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SOME ASPECTS OF THE FORMULATION OF HARD GELATIN CAPSULES

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Two kind of problems can arise in the liberation of a drug from a solid dosage form :
- an excessive short liberation time, so that the plasma concentration could reach a high value, with possible side effects, and the drug activity often remains only a short period of time ;
- a very long liberation time, frequently due to bad dissolution properties of the drug (wetting, solubility a.s.o.). In this case usually only a part of the drug is really dissolved, and the effect is not complete.

These two kind of problems were well investigated in the formulation of tablets, but there are only few publications treating more precisely the formulation of hard gelatine capsules. The present work only aims to show, with two selected examples, how the formulation of hard gelatine capsules can influence the in vitro

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drug liberation.

1) Materials and methods

The formulation of the capsules content was realised as described hereafter.

The dissolution of capsules content was analysed in vitro, using the paddle dissolution apparatus (U.S.P. XX) with a rotation speed of 50 r.p.m. The dissolution medium was diluted hydrochloric acid (pH = 1.2).

Samples of dissolution medium were taken at regular time interval (depending on the dissolution rate of the capsule content), and analysed by U.V. spectrophotometry. Each sample was replaced by an equivalent volume of new dissolution medium.

An identical procedure was followed for tablets.

The results are given in percent of dissolved drug as a function of time.

2) Example of an easily water soluble drug

The drug choosen as an example for easily water soluble product was tetracycline hydrochloride.

It is a crystalline yellow powder, odourless and bitter tasting.

The drug is very soluble in methanol (more than 20 mg/ml), chloroform, and practically insoluble in aceton or ether.

Tetracycline is stable in a dry stage when stored in darkness. In aqueous solutions, it is hydrolysed at low pH.

For these different reasons, tetracycline hydrochloride is presented in solid dosage forms.

In a first group of experiments, it was tried to prepare capsules and tablets containing 250 mg of tetracycline hydrochloride with diluants for direct compression (AVICEL 102[1], STARX 1500[2], EMDEX[3] and crystalline LACTOSE[4]; the composition of each

kind of capsule is given in table 1. The formula were calculated in such a manner to give a complete filling of 00 size capsules by simple flowing of the powder into the capsule. All formulas contain 1.5 % of magnesium stearate in order to allow a better compaction of the powder bed.

All the mixtures were homogeneized on a Turbula mixer, and the content uniformity controlled on ten samples.

The mixtures were, on one side, filled by hand into capsules size OO, O and 1 (so that various porosities of the powder beds could be observed).

On the other side, the mixtures were tabletted on a KORSCH EK/O tabletting machine, fitted out with strain gauges. Three kind of tablets were prepared : one presenting a low hardness (approx. 2 kg measured on an Erweka hardness tester), one with a medium hardness (4 to 7 kg) and one showing a high hardness (7 to 10 kg). These data are reported in table 2. In this table are also indicated the porosity of the powder beds in capsules, calculated according to the relation :

$$\varepsilon = 1 - \frac{b.d.}{t.d.}$$

where ε is the porosity ;
b.d. is the bulk density (apparent density) of the powder ;
t.d. is the true density of the powder (measured with an helium pycnometer)

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(1) F.M.C.
(2) Staley
(3) Ed. Mendell
(4) H.M.S.

TABLE 1

Composition of the mixtures tetracycline - direct compression diluents

Content	Quantity (mg)	Percent	Weight of one dosage unit (mg)
Tetracycline	250	64.9	
AVICEL 102	130	33.7	385.4
Mg stearate	5.4	1.4	
Tetracycline	250	47.8	
STARX 1500	265	50.8	522.5
Mg stearate	7.5	1.4	
Tetracycline	250	57.8	
EMDEX	176	40.8	432.2
Mg stearate	6.2	1.4	
Tetracycline	250	38.9	
LACTOSE F.C.	400	60.6	659.4
Mg stearate	9.5	1.4	

The results of dissolution experiments show low differences between the different formulations : With AVICEL 102, STARX 1500 and EMDEX the dissolution is complete after 15 minutes (for example, figure 1 gives the results of EMDEX capsules). The dissolution is faster with high porosity capsules and with tablets of low hardness. Figures 2 and 3 represent the examples of AVICEL 102 formulations. In the case of lacto-

