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ACcelerated Dissolution Rate Analysis (ACDRA) for controlled release drugs. Application to Roxiam®

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Abstract: Accelerated dissolution rate analysis by elevated temperature has been applied to the release of remoxipride from a controlled release drug, Roxiam®, and compared to the standard USP method. A PLS model has been used in evaluating the factors of importance of the release as well as for the comparison to the standard USP method. ACelerated Dissolution Rate Analysis (ACDRA) offers the possibility of substantial reduction of analysis time. The time needed for one analysis with ACDRA is less than 5% of the USP-method. The automated analytical procedure is well suited for use in process control as well as in the early stages of the formulation development.

Keywords: *Accelerated dissolution rate; remoxipride; controlled release; CR; slow release; PLS-modelling; in process control; IPC; process analytical chemistry; PAC.*

Introduction

The utility of oral controlled release dosage forms has been evident for years. Controlled release (CR) products maintain drug levels in blood within therapeutic concentrations for longer periods of time than traditional immediate release dosage forms. A common form of oral controlled release formulation is the use of film coated pellets [1]. In this study we investigated the drug Roxiam®. The active component of Roxiam® is remoxipride. Dissolution analysis of CR-drugs is time-consuming, *e.g.* for Roxiam® about 18 h. This is disadvantageous in early research and unacceptable for effective process control. A method to speed up the analysis would be desirable. One way to achieve this, is to accelerate the release by increasing the temperature. This approach is used in ACcelerated Dissolution Rate Analysis (ACDRA) and outlined in this paper.

The aim of this study was to develop a method for In Process Control (IPC) of remoxipride μ-capsules. An IPC method should reflect and discriminate between many different sources of variations in the manufacturing process. A deterministic approach to IPC would require the cumbersome determination of several physical characteristics such as diffusion coefficient, wetting and a kinetic description of dissolution near saturation within the pellet. We are using an empirical approach for fast development of an IPC method that allows interpretation and evaluation. In this case the process time for film coating is currently about 4 h. Thus the analytical result should be at hand at a much shorter time.

In this work we have chosen to describe the release profiles according to a general model, see Fig. 1:

(1) The primary phase, lagtime, where no active component could be detected in the dissolution media.
(2) The steady state phase, where the release rate is constant, *i.e.* the linear part of the curve.
(3) The exponential decay phase, where the release rate is continuously decreasing.

Materials

Reagents and standard solutions

Remoxipride Chemical Reference Standard (CRS) were obtained from ASTRA Arcus AB.

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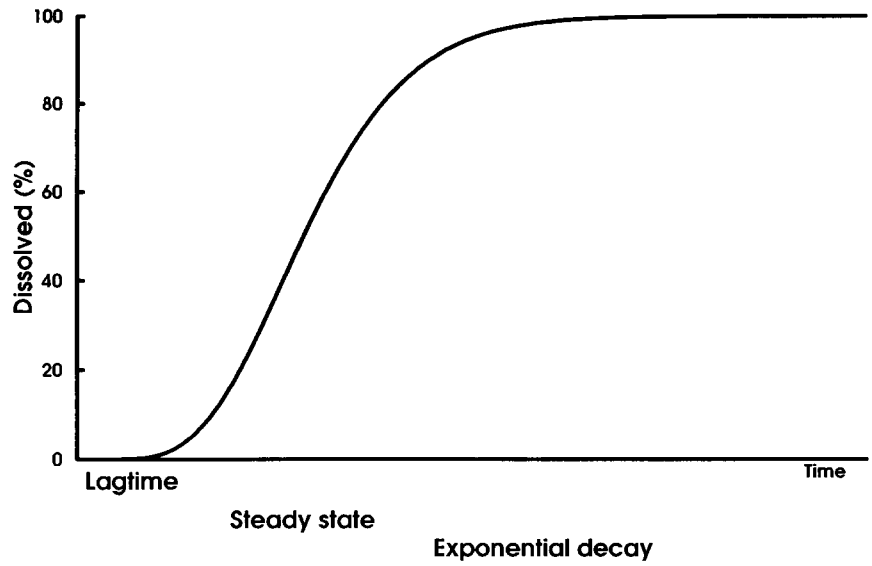

Figure 1
Dissolution profile phases.

