International Journal of Pharmaceutics, 60 (1990) 83–88
Elsevier

IJP 02008

An interpretation of the diffusion-type mechanism of drug release from microcapsules

Flavio Forni, Gilberto Coppi, Maria Angela Vandelli and Maria Teresa Bernabei

Department of Pharmaceutical Sciences, University of Modena, 19 via S. Eufemia, 41100 Modena (Italy)

Received 18 July 1989
Accepted 19 September 1989

Key words: Microcapsule; Salbutamol sulfate; Spray-drying technique; Drug release kinetics; Diffusion-type mechanism; Power law expression

Summary

Salbutamol sulfate microcapsules were prepared by a spray-drying technique. The release data were calculated approximately via standard equations (square root and first-order relationships), but unequivocal evidence in support of the cumulative release mechanism was not obtained. Even more stringent mathematical or statistical (Durbin-Watson analysis) methods did not allow any distinction to be made between the two release mechanisms. In contrast, on application of the simple power law expression $M_t/M_\infty = kt^n$ proposed by Peppas the value of the kinetic exponent of release (about 0.4) indicated a diffusion-type mechanism of the release process relative to the microcapsule shape. Therefore, it suggested here that this power law expression can be applied in order to confirm the actual diffusion-type mechanism of drug release from microcapsules.

Introduction

The analysis of the mechanism of drug release from pharmaceutical devices is an important but complicated problem. Therefore, several equations have been suggested for this purpose (Higuchi, 1963; Langenbucher, 1969, 1972; Cobby et al., 1974; Korsmeyer et al., 1983; Sinclair and Peppas, 1984). As far as the release from microcapsules is concerned, this problem is particularly evident. In fact, it should be borne in mind that cumulative drug kinetics can be altered and only the release from an individual microcapsule can provide a valid example of the true mechanism (Gross et al., 1986; Hoffman et al., 1986). Hence, the drug release profiles cannot be indicative of the true release kinetics. However, it is reasonable to consider the cumulative release kinetics as the release kinetics indicative of the therapeutic dose, i.e., of drug available for the absorption process. Consequently, the cumulative kinetics of drug release from microcapsules always represent an important parameter. Nevertheless, as described above, interpretation of this parameter is not always easy.

The present work suggests that the power law expression (Korsmeyer et al., 1983; Sinclair and Peppas, 1984) can be used as a tool in order to verify the diffusion-type mechanism of drug release from microcapsules, in cases where standard statistical and mathematical models do not allow one to distinguish between the release mechanisms. As an example analysis of the release data of salbutamol sulfate microcapsules prepared by a spray-drying technique was performed.

Correspondence: M.T. Bernabei, Department of Pharmaceutical Sciences, University of Modena, 19 via S. Eufemia, 41100 Modena, Italy

Materials and Methods

Chemicals

Salbutamol sulfate (B.P., Labochim) was used as received from the manufacturer. The drug density (1.30 ± 0.05 g cm^{-3}) was measured on a torsion balance (WDF, United) using crystals (size, approx. 2 mm) recrystallized from H_2O/H_2SO_4 (99 : 1, v/v). Ethylcellulose (EC) [Ethocel 100 SE (Dow Chemical); viscosity 90–110 cP; ethoxy content 48.0–49.6%; density 1.11 g cm^{-3} (Samejima et al., 1982)] was used as supplied by the manufacturer. All reagents were of analytical grade (Carlo Erba).

Microcapsule preparation

Salbutamol sulfate (1 g) was dispersed in 100 ml of an ethanolic solution of EC at drug/EC ratios of 1 : 1, 1 : 2, 1 : 5 and 1 : 7 (w/w). The dispersions were spray-dried with a Mini Spray-Dryer (model 190, Buechi) to prepare microcapsules characterized by the theoretical drug/EC ratio of the dispersions. The experimental parameters of the process were set as follows: inlet temperature, 150 °C, outlet temperature, 95–100 °C; aspirator setting, 5; pump setting, 4 ml min^{-1}; spray flow, 500 NLh^{-1}. A 0.5 mm nozzle was used throughout experiments.

Drug content

The amount of salbutamol sulfate in microcapsules was determined: (a) microanalytically, on the basis of the percentage of nitrogen (model 1102 Elemental Analyzer, Carlo Erba) and sulfur (White, 1962); (b) according to Merkle and Speiser (1973).

Microcapsule wall thickness

The wall thickness of microcapsules was calculated using the relationship proposed by Si-Nang et al. (1973).