TABLE 2

Hardness of tablets (kg Erweka), mean compression forces (kg/cm^2) and capsules porosity

FILLER	TABLETS		CAPSULES		
	Hardness (kg)	Mean compression force (kg/cm^2)	Porosity ε		
			Size 00	Size 0	Size 1
AVICEL 102	4	670	0.63	0.56	0.42
	7	1140			
	10	1530			
STARX 1500	2	1200			
	4	1740	0.60	0.45	0.35
	9	4060			
EMDEX	2	610			
	5	900	0.54	0.36	0.30
	7	2110			
LACTOSE FC	2	1100			
	4	2400	0.50	0.37	0.25
	high hardness could not be reached				

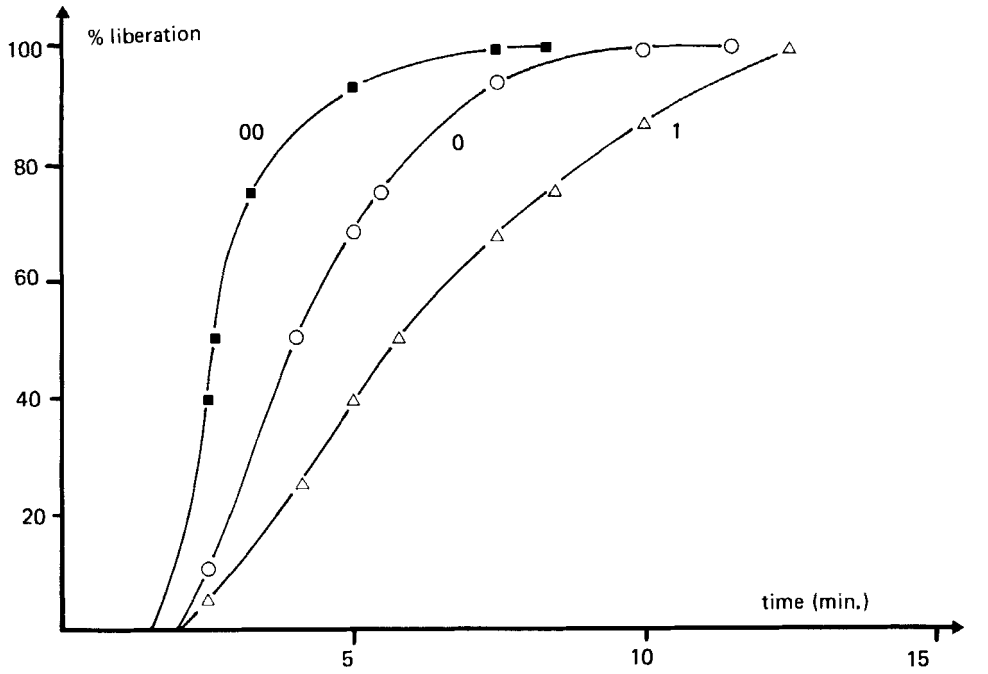

FIGURE 1

Dissolution rate of tetracycline - EMDEX capsules (size 00 : ε = 0.54 - size 0 : ε = 0.36 size 1 : ε = 0.30).

