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SOME CONSIDERATIONS ON THE LIBERATION OF DRUGS FROM INERT MATRICES

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ABSTRACT

The liberation of a drug from an inert matrix tablet is usually studied by plotting the percentage of drug released as a function of the square root of time, according to the equation proposed by Higuchi for the mechanism of drug release. In many cases this plotting does not give a straight line during all the liberation. In this paper matrices containing metoclopramide as an active drug and ethylcellulose as a polymer have been studied, and the origin of the non linear release at the end of the liberation discussed.

INTRODUCTION

The liberation of a drug from an inert matrix tablet is usually studied in vitro by plotting the percentage

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of drug liberated as a function of the square root of time, according to the relation proposed by HIGUCHI (4) for the mechanism of drug dissolution :

$$Q = (k.t)^{1/2} \qquad \text{(equation 1)}$$

where Q is the amount of drug dissolved
t is the time
k is the liberation constant

$$k = \left((D.e/T) .(2.A - e.Cs). Cs \right)^{1/2} \qquad \text{(equation 2)}$$

where D is the diffusion factor
e is the porosity factor of the matrix
T is the tortuosity factor of the matrix
A is the amount of drug in the matrix (weight/volume)
Cs is the solubility of the drug

These relations indicate that the liberation of drug is a linear function of the square root of time.

In practice there is often seen that the linear relationship between the amount of drug liberated and the square root of time is only true in a part of the dissolution curve (75 to 80 % of the time needed for complete liberation of the drug)

FARHADIEH, BORODKIN and BUDDENHAGEN (1,2) have mentioned that this slope change is related to the

geometrical shape of the tablet : according to these authors ,a flat tablet shows a linear liberation profile during a longer time than a curved one.

According to FESSI, PUISIEUX, MARTY and CARSTENSEN (3), the change in slope is due to a modification in the liberation process itself. This change appears when the tablet has been completely penetrated by the dissolution liquid : From this moment, the HIGUCHI law is no longer valid, and the drug dissolution occurs according to a simple diffusion model.

In this paper it was tried to verify if the modification of the slope in the liberation plot could not be due to the internal structure of the tablets.

MATERIALS

For this study Metoclopramide Hydrochloride (Methoxy-2 chloro-5 procainamide) - an antiemetic drug was choosen as the active component of the formulation : It is a drug which shows a good stability in acidic and alcaline medium, a short half life and a good absorption in the G.I.tract so that this drug is an interesting molecule to be put in a long acting formulation.

Inert matrices were manufactured with ethylcellulose (Ethylcellulose 20 cps - Hercules) as a matrix agent, lactose as an inert filler and porosity enhancer, and magnesium stearate as a lubricant.

METHODS

Inert matrices where manufactured according to the formula :

Metoclopramide ,1HCl,1H20.....	10,0 %
Lactose crystalline (E.F.C.)..	39,5 %
Ethylcellulose 20.....	50,0 %
Magnesium stearate	0,5 %

The tablets were manufactured on a Korsch EK/0 tabletting machine with 12 mm flat single punches. This equipment is fitted out with strain gauges and allows the recording of the compression forces. The tablets were manufactured at four different compression forces. The quantity of powder compressed was adjusted in order to give tablets of the same thickness (3 mm) at each compression pressure. So all the tablets show the same surface (3.3929 cm2). The hardness of the tablets was measured on an Erweka TBT hardness tester, and the true hardness was calculated according to the formula given by TIMOSHENKO and GOODIER (5). The properties of the tablets are given in table 1 (average of 20 measurements).

The dissolution of the manufactured tablets has been studied according to the U.S.P. XX Paddle method. The dissolution medium was 1000 ml of distillated water at 37 degres C because it could be seen that there is no significant difference in the dissolution profile when water is taken as medium instead of 0.1 N hydrochloric acid. The rotation speed of the paddle was 50 r.p.m.

