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Research Article

Modelling of drug release from ensembles of aspirin microcapsules of certain particle size distribution

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Abstract

Purpose: *In order to determine the drug release profile of an ensemble of aspirin crystals or microcapsules from its particle distribution a mathematical model that considered the individual release characteristics of the component single particles was developed. The model assumed that under sink conditions the release from individual (component) particles would be independent of each other and hence simply additive.*
Method: *The release parameters, m_t = the amount of drug released in time t, m_∞ = the maximum release and t_∞ = the time to attain it were determined for each single particle by simulation using previously derived mathematical models. To obtain the cumulative release curve for the ensemble the individual releases were summed up at each time scale and for the various time intervals. Values of m_∞ and t_∞ for the ensemble were obtained from the simulated cumulative curves. The release profiles of the ensembles were also determined experimentally and their m_∞ and t_∞ values deduced from the release curves.*
Results: *The observed cumulative curves of the ensembles compared favourably with the simulated data. The % difference in the observed and the simulated m_∞ and t_∞ values of the ensembles was within ± 20%, which indicated that the modelling was valid.*
Conclusion: *The study showed that the release profile of an ensemble can be determined from its particle distribution which has application in controlled release studies.*

Key words*: Aspirin microcapsules, drug release simulation, multiparticulate systems*

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Introduction

Water insoluble polymers such as the acrylate methacrylates have been frequently applied on drug microparticles to obtain controlled release[1, 2]. The resulting microcapsules are invariably inhomogeneous with respect to either the distribution of particle size, shape, nature of the wall (coating) material and/or wall thickness. A polydisperse system is therefore an ensemble of such inhomogeneously distributed particles. The release profile of an ensemble is dependent on the release characteristic of the individual (component) particles, and hence the particle distribution which may therefore be predetermined by computer simulation to optimize drug release[3].

The important parameters which define the release profile of a microencapsulated drug are the rate order kinetic, the diffusion coefficient, the maximum release, m_∞ and the time to attain it, t_∞. Whereas the ensemble of microcapsules invariably displays a first order rate kinetic the single (component) microcapsules display a zero order rate profile[3-7]. The individual particles were found to be inhomogeneous in the distribution of the release parameters, m_∞ and t_∞. Consequently summation of the individual releases from the single particles will give a cumulative release curve of he first order type, which was confirmed experimentally[3, 4]. The individual releases are additive only under a sink condition such that the release from the individual particles are independent of each other. This finding provides a basis for predicting the release profile of an ensemble of a given particle distribution. In the previous studies[3, 4], the release data on several single particles of various sizes and weights were first determined empirically and the data subsequently used to simulate the release profiles of the ensembles, which is tedious. In the first part of this report we showed that the release profiles of the single particles could be simulated applying certain derived mathematical models[8]. Also the previous study[3] was modelistic in design as one particle each of different sizes and weights were randomly selected to constitute the ensemble. In the present study the model was applied to an actual polydisperse system of an accidental particle distribution.

Modelling

Details of the derivation of the mathematical models for the simulation of the drug release profiles of the single particles of aspirin of an orthorhombic shape have been presented elsewhere in a recent publication[8]. The model allowed the estimation of the parameters m_∞, t_∞ and m_t (the amount released at time intervals, t) from each particle in the distribution. In the case of the single crystals only the simulated amount of drug that would be released at the transition point from zero to first order release was designated as m_1 and the time to attain it as t_1[8]. The data are used here to simulate drug release from the ensembles based on the model:

$$M_t = \sum_{i=1}^{N} n_i m_{i(t)} \qquad \text{..... (1)}$$

where M_t is the cumulative release from the ensemble in time t, n_i is the number of particles each of size i distributed between the 1st and the Nth term which in the system studied were 0.3 mm and 1.4 mm respectively (i.e. the particle size range), $m_{i(t)}$ is the individual release from each particle in time, t. The maximum value of $m_{i(t)}$ is predetermined as the calculated m_∞ of that particle achieved in time, t_∞. This model assumes that under sink conditions the release from individual particles in the ensemble would be independent of each other and therefore additive.

