The Use of Statistical Moment Analysis to Elucidate the Mechanism of Release of a Model Drug from Pellets Produced by Extrusion and Spheronisation

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The dissolution profile of a model drug (indomethacin) in pellets produced by extrusion and spheronisation has been evaluated according to the method described in the USP XXIII, apparatus II. The effects of the speed of the paddles, temperature, pH and size of the pellets, *i.e.*, the surface area have been examined. The study was complemented by coating the pellets with a polymer (ethylcellulose) in an aqueous dispersion and changes in the release of the drug were monitored. The analysis of the results was carried out by determination of two statistical moments mean dissolution time (*MDT*) of indomethacin and variance of dissolution time (*VR*) and an associated parameter, the relative dispersion of the concentration–time profile (*RD*). From these parameters, it was possible to relate the release of the drug to the dissolution mechanisms and models described in the literature. The present study has shown the possibility of analysing the complete release of the indomethacin as opposed to the traditional approach of considering only 40—60% of the drug released. The analysis has also shown that the mechanism of release of the drug changes throughout the test. Finally, for pellets coated with ethylcellulose, the coating altered the rate of release of the drug and changes in the release mechanism were also observed. Under certain conditions a zero order release rate was obtained.

Key words extrusion; mean dissolution time; release mechanism; statistical moment

The release of an active substance from a solid dosage form (such as pellets produced by extrusion and spheronisation) is a matter of primary concern for the formulator since the drug must be in solution in order for it to be absorbed. Ideally, the release of a drug should be monitored *in vivo*. However, due to practical and ethical limitations, *in vitro* tests are usually carried out. From the *in vitro* tests which can be used, the dissolution test (as described in major Pharmacopoeias) is probably the most important test in monitoring the variables associated with formulation excipients, design and manufacturing of dosage forms which have an influence on the release characteristics of the drug.[2] Probably, the most important parameter to be determined in these studies is the release rate (the amount of drug released per unit of time) which may be correlated to the permissible variations in processing and formulation variables in industry.[3]

Traditionally, the analysis of the results is carried out by curve fitting to a pre-established model and is based only on a portion of the release of the drug (about 45%) whereas the rest of the drug released is ignored, *i.e.*, the release of more than half of the dose is ignored. Moreover, it is common that burst effects at the beginning of the release of the drug occur providing a larger amount of drug to the patient than predicted by the models. Therefore, the analysis of data according to this approach presents some drawbacks, added to the fact that a correlation with the results *in vivo* is not easily established. Another drawback becomes evident when several release profiles of a drug have to be compared, because it is statistically incorrect to compare two or more curves based on the analysis of the individual points in a graph. In face of the disadvantages discussed above a different approach seemed necessary.

Statistical moment analysis has been commonly used in pharmacokinetics with the advantages of providing model-independent estimates of *in vivo* dissolution and absorption rates.[4] Examples of its use are studies of the bioavailability of drugs from dosage forms, *e.g.* theophylline from microcapsules,[5] rate of absorption for bioequivalence studies,[6] correlation of *in vitro* to *in vivo* release of a drug,[7] and correlation of *in vitro* dissolution data to plasma concentrations of orally administered drugs.[8] Statistical moment theory may also be used to determine the mean dissolution times (*MDT*) and absorption time for conventional oral dosage forms.[9]

The theory of statistical moments is based on the preliminary assumption that the movement of the individual drug molecules through the dosage form is governed by laws of probability and that the drug concentrations in the dissolution medium at a certain time, can be regarded as a statistical distribution curve. Thus, the residence time of the drug in the dosage form can be conceived as a frequency distribution with a mean and a variance about the mean.[10,11] In fact, the profile of the cumulative amount of the drug released from a solid dosage form, observed from an *in vitro* dissolution study, can be represented as the cumulative frequency of the residence times of the drug molecules in the dosage form.[11] A fraction of drug released (M_t/M_∞) represents the number of molecules of drug substance released from the dosage form up to the time t and can be regarded as a cumulative frequency function $F(t)$ in the sense of statistics. Once this frequency function has been found for a particular dissolution curve, the different statistical moments can be calculated. The statistical moments, such as the mean dissolution time (*MDT*), the variance associated with the *MDT* (*VR*), and the relative dispersion of the concentration–time profiles (*RD*), or the skewness of the curve can be used to characterize a dissolution

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Table 1. Equations to Characterize Different Release Models of a Drug, Based on Statistical Moment Analysis[12]

Release rate mechanism	Description	Release rate constant (k)	RD	Release class
First order	$M_t/M_\infty = 1-e^{kt}$	$1/MDT$	1.0	1
Pseudo first order	$M_t/M_\infty = kt^{0.5}$	$1/(3MDT)^{0.5}$	0.8	2
Cube root	$M_t/M_\infty = 1-(1-kt)^3$	$1/(4MDT)$	0.6	3
Zero order	$M_t/M_\infty = kt$	$1/(2MDT)$	0.3	0

profile[11,12] and compared with a well accepted dissolution model for a formulation processed under standard conditions. The statistical moments can also be used to compare different profiles,[13] or to establish relationships between *in vitro–in vivo* data[14] or between two dissolution profiles.[15] The release rates (k) for the different models can be calculated from the equations presented in Table 1,[12] and the RD-values are indicative of the physical model which would describe the dissolution process best.[12]

One way to check the validity of the values presented for the RD is to draw a curve with values known to represent one of the models under study, and then by using different values of RD to draw the different curves. The curve drawn using the value of RD related to the defined model (see Table 1) will show the best agreement between observed and predicted data, assessed by residual analysis, which can be summarized by the root mean square value (RMS). If the data fails to fit any of the models, the values of MDT, VR and RD can be used to describe the curve.[11] To calculate MDT and VR, simple integration procedures, *i.e.*, calculation of the area under the cumulative fractional release profile and the area between the curve (ABC) and unity can be employed.[12] In fact, the MDT is equal to ABC/M_∞, with M_∞ = the maximum amount of drug released throughout the time of the test.

One can assume that the dissolution models are strictly equivalent with respect to a dosage form, if the same total amount of drug is released from the dosage form and the normalized dissolution profiles are superimposable by a linear transmission of time. Although this approach proposed by Brockmeier and von Hattingberg[11] presents several advantages, for example consideration of the whole dissolution curve and one calculation procedure instead of trial-and error data fit to each single dissolution model, it presents, however, a problem in common with the other approaches, *i.e.*, experimental data only occasionally fit the model parameters. More often, the experimental data tend to obey neither of the proposed mechanisms in a strict manner, and thus a compromise has to be made, if one model only is sought.

The aim of the present work was to characterize the release of a model drug (indomethacin) from pellet formulations by statistical moment analysis.

