Drug Development and Industrial Pharmacy, 23(8), 749–760 (1997)

RESEARCH PAPER

Critical Dissolution Tests of Oral Systems Based on Statistically Designed Experiments. I. Screening of Critical Fluids and In Vitro/In Vivo Modelling of Extended Release Coated Spheres

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ABSTRACT

Different compositions of in vitro dissolution fluids have been developed and used in screening experiments during the development of ethylcellulose ER-coated spheres of the model drug remoxipride. The composititon were different with respect to pH, temperature, osmotic pressure, viscosity, agitation, ionic strength, polarity of the medium, type, and concentration of surfactant. By using a chemometric methodology all the variables were varied independently at the same time, and the results were connected in a mathematical model which described the experimental domain. The most significant main effects on the amount of remoxipride released at all timepoints were caused by polarity, temperature, and agitation. The mathematical model was used to predict the in vitro condititons that was best associated with the in vivo data, obtained after administration of the formulation to sixteen volunteers. A verifying experiment showed a close connection between the predicted and experimental in vitro dissolution profile up to 4 hr, but thereafter (up to 24 hr) the profiles deviated. It is obvious that the conditions need to be further optimized. However, the present approach to stress oral dosage systems during the development phase seems very promising.

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INTRODUCTION

In vitro dissolution testing of oral dosage forms is an important tool, not only to assure product uniformity, but to also screen and optimize formulations during product development. Stressed conditions are encouraged in the latter case to detect possible critical formulation variables. The tests are performed by several types of apparatus, e.g., the Paddle, the Basket, and the Flow-Through. Guidelines have been issued proposing compositions of media for use during product development (1,2,3). These liquids are aimed at mimicking the physiological conditions of the gastrointestinal tract considering pH, agitation, and temperature. Further additives could be considered in specific cases, i.e. fat, enzymes, bile, and surfactants (4). However, the complexity of the gastrointestinal environment is high, and its physico-chemical properties are too complicated to allow perfect modelling in vitro. Still, it is possible to identify and simulate some of the individual variables that a dosage form is exposed to. Because some of these are controlling each other (Figure 1), the choice of their levels is limited. In addition to these variables of physico-chemical nature, there are others present such as age, diet, health, and genetic background that might have an influence.

A correlation between drug dissolution in vitro and in vivo is necessary if the test is meant to assure batch-to-batch bioequivalence, but this is not always achievable. One possible reason for poor correlation is the choice of irrelevant in vitro testing conditions (3). However, when a meaningful correlation is obtained, the conditions apply to the specific drug formulation studied. It is therefore necessary to know which variables affect the in vitro dissolution in order to achieve a good correlation between dissolution in vitro and in vivo.

A classical approach to experimentation is to study the effects of one variable while keeping all other constant. The methodology of statistical experimental design (chemometry) has the ability to vary all the variables independently at the same time and connect the results in a mathematical model, which describes the investigated experimental domain. The model may also include

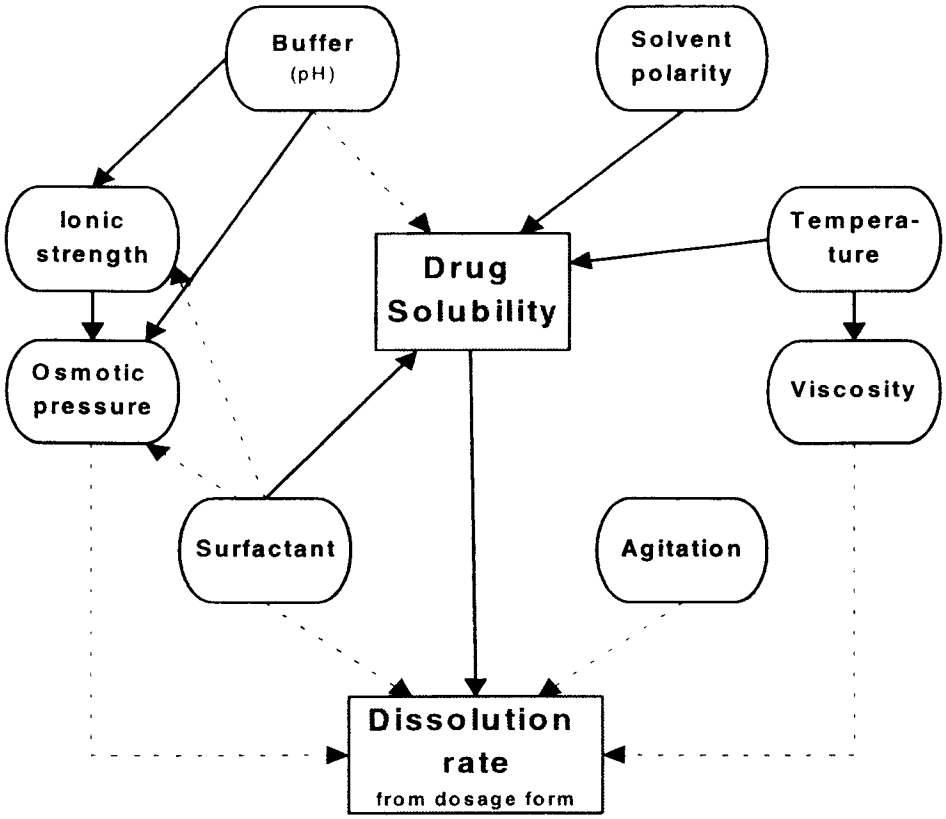

Figure 1. Variables that may affect the solubility and dissolution rate of a drug. The solid lines (——) indicate known interaction effects while the broken lines (---) only indicate possible effects.

quadratic and interaction relationships between the variables and the responses.