Standard solutions were prepared in deionized water. Series of standards of remoxipride in the interval 0–120%, by weight, of nominal amounts of drug release value were prepared. The detergent Brij-35, see below, was obtained from Technicon Chemicals CO (Belgium).

Samples

Remoxipride μ-capsules were obtained from ASTRA Arcus AB. The capsule core (pellet) consists of remoxipride (80%) and other non ionic constituents. The core is coated with a cellulose based polymer film with a thickness of about 20 μm. Samples were taken, during an upscaling process study, ranging from 60 to 125% of the nominal amount of film (from 40 mg polymer/g pellet to 90 mg polymer/g pellet). The size of the capsules were approximately normally distributed within 0.85–1.12 mm.

Apparatus

An ACDRA 2000 from GÖTALAB AB equipped with a PC was used. The software for control of the instrument, data sampling and calculations was also obtained from the same company. The ACDRA 2000 is a semiautomatic instrument designed for dissolution rate analysis in process environment. Therefore all liquid handling is fully automated under computer control, *e.g.* filling, thermostating, rinsing and emptying of the standard USP vessel. Temperature and stirring speed can be set in wide ranges. An in built conductivity sensor monitor the dissolution. All parameters including the dissolution rate curve are presented on the computer screen.

Methods and Models

Sampling plan

A sampling plan was constructed where temperature and degree of coating were varied in a grid pattern, according to Fig. 2. This is a type of factorial arrangement [2, 3] that allows the estimation of both non-linear (here quadratic) and interactive effects.

ACDRA method

The vessel of the ACDRA instrument is

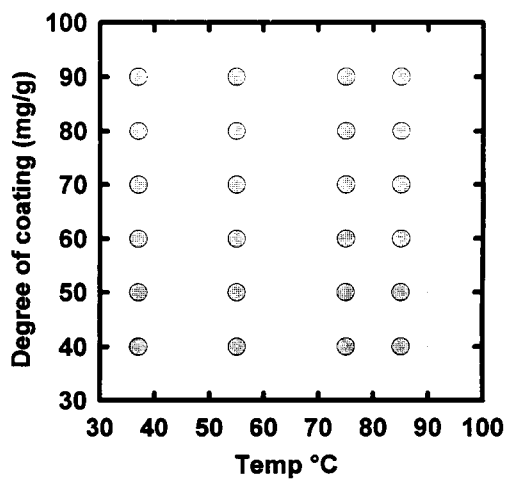

Figure 2
Sampling plan for the study.

automatically filled to a defined volume and the media thermostated to a preset temperature (±0.1°C). Four drops of Brij-35 were added to eliminate bubbles on the conductivity cell. The stirring speed was set to 150 rpm in all experiments. A weighed amount (~1 g) of remoxipride μ-capsules was added. Measurements were collected over time to characterize the accelerated dissolution profile.

USP method

The dissolution rate was determined by means of the flow-through technique [4]. The amount of remoxipride was determined spectrophotometrically. The flow-through apparatus has a thermostatic bath specified to 37 ± 0.5°C and a piston pump with flow rate of 9.0 ± 0.5 ml min^{-1}. Deaerated deionized water was used as dissolution medium. The system was calibrated with remoxipride CRS.