Table 1 : Properties of the tablets

Batch	Weight (g)	Hardness (kg)	Porosity (e) (%)
D1	0.3658	2.92 +/- 0.52	17.07
D2	0.4084	15.25 +/- 0.73	7.41
D3	0.4208	22.90 +/- 1.64	4.60
D4	0.4305	24.40 +/- 1.46	2.40

The amount of Metoclopramide dissolved was mesured by U.V. Spectrophotometry at 272 nm.

RESULTS

The results of the liberation of Metoclopramide are given in table 2 and figure 1.

The batch D1, which has a low hardness and a high porosity, gives a quick release of the drug. With high hardnesses, the liberation profiles are approximately the same.

The liberation constants show that the hardness and porosity of the matrices are of little influence on

Table 2 : Amount of drug dissolved from the tablets

Time	D1	D2	D3	D4
	Amount of drug dissolved per surface unit (mg.cm -2)			
10 minutes	2.17	2.18	2.21	2.22
20 minutes	3.17	3.10	3.07	3.15
30 minutes	4.06	3.80	3.73	3.83
60 minutes	6.08	5.26	5.17	5.34
90 minutes	7.40	6.45	6.24	6.48
120 minutes	8.32	7.49	7.20	7.36
	Dissolution constant (0.01 mg.cm^{-2} .s$^{-1/2}$)			
	10.43	8.72	8.23	8.53
Correlation coefficient	0.9987	0.9999	0.9999	0.9998

the dissolution of the drug when these values are over (for hardness) or under (for porosity) certain limits.

For each of these tablet batches, the amount of drug dissolved has been plotted vs the square root of time (figures 2, 3, 4 and 5)

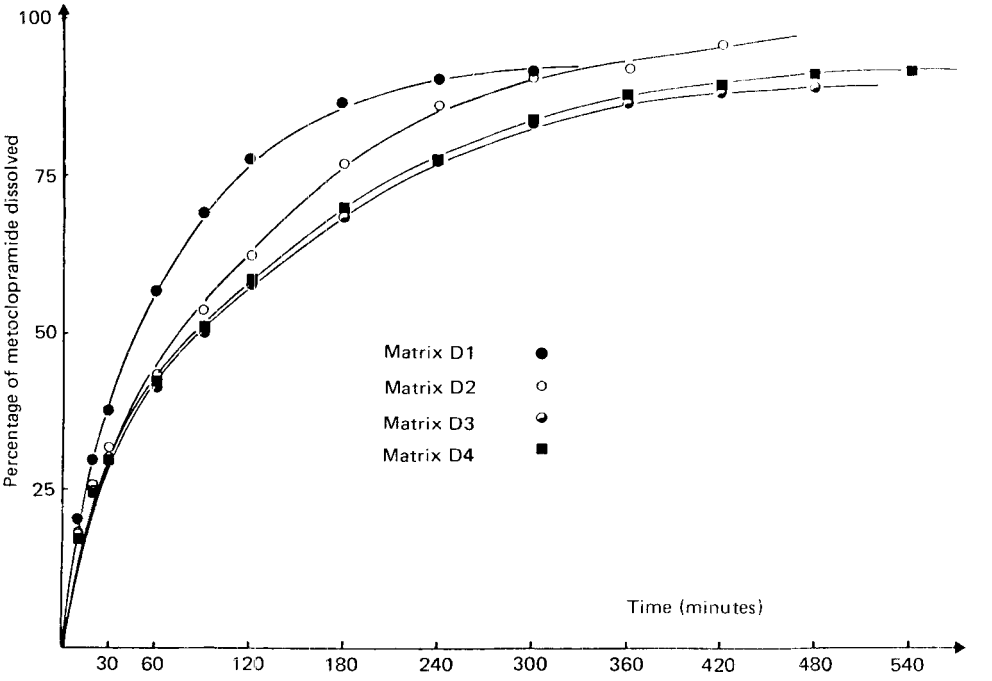

FIGURE 1 : Percentage of drug released as a function of time

In each case a linear relationship between the amount of drug dissolved and the square root of time could be observed during the begining of the dissolution. At the end there is a change in the slope of the curve. This change in the slope appears faster when the porosity of the matrix is high.