Although the present study is focused on an ER formulation, it is hoped that the approach of using statistical experimental design for stressing oral dosage forms in the development phase could be applicable on other systems. The aims of this project are:

- to develop different compositions of dissolution fluids, for stressing products in the development phase,
- to use statistical experimental design in the performance and evaluation of such in vitro dissolution tests, and
- to investigate if the obtained in vitro dissolution data correlates with the in vivo dissolution behavior of ER spheres containing a model drug, and if so, use the data to find a model that has the ability to predict appropriate in vitro testing conditions.

EXPERIMENTAL SECTION

Materials

All chemicals were of analytical grade. The used substances were hydrochloric acid 5 M, sodium chloride, sodium acetate anhydrous, magnesium chloride hexahydrate, acetic acid 100 %, tris(hydroxymethyl)-aminomethane, potassium oleate, glucose, ethanol 99.5%, polysorbate 20 (Tween® 20, ICI, Great Britain), povidone 90 (Kollidon®, BASF AG, Germany), taurocholic acid sodium salt (SIGMA Chemical Company, Sweden), and remoxipride spheres 300 mg (pKa 8.9), batch number TI 3020 (Astra, Södertälje, Sweden). The spheres, were manufactured by extrusion and spheronization of remoxipride HCl monohydrate, and microcristalline cellulose. Thereafter a coating was performed on the dried cores in a fluidized bed apparatus using the polymer ethylcellulose 10 cps (Dow Chemicals Inc., USA) and the plasticizer triethyl citrate. The solubility of remoxipride in water and in ethanol is is 0.30 g/ml and 0.40 g/ml, respectively (5). Milli-Q water was used as a solvent in the preparation of the fluids.

METHODS

In Vitro Dissolution Test

The in vitro dissolution test was performed using the Apparatus I (Basket) method (6). The apparatus was

Table 1

Dissolution Conditions and Compositions of the Fluids

Exp No	pH	Agitation (rpm)	Osmotic Pressure (mmol/kg)	Temperature (°C)	Conc. Surfactant (mM)	Surfactant	Viscosity (mPas)	Polarity (% ethanol)
1	1.2	50	300	36	0	nonionic	1	0
2	8.6	50	300	36	0.015	nonionic	30	50
3	1.2	150	300	36	0.015	anionic	1	50
4	8.6	150	300	36	0	anionic	30	0
5	1.2	50	500	36	0.015	anionic	30	0
6	8.6	50	500	36	0	anionic	1	50
7	1.2	150	500	36	0	nonionic	30	50
8	8.6	150	500	36	0.015	nonionic	1	0
9	1.2	50	300	38	0	anionic	30	50
10	8.6	50	300	38	0.015	anionic	1	0
11	1.2	150	300	38	0.015	nonionic	30	0
12	8.6	150	300	38	0	nonionic	1	50
13	1.2	50	500	38	0.015	nonionic	1	50
14	8.6	50	500	38	0	nonionic	30	0
15	1.2	150	500	38	0	anionic	1	0
16	8.6	150	500	38	0.015	anionic	30	50
17–19	4.9	100	400	37	0.0075	nonionic	15	25
20–22	4.9	100	400	37	0.0075	anionic	15	25
23	4.9	100	400	37	0.0075	nonionic	15	50
24	4.9	100	400	37	0.0075	nonionic	15	0

calibrated using USP prednisone and salicylic acid tablets. The liquids are apparent from Table 1, and were used in a randomized order. The volume of the vessels was 900 ml. Samples were taken at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 420, 480, 540, and 600 min. The amount remoxipride dissolved was detected spectrophotometrically (Philips spectrophotometer Unicam 8700, Great Britain) at 286 nm.

Dissolution Medium

The media were prepared by mixing all the components for at least two hours, by using a magnetic stirrer. In order to avoid evaporation, the ethanol was added after that a homogenous solution was obtained. Since it was not possible to deaerate the final medium composition, the deaeration by helium (20 min) was only performed on the used water.

pH

The pH-measurements of the aqueous fluids were performed by a digital pH-meter (pHM 92, Radiometer, Copenhagen) with a combined electrode (GK2321 C). The fluids that contained ethanol were measured by a glass electrode (G202B) and a lithium chloride reference electrode (K901) (7).

Buffer-Capacity

Hydrochloric acid and acetate-buffer were titrated with 100 mM sodium hydroxide and the tris-buffer was titrated with 100 mM hydrochloric acid. By using equation 1 the buffer-capacity, β, was calculated:

$$\beta = \Delta c/\Delta pH \quad (1)$$

where Δc is the number of moles of alkali or acid needed to change the pH of 1 litre of solution by an amount of ΔpH.

Ionic Strength

Magnesium chloride was used to adjust the ionic strength. Magnesium chloride was chosen instead of sodium chloride since it has a small effect on the osmotic pressure. The required amount was calculated by using Equation 2.

$$I = 1/2 * \Sigma (mz^2) \quad (2)$$

where m is the molality of the solution and z is the charge of the ion. The summation is continued over all the different components of the solution.

Osmotic Pressure

Glucose was used to adjust the osmotic pressure. The glucose was added according to a calculated starting point and then experimentally titrated to the obtained values by measurements of the osmotic pressure. The measurements were carried out at about 20°C, using an osmometer based on freezing point depression (Knauer osmometer, model M, Germany). Mean values of two measurements were calculated. The measured values differed 15% at the most from the set values. Because of limitations in the method, it was not possible to measure the osmotic pressure of fluids containing ethanol.