Model system

Temperature and degree of coating are known to influence the dissolution. The modelling consisted of two parts. The first part, covering the lagtime, was assumed to last until 15% of remoxipride was dissolved and is described in equation (1). In the second part, the phases steady state and exponential decay were modelled. Temperature, degree of coating and dissolution time were included in this model. In equation (2) a logarithmic time scale for the steady state and exponential decay phases was used according to equation (3).

$$\text{Lagtime} = t_{15\%} = f(\text{temperature, degree of coating}) \quad (1)$$

$$\text{Fraction dissolved} = f(\text{temperature, degree of coating, time in model}) \quad (2)$$

$$\text{Time in model} = {}^{10}\log(\text{time}) - {}^{10}\log(\text{lagtime}). \quad (3)$$

PLS model

The functional relations according to equations (1), (2) and the comparison between USP and ACDRA methods were established by the use of PLS-regression. PLS is an acronym for Projections to Latent Structures, that is a biased regression method based on disjoint bi-linear projections [5, 6]. The reason for using PLS is that our data, at least in comparison between USP and ACDRA methods, are known to be highly colinear and, therefore, traditional methods like MLR (Multiple Linear Regression) will not be reliable and in the comparison case even fail. PLS can be expressed in many ways, one convenient way is to use polynomials like equations (4) and (5). The β:s are here PLS regression coefficients and ε constitute residuals, *i.e.* the discrepancy between model and reality.

$$\text{lagtime} = \beta_0 + \beta_1{*}\text{temp} + \beta_2{*}\text{coating} + \beta_{11}{*}\text{temp}^2 + \beta_{22}{*}\text{coating}^2 + \beta_{12}{*}\text{temp}{*}\text{coating} + \epsilon \quad (4)$$

$$\text{Fraction dissolved} = \beta_0 + \beta_1{*}\text{temp} + \beta_2{*}\text{coating} + \beta_3{*}\text{time} + \beta_{11}{*}\text{temp}^2 + \beta_{22}{*}\text{coating}^2 + \beta_{33}{*}\text{time}^2 + \beta_{12}{*}\text{temp}{*}\text{coating} + \beta_{13}{*}\text{temp}{*}\text{time} + \beta_{23}{*}\text{coating}{*}\text{time} + \epsilon \quad (5)$$

Analogously a series of ten polynmomials, see equation (6), can be formulated (one for each USP-time) for the comparison of USP and ACDRA data.

$$\text{USP}_j = \beta_{0J}{*}\text{ACDRA}_i + \ldots \beta_{ij}{*}\text{ACDRA}_i + \epsilon_j, \quad (6)$$

where $j = 1,2 \ldots 10$ denotes USP time and $i = 1,2 \ldots 45$ denotes ACDRA time.

In order to obtain PLS models with maximum predictive power, *i.e.* the best selection of projections, a cross-validation procedure was used [7]. Every single PLS projection was the cross-validated using five cross-validating groups. Before applying PLS-modelling all data were scaled, to unit variance, and centred.

All calculations were carried out by the use of Matlab for Windows version 4.2b.

Results and Discussion

Conductivity measurements

The linearity, precision and reproducibility of the conductivity meter was controlled with KCl solutions [8, 9]. The conductivity of a ground and dissolved sample is more than 99% due to the conductance of remoxipride (amine-HCl), whereas the excipients contribute less than 1%. This is in agreement with earlier observations for this type of product [10]. Thus, the influence of the excipients can be neglected. The conductivity is highly dependent on the temperature (ion mobility). There-

fore, calibrations must be performed at every temperature of interest.

Results from analyses

The results from the USP analyses at 37°C for different degree of coating are shown in Fig. 3. The results from ACDRA analyses are given in Fig. 4. The sampling plan according to Fig. 2 induced large variation in dissolution time. Hence, it is convenient to use a logarithmic time-scale to show the dissolution profiles.

Lagtime model

The PLS model, composing one single projection, express the result as regression coefficients (β), see Fig. 5. The scaled coefficients show the relative influence on the dissolution rate. We conclude that temperature has a major influence on lagtime. The negative linear effect indicates that lagtime is decreasing with increasing temperature. However, due to the positive quadratic effect, there is a minimum lagtime at a certain temperature. Degree of coating is contributing to lagtime by a positive linear effect, *i.e.* lagtime will increase with increasing degree of coating. The interaction effect may be neglected. The observed lagtime values are plotted against calculated lagtime results in Fig. 6. The squared correlation coefficient, R^2, of this plot is 0.96. This indicates that the model is statistically sound and may be used for tentative predictions.

