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Influence of size polydispersity on drug release from coated pellets

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Summary

In this study, a previously demonstrated model for monodispersed pellets is extended to the case of polydispersed systems. To validate the model, ketoprofen pellets prepared using the extrusion-spheronisation process were coated with an acrylic membrane (Eudragit® RL and triacetin). The effect of pellet size polydispersity on drug release was investigated by screening the spherical matrices before coating. Dissolution testing was performed on each fraction and pellet batch before screening; it was possible to predict the release kinetics of the latter to a good approximation. Next the different fractions were separately coated with a polymeric membrane of nearly identical thickness and their drug release kinetics were interpreted according to the investigated model. The polydispersed system was also coated and screened. The results from the interpretation of the drug release kinetics of each fraction showed that there was apparently no significant influence of pellet size on the coating thickness.

Introduction

Coating of drug pellets with polymeric substances is a common method to obtain sustained release devices. Many theoretical models have been reported in the literature in order to describe the release properties of these systems (Droin et al., 1985; Jambhekar et al., 1987; Ritschel and Udeshi, 1987; Zhang et al., 1988).

In a previous paper (Husson et al., 1991a), we validated a theoretical model describing drug release kinetics from spherical coated matrices, where the membrane does not entirely control the release. The model derived from the Higuchi equation relative to spherical matrices (Higuchi, 1963) was used with the hypothesis of a monodispersed size distribution of beads. However, pellets whether manufactured by powder layering, solution layering or extrusion-spheronisation usually show size polydispersity. Therefore, especially in the case of pellets prepared by extrusion-spheronisation, screening is required after manufacture, in order to avoid pellet systems showing large size polydispersity.

Ragnarsson and Johansson (1988) studied the influence of the size of barrier-coated drug cores

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on their release properties. They showed that the release rate is directly proportional to the surface area of the cores. Consequently, for a set amount of pellets, the surface to be coated varies in inverse proportion to the radius. Thus, for a given amount of coating polymer, the coating thickness is thicker when the pellet size is larger. The drug release rate is consequently faster from smaller pellets, due to a larger release surface and also due to a thinner coating thickness.

Wesdyk et al. (1990) studied the influence of pellets' size polydispersity and mass on their release properties. In theory, pellets of a polydispersed system should receive an amount of coating solution proportional to the total surface area of the pellets. Under these conditions the coating thickness should be the same irrespective of the pellet size. However, the authors, observed that in the case of polydispersed systems, larger or heavier beads received a thicker film compared to smaller or lighter beads. According to the authors, this trend would be due to the fluidization patterns and velocities of the various sized pellets.

As pellets' release properties are very much dependent on their size, their polydispersity should affect their release properties. Thus, the aims of this work were to evaluate the effect of size polydispersity on coated drug release properties and to interpret this effect with a theoretical model.

Materials and Methods

Materials

Ketoprofen B.P. (Rhône-Poulenc Ltd, U.K.), microcrystalline cellulose (Avicel® PH-101, FMC, U.S.A.) and carboxymethylcellulose sodium (Courlose®, Courtaulds Acetate Ltd, U.K.) were used to make pellets. An acrylate-methacrylate copolymer (Eudragit® RL 100, Röhm Pharma, Germany) was used to coat the pellets. Triacetin (Janssen Chimica, Belgium) was used as a plasticiser. Acetone and isopropyl alcohol (Prolabo, France) were used as solvents of the copolymer.

Methods

Preparation of coated pellets The ketoprofen pellets were manufactured by extrusion-spheronisation, using the same procedure as described in a previous paper (Husson et al., 1991a). They comprised 75% ketoprofen, 24% microcrystalline cellulose and 1% carboxymethylcellulose sodium.

The pellets were then coated by spray-coating of an organic polymer solution in a fluid bed column (Aeromatic Strea 1). The composition of the coating solution was as follows: Eudragit® RL 100, 10% (w/w); triacetin, 1% (w/w); isopropyl alcohol, 53.4% (w/w); acetone, 35.6% (w/w).

Coating conditions were: batch size, 350 g of uncoated pellets; coating solution flow rate, 12 g/min; spray pressure, 1 bar; outlet temperature, 30°C; nozzle size, 1.1 mm; drying, 30°C for 15 min.