Interfacial Tension

An interfacial tensiometer (Kruss type K8, Germany) was used to check the interfacial tension of potassium oleate and polysorbate 20. The determinations were carried out in water at about 20°C. Mean values were calculated of three measurements. The interfacial tensions were within physiological range.

Viscosity

A rotational viscosimeter (Contraves rheomat 135, measuring system MS 0) was used to determine the viscosity of the fluids after addition of povidone 90 (24–46.5 g/l, depending on the presence of other components). The shear rate and shear stress were 184.1 s^{-1} and 5.7 N/m^2, respectively, and the measurements were repeated twice. The temperature of all the samples was 20°C, but since the in vitro tests were performed at 36 to 38°C, the viscosity was checked at these temperatures. The measured values at 36 to 38°C were about 5–10 mPas below the set levels (standard deviation of 3–8%) based on 20°C measurements.

Polarity

In addition to the ingredients effect on polarity, the polarity of the dissolution fluids were adjusted by adding ethanol 99.5%. A Q meter (Q metre type M803A, no 1833, voltmetre de Crete, type AC 103A, no 332, France) was used to check the dielectric constants of the fluids. However, since the apparature does not allow measurements of buffer-solutions, the measurements were carried on pure water-ethanol mixtures (25 and 50% ethanol). The temperature of the samples was 37°C.

Statistical Experimental Design

The computer program used to set up the statistical experimental design was Modde 2.1 (Umetri AB, Umeå, Sweden). All the variables were quantitative, except for the type of surfactant, which was qualitative (see Table 1). The effects of the variables, varied from a low to a high level, were expressed as percent dissolved remoxipride at specified timepoints from 30 to 600 minutes. The used fractional factorial design was a 2^{8-4} design leading to $2^4 = 16$ runs. In order to examine the reproducibility, replicates were added to the center of the design. Since two types of surfactants were used, the number of replicates were six, i.e. three experiments including each type. When evaluating the obtained in vitro dissolution data, two experiments were added to the design (exp. no. 23, 24) to investigate if ethanol was the source of the obtained curvature in the model. These experiments were run with all the variables at their mid-levels, except for ethanol which was varied at a low and a high level.

Multiple linear regression (MLR) was used for the test on fitting each of the responses to the variables. This was a design of resolution IV, which shows main effects and two-factor interactions, but confounds two-factor interactions with other two-factor interactions (8) (see Table 2). To explore the effects from the two-factor interactions it is therefore necessary to use another design, e.g, a full factorial design.

In Vivo Study

The in vivo study was performed at the Medeval Clinical Investigation Unit, University of Manchester, Manchester, England. Each volunteer was fully informed both in writing and verbally about the purpose, investigational events, and possible risks involved with the studies. The subjects were healthy according to medical history, physical examination, laboratory tests, and ECG. Sixteen male volunteers in the age of 20–45 years participated.

The study was conducted as a randomized, double-blind crossover design with two treatments separated by a washout period of one week. The treatments were a single 150 mg ER capsule and a single 1.5 ml (75 mg) dose of remoxipride solution (50 mg/ml stength). The subjects were fasted from 22.00 hr the night prior to drug administration, until one hour after dosing when a light standard breakfast was provided. A standardized light lunch was given about 4 hr post-dosing, a small meal at 7 hr and a hot evening meal 10 hr post-dosing. The capsules were administered with approximately 150 ml tap water. Venous blood samples (5 ml) were taken at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 30, 36, and 48 hr after dosing. They were immediately placed in tubes containing lithium heparin-coated interfacing granules and centrifuged at 3000 rpm for ten minutes. They were then transferred to plastic tubes and stored at approximately −18°C until assayed. Plasma concentrations of remoxipride were determined by means of reversed-phase HPLC after a base extraction (9).

Data Analysis

The mean in vivo release of remoxipride from the spheres was calculated by numerical deconvolution of the individual plasma concentration versus time curves (10). The algebraic deconvolution integral, Equation 3, is based on the theory that the body reacts as a linear system to drug input.

$$I(t) = R(t) \,//\, W(t) \tag{3}$$

The plasma concentration versus time curve following administration of the solution was defined as the weight-

Table 2

The Confoundings of the Interaction Terms Included in the Models. One Interaction Term May Be the Result of One of Three Combined Variables

Interaction Terms	Confoundings		
et*coA	os*te	sp*am	pH*vi
et*pH	sp*te	os*am	coA*vi
et*sp	pH*te	os*vi	coA*am
et*os	te*coA	pH*am	sp*vi
et*vi	sp*os	pH*coA	te*am
te*vi	pH*os	sp*coA	am*et

ing function (W(t)) of the system, the corresponding curve following the ER capsule was considered the response function of drug into the body (R(t)) and the obtained dissolution curve was the input function (I(t)).

The calculations were performed by a program developed within RS/1 Command language (BBN Software Products Corp.). The adaption of the in vitro data to the deconvoluted in vivo data was made by using the function Solver in Microsoft Excel 5.0 c.

RESULTS AND DISCUSSION

Development of the Dissolution Media

pH, Ionic Strength, and Osmotic Pressure

The pH values in the stomach and small intestine are 1–8, which correspond to the ionic strengths of 0.11–0.14 (11). Our initial aim was to use a low pH of 0.80, in accordance to the recommendations from the Commission of the European Communities. However, a hydrochloric acid buffer with such a pH has an ionic strength of 0.21 and an osmotic pressure of about 380 mmol/kg. Because of the dependance between the variables, the ionic strength was fixed at 0.10, with the possibility to have the low level of the osmotic pressure close to isotonicity. The low pH level was thereby increased to 1.2. Buffers of 80 mM hydrochloric acid, 50 mM tris and 50 mM acetate were used to control the pH levels to 1.2, 4.9, and 8.6, respectively.