Steady state model

Modelling of the steady state and the exponential decay using three PLS projections resulted in regression coefficients (β) that are described in Fig. 7. The model is clearly dominated by time. The second most important effect is temperature, while degree of coating only showed a minor contribution to the model. Observed values are plotted against the calculated results in Fig. 8. The squared correlation coefficient, R^2, of this plot is equal to 0.95. This again indicates a statistically sound model.

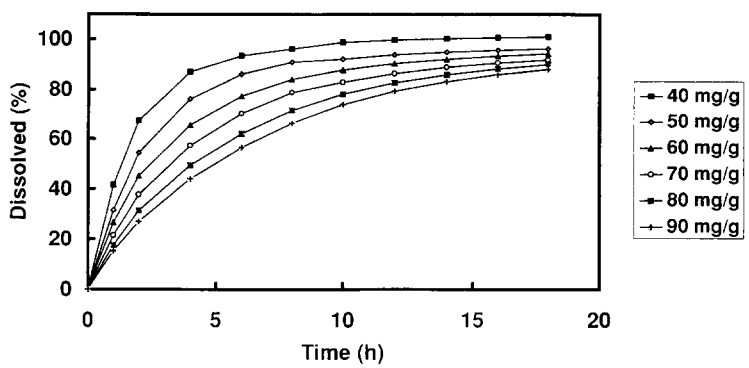

Figure 3
Results according to USP-conditions at 37°C.

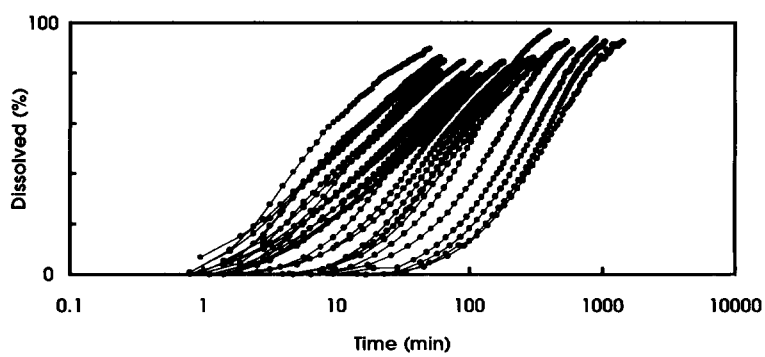

Figure 4
Measured data according to sampling plan: time scale is logarithmic.

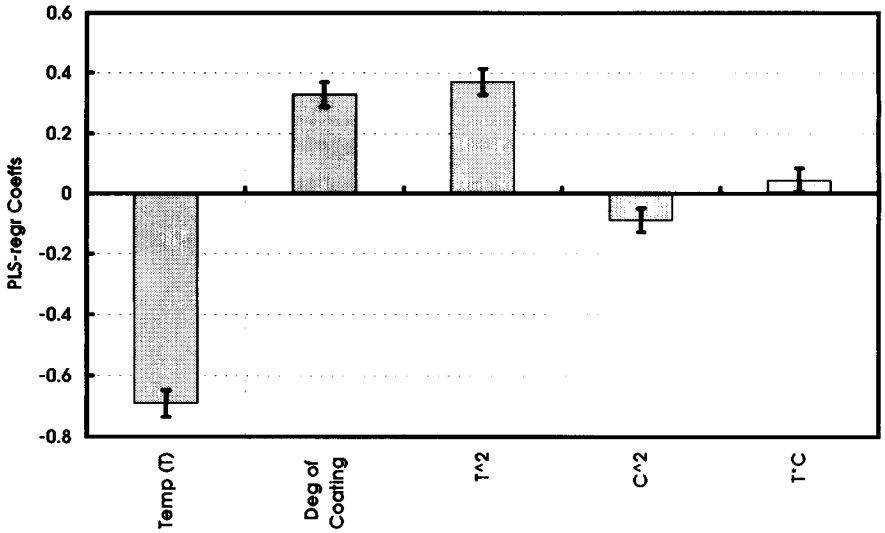

Figure 5
The factor influence in the lagtime model with the approximate 95% confidence level error bars included.