Particle size distribution Pellets were separated into five size fractions by sieving through 0.5, 0.71, 0.8, 1.0, 1.25 and 1.4 mm diameter screens. The testing was performed on a Fritsch vibratory sieve shaker using 200 g pellets at an amplitude of 4 for 10 min.

In vitro dissolution testing Dissolution tests of pellets were performed in 500 ml of pH 6.6 buffer, using the paddle method (Dissolutest Prolabo, France, U.S.P. XXI, 120 rpm, 37°C). The release of ketoprofen was analysed spectrophotometrically (Perkin Elmer lambda 5, U.S.A.) and continuously at 260 nm. The amount of coated pellets to be tested was adjusted in order to have 100 mg of ketoprofen in each solution vessel (sink conditions were maintained, since the solubility of ketoprofen in pH 6.6 buffer is 30 g/l).

Coating thickness determinations In a previous study (Husson et al., 1991b), we showed that there was an excellent correlation between the results of scanning electron microscopy and calculated coating thicknesses. Therefore, the latter technique, which consisted of determining the coating thickness from the weight of coating polymer applied and the surface area of the pellet bed, was employed.

Results

Uncoated pellets

Characterization of uncoated pellet size polydispersity

After screening, the different fractions of uncoated pellets were weighed and led to the weight distribution as a function of five diameter ranges (Fig. 1). There are two main fractions in the 0.8–1.25 mm range and smaller fractions of other sized pellets. This distribution is typical of pellets manufactured by extrusion-spheronisation. Calculation of the average diameter from this distribution led to the value of 1.03 mm.

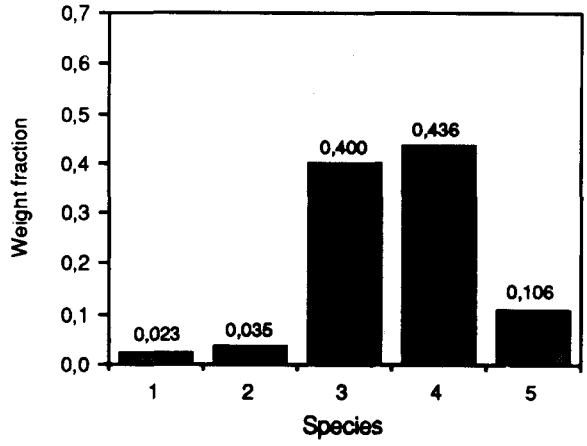

Fig. 1. Uncoated pellets: weight distribution. Species 1, 0.50 < Ø ⩽ 0.71 mm, average diameter = 0.605 mm; species 2, 0.71 < Ø ⩽ 0.80 mm, average diameter = 0.755 mm; species 3, 0.80 < Ø ⩽ 1.0 mm, average diameter = 0.900 mm; species 4, 1.0 < Ø ⩽ 1.25 mm, average diameter = 1.125 mm; species 5, 1.25 < Ø ⩽ 1.40 mm, average diameter = 1.325 mm.

In vitro drug release kinetics from uncoated pellets

The results of dissolution testing for the five size fractions of uncoated pellets and the polydispersed system (uncoated pellets before screening) are presented in Fig. 2. They show, as expected, a significant influence of the diameter on the release kinetics. The smaller pellets release drug at a much faster rate than the larger pellets. The drug release kinetics of the polydispersed system, of which the average diameter is 1.03 mm, is almost identical to that of species 3 of average diameter 0.9 mm.

The use of the Higuchi model (1963) related to spherical matrices with drug dispersed ($C_0 \gg C_s$), valid in the case of monodispersed systems (Eqn

