judgment of taste of two modified-release suspensions (B and C) and an aqueous solution of remoxipride.

Dissolution Rate Specifications

A plot of percentage remoxipride released *in vitro*, calculated by applying numerical deconvolution, *versus* percentage released *in vitro* from the two suspensions in Study 2 reveals a good correlation, and the regression line was calculated to be $Y = 1.1 \cdot X - 4.8$ ($r = 0.97$; MSE = 84.2) (Fig. 4). The slope of 1.1 indicates a similar release rate *in vitro* and *in vivo*. By using water and 0.5% SLS, it thus seems possible to predict the bioavailability and the release rate from the suspensions *in vivo*. Since the two suspensions were judged to be bioequivalent, the dissolution rates might be used as the lower and upper limit of the product specification.

The two production batches investigated have comparatively faster dissolution rates than the two suspensions tested in Study 2, but similar rates to the laboratory batch of Study 1 (Table I). The difference in release rate might be attributed to the scale of manufacturing, to batch-to-batch variability, and to the reproducibility of the dissolution method. However, since the taste of the production batches was judged to be good, it is not considered necessary to establish an upper dissolution rate limit. This is consistent with our previous experience with another extremely bitter compound that was taste-masked using a similar technique (14). The taste assessment versus *in vitro* dissolution rate was investigated in that case, and the taste was only slightly

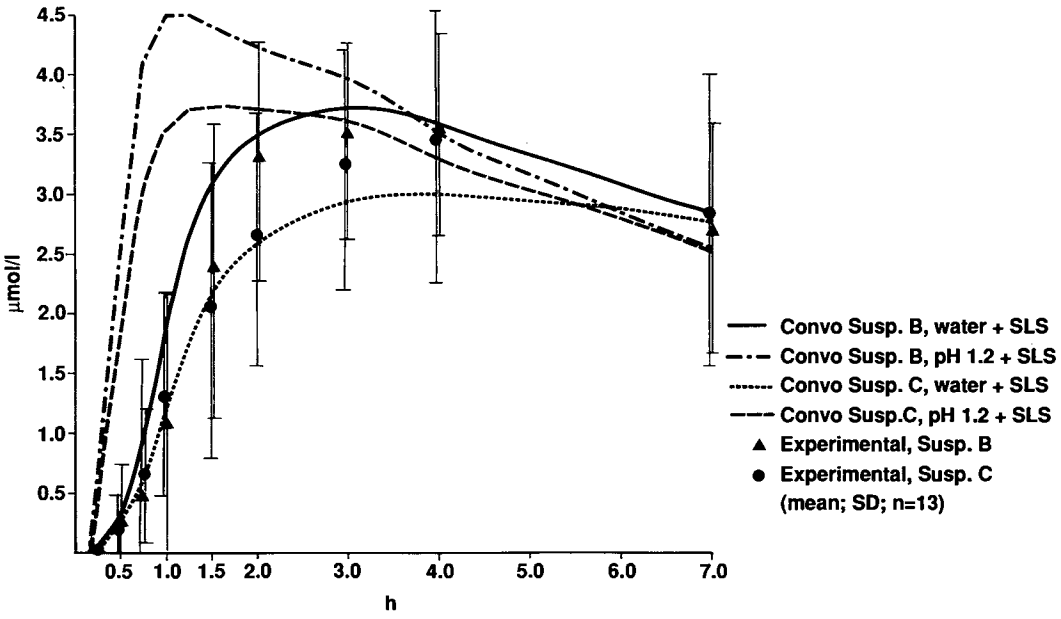

Fig. 3. Experimental plasma concentrations of remoxipride versus time (mean; SD; n = 13) after 100 mg remoxipride in the modified release suspensions B and C (Study 2). The curves are hypothetical levels derived by use of numerical convolution and two *in vitro* dissolution time functions, $I(t)$.

improved when using a more slowly dissolving modified release formulation. For remoxipride, one can now specify a lower release limit of the suspension that avoids impaired bioavailability.

In conclusion, a palatable suspension of the bitter-tasting neuroleptic compound, remoxipride, was developed based on microcapsules dispersed in an oily vehicle. Large-scale production batches are produced with reproducible release properties.

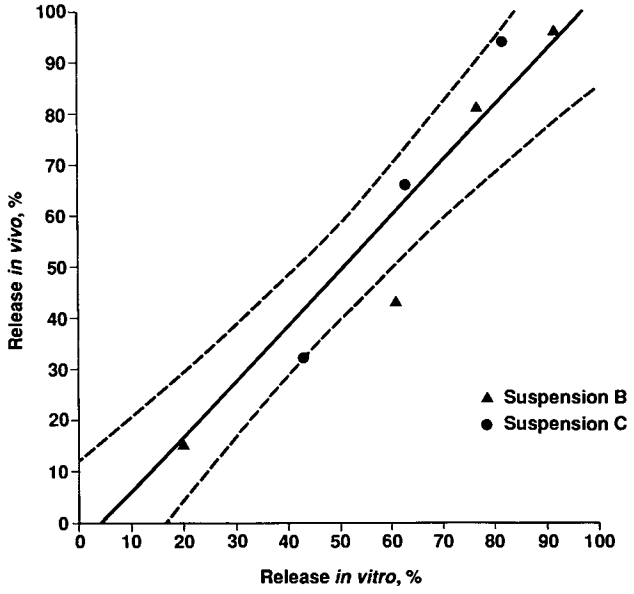

Fig. 4. Release rate of remoxipride *in vivo* versus *in vitro*, from the modified release suspensions B and C (confidence level, 95%).

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