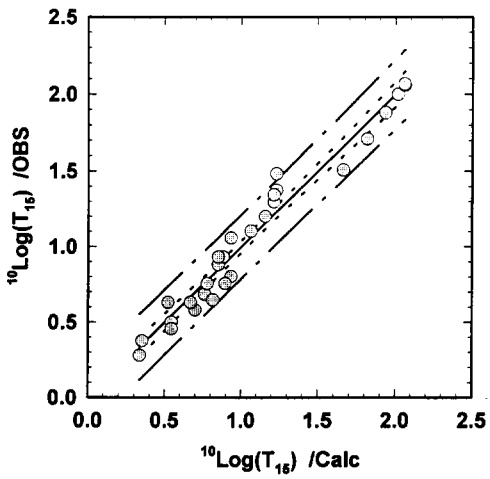

Figure 6
Observed results vs calculated values in the lagtime model.

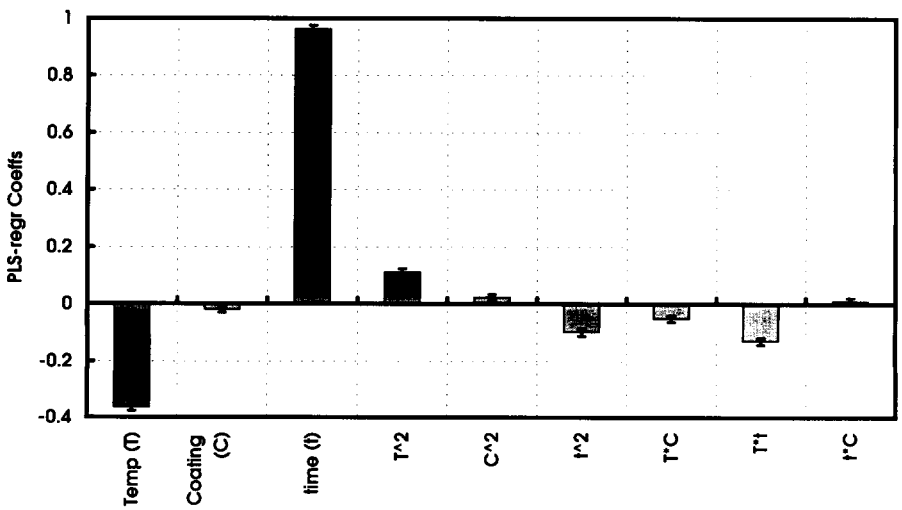

Figure 7
The factor influence in the steady state model with the approximately 95% confidence level error bars included.

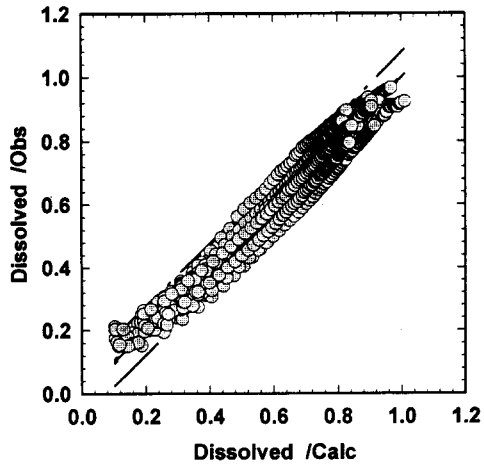

Figure 8
Observed results vs calculated values in the steady state model.