The time after which the change in the slope appears was evaluated on the figures 2 to 5, and plotted vs the porosity of the matrix (figure 6).

There is a linear relationship between the porosity of the matrices and the time needed for the change of

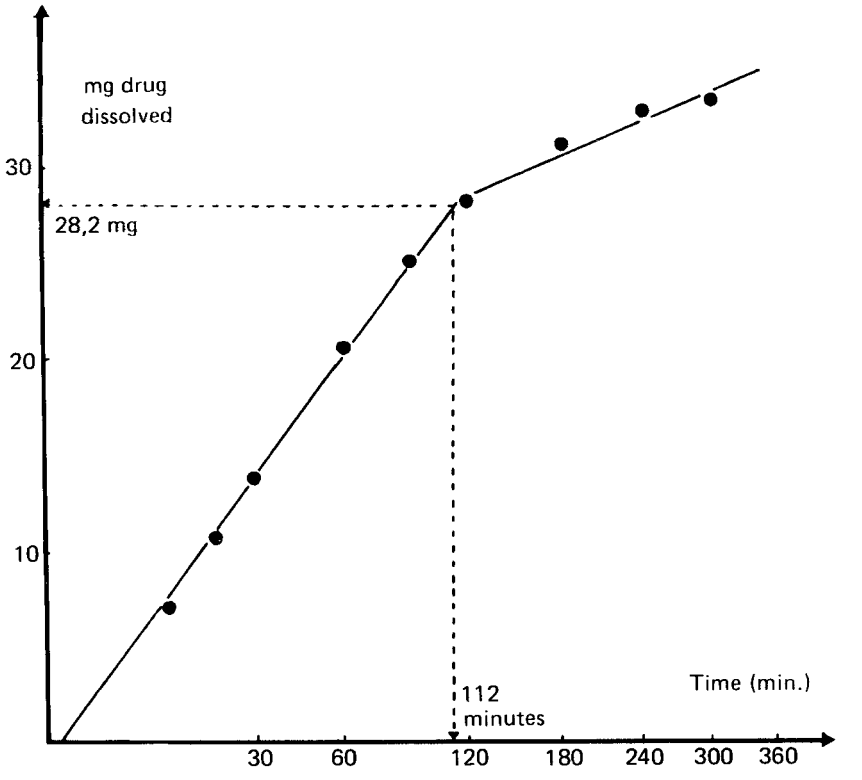

FIGURE 2 : Amount of drug dissolved as a function of the square root of time (Batch D1)

slope to appear, excepted for very low porosities, where the time reaches a maximal value.

DISCUSSION

The change in the slope of the liberation curve can be explained in different manners. It could be related to a change in the liberation mechanism, as mentioned by FESSI and al. (3), or it could be due to the internal structure of the tablets.