Interfacial Tension

A non-ionic and an anionic surfactant were used to simulate the interfacial tension of the gastrointestinal tract, which is 35–50 mN/m (11). A cationic surfactant is rarely seen in vivo, and was therefore excluded. The choice of the two surfactants was mainly based on the HLB-numbers, 16.7 and 20.0 respectively (12, 13, 14), which are similar to those of bile salts (15). The aim was to compare the effect of the two surfactants in an equal number of non-aggregated molecules, e.g. in a submicellular range, and therefore the chosen interval was 0 to 0.015 mM, which corresponds to an interfacial tension of about 47–70 mN/m (polysorbate 20) and 65–70 mN/m (potassium oleate). This is somewhat higher than the physiological values.

Viscosity

The chosen interval for viscosity is wider than explained by literature data, which say 1–3 mPas (stomach) and 5–8 mPas (small intestine), during fasted conditions (11). The high value of 30 mPas will, thus, stress towards possible food effects. Povidone was chosen as a viscosity increasing agent based on its ability to act in the used pH conditions and on its solubility in ethanol (16).

Polarity

In an earlier study, a slower initial release of remoxipride was shown in vitro compared to in vivo (17). Therefore we decided to chose the polarity of the medium as a way to stress the properties of the ethylcellulose ER-coated spheres, since both the solubility of the drug and the release from the dosage form are expected to vary due to this. Hence, the polarity was adjusted by adding ethanol in levels that were based on the solubility of remoxipride in water and in ethanol. The dielectric constants of 25 and 50 % ethanol-water solutions at 37°C are 66 and 50, respectively. The literature values of pure water and ethanol at 25°C are about 78 and 24, respectively (7). Ethanol is of course an unphysiological component but nevertheless the polarity might be an interesting factor when the aim is to stress the robustness of a formulation.

Evaluation of In Vivo Drug Release

The mean pharmacokinetic data of remoxipride after administration of the ER formulation to man, are presented in Table 3. The deconvolution of the individual plasma concentration versus time curves of the sixteen subjects resulted in a mean in vivo release profile, as shown in Figure 2. After 10 hr, 50% of the dose is released and almost the whole dose, 90%, is released after 24 hr.

Evaluation of In Vitro Drug Release

Due to the experimental design, eighteen different drug release profiles were obtained (Figure 2). It is apparent that the release from the spheres is affected by the tested variables. Three groups were obtained depending on whether ethanol was varied at a low or a high level in the experiments. Hence, the upper release profiles in the figure represents the experiments where ethanol was varied at a high level, whereas the lower profiles represents the experiments where ethanol was varied at a low level. The profiles in the middle are the center points.

Table 3

The Mean Pharmacokinetic Data of Remoxipride Following Administration of a Single 150 mg ER Capsule of Remoxipride to Young Healthy Male Volunteers

	C_{max} (μmol. L^{-1})	t_{max} (hr)	AUC (μmol. L^{-1}.h)	$t_{1/2}$ (hr)	Cl/F (Lh^{-1})	Vss/F (L)	MRT (hr)	Ae (μmol)	ClR (Lh^{-1})	F
Mean	2.46	5.95	47.01	7.63	8.43	122.22	14.88	64.95	1.49	0.98
s.d.	0.7	1.71	17.87	2.2	2.87	34.72	1.85	27.07	0.64	0.31
CV (%)	28.3	28.8	38	28.28	34	28.4	12.4	41.7	43.2	31.5

Modelling of the Data

The fitting of the dissolution responses required the use of four statistical models, where each model represents a time interval, as shown in Table 4.

Besides, it was necessary to add a quadratic term and interaction terms to get an adequate fitting. The addition of two experiments to the design (exp. no. 23, 24), see Table 1, confirmed that the polarity caused the quadratic term and contributed to the curvature. The fraction of the data that is explained by the model, R2, were over 0.90 in all four cases. The predictive measure, Q2, was found to be over 0.90 in all except in model IV, which had values between 0.82–0.93. Thus, the best prediction was obtained during the first two hours. A plot of the percent remoxipride dissolved in the different liquids at 30 min versus the predicted value, is seen in Figure 3. A relationship close to linearity is obtained, which indicates a good model. The plot is based on model I, but it is also representative of model II, III, and IV.