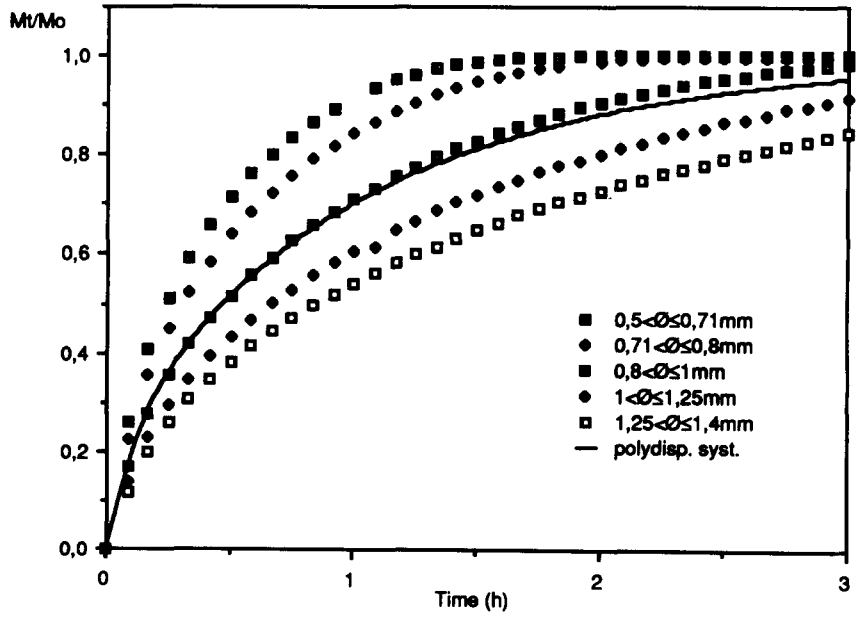

Fig. 2. Uncoated pellets: drug release kinetics.

TABLE 1

Values of the Higuchi constant B_i for the different fractions

Diameter (mm)	B_i (h^{-1})
$0.5 < \varnothing \leq 0.71$	0.597
$0.71 < \varnothing \leq 0.80$	0.466
$0.80 < \varnothing \leq 1.0$	0.289
$1.0 < \varnothing \leq 1.25$	0.200
$1.25 < \varnothing \leq 1.40$	0.152

1), allows the determination of the parameter B for each species (Table 1).

$$1 + 2\left(1 - \frac{M_t}{M_0}\right) - 3\left(1 - \frac{M_t}{M_0}\right)^{2/3} = Bt \qquad (1)$$

with

$$B = \frac{6D_cC_s}{C_0r_0^2} \qquad (2)$$

where M_t/M_0 is the fraction of drug remaining at time t, D_c denotes the drug diffusion coefficient in the core, C_0 is the initial drug concentration in the core, C_s represents the drug solubility in the matrix and r_0 is the pellet radius.

We can note that the values logically decrease when the diameter of the species increases as predicted by Eqn 2.

Influence of size polydispersity: theoretical considerations

The Higuchi theoretical model has been demonstrated and validated in the case of pellets having a monodispersed size distribution. This led to Eqn 1.

To extend this model to the case of polydispersed systems, we supposed that each species releases the drug according to a Higuchi-type law, and that a composite system corresponding to the blending of the different species also released the drug according to the Higuchi-type law.

In other words, the modelling of the release kinetics of polydispersed uncoated pellets consisted of determining a new parameter $B_{\text{polydisperse}}$ (B_{poly}) from the elementary characteristics of each species. The parameter B_{poly} allows one to describe the release kinetics of the polydispersed system according to Eqn 3:

$$1 + 2\left(1 - \frac{M_t}{M_0}\right) - 3\left(1 - \frac{M_t}{M_0}\right)^{2/3} = B_{\text{poly}}t \qquad (3)$$

The interpretation of the release kinetics of the polydispersed system according to Eqn 3 led to an experimental value of B_{poly} equal to 0.257 h^{-1}.

In order to derive an expression for the prediction of B_{poly} we considered an approximate theoretical modelling. In this approach, we attempted to find a theoretical expression for the parameter B_{poly} from boundary conditions. Therefore, we performed a limited development of the left-hand side of the Higuchi equation for $M_t/M_0 < 1$:

$$Y = 1 + 2\left(1 - \frac{M_t}{M_0}\right) - 3\left(1 - \frac{M_t}{M_0}\right)^{2/3}$$

$$\approx \frac{1}{3}\left(\frac{M_t}{M_0}\right)^2\left(1 + \frac{4}{9}\frac{M_t}{M_0} + \ldots\right)$$

This limited development shows, for example that during the early stages of the kinetics, as long as the percentage drug released is below 20%, a simplified expression (Eqn 4) of the Higuchi equation can be written with a 10% approximation as follows:

$$\frac{M_t}{M_0} \approx \sqrt{3Bt} \qquad (4)$$

For an extension of the Higuchi model, the relationship between the parameter B_{poly} and the parameters B_i of the different species must be verified for each time of the kinetics, and particularly for the early times. Thus, it is possible to write:

$$M_t = M_0\sqrt{3B_{\text{poly}}t} \qquad (5)$$

for the polydispersed system,

$$M_{ti} = M_{0i}\sqrt{3B_it} \qquad (6)$$

for each species i of the system.