Drug dissolution and drug release from microcapsules

Drug dissolution and drug release from microcapsules were examined using a column-type apparatus (Langenbucher, 1969) (Dissotest CE-1, Sotax) in 250 ml deionized water at a flow rate of 25 ml min^{-1}. All experiments were carried out under sink conditions at a temperature of 37 ± 0.2 °C using either 25 mg of salbutamol sulfate crystals or an amount of microcapsules corresponding to 25 mg of the drug. Drug content in the solution was determined spectrophotometrically (model 550, Perkin-Elmer) at fixed time intervals and a wavelength of 278 nm.

Morphological analysis

The morphology of the drug crystals and microcapsules was determined by observation on scanning electron microscopy (SEM 500, Philips). The particular size and circularity parameter (Kaye, 1986) were evaluated using, an image analysis apparatus equipped to enable the following of a computerized procedure (TESAK) on SEM micrographs showing at least 100 particles (either crystals or microcapsules).

Results and Discussion

The SEM micrographs showed the EC coating of the microcapsules to appear shrivelled irrespective of the drug/EC ratio (Fig. 1). The mechanism involved in the formation of a shrivelled coating owing to the spray-drying procedure has been discussed by Kawashima et al. (1972). The values of the particular size and circularity parameter of

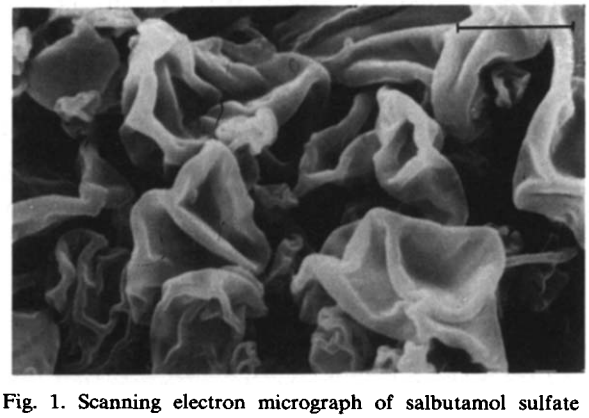

Fig. 1. Scanning electron micrograph of salbutamol sulfate microcapsules. Scale bar: 5 μm.

TABLE 1

Values of the particle size (μm) and circularity parameter (C) of salbutamol sulfate (SS) crystals and microcapsules prepared at different drug/EC ratios (± S.D., in parentheses)

	Diameter (μm)	C
SS plain crystals	4.7 (2.8)	0.67 (0.11)
SS spray-dried crystals	4.4 (2.0)	0.67 (0.10)
Microcapsules		
1:1	4.7 (3.2)	0.69 (0.08)
1:2	6.5 (3.1)	0.65 (0.06)
1:5	6.5 (4.3)	0.69 (0.09)
1:7	7.0 (3.0)	0.68 (0.11)

the microcapsules are identical to those of both plain salbutamol sulfate crystals and drug crystals after the spray-drying process in an ethanolic suspension without EC (Table 1). Therefore, the passage of salbutamol sulfate crystals through the pump and nozzle of the spray-drying apparatus affected neither size nor shape of the crystals forming the microcapsule core. Since the drug crystals and microcapsules are very similar in size and shape, it is reasonable to define the microcapsules as being of the 'film' type.

The drug content and calculated wall thickness of microcapsules prepared at various drug/EC ratios are listed in Table 2.

Drug release profiles in the dissolution medium (deionized water) from microcapsules as compared with drug dissolution are depicted in Fig. 2. Quantitative interpretation of the release data according to Langenbucher (1972) (Table 3) shows that the value of the shape parameter '*b*' is always less than unity, indicating a steeper initial slope

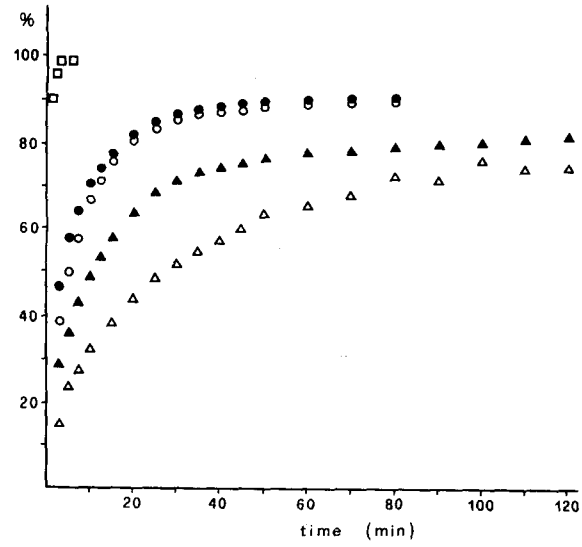

Fig. 2. Percentage release of salbutamol sulfate from microcapsules. Core/wall ratio: (●) 1:1; (○) 1:2; (▲) 1:5; (△) 1:7; (□) unmicroencapsulated salbutamol sulfate.

for the plot of the release process. The dissolution time, T_d, increased with decreasing drug/EC ratio.