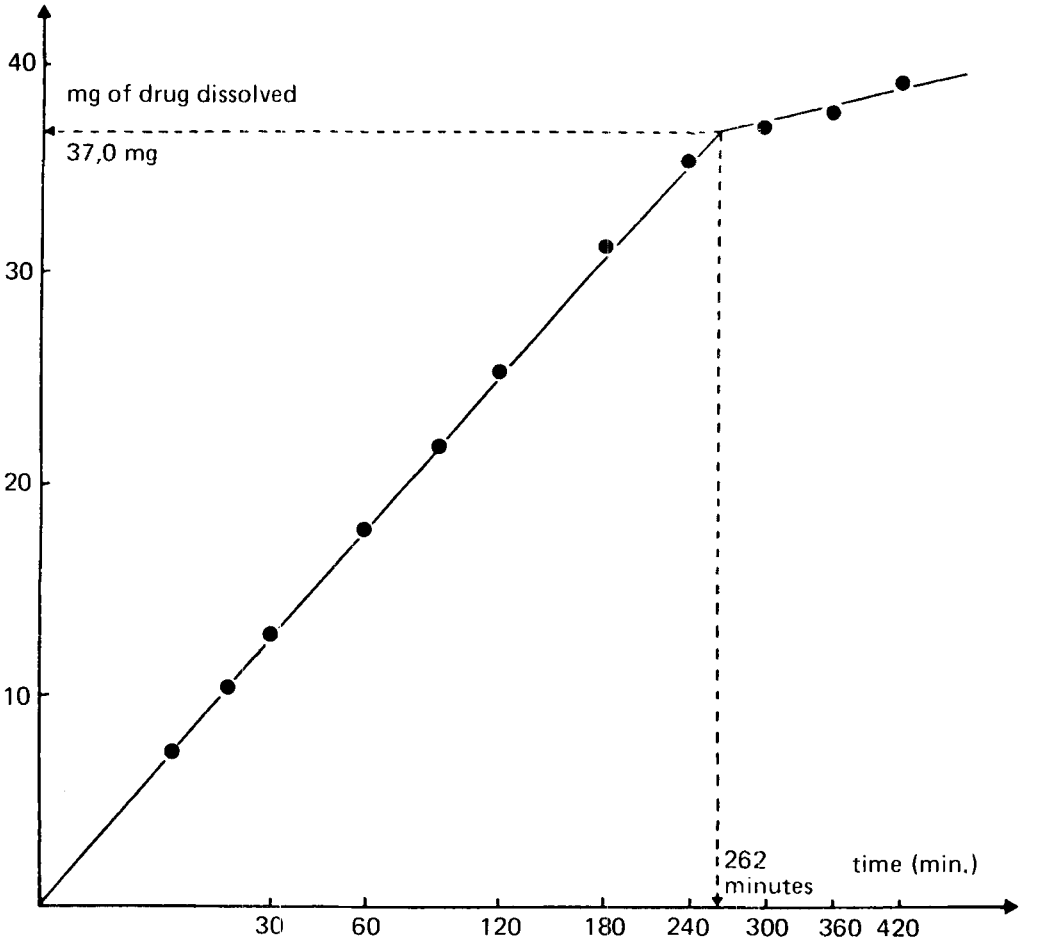

FIGURE 3 : Amount of drug dissolved as a function of the square root of time (Batch D2)

Change in the Mechanism of Liberation

The equation given by HIGUCHI assumes that the size of the solid in contact with the liquid is of infinite size. After a time equal to t, the dissolution medium has penetrated the matrix on a certain length equal to a. At the interface between the solid and the liquid,

