ELSEVIER

International Journal of Pharmaceutics 145 (1996) 61–64

international journal of pharmaceutics

Evaluation of mathematical models describing drug release from lipophilic matrices

Judit Dredán*, István Antal, István Rácz

Pharmaceutical Institute of the Semmelweis University of Medicine, Budapest, Hungary

Received 30 June 1996; accepted 29 August 1996

Abstract

Potassium chloride, as a highly watersoluble model drug was embedded into wax to produce sustained release dosage form. Samples were coated with different core:wall ratios to control the dissolution profile. The drug release from coated samples was tested by the rotating paddle method of USP and the dissolution data were analyzed assuming different kinetic models. Increasing the quantity of coating material may modify the drug liberation which was demonstrated by the correlation between proportion of the embedding material and mean dissolution time. It can be concluded that changing the quantity of embedding material both the dissolution rate and kinetic profile can be controlled.

Keywords: Sustained drug release; Lipophilic matrix; Highly watersoluble drug; Dissolution kinetics; Mathematical models; Statistical evaluation

1. Introduction

The embedding of a drug into lipophilic coating material is often applied to ensure sustained or slow release for a formulation containing a highly/freely watersoluble drug. The release mechanism of the embedded drug differs from other coated formulations. The erosion and/or decomposition of the coating material by enzymes, H^+ or body fluids precedes the contact of body fluids with the solid active ingredient, thereupon the dissolution process starts (Rácz, 1989; Huang et al., 1994).

The aim of our study was to evaluate the applicability and reliability of some mathematical kinetic models to describe the drug release from non-disintegrating, lipophilic matrix systems.

* Corresponding author.

PII S0378-5173(96)04725-4

2. Materials and methods

2.1. Materials

Potassium chloride of USP 23 grade was selected as highly watersoluble model drug for core material. The studied coating material was the white beeswax (melting range of 62–65°C) purchased from the Fluka Chemie AG (Buchs, Switzerland).

All other chemicals—such as those used for preparation of the artificial gastric juice for the dissolution test—were of analytical grade.

2.2. Preparation of the samples

The thermosoftening coating material in all cases was heated in a double jacketed vessel onto 70°C (± 1°C) to ensure the reproducibility of the sample-preparation. The crystals of the model drug were mixed into the melted mass in the proportions as follows: 2/1; 3/1; 4/1; 5/1; 9/1; 19/1.

When the quantity of the embedding material was small, continuous stirring while cooling was used, resulting in individually coated drug particles with a layer of the congealed thermosoftening waxy material. When the amount of wax was increased, the molten mass was filled into hard gelatine capsules before congealing to form a skeletal sustained release dosage form.

2.3. In vitro dissolution studies

The release of the model drug was studied using rotating paddle method of USP 23, in Pharmatest PTW2 dissolution-tester (Pharmatest Apparatebau GmbH, Hamburg). The amount of released model-drug was measured continuously using a digital pH-meter (Radelkis OP 211/1, Budapest), with chloride-selective electrode (Radelkis OP-CL 7111P type, Budapest).

2.4. Mathematical models

The following mathematical models were evaluated considering the dissolution profiles of the non-disintegrating lipophilic matrices (Blume et al., 1991).

2.4.1. Zero-order model

The drug release from the dosage form follows a 'steady-state release' (Ravelli and Rossi, 1995), running at a constant rate:

$$M_t/M_\infty = kt$$

where M_t amount of drug released at time t, M_∞ the maximal amount of the released drug at infinite time, k is the rate constant of drug release.