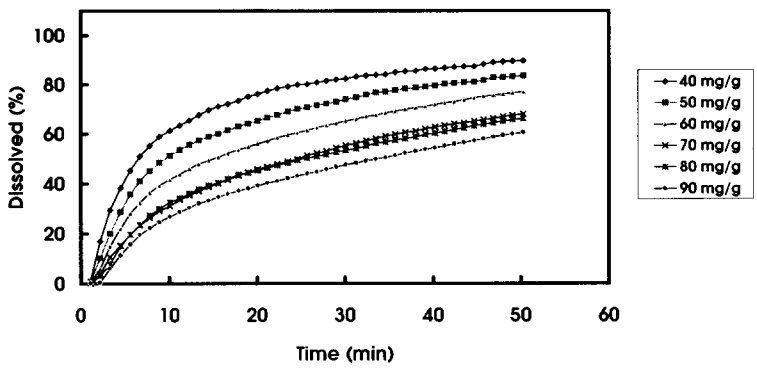

Figure 9
Results from ACDRA analyses at 85°C.

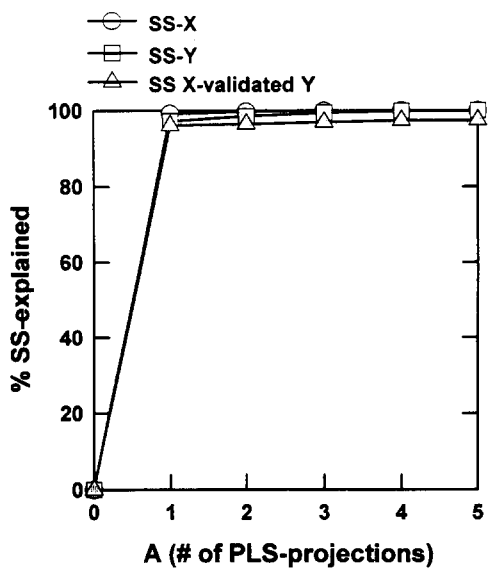

Figure 10
Sum of squares from when observed and calculated data were compared.

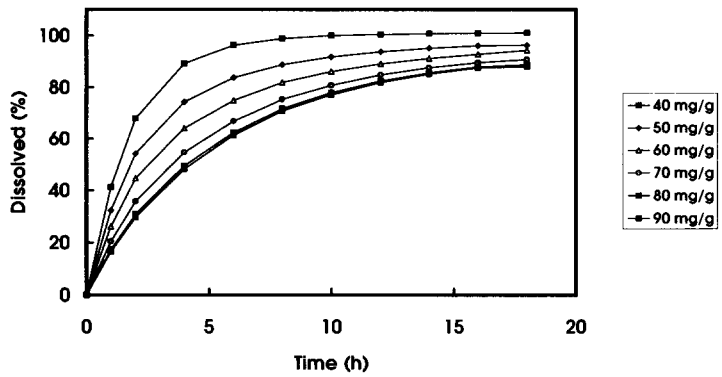

Figure 11
Predicted USP curve at 37°C calculated from results ACDRA analyses.

USP data compared with the ACDRA model

Since the models described above are statistically sound we conclude that they can be used for tentative predictions. The predictive power of accelerated dissolution rate analysis was, therefore, tested in a model where the USP data at 37°C (see Fig. 3) were correlated against ACDRA data at 85°C (see Fig. 9).

Figure 10 illustrates the quality of this model by means of cumulative explained sum of squares in the PLS model. *X*-block data here are the ACDRA data and correspondingly the *Y*-block is the USP-data. The cross-validated curve is indicating that the predictive power, *i.e.* the capacity of predicting "unknown" *Y*-data is high. The PLS model reaches almost 100% explained sum of squares after only one projection (*i.e.* $A = 1$) and, hence, we can conclude that therer is a direct correspondence between the USP data at 37°C and the ACDRA data at 85°C.

Figure 11 presents PLS predictions of the USP data in Fig. 3. There is a striking striking similarity between them.

Conclusions

The automated analytical procedure, ACDRA, is well suited for use in process control as well as in the early stages of the formulation development.

As a final remark we therefore conclude that for this system (ACDRA–USP) we can obtain some information about the USP profiles using ACDRA method that requires less than 5% of the analysis time in the USP method. We are currently working on extending this concept to more complex dissolution profiles.

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