Experimental

Materials Indomethacin (Bechpharm, UK) medium volume particle diameter $57.0 \pm 1.86\,\mu m$, melting range 155—156 °C (the drug was in the polymorphic form I[16]), lactose monohydrate EP (Meggle-Wasserburg, Germany) medium volume particle diameter $16.8 \pm 0.35\,\mu m$ and microcrystalline cellulose (Avicel PH 101, FMC Corp., U.S.A.) medium volume particle diameter $53.8 \pm 0.54\,\mu m$ were incorporated into the pellets. The water used was freshly distilled. Ethylcellulose in an aqueous dispersion was used to provide a coat to the pellets (Surelease, Colorcon, UK).

Methods Particle size analysis of the particles of the powders was carried out using a Malvern Master Sizer (Series 2600C, Malvern Instruments, UK). The melting range of indomethacin was determined with a Mettler hot stage (Mettler FP52) mounted on an Olympus microscope (model B201, Olympus, Japan).

Three different types of pellets were produced by extrusion and spheronisation. The pellets included the model drug (0.25—3 parts in the formulation), lactose (2—4.25 parts in the formulation), microcrystalline cellulose (3 parts in formulation) and water (3.36 parts in formulation). The combined amount of indomethacin and lactose was kept constant at 5 parts in each formulation. The powders were mixed for 20 min (Turbula T2C, Basel, Switzerland) and then transferred to a planetary mixer (Kenwood chef, UK) where the water was added.

The masses were extruded in a ram extruder fitted to a mechanical press (Lloyds Instruments, MX50 fitted to a 50 kN load cell, UK). The extruder was fitted with a die of 1 mm diameter and 4 mm length. The speed of displacement of the cross head was 400 mm/min. The extrudate was spheronized in a spheroniser (Caleva, UK) fitted with a radial plate, 225 mm diameter, at 1000 rpm for 10 min. The wet pellets were dried in a fluidized bed dryer (model FBD/L70, PRL Eng. Ltd., UK) for 20 min at 60 °C. The densities of the pellets, as measured by an air pycnometer (Beckman, U.S.A.), and the forces required to crush the pellets (measured by a CT-40, Eng. Systm., Nottingham, UK) were identical for the different formulations ($p<0.05$). The dissolution tests were carried out according to the USP XXIII (Pharmatest dissolution tester, Germany), paddle method at four different stirring speeds (20, 50, 100 and 200 rpm), four different temperatures (12, 25, 37 and 45 °C) and two pH values (4.5 and 7.4, phosphate buffer, BP 1993). Three different sizes of pellets, separated by sieving, were used in the study (0.71—1.00, 1.00—1.40 and 1.40—1.70 mm). Pellets in the range of 1.00—1.40 mm diameter were coated with an aqueous dispersion of ethylcellulose (Surelease, Colorcon, UK) in a coating equipment (Strea, Aeromatic, Switzerland) and three different types of pellets with three different percentages of coating material were produced (1.5, 3.0 and 7.0%, w/w of uncoated pellets) in a total number of preparations of nine.

Results

Tables 2 to 6 present the dissolution results after application of statistical moment analysis as proposed by Brockmeier and von Hattingberg.[11] The values for the areas under the curves (AUC), the MDT, the VR and the RD are presented for the different factors studied. Moreover, the analysis of the results was carried out in three portions of the curve percentage of drug released *versus* time as indicated by the subscripts t, 8 and 3 in order to check for changes of release mechanisms. The subscript t means that the complete release profile was considered. Thus, in formulations where 100% of drug was released before 8 h, the analysis of the results up to 8 h was not carried out and blank spaces are found in Tables for some formulations and for subscript 8. Finally, the subscript 3 means that the release rates up to 3 h were considered. In this way the analysis of the results was carried out at earlier stages, middle stages and for the whole release profile of the drug. Splitting the release in stages results in only some fractions of the release of the drug being analyzed in a consistent and unbiased manner without making any attempt to analyze the 'best' or more 'convenient' portion of the curve. From the RD the release mechanism is proposed, when possible, (results in Tables 2 to 6) and the release constants are calculated from the equations presented in Table 1 for the models considered. The values obtained for RD do not always fit the values proposed for the models. Therefore, approximations to the values presented in Table 1 had to be made. Once the

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Table 2. Assessment of Statistical Moment Analysis Models of Dissolution as a Function of Paddle Speed

	Paddle speed (rpm)											
	20			50			100			200		
Formulation	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
AUC_t	2.8	25.8	96.0	2.2	20.7	81.0	2.3	20.7	91.6	2.1	22.6	89.0
MDT_t	1.1	2.6	4.0	0.9	2.1	3.1	0.9	2.1	3.4	0.8	2.2	3.4
VR_t	1.2	6.0	10.7	0.7	4.5	8.9	0.8	4.5	10.9	0.6	5.7	11.0
RD_t	1.0	0.9	0.7	0.8	1.0	0.9	1.0	1.1	0.9	0.9	1.2	1.0
Release class	1	2	3	2	1	1	1	1	1	2		1
Release const. (h^{-1})	0.91	0.36	0.06	0.61	0.48	0.32	1.11	0.48	0.29	0.65	0.46	0.29
AUC_8		22.0	60.0		19.2	56.2		19.1	57.1		19.5	48.3
MDT_8		2.3	2.9		2.0	2.4		1.9	2.4		1.9	2.2
VR_8		4.1	5.1		3.8	4.8		3.7	5.0		3.8	4.0
RD_8		0.8	0.6		1.0	0.8		1.0	0.8		1.0	0.8
Release class		2	3		1	2		1	2		1	2
Release const. (h^{-1})		0.31	0.09		0.50	0.37		0.53	0.37		0.53	0.39
AUC_3	2.2	7.5	15.3	2.0	7.6	17.1	1.9	7.3	16.1	1.9	7.3	15.9
MDT_3	0.9	1.1	1.3	0.9	1.0	1.1	0.8	1.0	1.0	0.8	1.0	1.0
VR_3	0.6	0.7	0.7	0.6	0.7	0.7	0.5	0.6	0.7	0.4	0.7	0.7
RD_3	0.6	0.5	0.4	0.7	0.6	0.6	0.8	0.7	0.6	0.8	0.7	0.7
Release class	3	3	0	2	3	3	2	2	3	2	2	3
Release const. (h^{-1})	0.58	0.51	0.41	0.61	0.25	0.23	0.65	0.58	0.25	0.65	0.58	0.25

Formulation, indomethacin : lactose : microcryst. cellulose (in parts of each ingredient): (1) = 0.25 : 4.75 : 3, (2) = 1 : 4 : 3, (3) = 3 : 2 : 3.