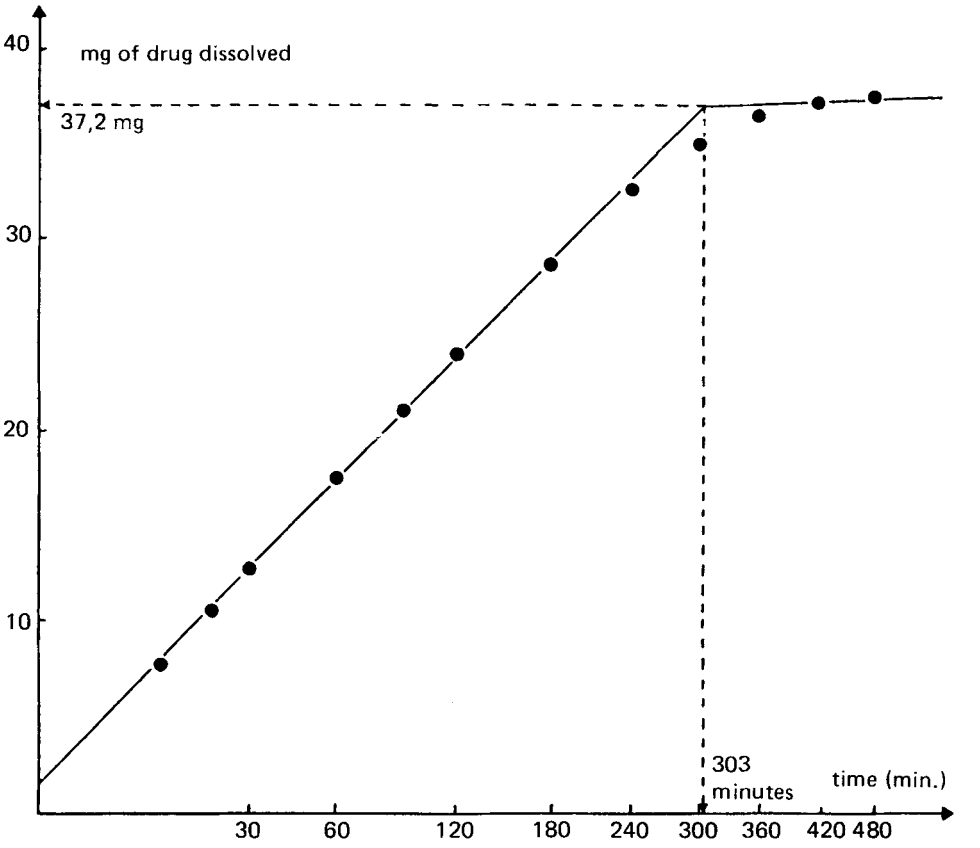

FIGURE 4 : Amount of drug dissolved as a function of the square root of time (Batch D3)

the concentration in dissolved drug is equal to the solubility of the drug. In the dissolution medium, outside of the solid matrix, the concentration is equal to zero ("sink" conditions). According to FESSI and al. (3) there is a concentration gradient in the tablet, from C = S at the solid-liquid interface to C = 0 at the outside of the tablet.

In fact the dimension of the tablet is not infinite : as long as there remains a part of the tablet which

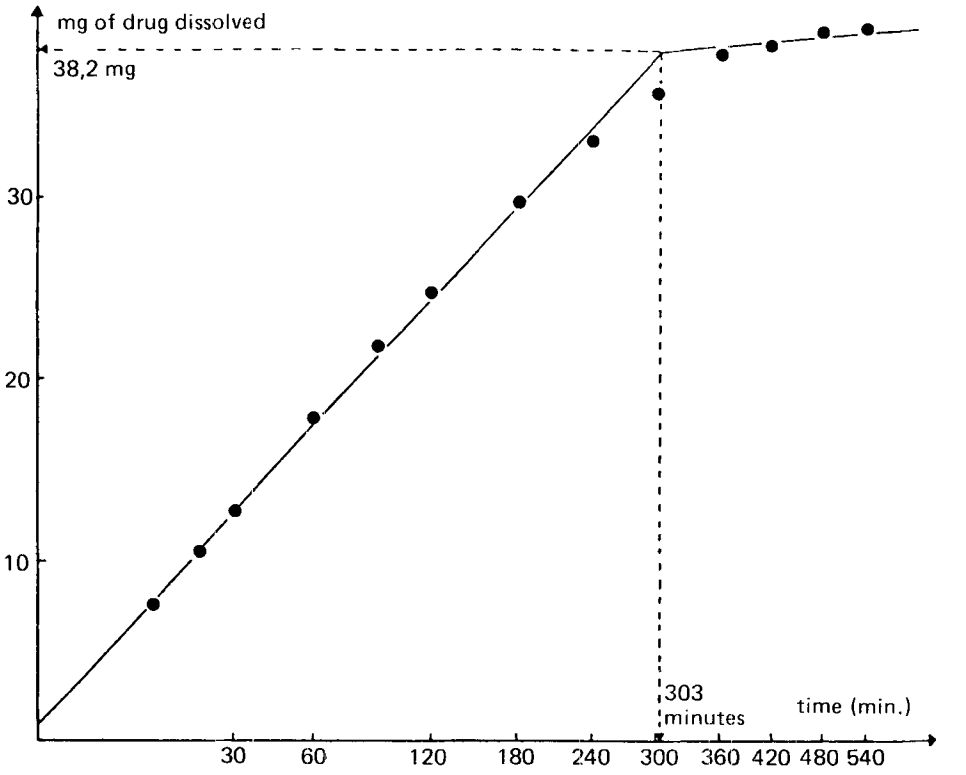

FIGURE 5 : Amount of drug dissolved as a function of the square root of time (Batch D4)

has not been wetted by the dissolution medium, the equation given by HIGUCHI is valid. When the tablet is completly wetted, C becomes lower than the solubility S, and the relation of HIGUCHI can no longer be used : at that time the change in the slope occurs.

