International Journal of Pharmaceutics, 60 (1990) 229–234
Elsevier

IJP 02048

Modelling drug release from hydrophobic matrices by use of thermodynamic activation parameters

Manuel Efentakis * and Graham Buckton

Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX (U.K.)

(Received 26 October 1989)
(Accepted 24 November 1989)

Key words: Controlled drug release; Diffusion; Thermodynamics; Indomethacin; Eudragit; Dissolution

Summary

Sustained release tablets of indomethacin were prepared using Eudragit RS. Two types of formulation were considered, one was a directly compressed powder mixture which produced a matrix system, and the other was prepared by granulation, such that the drug was to some extent sealed within a cast film of the polymer. Dissolution studies (USP paddle) revealed that the drug release from the matrix was directly proportional to the concentration of the polymer that was used. Drug release from the granulated system was much slower than from the directly compressed matrix. Conventional analysis of the dissolution data showed that the release was best described as an anomalous diffusion process and that it fitted zero-order release kinetics. By undertaking dissolution studies at different temperatures, and by monitoring the temperature dependence of the release rate constant it was possible to calculate the thermodynamic parameters of activation for the release. The release of drug from the granulated product has a greater entropic hindrance than that from the directly compressed tablet. This provides a probable explanation for the large difference in release rates between the two products.

Introduction

The use of polymeric additives to achieve sustained or controlled release of drug from a solid oral dosage form has been established for over two decades. Many workers have tried to develop models to describe the release profiles from such systems (for example: Higuchi, 1963; Cobby et al., 1974; Fessi et al., 1978; Bamba et al., 1979; Gurny et al., 1982, Korsmeyer et al., 1983; Lee and Peppas, 1987). Even though a vast body of literature exists on the subject of drug release from matrix systems, we are not aware of many attempts to model drug release profiles by use of thermodynamic parameters.

Buckton and Francis (1987) demonstrated that the thermodynamic parameters of activation could be used to help to describe the mechanism of dissolution of a commercially available sustained release theophylline preparation (Nuelin SA).

In the work presented here the drug release profiles of different preparations containing indomethacin in an acrylic/methacrylic copolymer (Eudragit RS) have been investigated. The mechanisms of release have been described in terms of values obtained for the thermodynamic parameters for activation and by reference to other published work.

Correspondence: G. Buckton, Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, U.K.

* *Permanent address*: Department of Pharmacy, University of Athens, Solonos 104, Athens, Greece.

Materials and Methods

Tablets were made by either direct compression or a 'granulation' technique. The directly compressed tablets were prepared from a mixture of indomethacin (Sigma), lactose (Zaparox), Eudragit RS 100 (Rohm Pharma) and magnesium stearate (BDH). Three different formulations were prepared, containing varying amounts of indomethacin and lactose (A–C). The proportions are shown in Table 1. The dry powders were mixed for 15 min (Turbula T2C, Bachofern, Basel) and filled by hand into a Manesty F3 tabletting machine. The tablets were of average weight 280 mg with a diameter of 11.5 mm and a thickness of 2.8 mm. The hardness of the tablets was such that they would break under a load of between 7 and 8 kg (CT 40 hardness tester).

The granulated sample (formulation G in Table 1) was prepared in a similar manner to the method used by Martinez-Pachero et al. (1986). The lactose and indomethacin were mixed as above, and then formed into a slurry with a 12.5% solution of Eudragit RS in a 1 : 1 mix of acetone and propan-2-ol. This was passed through a 1 mm mesh and tray dried at 25 °C for 3 h (considerably longer than the time used by Martinez-Pachero et al. (1986)). Magnesium stearate and sufficient powdered Eudragit were added to make up the quantities to the required content, which was then mixed for 30 min (Turbula). The tablets were then made in the same manner as the directly compressed mixture.