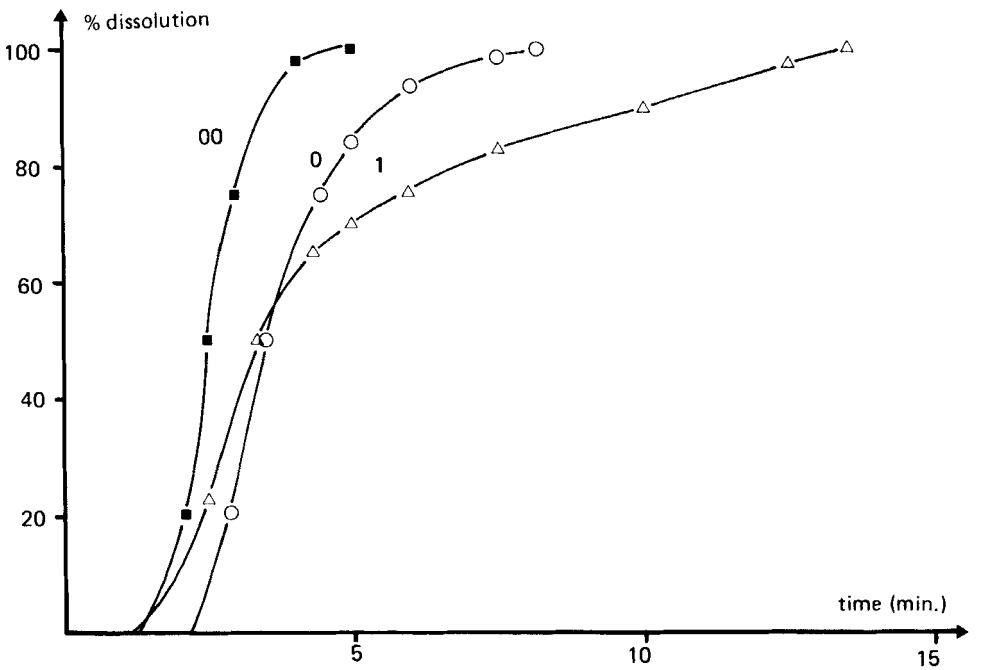

FIGURE 2

Dissolution rate of tetracycline - AVICEL 102 capsules (size 00 : ε = 0.63 - size 0 : ε = 0.56 size 1 : ε = 0.42).

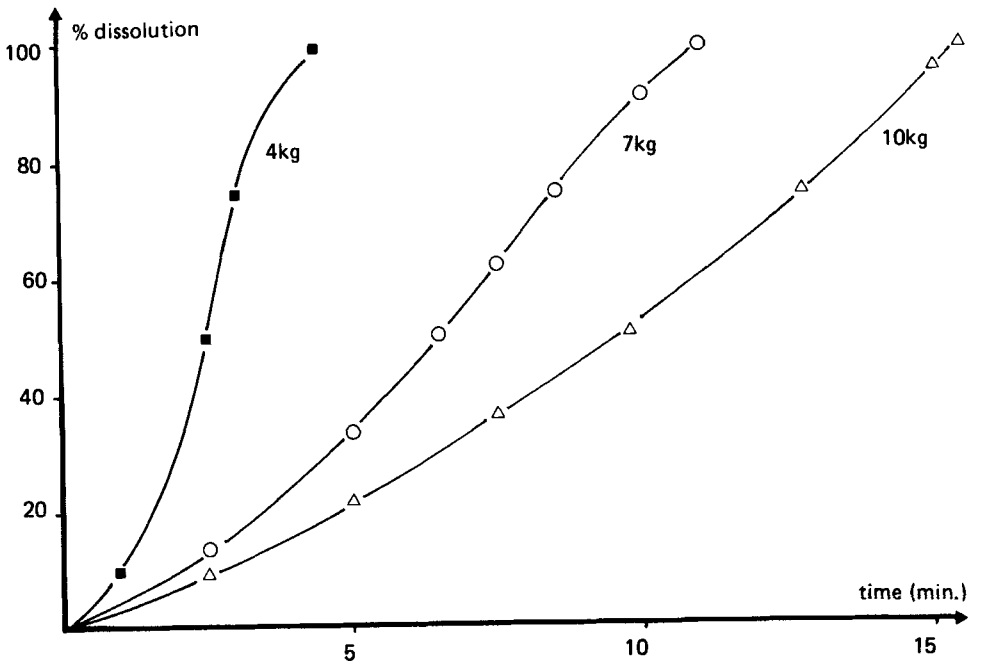

FIGURE 3

Dissolution rate of tetracycline - AVICEL 102 tablets.