Table 3. Assessment of Statistical Moment Analysis Models of Dissolution as a Function of Temperature

	Temperature (°C)											
	12			25			37			45		
Formulation	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
AUC_t	6.9	24.3	51.2	3.0	30.1	73.4	2.3	20.7	91.6	1.7	12.7	73.9
MDT_t	3.0	3.9	4.3	1.3	3.3	3.8	0.9	2.1	3.4	0.6	1.3	2.5
VR_t	10.6	12.3	12.7	1.4	9.9	11.1	0.8	4.5	10.9	0.6	2.2	7.2
RD_t	1.1	0.8	0.7	0.8	0.9	0.8	1.0	1.1	0.9	1.7	1.3	1.1
Release class	1	2	3	2	1	2	1	1	1			1
Release const. (h^{-1})	0.33	0.29	0.06	0.51	0.30	0.30	1.11	0.48	0.29	1.67	0.77	0.40
AUC_8	3.9	13.3	26.5	4.7	19.9	42.0		19.1	57.1		12.0	59.5
MDT_8	2.0	2.6	2.9	1.8	2.4	2.6		1.9	2.4		1.2	2.1
VR_8	4.2	5.2	5.4	3.8	4.9	5.1		3.7	5.0		1.6	4.7
RD_8	1.0	0.8	0.6	1.2	0.8	0.8		1.0	0.8		1.1	1.0
Release class	1	2	3		2	2		1	2		1	1
Release const. (h^{-1})	0.50	0.39	0.09	0.56	0.37	0.36		0.53	0.37		0.83	0.48
AUC_3	2.0	3.9	6.6	2.2	5.7	10.8	1.9	7.3	16.0	1.3	7.8	19.6
MDT_3	1.2	1.1	1.2	1.0	1.0	1.1	0.8	1.0	1.0	0.5	0.9	1.0
VR_3	0.9	0.7	0.8	0.7	0.7	0.7	0.5	0.6	0.7	0.3	0.6	0.7
RD_3	0.6	0.6	0.5	0.6	0.6	0.6	0.8	0.7	0.6	1.0	0.8	0.7
Release class	3	3	3	3	3	3	2	2	3	1	2	2
Release const. (h^{-1})	0.21	0.23	0.21	0.25	0.25	0.23	0.65	0.58	0.25	2.00	0.61	0.58

Formulation, indomethacin : lactose : microcryst. cellulose (in parts of each ingredient): (1) = 0.25 : 4.75 : 3, (2) = 1 : 4 : 3, (3) = 3 : 2 : 3.

values for *RD* were found, the release mechanisms and the release constants could be obtained. Simulations were carried out based on the proposed models, and Figs. 1 to 7 (open symbols and dotted lines) compare simulated and experimental release profiles.

Discussion

Table 2 and Fig. 1 (a to d) present the results for the release of indomethacin studying the effect of different paddle speeds. Obviously, the release mechanism changes with the load of drug in the spheres and with the speed of the paddle. First order mechanism dominates when the speed of the paddle increases, and for later stages of the release. Figure 1 (a to d) shows the results for the release of drug under different test conditions. The analysis provides a good prediction of the release in practice and, except for a high paddle speed combined with a higher drug load the predictions match the experimental data. In these 2 cases it appears as though in the earlier stages the release of indomethacin is faster than predicted, suggesting that the surface of the spheres may contain drug which is released more quickly than the rest of the drug (so-called burst effect). The burst effect is associated with the amount of drug at the surface, *i.e.*, a higher drug load corresponds to more drug covering the surface. Furthermore, the burst effect depends on the thickness of the diffusion layer, which varies with aggitation conditions, *i.e.*, decreases with an increase in paddle speed. Thus, a higher drug load and paddle speed promote a burst effect. For a medium and high drug load, the increase

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Table 4. Assessment of Statistical Moment Analysis Models of Dissolution as a Function of pH

	pH					
	4.5			7.4		
Formulation	(1)	(2)	(3)	(1)	(2)	(3)
AUC_t	1.2	1.6	2.7	2.3	20.7	91.6
MDT_t	2.2	2.4	3.3	0.9	2.1	3.4
VR_t	13.9	10.4	10.9	0.8	4.5	10.9
RD_t	2.9	1.8	1.0	1.0	1.1	0.9
Release class			1	1	1	1
Release const. (h^{-1})	0.45	0.42	0.30	1.11	0.48	0.29
AUC_8					19.1	57.1
MDT_8					1.9	2.4
VR_8					3.7	5.0
RD_8					1.0	0.8
Release class					1	2
Release const. (h^{-1})					0.53	0.37
AUC_3	0.2	0.3	0.4	1.9	7.3	16.0
MDT_3	0.4	0.7	0.6	0.8	1.0	1.0
VR_3	0.2	0.5	0.5	0.5	0.6	0.7
RD_3	0.8	1.2	1.2	0.8	0.7	0.6
Release class	2			2	2	3
Release const. (h^{-1})	0.91	1.43	1.67	0.65	0.58	0.25

Formulation, indomethacin : lactose : microcryst. cellulose (in parts of each ingredient): (1) = 0.25 : 4.75 : 3, (2) = 1 : 4 : 3, (3) = 3 : 2 : 3.

Table 5. Assessment of Statistical Moment Analysis Models of Dissolution as a Function of Different Sizes of Pellets

	Size of the pellet (mm)								
	0.71—1.00			1.00—1.40			1.40—1.70		
Formulation	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
AUC_t	1.2	9.5	98.6	2.3	29.8	91.8	2.4	27.3	7.9
MDT_t	0.5	1.0	3.4	0.9	2.0	3.4	1.0	2.9	3.5
VR_t	0.2	1.2	10.8	0.8	4.1	10.9	1.2	8.7	8.8
RD_t	0.9	1.4	1.0	0.9	1.0	0.9	1.3	1.0	0.7
Release class	1		1	1	1	1		1	2
Release const. (h^{-1})	2.00	1.00	0.29	1.11	0.48	0.29	1.00	0.35	0.31
AUC_8			62.8		19.1	57.1		18.8	59.6
MDT_8			2.4		1.9	2.4		2.2	2.9
VR_8			5.3		3.7	5.0		4.5	5.5
RD_8			0.9		1.0	0.8		0.9	0.6
Release class			1		1	2		1	3
Release const. (h^{-1})			0.42		0.53	0.37		0.46	0.09
AUC_3	1.1	6.8	15.7	1.9	7.3	16.0	1.6	5.5	13.8
MDT_3	0.5	0.7	0.9	0.8	1.0	1.0	0.7	1.0	1.2
VR_3	0.2	0.5	0.7	1.5	0.6	0.7	0.4	0.7	0.7
RD_3	0.8	0.9	0.7	0.8	0.7	0.6	0.8	0.7	0.5
Release class	2	1	2	2	2	3	2	2	3
Release const. (h^{-1})	0.82	1.43	0.61	0.65	0.58	0.25	0.69	0.58	0.21

Formulation, indomethacin : lactose : microcryst. cellulose (in parts of each ingredient): (1) = 0.25 : 4.75 : 3, (2) = 1 : 4 : 3, (3) = 3 : 2 : 3.