FESSI and al. (3) have calculated the amount of drug remaining in the tablet at the "critical time" (time at which the slope of the curve changes).

$$J = e \cdot S \cdot \frac{3.1416}{------} \cdot h \cdot r \qquad \text{(equation 3)}$$

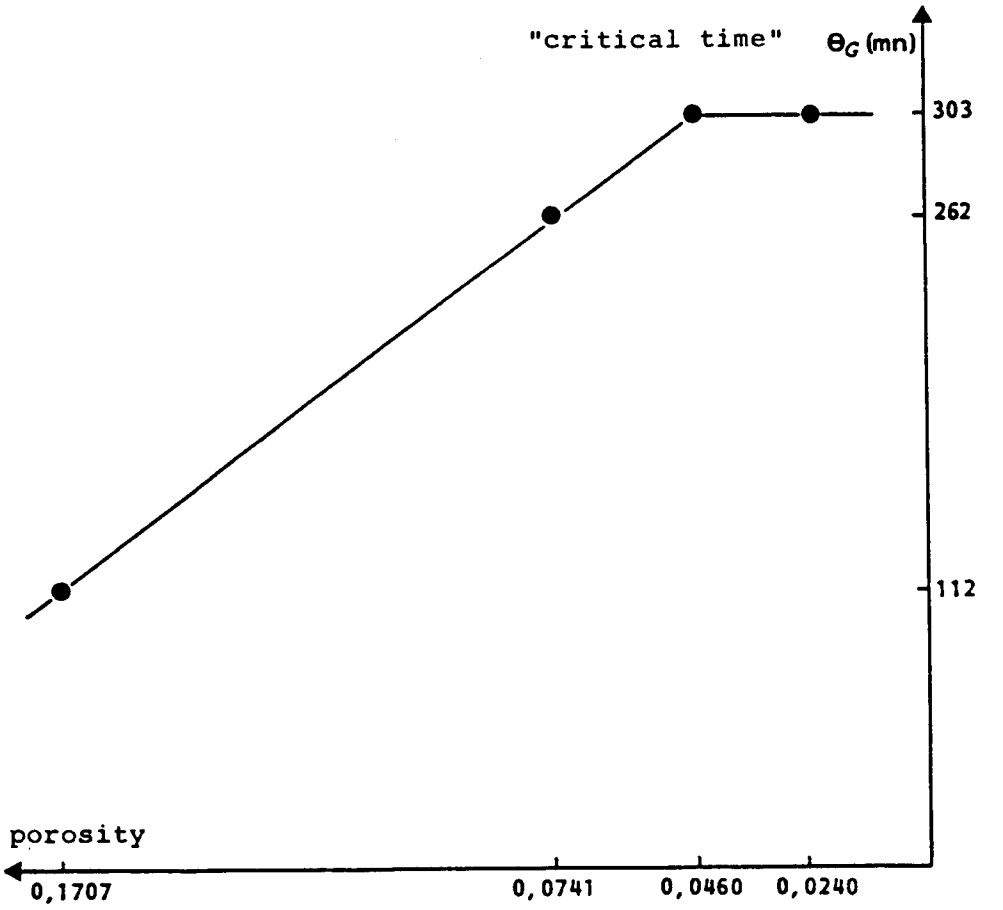

FIGURE 6 : Critical time as a function of the porosity of tablets

where : J is the amount of drug remaining in the tablet
e is the porosity of the tablet
S is the solubility of the drug
h is the thickness of the matrix tablet
r is the radius of the matrix tablet

In the case of Metoclopramide tablets studied here, the amount of remaining drug in the tablet at the

Table 3 : Amount of drug remaining in the matrices at the "critical time"

Batch	Porosity (%)	Thickness (cm)	J (mg) calculated	J (mg) graphic
D1	17.07	0.3	8.53	8.38
D2	7.41	0.3	3.70	3.84
D3	4.60	0.3	2.30	4.88
D4	2.40	0.3	1.20	4.85

critical time has been calculated, according to the equation (3) and has also been evaluated from the figures 2, 3, 4 and 5.