An aspect which was not considered in the first part of this study[8] is the development of mathematical models for the simulation of the release profiles of single microcapsules at different wall thicknesses. The published values of m_∞ and t_∞ relate to single microcapsules of wall thickness, 11 μm[8]. Values of these parameters at other wall

thicknesses e.g. 27 μm were estimated in the present study from the modified Fick equation, applicable to drug release from microcapsules[9], thus:

$$m = \frac{K}{L}t \qquad \ldots\ldots\ldots (2)$$

where K is the proportionality constant for mass transfer through a wall barrier of thickness, L; m is the mass transferred in time, t. At the point of maximum release m = m_∞ and t = t_∞ in equation 2. Thus the maximum release $m_{\infty(1)}$ and $m_{\infty(2)}$ of two microcapsules of same core weight but of different wall thicknesses, L_1 and L_2 respectively, can be compared by the ratios:

$$\frac{m_{\infty(2)}}{m_{\infty(1)}} = \frac{L_1}{L_2} \qquad \ldots\ldots\ldots (3)$$

and similarly,

$$\frac{t_{\infty(2)}}{t_{\infty(1)}} = \frac{m_{\infty(2)}}{m_{\infty(1)}} \qquad \ldots\ldots\ldots (4)$$

These expressions are based on the inverse relationship between m_∞ and L and the direct relationship between m_∞ and t_∞, (equation 2) since the m_∞ and t_∞ values of microcapsules of wall thickness 11 μm (represented by L_1) were already known [8] the corresponding values for microcapsules of same core weight but of wall thickness 27 μm (represented by L_2) were easily computed. The simulated values were used to compute the release profile of the ensembles.

Materials and Methods

Aspirin crystals (Synopharm Ltd., Germany) were selected as the core material primarily because of the ease of their micro-encpsulation by spray coating methods, thus obviating the need for preliminary pelletization, as would be the case with a fine powder. The particles were mainly orthorhombic with size range 0.3 to 1.4 mm; the most frequent size was 0.7 to 0.8 mm (frequency, 70%)[8]. The frequency – size distribution in a sample of the aspirin crystals (100 mg) is given in Table 1. Acetone (analar grade, BDH Poole, England) was used as solvent in the preparation of the polymeric coating fluid, while dibutylphthalate (reagent grade, BDH) was used as plasticizer.

Microencapsulation technique

The polymer films were applied on the aspirin crystals by a spray coating method, details of the technique have been described elsewhere[8]. Resulting microcapsules were of coating thickness 11 and 27 μm. The cores (i.e. the aspirin crystals) varied in size, 0.3 to 1.4 mm.

Determination of drug release

The procedure for single particles has been described earlier[8]. To determine release from the ensembles, a sample of the crystals or the microcapsules (100 mg) was placed in 1000 ml water in a conical flask and stoppered. The flask was mounted on a shaker bath which was agitated 50 rev. min^{-1} and maintained at a temp. 37 °C. At pre-determined time intervals 3 min (crystals) or 30 min (microcapsules) samples (2ml) were withdrawn from the leaching fluid with a pipette fitted with a cotton wool plug. The samples were analyzed with a spectro-photometer (Hitachi U – 1100, Tokyo, Japan) at λ_{max} 267 nm. Each experiment was carried out in triplicate and the mean results reported. The cumulative amounts of drug released were plotted against time and from the curves the values of m_∞ and t_∞ were obtained.