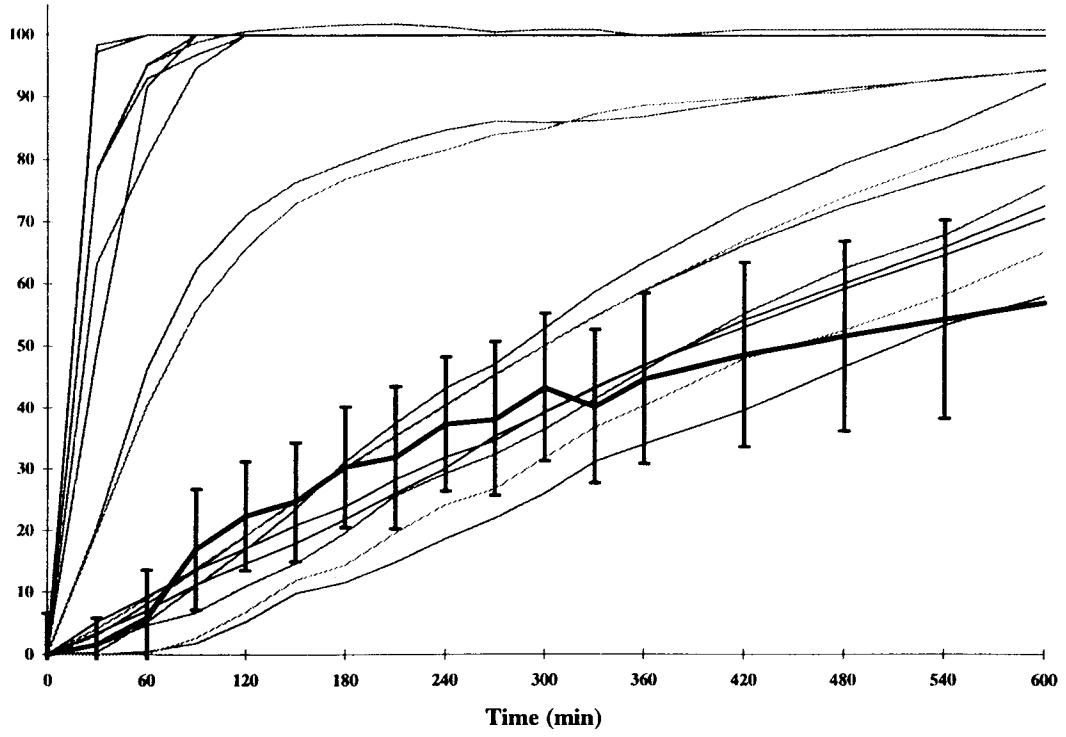

Figure 2. The dissolution profiles of 300 mg remoxipride spheres in fluids according to Table 1. The in vivo dissolution curve was calculated by deconvolution (N = 16). Error bars denoted as standard deviations.

Table 4

The Linear Interaction—and Quadratic Terms Included in Each MLR Model. R2 and Q2 Values Greater Than 0.9 Indicate Excellent Models

Statistical model	Responses (min)	Variables	Interaction Terms	Quadratic Term	R2	Q2
I	30	all	et*CoA et*te et*os, te*vi	et*et	0.979	0.867
II	60	-coA, Am	et*os te*vi	et*et	0.990	0.964
III	90	-coA, Am, os	et*vi	et*et	0.992	0.982
IV	120–600	all	et*pH et*sp et*te et*vi	et*et	0.987–0.996	0.816–0.933

- = these variables were not included; te = temperature; et = etanol; os = osmotic pressure; sp = agitation; vi = viscosity; coA = surfactant concentration; Am = type of surfactant.

Replicates

The variance within the replicates, which is shown in Table 5, supports a good reproducibility at the investigated timepoints except at 30 min for the replicates based on the anionic surfactant (potassium oleate). A two-factor Anova test ($p = 0.05$, $n = 3 + 3$) with replication showed a significant difference between the replicates including a nonionic surfactant and those including an anionic surfactant at 300 and 600 min. No difference was detected between the different vessels.

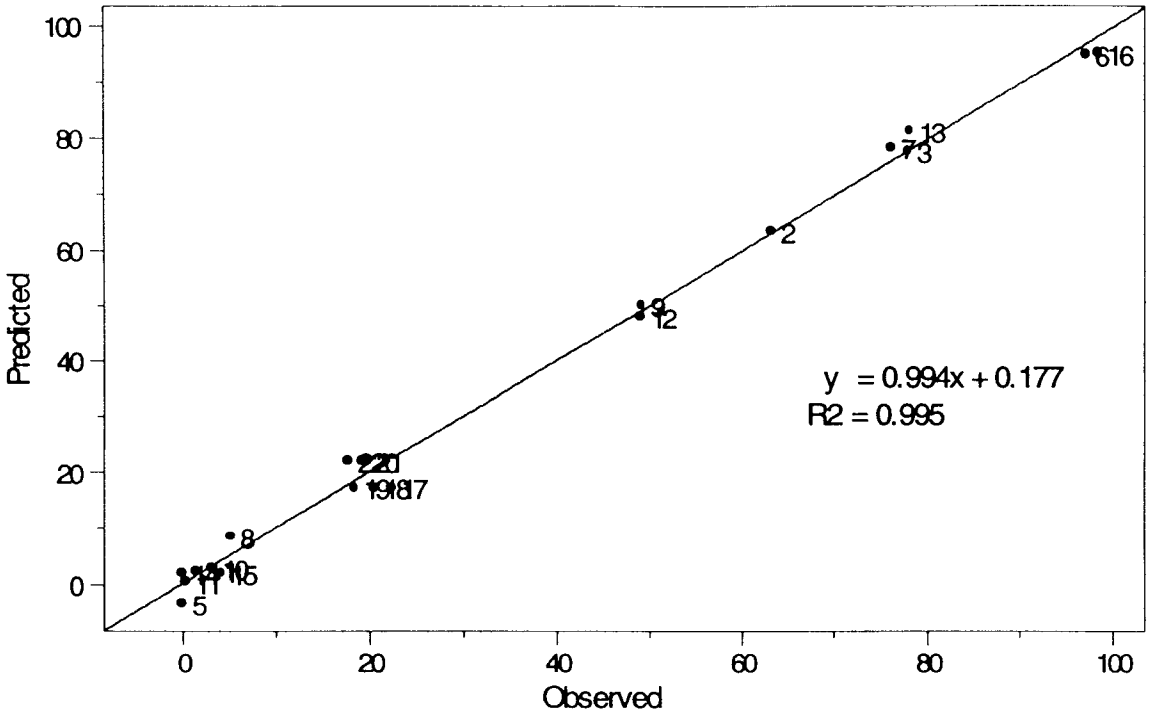

Figure 3. A plot of the observed values versus the predicted values at 30 min. The numbers which form the line are the experiments numbers.