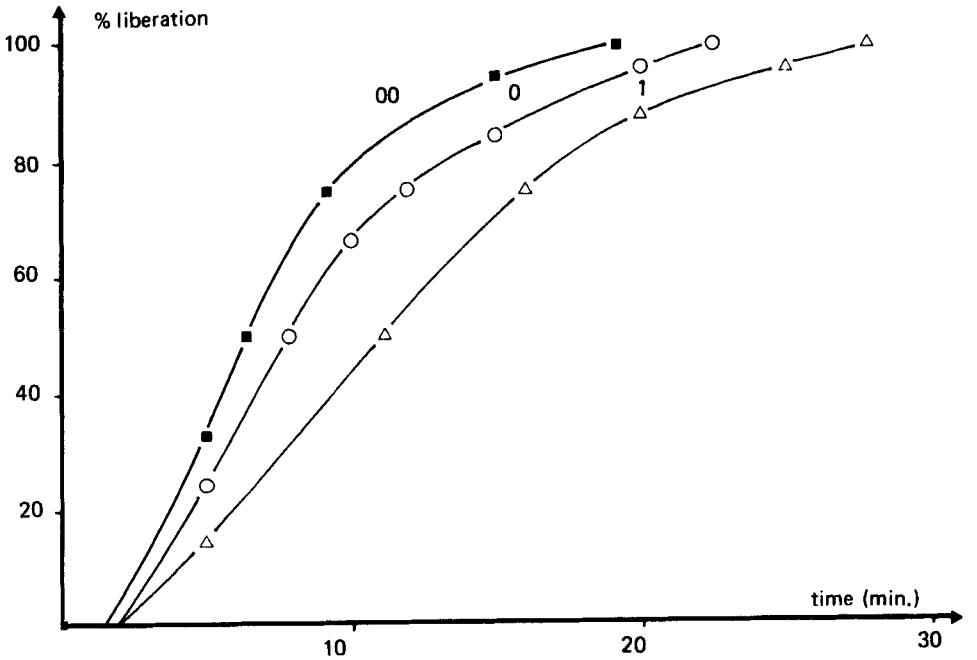

FIGURE 4

Dissolution rate of tetracycline - LACTOSE FC capsules (size 00 : ε = 0.50 - size 0 : ε = 0.37 size 1 : ε = 0.25).

se used as a filler, the drug liberation is slower (figure 4), but complete after 25 to 35 minutes.

So it seems that even in the case of capsules of low porosity or tablets of great hardness, the liberation rate is high because of the very good solubility of tetracycline in water.

In order to prolong the liberation of the drug, different kind of matrixes were prepared by wet granulation.

Some were lipidic matrixes ; for these formulations PRECIROL(5) and CUTINA(6) were used.

PRECIROL is a glycerol palmitostearate containing approximately 40 % of triester, 45 % of diester, 14 % of monoester and 1 % of free glycerol; it is available as an atomised free flowing powder ; it gives prolonged effect when used in a concentration of 10 to 40 % in the formula.

Two kind of methods were used to prepare the granules : In the method A (containing 30 % of PRECIROL), the fatty component was melt at 60 - 65°C, mixed with the other ingredients and cooled. When the mixture became solid, it was granulated through a screen. In the method B (20 % of PRECIROL), the fatty component was dissolved in six parts of chloroform. The other ingredients were added to this solution, and the solvent evaporated under continuous stirring.

CUTINA HR is an hydrogenated castor oil, and can be used for the preparation of matrixes by direct compression when used in a proportion of 10 to 15 %. When the mixture is granulated smaller amount can be used.

The granules were prepared according to the two methods (A and B) described for PRECIROL. In the case

(5) Gattefossé

(6) Henkel

of method B the solvent was alcohol instead of chloroform.

Other matrixes were hydrophilic ones. For these formulations P.V.P. and H.P.M.C. (PHARMACOAT 606[7]) were employed. The granules were prepared by wet granulation, using alcohol as a solvent.

A plastic matrix was also prepared, using an acrylic resin (EUDRAGIT RL [8]). In this case, the granules were prepared by mixing EUDRAGIT powder with the other ingredients, and using an EUDRAGIT solution as binder.

All the granules were passed through 250 μm and 1000μm screens, and only the fraction between these sizes was used for the experiments.

The composition of the different mixtures is given in table 3. These formulas were studied to fill exactely a 00 size capsule with 250 mg of tetracycline.

The capsules were prepared using different capsules sizes (00, 0 and 1) in order to study the influence of the capsule content porosity.

Tablets were also prepared at three different hardnesses as mentioned for direct compression diluent formulations.