By summation of the latter equation, we obtain the total amount of drug release at time t:

$$M_t = \sum_i M_{ti} = \sum_i M_{0i}\sqrt{3B_i t} \quad (7)$$

Assuming that the drug is uniformly distributed in pellets (identical concentrations from one pellet to another), the weight fraction of the species i (m_i) can be evaluated from the initial weight fraction of the drug:

$$m_i = \frac{M_{0i}}{M_0} \quad (8)$$

Eqn 7 becomes:

$$M_t = M_0 \sum_i m_i\sqrt{3B_i t} \quad (9)$$

Comparison of Eqn 9 with Eqn 5 gives the theoretical expression of the parameter B_{poly} (Eqn 10):

$$B_{poly} = \left(\sum_i m_i\sqrt{B_i}\right)^2 \quad (10)$$

This relation has been demonstrated for the early stages of the release kinetics. It should logically remain valid for the later times if behaviour specific to certain fractions does not appear during the release kinetics. Regarding this matter, one can anticipate that in the case of smaller pellets, the Higuchi model will cease to be valid more quickly subsequently to a significant depletion of drug. Such a phenomenon can lead to differences between the theoretical predictions and the experimental results.

The use of Eqn 10 allows one to predict the theoretical value of B_{poly}:

$$B_{poly(theo)} = 0.243\ h^{-1}$$

The good approximation of the experimental value of B_{poly} (0.257 h^{-1}) obtained with our approximate theoretical model provides evidence of its validity.

Comparison between the uncoated system experimental release kinetics with the theoretical release kinetics obtained from the approximate theoretical model is given in Fig. 3. The theoretical curve results from the use of Eqn 3 with a value of B_{poly} calculated using Eqn 10 (B_{poly} = 0.243 h^{-1}). The good superposition of the curves confirms the validity of the extension of the

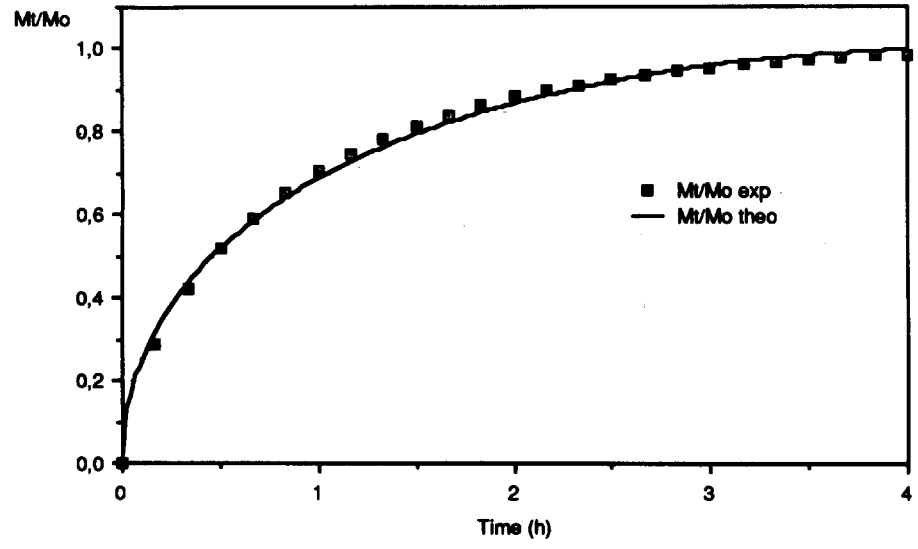

Fig. 3. Extension of the Higuchi model to the case of polydispersed systems. Correlation between theory and experiment in the case of uncoated pellets.

Higuchi model for polydispersed uncoated spherical matrices with drug dispersed and the accuracy of our theoretical prediction.