Table 5

The Variance Within the Replicates at 30, 300, and 600 Minutes

Time (min)	30	300	600
Polysorbate 20	5.6	8	4.7
Potassium oleate	30.2	5.7	6.4

Effects of Investigated Variables

The present study is a screening and all the variables were expected to contribute to the dissolution profiles. However, based on the results only the polarity, agitation, and temperature, were observed to have significant effects at almost all time intervals (Figure 4).

The following effects were seen during the interval of 30–600 min:

— polarity, i.e. an addition of 50% ethanol contributed to a large increase in the amount remoxipride released. The effect reached a maximum of 94 ± 4.3% at 90 min. The remoxipride spheres are coated with an ethylcellulose film, and one probable explanation is that the properties of the film are changed in the solvent. However, the shape factors of the different dissolution profiles, calculated according to the Weibull function (18), were almost the same when less than 25% ethanol was used. On the contrary, the experiments that contained up to 50% ethanol produced curves with shape factors that deviated.

— an increased agitation affected the release from the spheres positively after 150 min. The maximum increase was 7 ± 3.1% (600 min). This effect is consistent to our previous observations (18) and is caused by the decreasing thickness of the diffusion layer around each sphere.

— a higher temperature had a significant effect only after 150 min. The maximum increase of the amount of remoxipride released was 7 ± 3.2% (420 min). The effect is explained by the increased solubility of the drug. However, the temperature may also affect the permeability of the ethylcellulose film.

— an increase of the osmotic pressure from 300 to 500 mmol/kg increased the release from the

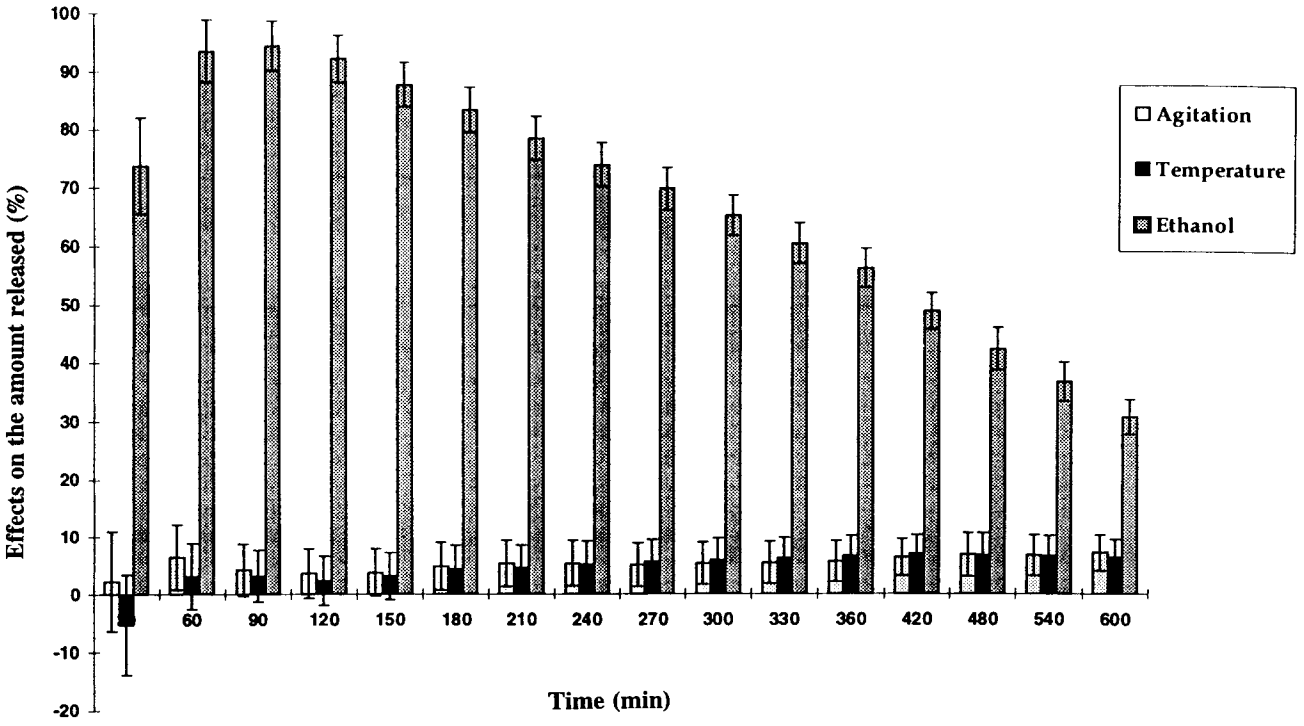

Figure 4. The effects of the most significant variables during all timepoints, from 30 to 600 min on remoxipride spheres. The error bars indicate confidence intervals.

spheres with 14 ± 8.7% during the first 30 min, but had no significant effect at other timepoints.
— the quadratic term ethanol and ethanol was significant at all the timepoints except at 90 min. The effect, which was 39 ± 16.4% at the most, was positive initially but became negative at the other timepoints.