The determination coefficients of the Higuchi and first-order relationships did not allow unambiguous distinction to be made between the two release kinetics (Table 4). Therefore, the more stringent mathematical treatment proposed by Benita and Donbrow (1982) and Donbrow and Benita (1982) was applied (Table 5). As previously reported (Forni et al., 1988), this procedure failed to give satisfactory results when rupture of the walls occurred during the release process. In contrast, the SEM micrographs of the salbutamol sulfate microcapsules showed neither fractures nor cracks in the wall subsequent to the release pro-

TABLE 2

Parameters of microcapsules prepared at different core/wall ratios (± S.D. in parentheses)

Core/wall ratio	Drug content (%)	Wall thickness (μm)
1:1	67.7 (1.2)	0.29 (0.20)
1:2	37.2 (2.3)	0.72 (0.35)
1:5	16.2 (2.9)	0.93 (0.61)
1:7	13.0 (0.9)	1.04 (0.44)

TABLE 3

Parameters of the release process from microcapsules prepared at different core/wall ratios calculated according to the Weibull function (95% confidence limits in parentheses)

Core/wall ratio	*b*	T_d (min)
1:1	0.54 (0.03)	7.3 (0.6)
1:2	0.61 (0.02)	8.8 (1.0)
1:5	0.51 (0.03)	20.8 (4.4)
1:7	0.57 (0.02)	53.0 (7.8)

TABLE 4

Mechanism of salbutamol sulfate release from microcapsules prepared at different core/wall ratios – comparison between linearization of release rate data by first-order and matrix equations (determination coefficients in parentheses)

Core/wall ratio	K_1 [a] (min^{-1})	K_H [b] (mg $min^{-1/2}$)
1:1	−0.1186 (0.9769)	22.865 (0.9864)
1:2	−0.0903 (0.9942)	19.785 (0.9982)
1:5	−0.0423 (0.9882)	12.788 (0.9970)
1:7	−0.0179 (0.9504)	9.147 (0.9771)

[a] Calculated from $\ln Q = \ln Q_0 - K_1 t$.
[b] Calculated from $Q = K_H t^{1/2}$.

TABLE 5

Determination coefficients for plots of release rate (dQ'/dt) vs. amount (Q') and reciprocal amount ($1/Q'$) of drug released

Core/wall ratio	vs. Q'	vs. $1/Q'$
1:1	0.9981	0.9875
1:2	0.8590	0.9730
1:5	0.6410	0.8804
1:7	0.9253	0.8268

cess and the release data appeared to conform with both of the applied equations.

Van der Voet et al. (1983) proposed using the statistical method of Durbin and Watson (1951) for serial correlation to test the validity of kinetic models. As reported in Table 6, the results of this method agree with both diffusion and dissolution models. For both models, the linear time intervals of drug release increased with decreasing drug/EC ratio. The drug release data from the 1:5 and 1:7 microcapsules fitted Higuchi kinetics over a greater duration of time than that calculated for the first-order relationship. Therefore, it could be suggested that the release data for the 1:5 and 1:7 microcapsules appear to be consistent with kinetics of the diffusion type rather than of dissolution. Nevertheless, definite conclusions concerning this factor could not be drawn.

Recently, a simple power law expression was proposed for the treatment of the experimental release data (Korsmeyer et al., 1983) as follows:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t/M_∞ denotes the drug fraction released at time t, k and n being the rate constant and kinetic exponent of release, respectively. The value of kinetic exponent n defines the mechanism of the release process (Sinclair and Peppas, 1984). This equation was applied to the release from matrices of several geometries (slabs, cylinders,

TABLE 7

Values of kinetics exponent of release (n) for microcapsules prepared at different core/wall ratios (95% confidence limits in parentheses)

Core/wall ratio	n
1:1	0.45 (0.08)
1:2	0.45 (0.02)
1:5	0.41 (0.04)
1:7	0.41 (0.02)

TABLE 6

Durbin-Watson statistics for salbutamol release from microcapsules prepared at different core/wall ratios – comparison between linearization of release rate data by first-order and matrix equations

Core/wall ratio	First-order law			Square-root law		
	Time (min)	Fraction released (M_t/M_∞)	Durbin Watson statistic	Time (min)	Fraction released (M_t/M_∞)	Durbin Watson statistic
1:1	1– 7	0.27–0.64	2.00	1– 7	0.27–0.64	1.98
1:2	1– 7	0.24–0.57	2.01	1– 7	0.24–0.57	2.35
1:5	1–12	0.21–0.47	1.94	1–20	0.21–0.63	1.50
1:7	5–20	0.24–0.44	1.50	5–27	0.24–0.50	1.94

spheres, discs), but to our knowledge it has never been applied to release from microcapsules (reservoir systems). With respect to salbutamol sulfate release from microcapsules, the value of the kinetic exponent of release (about 0.4) indicated diffusion-type kinetics (Fickian-type release), irrespective of the wall thickness (table 7). It should be noted that the Higuchi equation can be considered as one particular case of the power law expression ($n = 0.5$) and that the value of n indicating the release mechanism is dependent on the geometry of the systems (Ritger and Peppas, 1987). As concerns microcapsules, we consider the shape of the microcapsule to be spherical.