Simulation of drug release

A computer program, GW-BASIC (Microsoft Corporation, USA) was employed in the simulation. The computation was based on equation 2 which was built into the program. Values of the release parameters, m_t, m_1, t_1, m_∞, t_∞, of the single particles which are needed for the simulation of the cumulative release of the ensembles have been published earlier[8], except the data on single microcapsules of wall thickness of 27 μm

Table 1a: Simulated cumulative release data for ensembles of the crystals

Particle size (mm)	No. Particle (n_i)	Simulated release (µg) from particles of each size fraction ($n_i m_i$) at various time intervals (min)									
		0	3	6	9	10	12	13	14	15	17
0.3	27	0	42	56	57	57	57	57	57	57	57
0.4	27	0	74	74	134	136	136	136	136	136	136
0.5	67	0	291	291	647	653	662	662	662	662	662
0.6	281	0	178	178	4621	4694	4778	4806	4806	4806	4806
0.7	1058	0	908	908	27010	27645	28386	2858	28756	28756	28756
0.8	884	0	9915	991	29744	33049	34454	35001	35346	35832	35832
0.9	254	0	3624	3624	1087	12077	13810	14077	14346	14496	14669
1.0	80	0	1409	1409	4227	4697	5636	5971	6112	6209	632
1.1	30	0	6	6	1919	2132	2558	2772	2980	3052	3151
1.2	17	0	424	424	1271	1413	1695	1836	1977	2150	2235
1.3	12	0	348	348	1043	1159	1390	1506	1622	1738	1972
1.4	7	0	230	230	691	766	922	998	1075	1152	1306
Cumulative release (mg)	2743	0	28	28	82	88	94	96	98	99	100

which are presented in the present report in Figure 2b.

To obtain the simulated release from particles of each size fraction, the individual release at a particular time interval from a single particle of a given size was multiplied by the number of particles of that size represented by $n_i m_{i(t)}$ in equation 1. These were in turn summed up at each time scale and for the various time intervals to obtain the cumulative release curves. The system simulated was the accidental distribution of particles in a 100 mg samples (Table 1). For the ensembles of the crystals the results are presented in Table 1. The cumulative release data were plotted versus time and from the curves the values of m_∞ and t_∞ were obtained.

Determination of the rate order of release

Most drug delivery systems release their drug content by either zero or first order rate kinetic. Consequently in the present study, the cumulative release data on the ensembles were analyzed on the basis of zero or first order rate kinetic. The release was considered to follow a particular kinetic if the correlation coefficient was ≥0.90.

Table 1b: Simulated cumulative release data for ensembles of the crystals *contd.*

Particle size (mm)	No. Particle (n_i)	Simulated release (µg) from particles of each size fraction ($n_i m_i$) at various time intervals (min)								
		18	19	20	21	22	23	24	27	30
0.3	27	57	57	57	57	57	57	57	57	57
0.4	27	136	136	136	136	136	136	136	136	136
0.5	67	662	662	662	662	662	662	662	662	662
0.6	281	4806	4806	4806	4806	4806	4806	4806	4806	4806
0.7	1058	28756	28756	28756	28756	28756	28756	28756	28756	28756
0.8	884	35832	35832	35832	35832	35832	35832	35832	35832	35832
0.9	254	14674	14674	14674	14674	14674	14674	14674	14674	14674
1.0	80	6356	6356	6356	6356	6356	6356	6356	6356	6356
1.1	30	3156	3173	3172	3173	3173	3173	3173	3172	3172
1.2	17	2259	2275	2288	2288	2288	2288	2288	2288	2288
1.3	12	1958	1989	2011	2025	2036	2036	2036	2036	2036
1.4	7	1365	1398	1420	1435	1445	1453	1453	1453	1453
Cumulative release (mg)	2743	100	100	100	100	100	100	100	100	100

Validation of the models

The models employed in the simulation were considered valid if the observed results were in the same order of magnitude as the simulated data. The data were compared by means of a proportional difference given by:

$$\frac{S-E}{S}\times 100 \qquad \ldots\ldots\ldots (5)$$

where S = simulated data and E = the empirical or observed data.

The parameters compared were the correlation coefficient, r, for the rate order of release, m_∞ and t_∞ which define the release profiles of the ensembles. The proportional difference is a measure of the % deviation of the empirical from the simulated data. The results are presented in Table 2. The simulation was considered valid if the % deviation of the observed from the simulated data were within ± 20%.