In accordance with our previous study (17), no significant effect of the pH was observed. Neither was there any effect due to the type and concentration of surfactant used. Since the use of bile salts is common, an additional in vitro test was made to compare the effects of the bile salt taurocholic acid sodium salt, and the nonionic surfactant polysorbate 20. The tested in vitro conditions were pH 8.6, osmotic pressure 300 mmol/kg, agitation 100 rpm and temperature 37°C. The surfactants were added to the media in concentrations that correspond to 2%, 0.016 mM (polysorbate 20) and 0.037 mM (Na-taurocholate), which are well below the critical micelle concentrations 0.049 mM and 3–11 mM, respectively. The dissolution rate was equally affected by both, which means that the profiles differed 2.7% at the most and consequently there was no significant difference between the surfactants.

In Vitro/In Vivo Correlation

The different dissolution data in vitro, and the calculated dissolution curve in vivo, were used in the search for a model that can predict the in vitro conditions that are best associated with the in vivo dissolution behavior. The equation used was:

$$\begin{aligned}\%\ \text{Dissolved} = {} & \text{Constant} + (\beta_{pH} * pH) + (\beta_{sp} * sp) \\ & + (\beta_{os} * os) + (\beta_{te} * te) \\ & + (\beta_{coA} * coA) + (\beta_{am(K\text{-}pleat)} \\ & * am(k\text{-}oleat)) + (\beta_{vi} * vi) \\ & + (\beta_{et} * et) + (\beta_{et}^2 * et * et) \\ & + (\beta_{et} * \beta_{pH} * et * pH) \\ & + (\beta_{et} * \beta_{sp} * et * sp) \\ & + (\beta_{et} * \beta_{os} * et * os) \\ & + (\beta_{et} * \beta_{te} * et * te) \\ & + (\beta_{et} * \beta_{vi} * et * vi) \\ & + (\beta_{et} * \beta_{coA} * et * coA) \\ & + (\beta_{te} * \beta_{vi} * te * vi)\end{aligned} \quad (4)$$

where β corresponds to the unscaled and regular coefficients calculated in Modde and the constant represents the mean value of all the coefficients. Other expressions are explained in Table 2. The difference sum of squares, which is the difference between the in vivo curve, and the predicted in vitro curve, was calculated according to Equation 5 and had a value of 224.5.

$$\Sigma_i = (y_{\text{in vivo}} - y^A_{\text{predicted}})^2 \quad (5)$$

The best in vitro conditions predicted by the model were temperature 37.0°C, agitation 50 rpm, pH 1.2, osmotic pressure 600 mmol/kg and ethanol 6%.

A verifying experiment showed a close connection between the predicted and the experimental in vitro dissolution profile up to 4 hr (Figure 5). Thereafter there was a deviation of 10–15% between the two curves. The difference sum of squares was 1551.1, indicating a poor conformity with the predicted in vitro curve.

An additional test of the model was made after excluding the dissolution media containing povidone and surfactants. The predicted in vitro conditions obtained in this case were temperature 38.0°C, agitation 100 rpm, pH 1.2, osmotic pressure 300 mmol/kg and ethanol 20%. During these conditions the predicted and the experimentally obtained dissolution curves were close (Figure 6). The difference sum of squares was reduced to 376.3.

The reason for this improvement is unknown but may be explained by interactions between some physicochemical factors which are not detected by the applied experimental tests, or with the naked eye. The present study was designed as a screening experiment to identify critical in vitro factors and the design did not allow us to explore the effects from the confounded two-factor interactions. To optimize the prediction conditions it is therefore necessary to go on and perform a full factorial design and construct response surfaces.

CONCLUSIONS

The complex nature of the digestive juices during fasted, fed, and unhealthy conditions is difficult to mimic an in vitro dissolution test. We have chosen to compose liquids for the stressed in vitro tests during drug development which are based on a number of physico-chemical variables known to have a possible influence on the solubility and/or dissolution rate of solids (i.e. pH, temperature, agitation speed, osmotic pressure, viscosity, polarity of the medium and type, and concentration of surfactant). By applying a statistical experimental design it was possible to study the individual effects of these variables on the dissolution rate of the model drug remoxipride from ethylcellulose ER-coated spheres. On the basis of these stressed screening experiments it was concluded that the polarity, agitation,