Dissolution experiments were undertaken in a USP apparatus (paddle, 100 rpm), using 750 ml of pH 7.4 phosphate buffer (USP) at 37.5 °C for all formulations, and also at temperatures of 26.0, 31.0 and 43.0 °C, for formulations B (as an example of the directly compressed tablets) and G (granulated). Samples were taken over an 8 h period, filtered and analyzed using UV spectrophotometry at 318 nm. The thermodynamic functions of activation were calculated by plotting ln k (k = rate constant for dissolution) as a function of the reciprocal of absolute temperature (T), in order to calculate the activation energy and thus the enthalpy of activation ($\Delta H^{\ddagger}$) (Atkins, 1988). By measuring the intercept on the ln k axis it is possible to calculate the entropy of activation ($\Delta S^{\ddagger}$), and thus the Gibbs function for activation ($\Delta G^{\ddagger}$) (Atkins, 1988).

TABLE 1

Composition (%) of the formulations that were investigated (A–C, directly compressed; G, granulated)

Ingredient	Formulation			
	A	B	C	G
Indomethacin	27.0	27.0	27.0	27.0
Lactose	43.2	51.1	52.2	51.1
Eudragit RS	28.8	20.9	19.8	20.9
Mag. Stearate	1.0	1.0	1.0	1.0

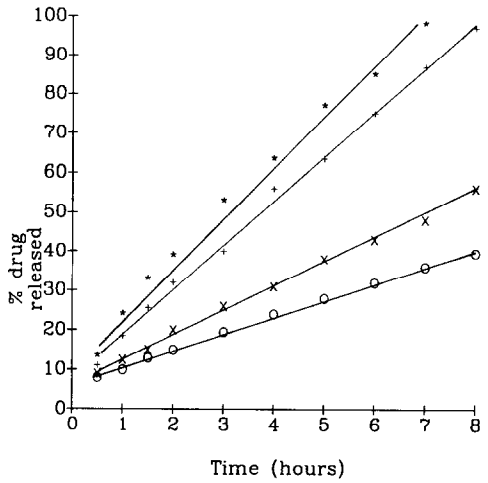

Fig. 1. Drug release (%) as a function of time at 37.5 °C for formulations A (×), B (+), C (*) and G (○).

Results

Fig. 1 shows the dissolution profiles for three batches of directly compressed tablets (A–C), the compositions of which are described above. The results demonstrate that even though all three dissolution profiles approximate to zero-order release kinetics, the best fit is obtained with the highest concentration of the polymer (A). Batch C (lowest polymer concentration) shows the greatest deviation from zero-order kinetics. The drug release profile obtained for the granulated sample is

TABLE 2

Apparent zero-order release constants for the different formulations at 37 °C

The correlation coefficient is of the linear regression line of drug release as a function of time.

Formulation	Rate constant ($mg\ ml^{-1}\ s^{-1}$) ($\times 10^3$)	Correlation coefficient
A	1.70	0.999
B	3.14	0.998
C	3.50	0.996
G	1.18	0.999

also shown in Fig. 1. The apparent zero-order rate constants are listed in Table 2. In Fig. 2, the % polymer content of the three directly compressed formulations is plotted as a function of the time taken to achieve 50% drug release (t_{50}) and the apparent zero-order rate constant; a linear relationship exists for both parameters as a function of polymer concentration.

The dissolution profiles for formulations B and G obtained at each of the test temperatures are presented in Figs 3 and 4 (for the directly compressed and granulated formulations, respectively). The profiles provide a good fit to zero-order release kinetics ($r = 0.992$ or better for each case).

Fig. 5 shows a plot of ln k as a function of $1/T$ for the two samples. In both cases a good fit to a straight line is observed ($r = 0.977$ for the directly compressed and 0.985 for the granulated preparation).

The calculated values for the thermodynamic parameters (using $T = 310$ K) are $\Delta H^{\ddagger} = 40.7$ kJ/mol, $\Delta S^{\ddagger} = -164.5$ J/mol per K and $\Delta G^{\ddagger} = 91.7$ kJ/mol for formulation C, and $\Delta H^{\ddagger} = 16.1$ kJ/mol, $\Delta S^{\ddagger} = -250.7$ J/mol per K and $\Delta G^{\ddagger} = 93.8$ kJ/mol for formulation G.