Results

Simulated release data on the single particles

The release curves of the single crystals already published earlier[8] are represented here (Figure 1), as the data would contribute to the understanding of how the release data in Table 1 were generated. As noted in the previous report the curves fitted into an initial zero order followed by a first order release profile. The linear portion of the plot represents the zero order flux and the curved

Table 2: Comparison of the release parameters (m_∞ and t_∞) values obtained from the simulated (S) and the empirical (E) cumulative curves

Wall thickness	M_∞(mg)			t_∞(min)		
(μm)	S	E	% deviation	S	E	% deviation
0	100	100	0	20	20	0
11	48	58	-21	150	120	20
27	18	22	-22	340	280	18

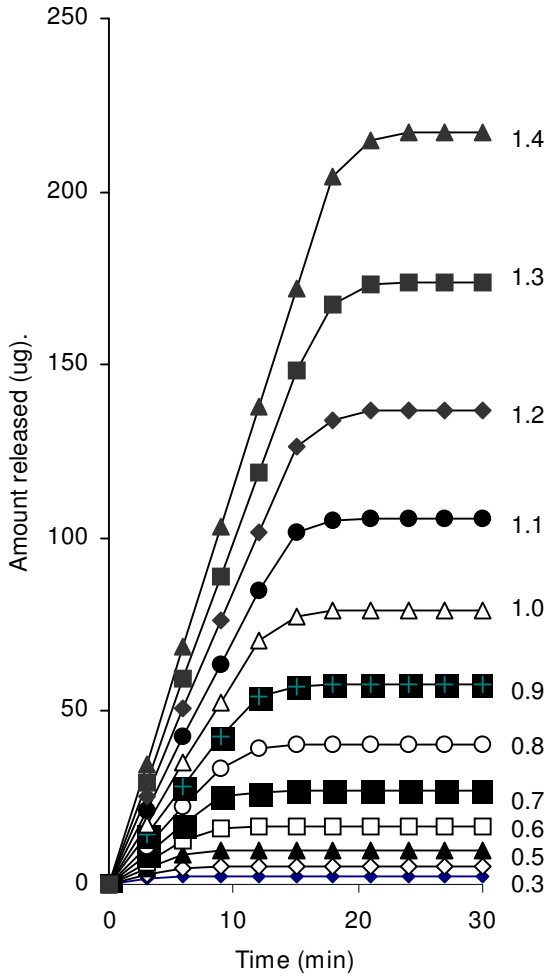

Figure 1: Simulated release profiles of hypothetical single crystals of various particle sizes (mm)

portion the first order phase.

The release data on the single microcapsules are presented in Figure 2. The data generally fitted into a zero order release profile. An increase in wall thickness from 11 to 27 μm brought about a profound decrease in the maximum release, m_∞ while the time to attain it, t_∞ increased considerably (compare Figures 2A and 2B). These parameters also varied with core weight or size. This means that the point of maximum release (the extent and duration) can be controlled by variation in the microcapsule core weight and/or the wall thickness.

Simulated cumulative release profiles of the ensembles

The releases from particles of each size fraction of the crystals (taking into account the release from each particle (Figure 1) and the number of particles of each size) are presented in Table 1, from which the cumulative curve of the crystals was obtained; the curves for the two sets of ensembles of the microcapsules were similarly deduced. The cumulative curves of the three sets of ensembles are shown in Figure 3. The points for maximum release (m_∞, and t_∞) were obtained from these curves; the values are given in Table 2. The release profiles (Figure 3) generally fitted into an initial zero order flux followed by a first order release, as was the case with the single crystals (Figure 1).