in paddle speed from 50 to 200 rpm does not change the release constants significantly, whereas the release constant is clearly smaller at a paddle speed of 20 rpm. This observation suggests that the diffusion layer for the drug around the spheres—a saturated layer of dissolved drug and lactose—is important in controlling the release of the indomethacin. Looking at the earlier stages of the release of the drug, a diffusion mechanism becomes more relevant in controlling the release of the drug (compare release mechanisms, Table 2). For the higher paddle speeds (100 and 200 rpm), the release rate was not different, although it is proposed that the release of the drug is controlled by a diffusion mechanism. The fact that the thickness of the layer around the spheres does not control the diffusion, suggests that the diffusion through the pores in the spheres controls the release of the drug. Comparing the release of drug for the same formulation, especially for higher loads (Table 2, formulation with 3 parts of indomethacin, 50, 100 and 200 rpm), at different stages of release, it can be seen that for later stages a first order is observed, whereas at early stages, dissolution of indomethacin seems to be the limiting step. However, as it can be seen from the same Table, the release of indomethacin does not follow a single mechanism, but several mechanisms are competing at the same time or sequentially. In fact, when the whole test is divided into stages and each one analyzed, (Table 2) one observes that up to 3 h the different formulations with different loads present different mechanisms. At the beginning, a diffusion process seems to occur for lower drug loads, whereas for the

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Table 6. Assessment of Statistical Moment Analysis Models of Dissolution as a Function of Spheres with Different Drug Loads for Different Amounts of Coating (1.5, 3.0 and 7.0%)

	Formulation (Parts of indomethacin, lactose and microcrystalline cellulose in the formulation)								
	0.25:4.75:3			1:4:3			3:2:3		
Percentage of coating	1.5	3.0	7.0	1.5	3.0	7.0	1.5	3.0	7.0
AUC_t	3.9	6.3	1.3	10.9	11.5	1.7	30.6	17.4	1.6
MDT_t	1.62	2.63	3.03	4.41	5.42	2.90	5.45	6.51	2.52
VR_t	1.71	3.47	8.41	14.0	11.7	6.35	9.58	12.9	5.15
RD_t	0.6	0.5	1.8	0.7	0.4	1.5	0.3	0.3	1.6
Release class	3	3		2	0		0	0	
Release const. (h^{-1})	0.15	0.10	0.33	0.27	0.09	0.34	0.09	0.08	0.41
AUC_8		5.9	0.7	4.4	5.9	0.7	21.4	6.4	1.0
MDT_8		2.51	1.75	2.43	3.79	1.55	4.53	4.01	1.75
VR_8		2.58	6.45	4.4	5.43	3.93	5.85	5.34	4.89
RD_8		0.4	2.1	0.8	0.3	1.6	0.3	0.3	1.6
Release class		0		2	0		0	0	1
Release const. (h^{-1})		0.20	0.57	0.37	0.13	0.65	0.11	0.12	0.53
AUC_3	2.5	2.5	0.2	1.2	0.90	0.3	2.2	0.80	0.2
MDT_3	1.2	1.56	0.54	1.06	1.36	0.69	1.5	1.39	0.56
VR_3	0.63	0.57	0.38	0.77	0.77	0.42	0.82	0.88	0.47
RD_3	0.4	0.2	1.2	0.6	0.4	0.9	0.3	0.4	1.4
Release class	0	0		3	0	1	0	0	
Release const. (h^{-1})	0.42	0.32	1.85	0.24	0.37	1.45	0.33	0.36	1.79

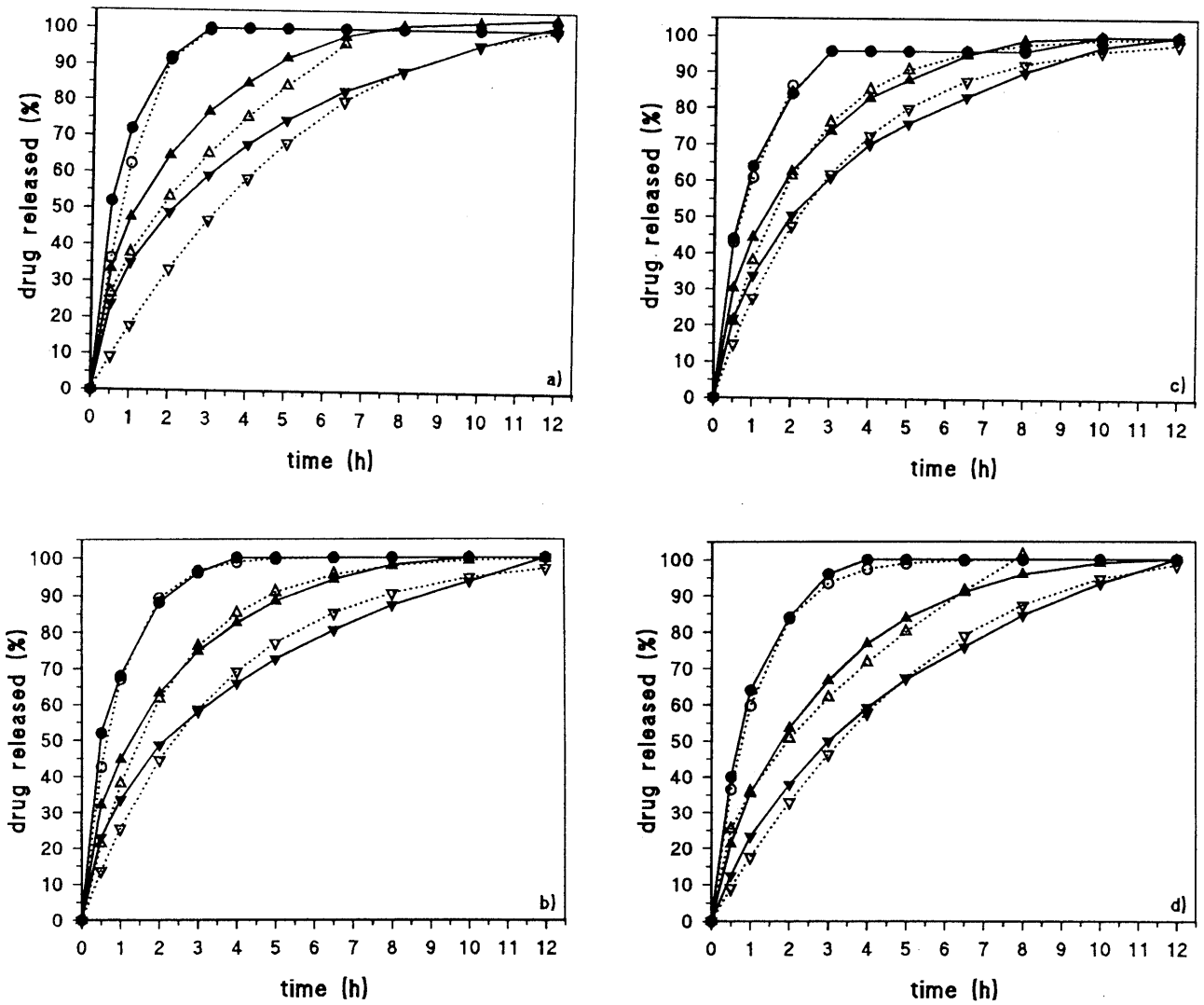

Fig. 1. Release of the Drug as a Function of Time, the Speed of the Paddle and Drug Load

a) 200 rpm, b) 100 rpm, c) 50 rpm and d) 20 rpm. Formulation (indomethacin : lactose : microcryst. cellulose): ●○, -0.25:4.75:3; ▲△, -1:4:3, ▼▽, -3:2:3. Solid symbols—experimental results, open symbols—predictions.