Conclusions

Even when mathematical and statistical models were applied, the results did not allow determination of the kinetics of cumulative drug release from microcapsules. Therefore, the power law expression $M_t/M_\infty = kt^n$ (Korsmeyer et al., 1983) was applied and diffusion-type kinetics were confirmed.

Clearly, as the value of the kinetic exponent differs from that corresponding to diffusion-type kinetics, no conclusions are possible with regard to the specific mechanism of drug molecular transport. In this case, only a phenomenological analysis of drug release (Peppas, 1985) can be carried out and non-diffusion release kinetics can be demonstrated.

Acknowledgement

This work has been supported by the Ministero della Pubblica Istruzione, Rome, Italy.

References

Benita, S. and Donbrow, M., Release kinetics of sparingly soluble drugs from ethyl cellulose-walled microcapsules: theophylline microcapsules. *J. Pharm. Pharmacol.*, 34 (1982) 77–82.

Cobby, J., Mayershon, 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.

Donbrow, M. and Benita, S., Release kinetics of sparingly soluble drugs from ethyl cellulose-walled microcapsules: salicylamide microcapsules. *J. Pharm. Pharmacol.*, 34 (1982) 547–551.

Durbin, J. and Watson, G.S., Testing for serial correlation in least squares regression II. *Biometrika*, 38 (1951) 159–178.

Forni, F., Coppi, G., Iannuccelli, V. and Bernabei, M.T., Papaverine hydrochloride release from ethyl cellulose-walled microcapsules. *J. Microencapsulation*, 5 (1988) 139–146.

Gross, S.T., Hoffman, A., Donbrow, M., and Benita, S., Fundamentals of release mechanism interpretation in multiparticulate system: the prediction of the commonly observed relase equations from statistical population models for particle ensembles. *Int. J. Pharm.*, 29 (1986) 213–222.

Higuchi, T., Mechanism of sustained-action medication; theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Hoffman, A., Donbrow, M. and Benita, S., Direct measurements on individual microcapsule dissolution as a tool for determination of release mechanism. *J. Pharm. Pharmacol.*, 38 (1986) 764–766.

Kawashima, Y., Matsuda, K. and Takenaka, H., Physicochemical properties of spray-dried agglomerated particles of salicylic acid and sodium salicylate. *J. Pharm. Pharmacol.*, 24 (1972) 505–512.

Kaye, B.H., Fractal description of fineparticle systems. In Beddow, J.K. (Ed.), *Particle Characterization in Technology, Vol. I, Application and Microanalysis*, CRC Press, Boca Raton, FL, 1986, pp. 81–100.

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.

Langenbucher, F., In vitro assessment of dissolution kinetics: description and evaluation of a column-type method. *J. Pharm. Sci.*, 58 (1969) 1265–1272.

Langenbucher, F., Linearization of dissolution rate curves by the Weibull distribution. *J. Pharm. Pharmacol.*, 24 (1972) 979–981.

Merkle, H.P. and Speiser, P., Preparation and in vitro evaluation of cellulose acetate phthalate coacervate microcapsules. *J. Pharm. Sci.*, 62 (1973) 1444–1448.

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta Helv.*, 60 (1985) 110–111.

Ritger, P.L. and Peppas, N.A., A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Controlled Release*, 5 (1987) 23–36.

Samejima, M., Hirata, G. and Koida, Y., Studies on microcapsules. I. Role and effect of coacervation-inducing agents in the microencapsulation of ascorbic acid by a phase separation method. *Chem. Pharm. Bull.*, 30 (1982) 2894–2899.

Si-Nang, L., Carlier, P.F., Delort, P., Gazzola, J. and Lafont, D., Determination of coating thickness of microcapsules

and influence upon diffusion. *J. Pharm. Sci.*, 62 (1973) 452–455.

Sinclair, G.W. and Peppas, N.A., Analysis of non-Fickian transport in polymers using simplified exponential expressions. *J. Membrane Sci.*, 17 (1984) 329–331.

van der Voet, H., De Haan, P. and Doornbos, D.A., The use of the Durbin-Watson statistic for testing the validity of kinetic models for dissolution. *Int. J. Pharm.*, 14 (1983) 291–298.

White, D.C., Simultaneous determination of sulphur and chlorine in organic compounds. *Mikrochim. Acta*, (1962) 807–812.