The evidence which suggests this profile for the ensembles is that the linear correlation coefficient was generally ≥ 0.95 when the data were analyzed on the basis of an initial zero

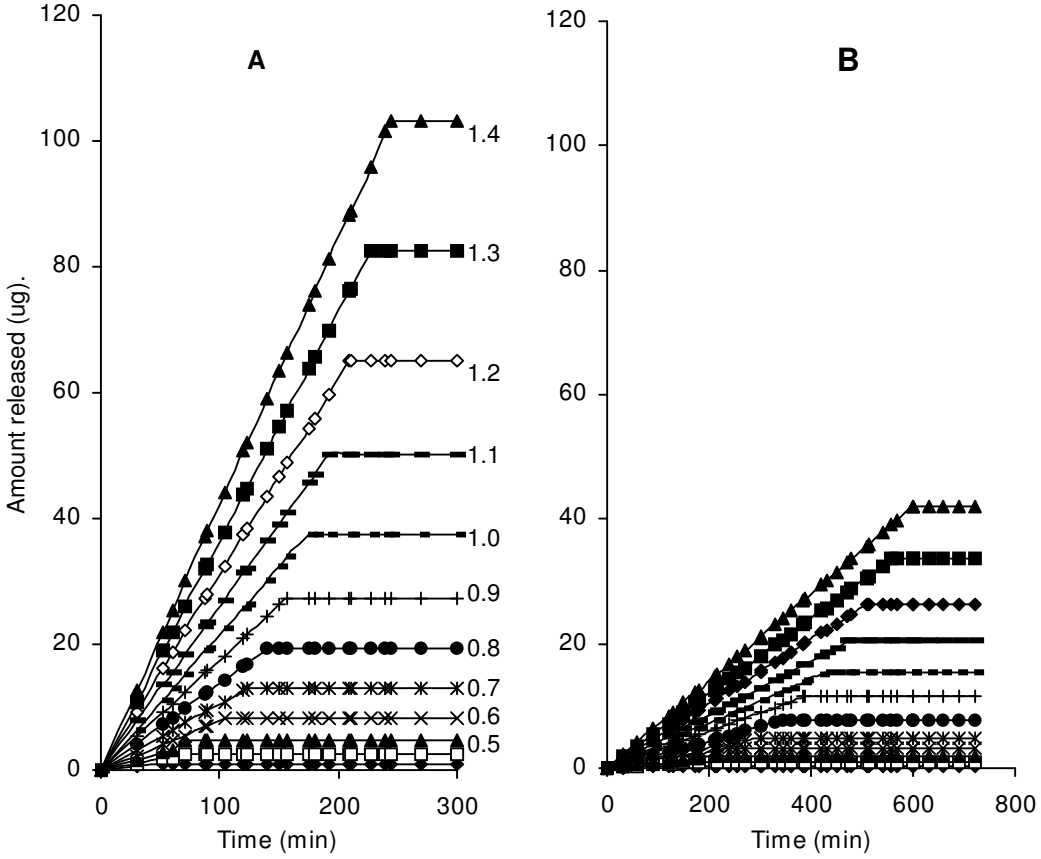

Figure 2: Simulated release profiles of single microcapsules of different wall thicknesses, A (11 μ), and B (27 μm) each of different core sizes of 0.3 to 1.4 mm

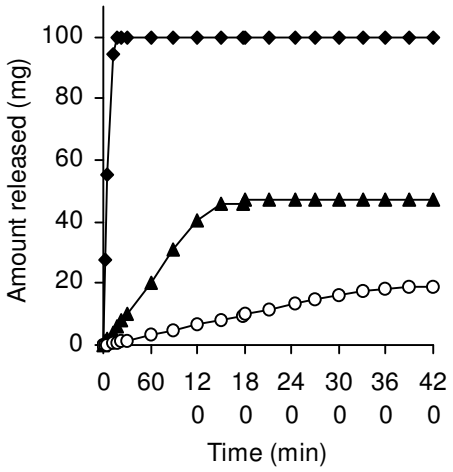

Figure 3: Simulated cumulative release curves of ensembles of the crystals (υ), and the micro-capsules of wall thickness: 11μm (π), and 27μm (ϒ).