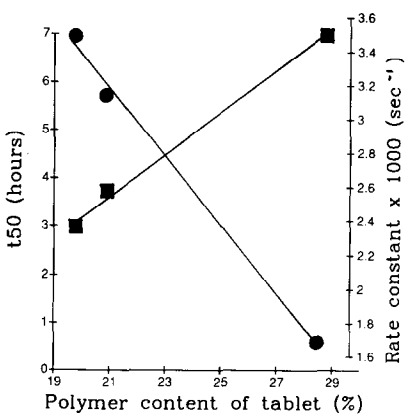

Fig. 2. Time taken for 50% drug release (■) and zero-order rate constant (●), as a function of % polymer content of the three directly compressed formulations.

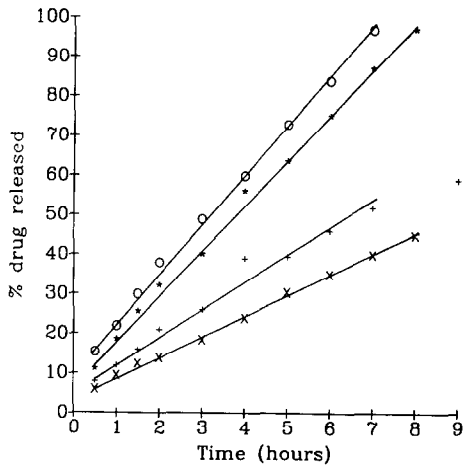

Fig. 3. Drug released (%) as a function of time for the directly compressed formulation B, at 26 (×), 31 (+), 37.5 (*) and 43 °C (○).

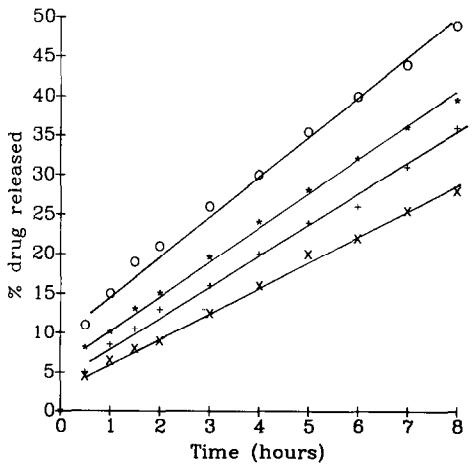

Fig. 4. Drug released (%) as a function of time for the granulated formulation G, at 26 (×), 31 (+), 37.5 (*) and 43 °C (○).

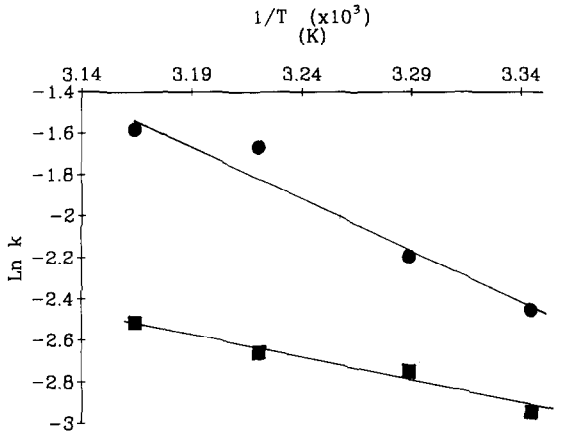

Fig. 5. Natural log of the rate constant as a function of $1/T$ for formulation B (●) and G (■).

In Fig. 6 the dissolution profiles are plotted as percentage undissolved as a function of the square root of time according to Higuchi (1963).

A double-logarithmic plot of drug release as a function of time (after Korsmeyer and Peppas, 1983), for the drug release from the different formulations (not shown), resulted in a good fit to a straight line for each case. Correlation coefficients ranged from 0.993 to 0.999 and the gradients were 0.604 for the granulated and 0.673 (A), 0.785 (B) and 0.737 (C) for the directly compressed tablets.