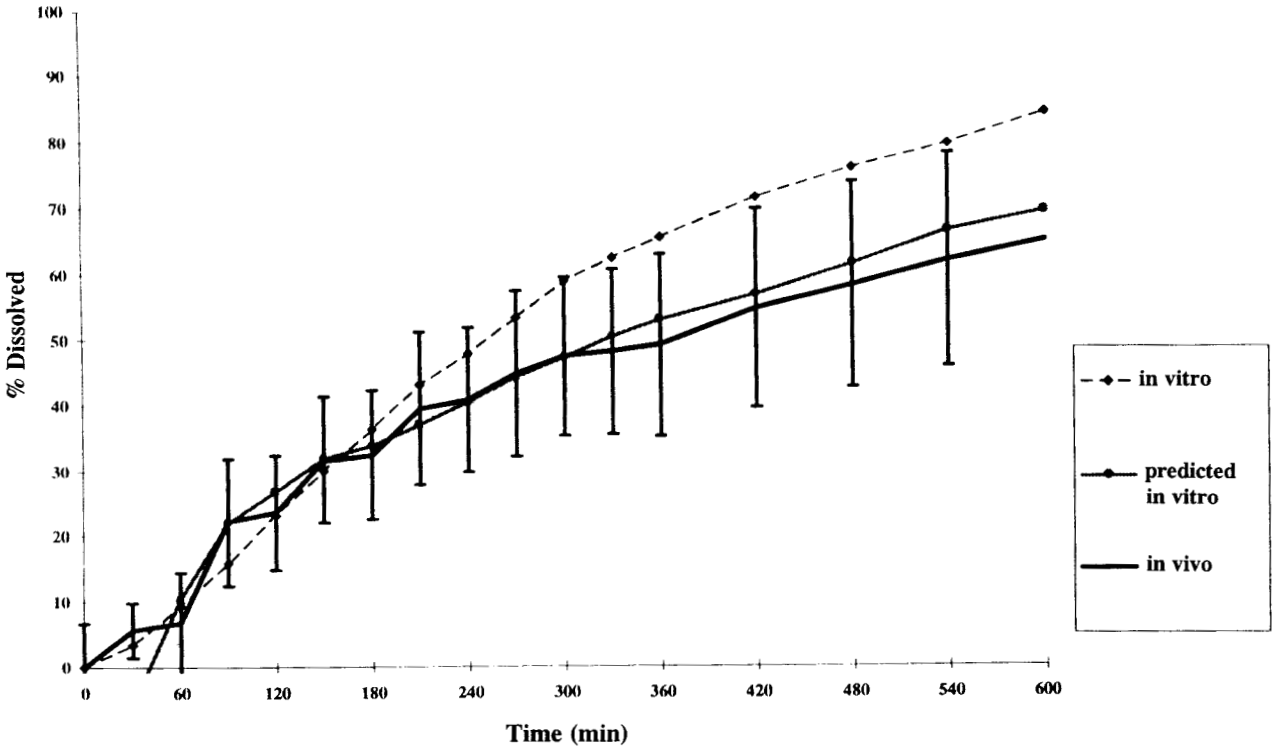

Figure 5. A comparison between the predicted in vitro dissolution profile of 300 mg remoxipride spheres, the verifying in vitro profile, and the in vivo dissolution curve.

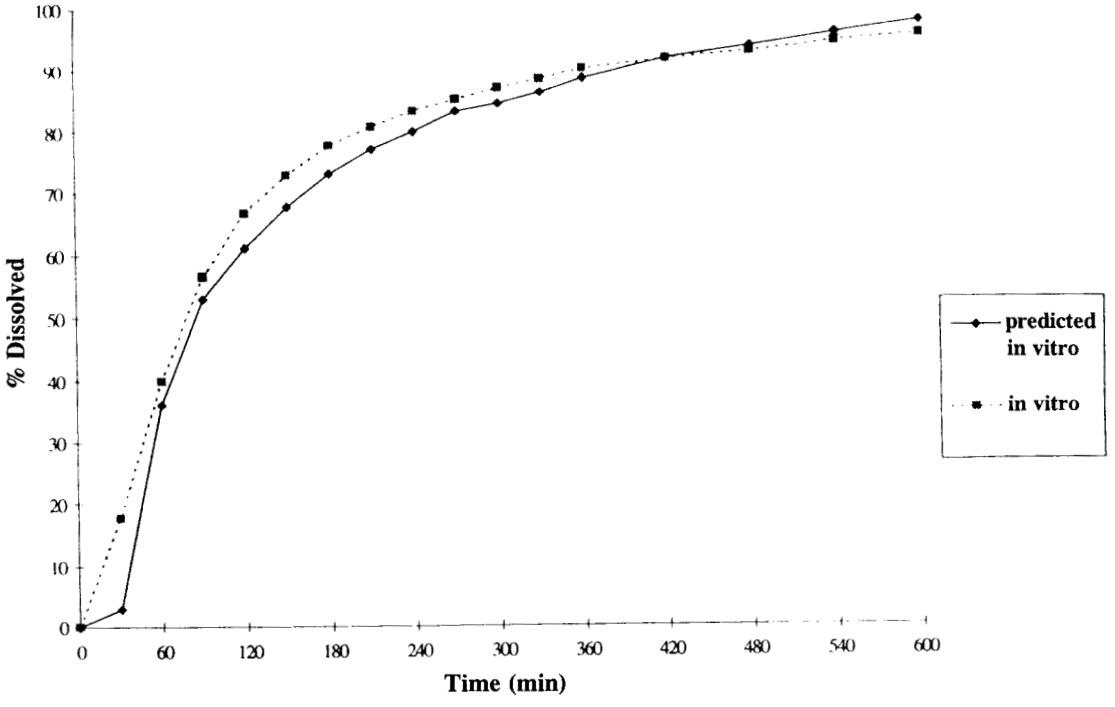

Figure 6. A comparison between the predicted dissolution profile in vitro and the verifying dissolution profile after excluding dissolution media containing povidone and surfactants.

and temperature were the main variables that had statistically significant effects during almost the whole dissolution phase.

A model was calculated based on the obtained dissolution data in vitro, and the calculated dissolution in vivo, that had the ability to predict the in vitro conditions that were best associated with the in vivo dissolution behavior. A successful correlation was obtained up to about four hr after drug administration to healthy volunteers. Thereafter, however, the in vitro data tend to overestimate the in vivo release with 10–15%. There is, thus, reason for an optimizing experiment based on the present screening studies.

ACKNOWLEDGMENTS

The authors would like to thank Mr Joakim Lindström and Mr Kiomars Karami for their technical assistance during the preparations of the fluids, and Dr. Bert Skagerberg for support in the statistical experimental design evaluation. We also wish to express our gratitude to Prof. Sylvan Frank at the College of Pharmacy, at The Ohio State University for stimulating discussions during the preparation of this manuscript.

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