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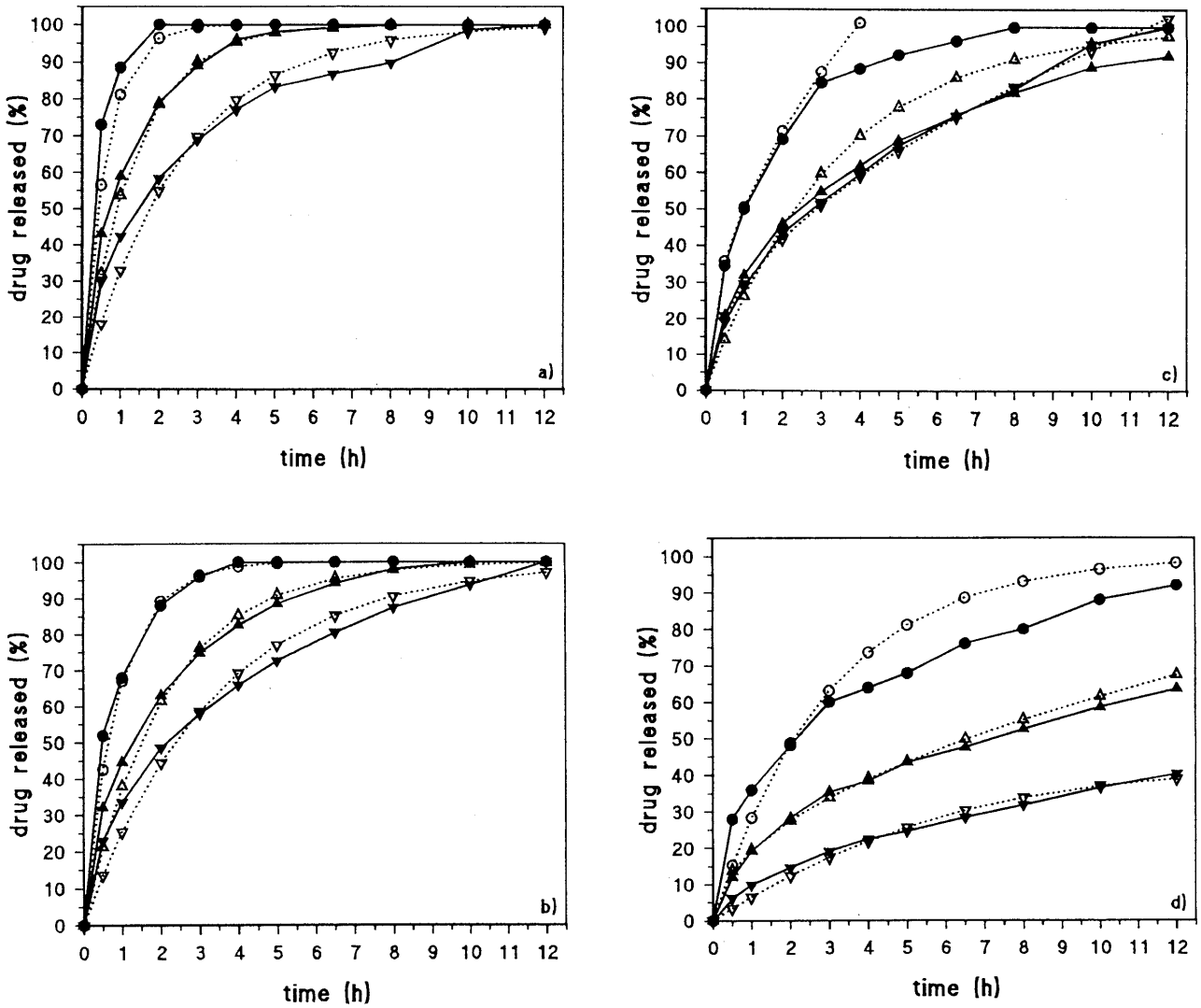

Fig. 2. Release of the Drug as a Function of Time, Temperature and Drug Load

a) 45 °C, b) 37 °C, c) 25 °C and d) 12 °C. Formulation (indomethacin : lactose : microcryst. cellulose): ●○, -0.25 : 4.75 : 3; ▲△, -1 : 4 : 3; ▼▽, -3 : 2 : 3. Solid symbols—experimental results, open symbols—predictions.

highest drug load a cube root mechanism predominates. It is thus possible to suggest that for lower drug loads the pores in the matrix are the route for drug diffusion as the solvent penetrates into the matrix. For higher loads the dissolution of the drug is the limiting step of the release, as suggested by the cube root mechanism. At later stages, the release becomes dependent on the amount of drug remaining in the matrix, as suggested by the first order mechanism. The group of results discussed indicates that for the initial phase of the dissolution a cube root mechanism controls the release in most cases, then it changes to a pseudo first order and at the final stages of the test, a first order mechanism controls the release of indomethacin from the spheres. A typical case to illustrate this general conclusion is formulation 3 tested at paddle speeds between 50 and 200 rpm (compare release class, Table 2). It should be pointed out that the presence of lactose, a much more soluble material than indomethacin, makes the interpretation of the results more complex as the changes occurring in the spheres are to a large extent due to the simultaneous dissolution of lactose, and changes of the porosity and/or tortuosity of the pores in the spheres.

Table 3 presents the results of the release of indomethacin at four different temperatures. The release rate for the different formulations increases with the temperature, with a highest at 45 °C. When maximum release of the drug is considered (subscript t in Table 3), the release mechanism can in the majority of cases be predicted by a first order model, suggesting that the release was dependent on the amount of drug remaining in the spheres, especially at the end of the test. However, at lower temperatures, and for higher drug loads, the release was controlled by the dissolution of the drug. The interpretation of the results is supported by the predictions made which are in good agreement with the experimental results (Fig. 2a to d, open symbols *versus* closed symbols). Regarding the results for the middle stages of the test, (Table 3, subscript 8) and for the tests where the release was nearly complete, *i.e.*, higher temperatures or lower loads, again a first order mechanism mostly controls the release of indomethacin. On the other hand, for higher loads, or lower temperatures the release seems to be controlled by diffusion or dissolution of the molecules of