The results, reported in table 3 show that the calculated values are close to the experimental ones for the batches D1 and D2. This confirms the hypothesis of FESSI and al. (3).

For matrices of great hardness (batches D3 and D4), the differences between calculated and experimental values are more important. It seems (figure 6 and table 3) that the hypothesis of FESSI and al. is valid for tablets of weak or medium hardness (high or medium porosity) but not for very hard tablets with low porosity.

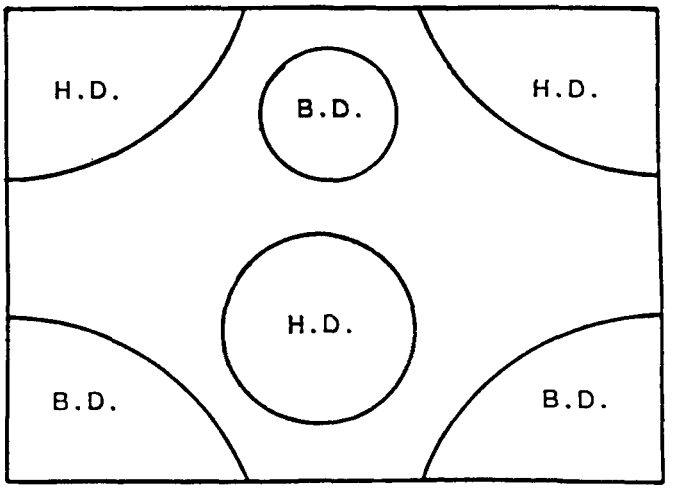

FIGURE 7 : Density zones in a tablet prepared on an alternative tabletting machine (H.D. = high density ; B.D. = low density)

High Density Nucleus

An other hypothesis could explain the change in the slope of the drug liberation curve : Train (6) has shown that the density of a tablet produced on an alternative press is not homogeneous, because the force transmission in a powder under pressure is not uniform. In the tablets there are parts with low density and others with high density. There is especially a zone of high density in the center of the tablet (figure 7).

This high density zone in the middle of the tablet could explain the change in the slope of the liberation profiles.