2.4.2. First-order model

The drug activity within the reservoir is assumed to decline exponentially and the release rate is proportional to the residual activity:

$$M_t/M_\infty = 1 - \exp(-kt)$$

2.4.3. Higuchi square root time model

The most widely used model to describe drug release from matrices, derived from Higuchi for a planar matrix, however it is applicable for systems of different shapes too:

$$M_t/M_\infty = kt^{1/2}$$

2.4.4. Hixson and crowell cube-root equation

This model describes the release from systems showing dissolution-rate limitation and does not dramatically change in shape as release proceeds (Su et al., 1994)

$$(1 - M_t/M_\infty)^{1/3} = 1 - kt$$

2.4.5. Weibull distribution

The Weibull distribution can be assigned as a generalized form of the exponential function (Langenbucher, 1976), hence it can be widely used for the analysis and characterisation of drug dissolution process from different dosage forms (Carstensen, 1977)

$$M_t/M_\infty = 1 - \{\exp - [(t - t_0)/\tau]^\beta\}$$

where t_0 is the lag time of the drug dissolution, τ the mean dissolution time, when 63,2% of M_∞ has been released, β shape parameter of the dissolution curve.

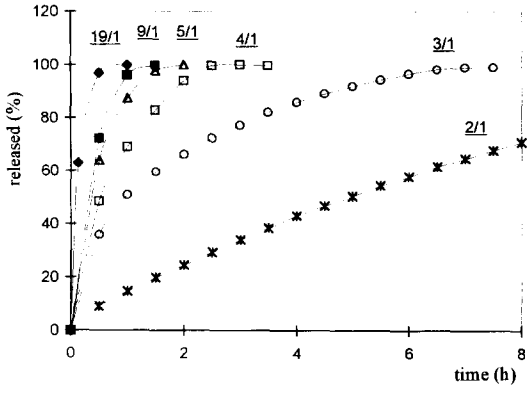

Fig. 1. Influence of the drug/excipient ratio on the release of KCl from wax matrix.

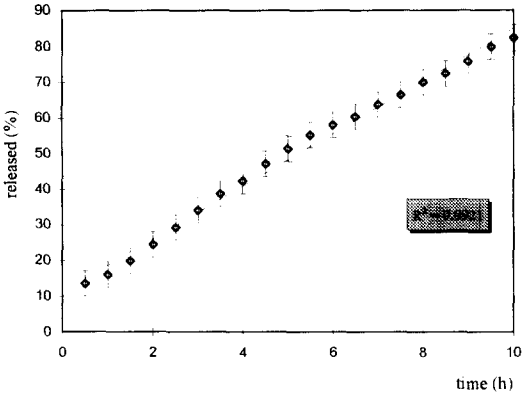

Fig. 2. Dissolution of 2/1 drug/excipient ratio sample (insert linear trendline representing zero-order release, S.E.: ± 3.6).

3. Results and discussion

The dissolution data of different drug:excipient ratio samples are shown in Fig. 1. Changing the core:wall ratio at the embedding procedure results in dissolution curves of manifold shapes, which can be characterized only with different mathematical models. The non-linear parameter estimation of the above listed model equations was made with the Solver function of Microsoft Excel 5.0.

The correlation coefficients of different kinetic equations are included in Table 1. and demonstrate that these models are suitable for describe the dissolution of embedded drug almost independently from the quantity of coating material. However, the characterization of the dissolution process of the samples with different wall thickness shows the next tendency:

(1) The release form samples of 4/1 and 5/1 ratio fits mostly to the first order kinetic model.
(2) The diffusion-controlled matrix release is most close to the samples of 3 /1 and 4/1 ratio.
(3) The 19/1 ratio sample seems to be a mass of individual spherical particles, like microcapsules.

At higher a amount of embedding material, 2/1 ratio, the cube-root law lost its applicability referring to the significance of matrix erosion. At this core/wall ratio the dissolution process can be characterized preferably by a two-phase dissolution kinetic. In the first phase (beginning half hour-period) less than 15% of drug is released following first order kinetic (correlation coefficient: 0.995). In the second phase a closely constant rate of drug dissolution can be observed demonstrating 'zero order' or steady state release (Fig. 2), which is possibly followed by a uniform and concentration-independent absorption of the drug from the dosage form (Evers, 1996).