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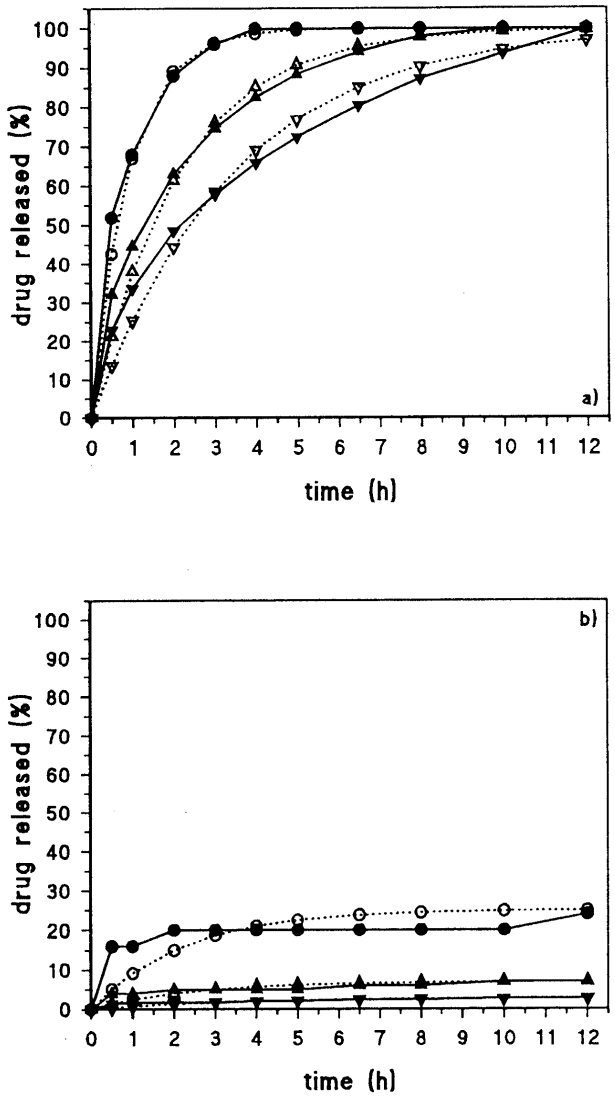


Fig. 3. Release of the Drug as a Function of Time, pH and Drug Load

a) pH = 7.4, b) pH = 4.5. Formulation (indomethacin : lactose : microcryst. cellulose): ●○, -0.25 : 4.75 : 3; ▲△, -1 : 4 : 3; ▼▽, -3 : 2 : 3. Solid symbols—experimental results, open symbols—predictions.

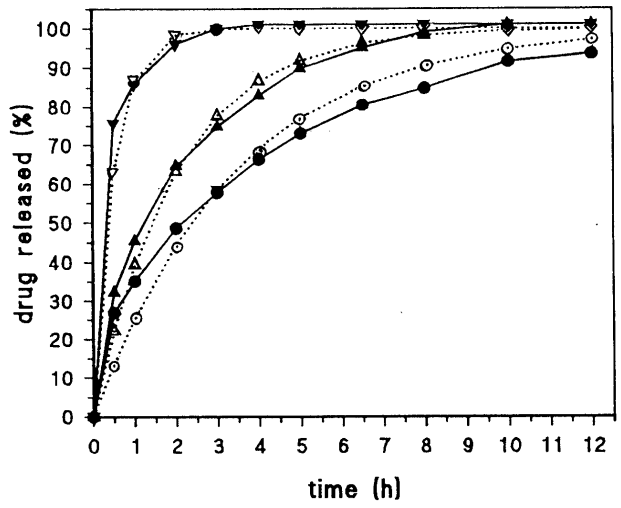
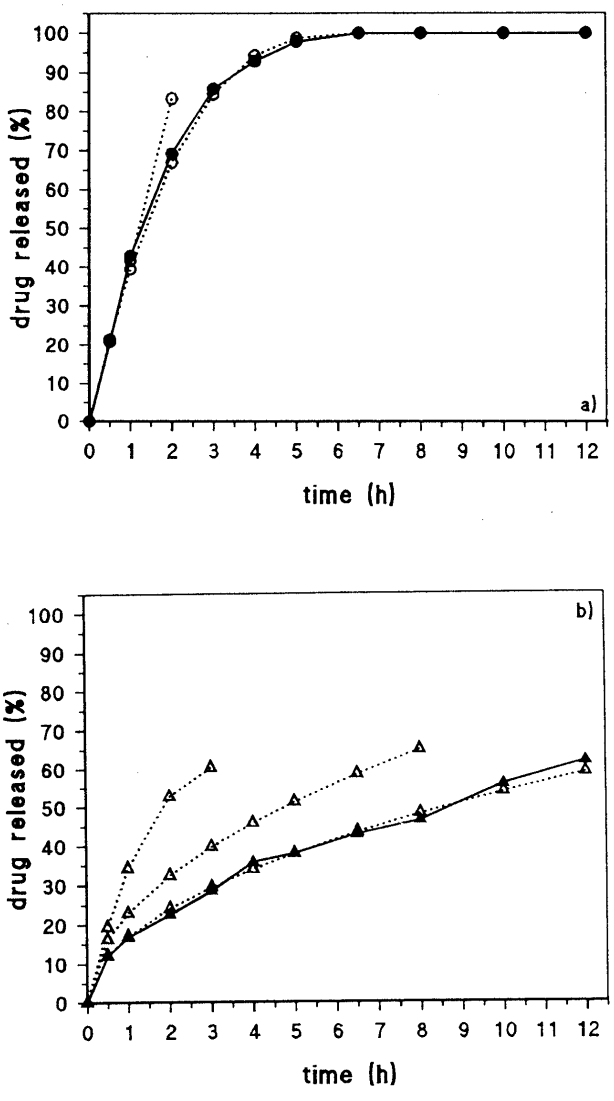


Fig. 4. Release of the Drug as a Function of Time, Size of the Sphere and Drug Load

Size of the spheres (mm): ●○, -0.71—1.00; ▲△, -1.00—1.40; ▼▽, -1.40—1.70. Formulation (indomethacin : lactose : microcryst. cellulose): 1 : 4 : 3. Solid symbols—experimental results, open symbols—predictions.



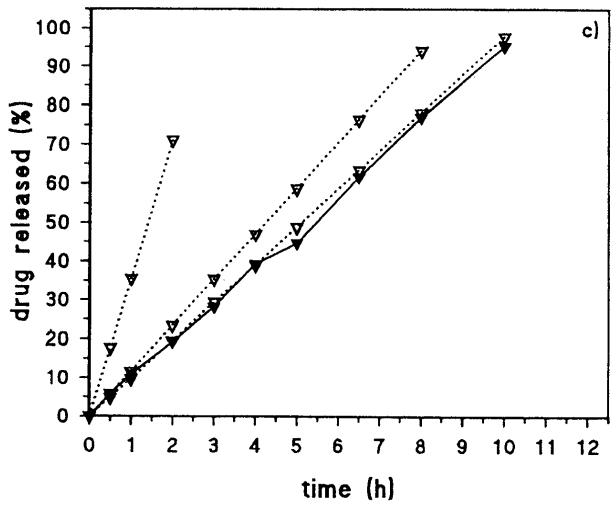


Fig. 5. Release of the Drug as a Function of Time, Coat (1.5%) and Drug Load

Formulation (indomethacin : lactose : microcryst. cellulose): a) ●○, -0.25 : 4.75 : 3; b) ▲△, -1 : 4 : 3; c) ▼▽, -3 : 2 : 3. Solid symbols—experimental results, open symbols—predictions.