With PRECIROL 30 % matrice, prepared by melting (method A) the dissolution of tetracycline is complete within 15 minutes (figures 5) when the granule is not strongly packed in the capsules (size 00 and 0). The liberation can be prolonged up to 2 hours when the granule is packed in capsules size 1.

The influence of packing can well be seen on the figure 5 : the 0 size capsule was normally packed (ε = 0.56) and also strongly packed (ε = 0.41) : the liberation rate decreased.

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(7) Shin Etsu
(8) Röhm Pharma

Table 3 : Composition of the different matrixes

	Quantity (mg)	Percent	Weight of one dosage unit
Tetracycline PRECIROL Mg stearate (method A)	250 107 3.5	69.3 29.7 1.0	360.5
Tetracycline PRECIROL Lactose Mg stearate (method B)	250 71.4 71.4 5.4	62.8 17.9 17.9 1.4	398.2
Tetracycline CUTINA Lactose Mg stearate (method A)	250 12 147.4 6.2	60.1 2.9 35.5 1.5	415.6
Tetracycline CUTINA Lactose Mg stearate (method B)	250 20.2 143 6.1	59.7 4.8 34.1 1.4	419.3
Tetracycline EUDRAGIT RL Lactose Mg stearate	250 65 16.5 3.2	74.7 19.4 4.9 1.0	334.7
Tetracycline Lactose P.V.P. Mg stearate	250 107 14.2 5.3	66.4 28.4 3.8 1.4	376.5
Tetracycline PHARMACOAT 606 Lactose Mg stearate	250 35.6 71.2 3.5	69.4 9.9 19.8 1.0	360.3

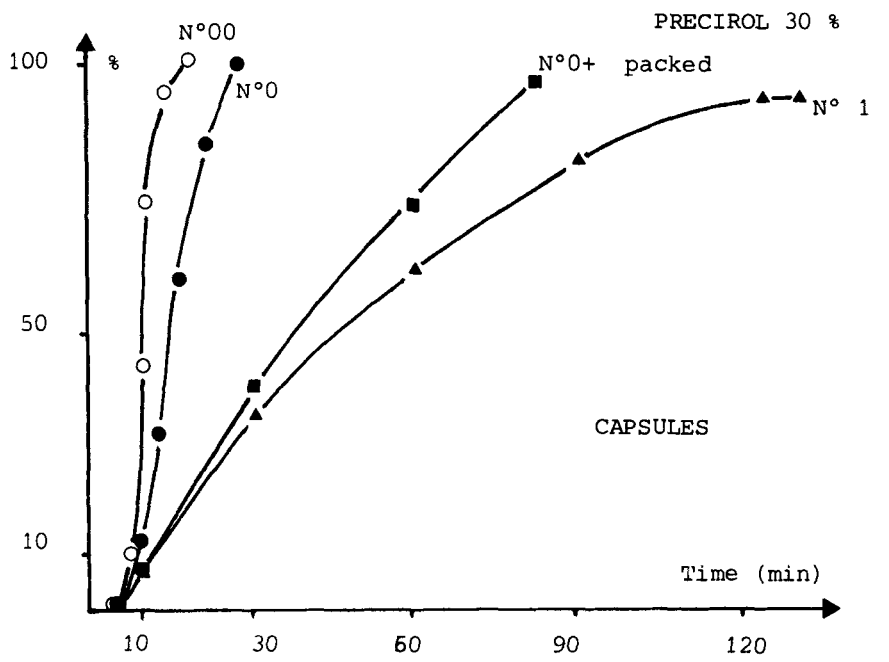

FIGURE 5
Dissolution of tetracycline- PRECIROL Capsules (method A).

With tablets (figure 6), the liberation is not completely achieved, even after 7 hours. Tablets hardness does not have a grean influence.

The capsules containing 20 % of PRECIROL, and prepared by the solvent method (method B) (figure 7) show a high liberation rate, in the case of loose packed granules (size OO : $\varepsilon = 0.59$) as also in the case of strongly packed ones (size 1 : $\varepsilon = 0.39$). This concentration of PRECIROL is not sufficient to achieve a prolonged release form in capsules. The tablets containing the same quantity of PRECIROL show, on the contrary, a good prolonged liberation.