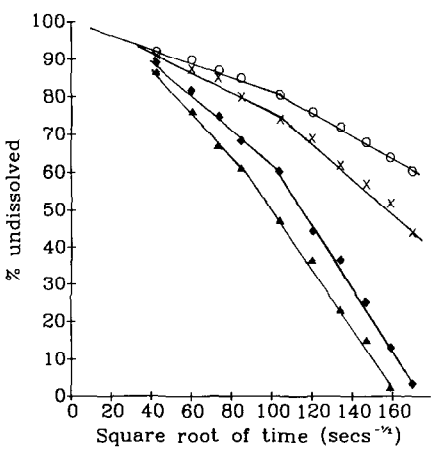

Fig. 6. Percentage undissolved as a function of the square root of time. Formulation: (×) A, (◆) B, (▲) C, (○) G.

Discussion

In the published literature, considerable effort has been devoted to describing the release mechanisms of drug molecules from polymeric matrix systems by use of various models. A typical approach is that of Gurny et al. (1982) who reported how a combination of dissolution and diffusion processes controlled the release from matrices.

The role of wetting must be considered as being at least partly responsible for differences between the release rates from any two different dosage forms. Carli et al. (1984) investigated the wettability of tablets produced from Eudragit polymers. It was noted that the contact angle was independent of the compression force used to prepare the tablet and that even when 10% of aspirin was added the contact angle was not altered significantly. In this paper the wettability has not been measured, but on the basis of the study by Carli et al. (1984) it is assumed that the contact angle will be of the order of 98° irrespective of whether the tablet was made by granulation or direct compression. As wettability is assumed to be a constant factor for the different formulations it will not be discussed further below.

Eudragit forms a non-disintegrating matrix which will only swell to a limited amount when placed in an aqueous environment. Drug release from Eudragit matrices will be governed by diffusion of liquid into the matrix, dissolution of the indomethacin and then diffusion of dissolved drug out of the tablet.

From Figs 1 and 6 it can be seen that the indomethacin release profiles are best described by zero-order release kinetics. This is contrary to the work of Carli et al. (1984), who studied the release of aspirin from Eudragit matrices and noted that the release profile was best described by a root time plot. In the current work, deviation from linearity of the root time plot was observed after about 3 h (Fig. 6). According to the model of Higuchi (1963), this would indicate that diffusion of the drug through the pores of the matrix may be a controlling factor in the early stages (0–3 h), and that a second, but different, diffusive process occurs at later times.

The extremely good fit of the drug release data

to a double-logarithmic plot (not shown) indicates a drug diffusion release mechanism, although the gradients (in the region of 0.7) provide evidence of a deviation from simple Fickian diffusion.

The approaches described above provide some information about the mechanism of drug release from the directly compressed and granulated formulations. The implication is that the mechanism by which indomethacin is liberated is the same for both formulations, but that only the rate alters. If the thermodynamic functions for the activation process are also considered, then it is possible to describe the process in terms of entropic and enthalpic driving forces, and also to utilise the values as a quantitative numerical descriptor from which comparisons can be effected.

For both the granulated and directly compressed systems the thermodynamic functions of activation are indicative of a disfavoured process. The total free energy change is disfavoured and of similar magnitude for each product. For both the granulated and directly compressed formulations, the value for the entropy change is disfavoured; the granulated sample having the largest entropic hindrance. For the directly compressed system the large disfavoured value for the enthalpic factor may be of most significance.

The directly compressed system will inevitably have a more open porous structure than the cast film produced during granulation. The release of drug from the less porous system may be expected to have a higher entropic hindrance as molecules will have to be ordered to pass through the membrane. Such entropic hindrance can be used to explain the greatly reduced rate of drug release from the granulated, as compared to the directly compressed, product.

The changes in the thermodynamic parameters are composite changes for the entire process, i.e., they will be related to the behaviour of not just the drug, but also the polymer, diluent, lubricant and dissolution fluid. A variation in the enthalpy change between the two formulations could be a result of an alteration in the behaviour of any component. In this case, it is probable that a different interaction will exist within the polymer/drug/lactose system depending upon whether they are directly compressed or granulated. From the results that have been presented, the directly compressed sample has to overcome a larger enthalpic barrier to dissolution than the granulated sample. This could be due to a thermodynamically disfavoured interaction having been enforced during granulation, hence reducing the enthalpic activation barrier.