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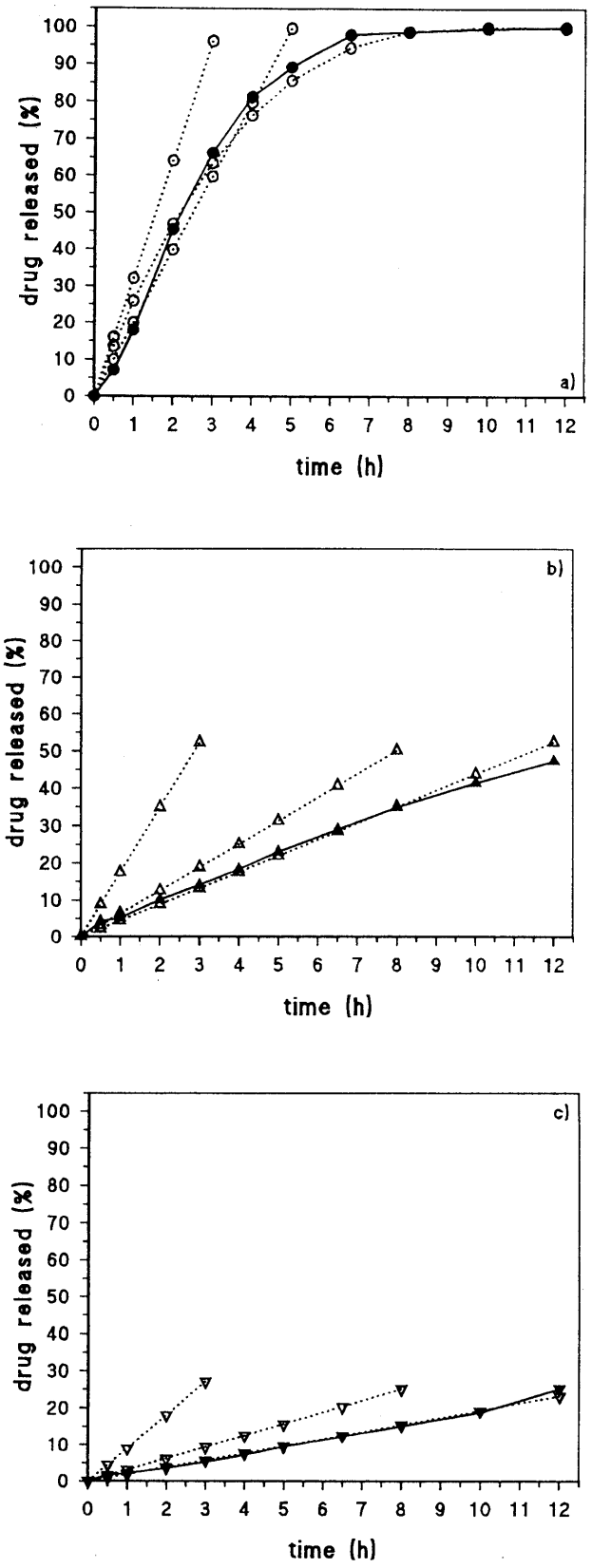

Fig. 6. Release of the Drug as a Function of Time, Coat (3.0%) and Drug Load

Formulation (Indomethacin : lactose : microcryst. cellulose): a) ●○, -0.25 : 4.75 : 3; b) ▲△, -1 : 4 : 3; c) ▼▽, -3 : 2 : 3. Solid symbols—experimental results, open symbols—predictions.

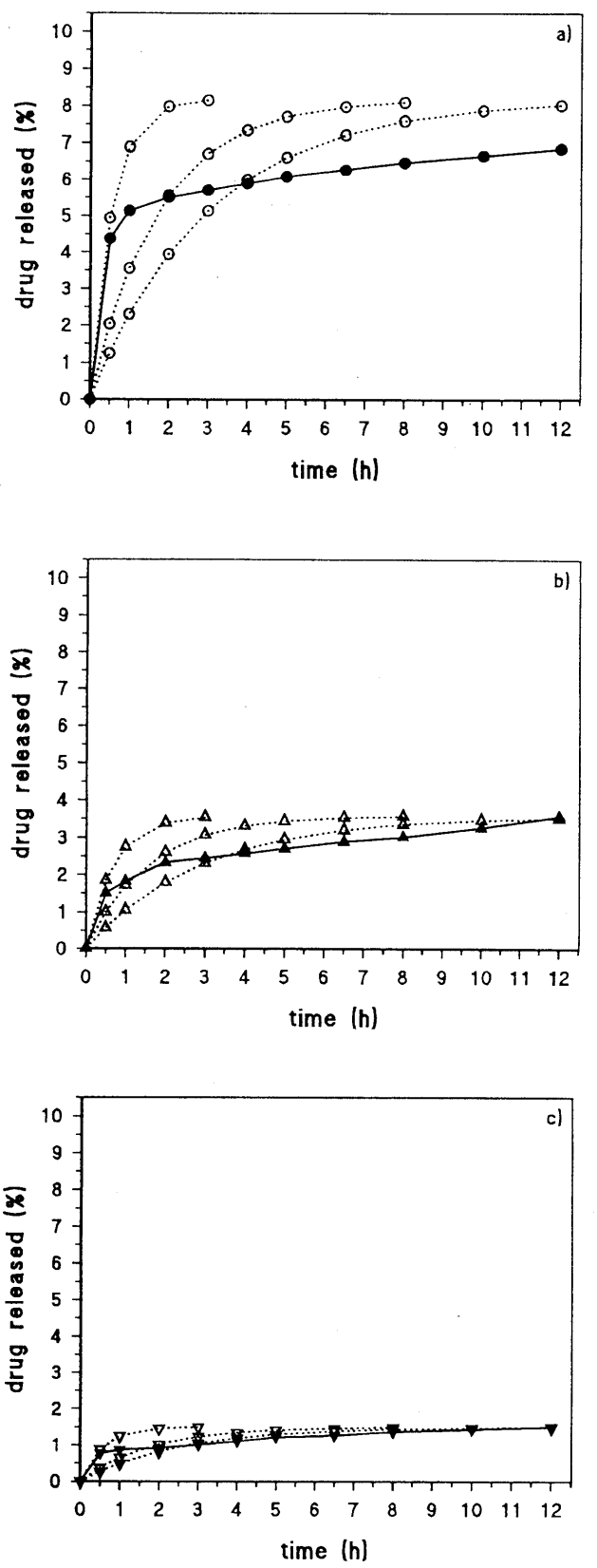

Fig. 7. Release of the Drug as a Function of Time, Coat (7.0%) and Drug Load

Formulation (indomethacin : lactose : microcryst. cellulose): a) ●○, -0.25 : 4.75 : 3, b) ▲△, -1 : 4 : 3, c) ▼▽, -3 : 2 : 3. Solid symbols—experimental results, open symbols—predictions.