Coated pellets

In a previous work (Husson et al., 1991a), we developed a theoretical model to describe the drug release kinetics of monodispersed coated pellets according to Eqns 11 and 12:

$$1+2\left(1-\frac{M_t}{M_0}\right)-3\left(1-\frac{M_t}{M_0}\right)^{2/3}+A\frac{M_t}{M_0}=Bt \tag{11}$$

with

$$B=\frac{6D_cC_s}{C_0r_0^2} \quad A=\frac{2hD_c}{r_0KD_p} \tag{12}$$

This equation is a modification of the Higuchi model with an additional dimensionless term AM_t/M_0. The parameter B is identical to the parameter of the Higuchi equation related to spherical matrices with drug dispersed. It is a parameter characteristic of the uncoated pellets. The parameter A can be correlated to the permeability of the membrane KD_p/h, where D_p is the drug diffusion coefficient in the membrane, K denotes the partition coefficient between the membrane and the core and h is the membrane thickness.

In this study we attempted to extend the theoretical model to the case of polydispersed systems. Therefore, we firstly considered a polydispersed model system comprising a blend of different sized species separately coated. Secondly, we studied a real polydispersed system, of which the different sized species were simultaneously coated.

Polydispersed coated model system: experimental results

The polydispersed model system was prepared by blending the species separately coated, according to the uncoated pellet size distribution.

The different species were separately coated with a 19 μm thick membrane comprising Eudragit® RL and triacetin as a plasticiser (10% by weight of polymer). Fig. 4 shows the experimental release kinetics of the different coated species in comparison with those of the polydispersed model system.

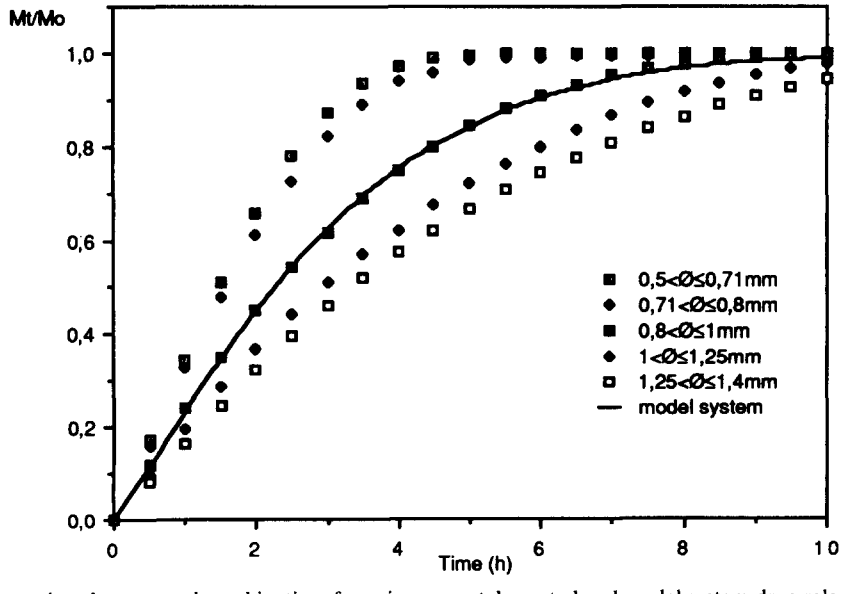

Fig. 4. Comparison between release kinetics of species separately coated and model system drug release kinetics.

TABLE 2

Values of the parameter A_i of the different coated fractions

Diameter (mm)	A_i
$0.5 < \varnothing \leqslant 0.71$	1.453
$0.71 < \varnothing \leqslant 0.80$	1.200
$0.80 < \varnothing \leqslant 1.0$	1.153
$1.0 < \varnothing \leqslant 1.25$	1.013
$1.25 < \varnothing \leqslant 1.40$	0.806

The use of the theoretical model valid in the case of monodispersed systems allows the determination of the parameters A_i of each species. The parameters A_i, of which the values are listed in Table 2, appear as a decreasing function of the radius according to Eqn 12.

The interpretation of the release kinetics of the model system with the theoretical equation (Eqn 11), valid in the case of monodispersed systems and assumed to be verified by polydispersed systems, leads to the following experimental value of $A = 0.915$.