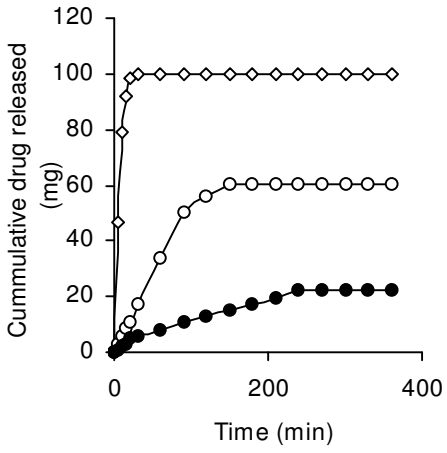

Figure 4: Empirical cumulative release profiles of the 3 sets of ensembles-crystals (↓), and the microcapsules of wall thickness 11um (ϒ), and 27um ( ).

oerder plot (up to 90% release) followed by first order plot for the remaining portion up to the maximum release. The correlation index fell below 0.8 when the data were analyzed entirely either as a zero order or as a first order plot.

Empirical release profiles of the ensembles: The curves are presented in Figure 4. The profiles are in many respects similar to the simulated curves for the ensembles (Figure 3). The observed m_∞ and t_∞ values are presented in Table 2; they differed from the simulated values by a maximum of ± 22% (Table 2). The simulation predicted a decrease in m_∞ from 48 to 18 μg and an increase in t_∞ from 150 to 340 min during increase in wall thickness from 11 to 27 μm. The actual change in m_∞ was 58 to 22 μg and in t_∞, 120 to 280 min. These results lend credence to the models used in the simulation.

Discussion

Interpretation of the release kinetics

The simulation revealed that the single crystals would give an initial zero order release (about 90% of initial particle weight) followed by a first order profile while the single microcapsules would display a total zero order release. The release parameters m_∞ and t_∞ were inhomogeneously distributed among the particles due to individual differences in particle weight and/or wall thickness (in the case of the microcapsules). Based on the previous observation[3, 4] that such inhomogeneous distribution in the m_∞ and t_∞ values would result in a first order release profile for the ensembles, this release profile for the ensembles studied here was expected. Instead what emerged was an initial zero order followed terminally by a first order profile. Unlike previous system[3, 4] where the different particles were in the ensemble in equal number, the present system was characterized by a dominant size fraction both in terms of their number and weight in the particle size distribution (Table 1). The smallest and the largest particles were very few compared with the mid size (0.7 – 0.8 mm) particles. Number of these mid size particles was up to 2000 out of a total of about 2700 particles. The data in Table 1 also show that this size fraction contributed predominantly to the overall release from the ensemble. Moreover the point for maximal release (m_∞ and t_∞) of this size fraction was close to that of the ensemble. As a result of this dominance, the release kinetic from the single crystals will be similar to that of their ensembles. The effect in the microcapsules would be that their ensembles would display a first order release profile only after the release from the dominant size fraction has attained a maximum. Hence, the initial zero order release followed by a first order profile observed for the ensembles of the microcapsules.

Influence of particle distribution on the release profile from the ensembles

From the results of this study the main factor that determined the release profile of the ensemble was the particle distribution. The evidence is that the release profiles of the ensembles which were deduced from their particle distribution were comparable to the empirical release profiles. The particles may be distributed with regards to particle size, shape and/or wall thickness, thus giving a flexible approach for optimizing drug release by predetermining the particle distribution in simulation studies. The selection of the particles will be based on their individual m_∞ and t_∞ values (Figures 1 and 2). For instance a distribution which is predetermined to contain equal number of particles, say 884 of size, 0.8 mm each of the single crystals (Table 1) and of the single microcapsules of wall thickness 11 μm (Figure 2A) will display a cumulative curve of the type in Figure 5, which is characterized by a prompt release from the crystal and a sustained release from the microcapsule fractions. The maximum release of the ensemble and the time to attain it can be predetermined as