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the drug substance as reported before. Analysing the initial phase of the release (Table 3, subscript 3), it can be seen that only one set of results follows a first order mechanism. In the majority of cases, either a pseudo first order or cube root model was predicted. This shows that the release of the drug follows different mechanisms, depending on the phase of the process considered and the processing conditions. For high loads of drug in the spheres, thus at the beginning of the test, dissolution of the drug is the limiting step. Later, as the drug is depleted from the surface of the spheres, diffusion is the controlling mechanism. Finally, near the end, the amount of drug remaining in the spheres, controls the process. Both the dissolution of the drug in the media, and the diffusion of the drug molecules in the media are processes highly dependent on the temperature. Therefore, the changes in mechanism, and, especially in the release rate, reflected in the results presented in Table 3, are not surprising.

Results presented in Table 4 and Fig. 3 (a and b) show the release of indomethacin from the spheres as a function of pH. The study was carried out at three different pH's. However, only the results for the higher values of pH (pH = 4.5 and 7.4) where considered as the release of drug at pH = 1.2 was minimal due to the chemical nature of the drug. The release of indomethacin tended to be faster and more complete for higher values of pH which is not surprising as indomethacin is a weak acid ($pK_a = 4.5$). The release of the drug at pH = 7.4 has been discussed previously when considering the effect of paddle speed (100 rpm) and temperature (37 °C) on the release of indomethacin. Although the drug was released under sink conditions, and the amount of the indomethacin in the spheres was well below the saturation concentration at pH = 4.5 when released, the results in Fig. 3b, show that a plateau was reached after the first hour of the dissolution test, which suggests that the driving force responsible for the release of the drug decreased dramatically. This can be explained if it is considered that during the first hour it is the drug at the surface, or close to the surface that is dissolved under sink conditions. However, there are no such sink conditions inside the pellets, and dissolution is therefore limited. It may be concluded that there was no dissolution and diffusion of the drug molecules inside the spheres, and consequently the drug was not released. The predictions for the release (Fig. 3b, dotted lines) which take into consideration the initial release, differ greatly from the experimental values as a consequence of the prediction being affected largely by the burst effect observed and discussed previously. Large differences between the values of *RD* and the reference values presented in Table 1 for the different models were found in these experiments. Therefore, these values are not presented in Table 4 (pH 4.5).

The surface area of the spheres available to come into contact with the dissolution media is a factor of major importance, and it has been accepted that the process of dissolution is a surface phenomena. The sizes chosen are within the range acceptable for a production of spheroids with high sphericity. Table 5 and Fig. 4 present the results for the different sphere sizes. The analysis of the full data (subscript *t* on Table 5) shows that, except for the spheres with higher drug load, the release followed a first order model. For the highest sphere size and load, release is controlled by the diffusion step, which suggests a slower and more incomplete release of drug, following previous observations for the other factors. Comparing the release rates for low and medium drug loads, the release rates decrease as the size of the spheres increases, due to a decrease in the surface area available for the release of the drug. The results for the initial 3 h (Table 5, subscript 3), indicate that the mechanism controlling the initial release of the drug varies between pseudo first order and cube root law. The amount of drug released also decreased as the size of the spheres increased (Fig. 4). The spheres with higher loads and larger diameters show a dissolution dependence for the release of the indomethacin. When the first 8 h were taken into account, (Table 5, subscript 8), it was found that the release of drug from the lower loads and for the different sizes was complete before that time. The observations have shown that the release rate decreases when the size of the spheres increases and with the time of the dissolution test. The release mechanism changes also during the time of the test, as the analysis of the different phases of the analysis of the results shows. The release mechanism tends to change from a cube root to a diffusion controlled release and for the later stages of dissolution to a first order mechanism. At the beginning the release of the drug is dependent on the drug itself, in an intermediate phase it depends on the system and finally when the matrix was partially depleted of the drug a first order mechanism was observed.

To provide more information about the applicability of this approach, it was thought as relevant to coat the spheres and to see whether the release mechanism and rate were changed. Different amounts of ethylcellulose in an aqueous dispersion (1.5, 3.0 and 7.0%, w/w of pellets) were used to provide such coat. Below 1% the coat was not effective as the percentage of drug released was similar to the results obtained for uncoated spheres. On the other hand, the release from spheres coated with more than 7.0% of coating material was negligible. The release of drug was delayed by the coat, as the values for the *MDT* show (to compare with the values of *MDT* for formulation with 1 part of indomethacin in Table 2, 100 rpm) represented in Figs. 5 to 7. The interpretation of the results is not a straightforward process as there are two variables involved (amount of coat and load of indomethacin and lactose), which interfere with the release process, the former by increasing the thickness of the coating barrier and the latter by changing the gradient of indomethacin between the matrix and the dissolution medium. Table 6 presents the results for different amounts of coating material applied to pellets with different drug loads as a function of three different duration times allowed for the release of the drug. As expected, an increase of the amount of coating material applied provided a barrier, whose thickness and porosity was proportional to the amount of coat applied, and which delayed the release of the indomethacin from the pellets. This observation can be supported when the areas under the curves are compared for the same formulation and time span of the analysis. The release of the drug, in many cases is controlled by

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both the coating and the matrix, and in fact by the dissolution of the drug as the proposed mechanism suggest. The release mechanism of the indomethacin changes with time suggesting that the parameters affecting the release of indomethacin also change with time. In some cases, the release of the drug tended to follow a zero order mechanism changing at latter stages into different mechanisms dependent on the dissolution of the drug, or the time, of the test. However, when the amount of drug increased it seemed that the gradient of concentrations between the two sides of the coating membrane remained constant throughout the whole release time of the indomethacin allowing the release to follow a Fickian diffusion. However, when the amount of coat was increased to its maximum, first a burst effect was found, probably due to drug at the surface of the matrix of the coated pellets which was released immediately, and then a slow diffusion was observed for most of the time during the tests. The burst effect observed suggests that drug has penetrated into the coat due to favourable permeability properties, and that this drug migration was enhanced by larger amounts of film coating. The overall release mechanism suggested was a first order mechanism (Table 6, 7.0% coating). Finally, the higher the amount of lactose in the formulation the faster the release of the drug. The higher solubility of lactose in water, compared to the solubility of indomethacin, was responsible for a rapid increase of the porosity of the matrix once the pellets were placed in the dissolution medium increasing the possibility of the medium to penetrate quickly into the matrix. Therefore, using a balanced ratio between drug load, lactose and thickness of the coat, a suitable release of indomethacin can be achieved.

Conclusion

It can be concluded that the application of statistical moment analysis to dissolution profiles to describe the release of a drug from pellet formulations has potential to be a method able to clarify the mechanism of release of a drug. The method provides values for parameters such as the release mechanism, the release rate, and the mean dissolution time, which allows the formulator to compare the results of different formulations.

The conditions of a dissolution test such as speed of agitation, temperature or pH are able to change both the release rate and the release mechanism. Furthermore, formulation specific variables such as surface area or drug load will also alter the dissolution in terms of the physical mechanisms involved. Film coating can alter the dissolution properties of pellets completely, and a zero order release becomes possible.

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References and Notes

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