Theoretical considerations

For the extension of the theoretical model to the case of polydispersed systems, we suppose that the membrane thickness is constant, and that the release kinetics of the blend of different species still follows the same type of equation as Eqn 11.

According to these assumptions, the parameters A_{poly} and B_{poly} of the blend can be written as a function of the parameters A_i and B_i of the fractions. In the case of uncoated pellets we gave a relationship between the parameter B_{poly} and the parameters B_i in the Higuchi model, these relationships remain valid for coated systems, thus the extension of the model consists of obtaining an expression for A_{poly}. Similarly to the case of uncoated pellets, we considered an approximate theoretical modelling.

As for the extension of the Higuchi model, in order to obtain an absolute relationship between the parameters of the polydispersed system and those of the fractions, we considered a particular part of the kinetics: the early stages of release.

During the early stages of the release kinetics, drug depletion in the matrix is negligible and the drug concentration gradient through the membrane corresponds to a concentration difference C_s of the drug mobile fraction through a thickness h of the membrane.

According to Fick's first law, the initial flux of drug is given by the expression:

$$J = \frac{KC_s D_m}{h} \tag{13}$$

Thus, the amount of drug released at time t (M_t) from a pellet of radius r_0 is given by Eqn 14:

$$M_t = 4\pi r_0^2 \frac{KC_s D_m t}{h} \tag{14}$$

By consideration of the initial amount of drug in the matrix M_0, the drug fraction released at time t can be written as follows (Eqn 15):

$$\frac{M_t}{M_0} = \frac{3KC_s D_m}{C_0 r_0 h} t \tag{15}$$

According to the definitions of A and B, Eqn 15 can be expressed as Eqn 16:

$$\frac{M_t}{M_0} = \frac{B}{A} t \tag{16}$$

Applied to the species i of the polydispersed system, Eqn 16 becomes:

$$M_{ti} = M_{0i} \frac{B_i}{A_i} t \tag{17}$$

The total amount release from the polydispersed system at time t is obtained by summation over all the species:

$$M_t = \sum_i M_{ti} = \sum_i M_{0i} \frac{B_i}{A_i} t \tag{18}$$

Using Eqn 8 related to the weight fraction m_i of the species i, Eqn 18 can be expressed as follows:

$$\frac{M_t}{M_0} = \sum_i m_i \frac{B_i}{A_i} t \tag{19}$$

For an extension of the model to the case of polydispersed systems, we supposed that a relationship such as Eqn 16 is valid in the case of a species blend:

$$\frac{M_t}{M_0} = \frac{B_{\text{poly}}}{A_{\text{poly}}} t \tag{20}$$

An expression of A_{poly} is obtained by equating Eqns 19 and 20.

$$A_{\text{poly}} = B_{\text{poly}} \left(\sum_i m_i \frac{B_i}{A_i} \right)^{-1} \tag{21}$$

Thus, the theoretical calculation of A_{poly} according to the values of B_i and A_i given in Tables 1 and 2 and the theoretical value of $B_{\text{poly}} = 0.243$ h^{-1} leads to the determination of $A_{\text{poly(theo)}}$:

$$A_{\text{poly(theo)}} = 1.059$$

The theoretical estimation of the parameter A_{poly} is not as good as that of the parameter B: the deviation between the theoretical and experimental values is around 15% in the case of A and only 5% in the case of B. However, taking into account the unavoidable experimental inaccuracy, the theoretical modelling appears very satisfactory based on its validation on the polydispersed model system.

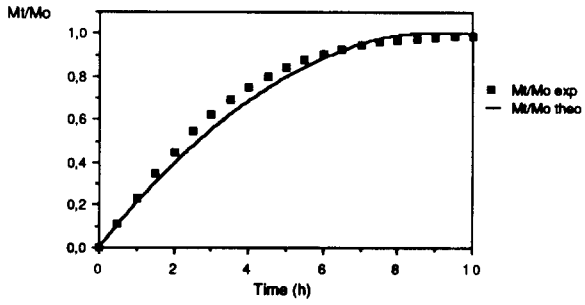

Fig. 5. Comparison between the model system release kinetics with the theoretical release predicted with the approximate theoretical model.

Comparison of the model system experimental release kinetics with the theoretical kinetics obtained from the approximate theoretical model (Fig. 5) shows the validity of the theoretical model.