The values obtained for the change in Gibbs free energy are similar, showing that the dissolution from the two products of identical chemical composition is disfavoured to a similar extent. The disfavoured free energy change is in line with the sustained release action of the product. The change in the processing of the two different products alters the rate to a large extent (Fig. 1), but not in line with the overall free energy change.

Korsmeyer and Peppas (1981) have attempted to describe the effect of morphology of the matrix on the release of water soluble drugs. As might have been expected, the macromolecular structure affected the drug release process. The changes were interpreted as being due to the need for relaxation in the macromolecular chains. If this finding is applied to the results reported in the current study, then the thermodynamic parameters can be explained as follows. With the granulated system, the polymer may have solidified in a disordered and predominately amorphous form. To go from an amorphous solid to a more ordered system with incorporated water would require a large entropic barrier to be overcome. The directly compressed system may well exist in a more crystalline state, i.e. more ordered than an amorphous cast film, to form a swollen matrix would not involve such an entropic barrier.

The above hypothesis indicates that there is considerable merit in using thermodynamic parameters in parallel with techniques which can adequately characterise morphology, in order to describe the mechanism of release from polymeric matrices. This approach provides an outline for further work in the field.

Conclusions

The dissolution of indomethacin from Eudragit RS matrices followed zero-order release kinetics.

The release rate from the granulated product was much slower than that from the directly compressed equivalent. The release rate from the directly compressed formulations varied in a linear manner with respect to % content of Eudragit.

An anomalous Fickian diffusion process was implicated as the release mechanism for all formulations.

The thermodynamic parameters of activation reveal that the release from the granulated product has a greater entropic hindrance than that from the directly compressed tablets. By reference to published work (Korsmeyer and Peppas, 1981) it is possible to attempt an explanation of the results in terms of the potential morphology of the polymer. Comparisons of the thermodynamic activation parameters with studies on the morphology of polymeric systems provide scope for further work.

Acknowledgement

The Wellcome Foundation Ltd are gratefully acknowledged for providing a financial contribution to assist M.E. in his visit to the U.K.

References

Atkins, P.W., *Physical Chemistry*, 3rd Edn, Oxford University Press, Oxford, 1988, pp. 700–750.

Bamba, M., Puisieux, F., Marty, J.P. and Carstensen, J.T., Release mechanisms in gel forming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Buckton, G. and Francis, M.R., Use of thermodynamic functions to describe the mechanism of drug release from a sustained release dosage form. *J. Pharm. Pharmacol.*, 39 (1987) 132P.

Carli, F., Capone, G., Colombo, I., Margotto, L. and Motto, A., Surface and transport properties of acrylic polymers influencing drug release from porous matrices. *Int. J. Pharm.*, 21 (1984) 317–329.

Cobby, J., Mayersohn, M. and Walker, G.C., Influence of shape factors on kinetics of drug release from matrix tablets I: Theoretical. *J. Pharm. Sci.*, 63 (1974) 725–732.

Fessi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T., The Higuchi square root equation applied to matrices with high content of soluble drug substance. *Int. J. Pharm.*, 1 (1978) 265–274.

Gurny, R., Doelker, E. and Peppas, N.A., Modelling of sustained release of water-soluble drugs from porous hydrophobic polymers. *Biomaterials*, 3 (1982) 27–32.

Higuchi, T., Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15 (1983) 25–35.

Korsmeyer, R.W. and Peppas, N.A., Effect of the morphology of hydrophilic polymeric matrices on the diffusion and release of water soluble drugs. *J. Membrane Sci.*, 9 (1981) 211–227.

Korsmeyer, R.W. and Peppas, N.A., Macromolecular and modelling aspects of swelling-controlled systems. In Roseman, T.J. and Mansdorf, S. (Eds), *Controlled Release Delivery Systems*, Dekker, New York, 1983, pp. 77–90.

Lee, P.I. and Peppas, N.A., Prediction of polymer dissolution in swellable controlled release systems. *J. Contr. Release*, 6 (1987) 207–215.

Martinez-Pachero, R., Vila-Jato, J.L., Souto, C. and Ramos, T., *Int. J. Pharm.*, 32 (1986) 99–102.