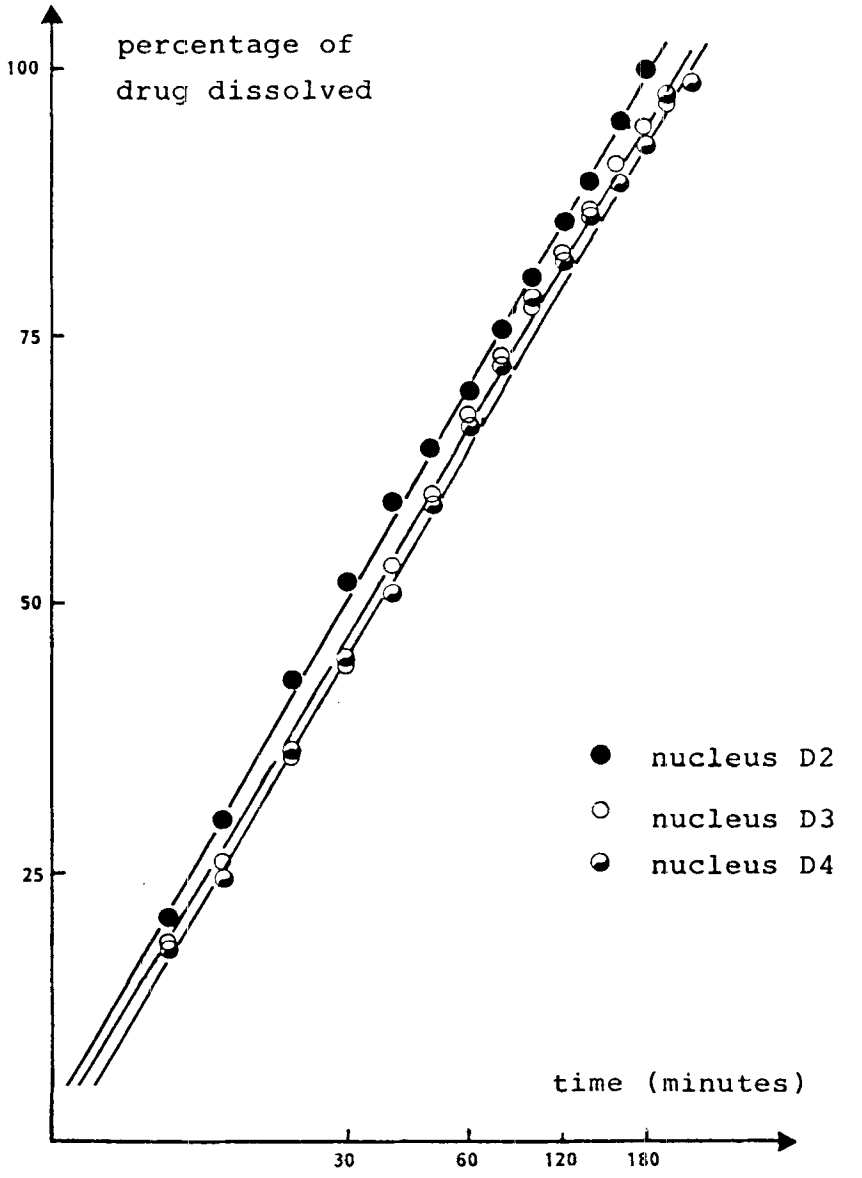

FIGURE 8 : Percentage of drug dissolved as a function of the square root of time (nucleus D2, D3 and D4)

In order to verify this possibility, tablets from the different batches were cut in order to insulate the central nucleus (approx. 90 mg, 20 % of the weight of the original tablet). This experiment could not be achieved with the batch D1, because of the low hardness of the batch.

The liberation profile was studied as mentioned previously, and the plot of the percentage of drug dissolved as a function of the square root of time is given in figure 8.

Each nucleus can be considered as a whole tablet, which liberates the whole quantity of drug contained in it. The nucleus shows a linear liberation profile, without any change in the slope of the curve.

So it can be assumed that the nucleus prepared has a higher homogeneity in density than the whole tablet, and that the change in the liberation profile slope is probably due to the differences of density in the tablets.

CONCLUSION

The plotting of the liberation of a drug from an inert matrix vs square root of time often shows a change in the slope of the curve at the end of the dissolution. It was tried in this paper to verify if this change is due to a modification of the liberation mechanism or to the difference of densities in the tablets.

For tablets showing a high porosity (low hardness), the change in the slope is probably due to a change in the liberation mechanism, but for tablets with low porosity (high hardness), the differences of density in the tablets are responsible of the change of slope.

REFERENCES

1) B. Faradieh, S. Borodkin , J.D. Buddenhagen, J.Pharm.Sci., 60, 209 (1971)
2) B. Faradieh, S. Borodkin , J.D. Buddenhagen, J.Pharm.Sci., 60, 212 (1971)
3) H. Fessi, F. Puisieux, J.P. Marty , J.T. Carstensen, Pharm. Acta Helv., 55, 261 (1980)
4) T. Higuchi, J.Pharm.Sci., 52, 1145 (1963)
5) G.P. Timoshenko, J.N. Goodier, "Theory of elasticity",2nd Ed. Mc Graw Hill Ed. London (1951)
6) D. Train, Trans. Instn. Chem. Engrs, 32, 258 (1957)