Real polydispersed coated systems

The real polydispersed system was prepared by simultaneous coating of all the uncoated fractions. The average coating thickness (19 μm) is

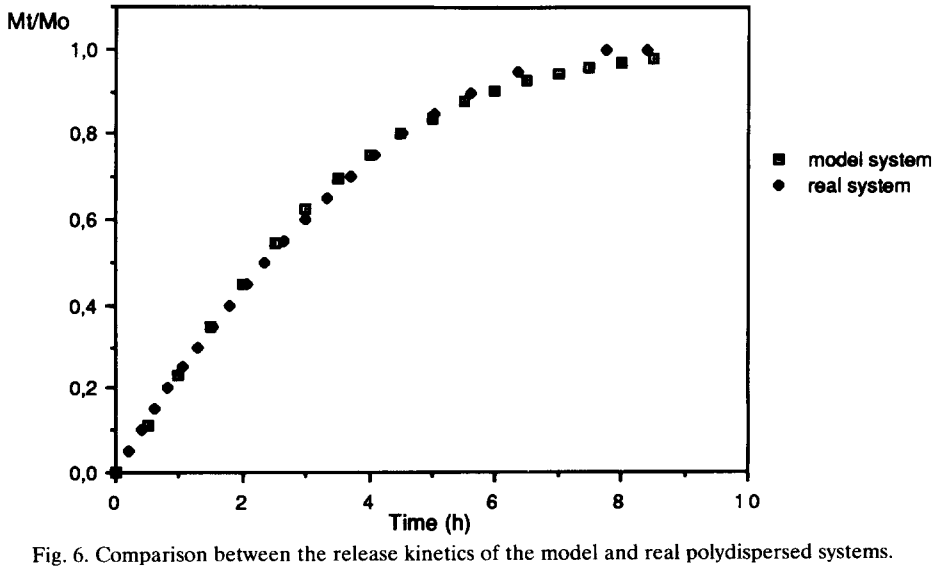

Fig. 6. Comparison between the release kinetics of the model and real polydispersed systems.

TABLE 3

Comparison of the values of A_i and A'_i characteristic of the fractions coated separately and as a composite batch, respectively

Diameter (mm)	A'_i	A_i
$0.5 < \varnothing \leqslant 0.71$	1.236	1.453
$0.71 < \varnothing \leqslant 0.80$	1.201	1.200
$0.80 < \varnothing \leqslant 1.0$	0.995	1.153
$1.0 < \varnothing \leqslant 1.25$	0.953	1.013
$1.25 < \varnothing \leqslant 1.40$	0.930	0.806

comparable with the model system membrane thickness.

Fig. 6 shows a comparison between the release kinetics of the model system and the real system. The good superposition of the curves appears to show that the coating conditions of the different fractions do not seem to notably affect the average release kinetics.

In order to examine this effect more accurately, we compared one by one the different fractions which had been coated either separately or as a composite batch. Therefore, we screened the real polydispersed coated system and investigated the drug release kinetics of the different fractions and interpreted these kinetics with the theoretical model valid for monodispersed systems. It led to the determination of the parameters A'_i. Table 3 shows the comparison of the A'_i values with the A_i values of the fractions separately coated.

There is a relatively good agreement between the values of A_i and A'_i. As the parameter A is proportional to the membrane thickness, we believe that there is not a great size influence on the coating thickness, which validates our hypothesis (constant membrane thickness). However, the parameter A'_i is greater than A_i for the larger pellets and lower for the smaller pellets, consequently when a polydispersed system is coated, larger pellets could possibly acquire a thicker coating.

Conclusion

In this work, we considered an extension of a theoretical model describing the drug release from coated matrices monodispersed in size to the case of coated matrices showing size polydispersity.

Our theoretical model was very satisfactorily validated in the case of pellets coated with an acrylate-methacrylate membrane. The results showed that the model permitted the prediction of drug release from spherical coated matrices, of which the size was within the experimental size range ($0.50 < \varnothing < 1.40$ mm). Furthermore, it showed that there was no significant coating selectivity with respect to the pellet size. For this reason, our model which only takes into account the latter parameter, allows one to interpret the drug release kinetics of real systems usually showing size polydispersity.

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