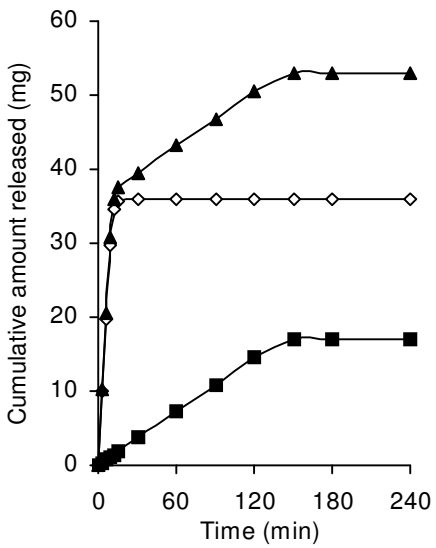

Figure 5: A plot of cumulative release from a predetermined distribution of aspirin crystals and microcapsules of 0.8 mm

follows. The maximum release from the crystal particles is given by:

$n_{(0.8)}m_{\infty(0.8)}$ = 884 x 41µg = 36244µg

where $m_{\infty(0.8)}$ is the maximum release of a single crystal particle (Figure 1). Similarly the maximum release from all the single microcapsules will be 884 × 19 µg = 16596 µg, 19 µg being the maximum release of a single microcapsule (Figure 2A)). Hence the maximum release of the ensemble is given by summation 36244 + 16596 µg = 52840 µg. Its t_∞ of the ensemble will be determined by the t_∞ of the microcapsule (the slow release fraction) which is 140 min (Figure 2). Unlike the m_∞ the t_∞ of a particle is independent of the number of particles (Table 1).

Conclusion

This study has shown that the release profile of a polydisperse multiparticulate system can be reliably deduced from its particle distribution and the release profiles of the individual (component) particles in the distribution. Hence, the particle distribution may be predetermined in simulation studies to optimize drug release. The release parameters (m_∞ and t_∞) of the single particles can be theoretically derived which provides a rationale basis for the selection of the particles in the simulation process.

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References

1. Lehmann K. Controlled delivery with eudragit retard lacquer films. Drugs made in Germany 1968; 11: 34-36.
2. Okor RS. Drug release through aqueous-based film coatings of acrylatemethacrylate, a water insoluble copolymer. Int J Pharm 1990; 58: 89-91.
3. Hoffman A, Donbrow M, Gross ST, Benita S, Bahat. R. Fundamentals of release mechanism interpretation in multiparticulate systems: determination of substrate release from single microcapsules and relation between individual and ensemble release kinetics. Int J Pharm 1986; 29: 195-211.
4. Donbrow M, Hoffman A, Benita, S. Variation of population release kinetics in polydisperse multiparticulate systems (microcapsules, microsphere, droplets, cells) with heterogeneity of one, two, three parameters in the population of individuals, J Pharm Pharmacol 1988; 40: 93-6.
5. Thies C. Microcapsules as drug delivery devices. Crit Rev Biomed Eng. 1982; 8: 335-338.
6. Donbrow M, Benita S. Release kinetics of sparingly soluble drugs from ethyl cellulose-walled microcapsules: salicylamide microcapsules, J Pharm Pharmacol 1982; 34: 547-51.
7. Benita S, Donbrow M. Release kinetics of sparingly soluble drugs from ethylcellulose walled microcapsules: theophylline microcapsules, J Pharm Pharmacol 1982; 34: 77-82.
8. Eichie FE, Okor RS. Parameters to be considered in the simulation of drug release from aspirin crystals and their microcapsules, Trop J Pharm Res 2002; 1(2): 99 – 110.
9. Dappert T, Thies C. The heterogeneous nature of microcapsules, Proc. 5th Int. Symp. Controlled Release of Bioactive Materials, University of Akron, Akron, Oh 1978; 2.18-24.