Table 1
Correlation coefficients of different parameters measured and estimated applied the mathematical models

Core/wall ratio	First-order model	Higuchi square-root of time model	Hixson-Crowell cube-root equation
2/1	0.9858	0.9881	0.9051
3/1	0.9911	*0.9951*	0.9814
4/1	*0.9961*	*0.9962*	0.9773
5/1	*0.9985*	0.9794	0.9823
9/1	0.9821	0.9661	0.9898
19/1	0.9898	0.9776	*0. 9959*

Table 2
Characteristic parameters of RRBSW distribution

Core/wall ratio	β shape-parameter	τ_d value (min)	M_∞ (%)	Correlation coefficient
2/1	1.1101	393.1	97.3	0.8923
3/1	0.8099	84.1	99.1	0.9911
4/1	0.9789	49.5	99.6	0.9964
5/1	0.9876	27.6	100.0	0.9986
9/1	1.2536	23.0	99.8	0.9980
19/1	1.6189	7.8	100.0	0.9996

The shape parameter values of the Weibull distribution in Table 2 refer to first order release ($\beta \approx 1$) at the 4/1 and 5/1 samples, justifying the results of Table 1. The β values increased significantly decreasing the proportion of the lipophilic excipient, except the 2/1 core/wall ratio sample, where the existing zero order kinetic—being not a natural growth process—makes it inapplicable. The τ_d values are tendencially higher when the amount of coating is increased following exponential regression as shown on the Fig. 3. There were no identified interpretable t_0 values.

4. Conclusions

The development of a controlled release dosage form has great importance in pharmaceutical research (Ravelli and Rossi, 1995). Except for the simple osmotic pump, the mechanism of drug dissolution usually cannot be defined uneqivocally (Blume et al., 1991).

In this study some opportunities are given for the characterization of dissolution parameters and description of drug release processes.

Although all of the kinetic models have the limit of their applicability, the presence of spherical individual particles as well as a matrix can be easily determined analysing of dissolution profiles according to the appropiate mathematical model.

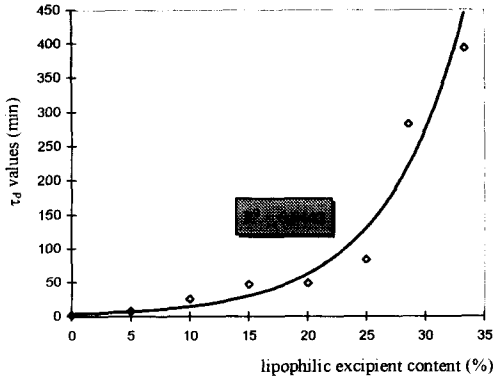

Fig. 3. The effect of drug/excipient ratio on the τ_d values of the RRSBW distribution (exponential regression).

References

Blume, Gundert-Remy and Möller, *Controlled/Modified Release Products*, Wissenschafliche Verlaggesellschaft, Stuttgart 1991, pp. 16–29.

Carstensen, J.T., *Pharmaceutics of Solids and Solid Dosage Forms*, John Wiley and Sons, New York, 1977, pp 63–76.

Evers, P., Drug delivery technology: responding to medical and market needs. *Pharmaceut. Technol. Eur.*, 8/3, (1996), 3 8–44.

Huang, H-P., Mehta, S.C., Radebaugh, G.W. and Fawzi, MB., Mechanism of drug release from an acrylic polymer-wax matrix tablet. *J. Pharm. Sci.*, 83/6 (1994), 795–797.

Langenbucher, F., Parametric representation of dissolution-rate curves by the RRSBW distribution. *Pharm Ind*, 38/5, (1976), 472–477.

Ravelli, V. and Rossi, R., Prolonged release formulation technology, *Pharm. Manufact. Int.*, 1995, pp. 171–172.

Rácz, I., *Drug Formulation*. Wiley, New York, 1989, pp. 367–369.

Su, X.Y., Al-Kassas, R and Li Wan Po, A., Statistical Modelling of Ibuprofen Release from Spherical Lipophilic Matrices. *Eur. J. Pharm Biopharm.*, 40/2, (1994) 73–76.