The results observed with CUTINA 3 % (figure 9) are similar to those obtained with melted PRECIROL. The results of CUTINA 5 % (method B) are in the same

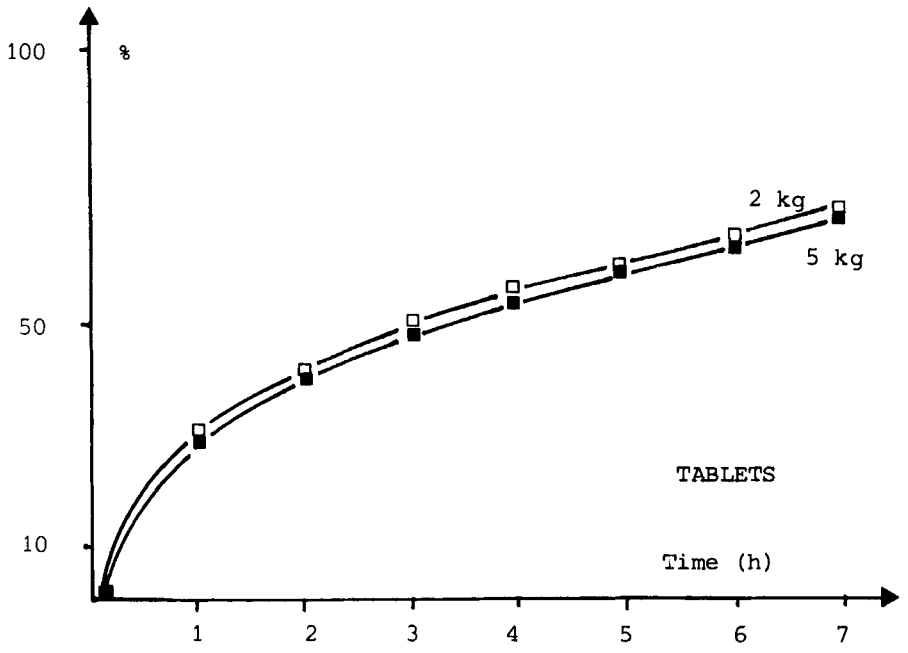

FIGURE 6

Dissolution of tetracycline - PRECIROL Tablets (method A).

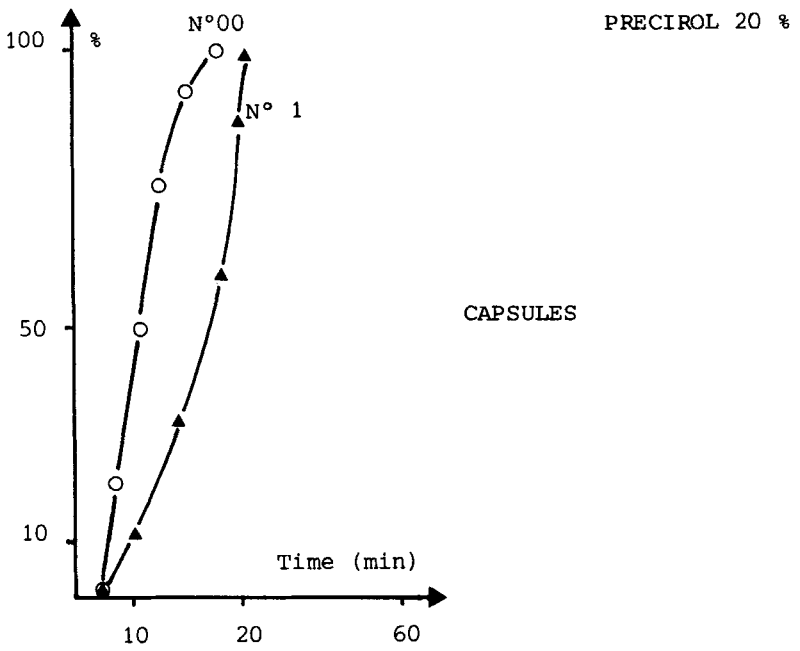

FIGURE 7

Dissolution of tetracycline - PRECIROL Capsules - PRECIROL Capsules (method B).

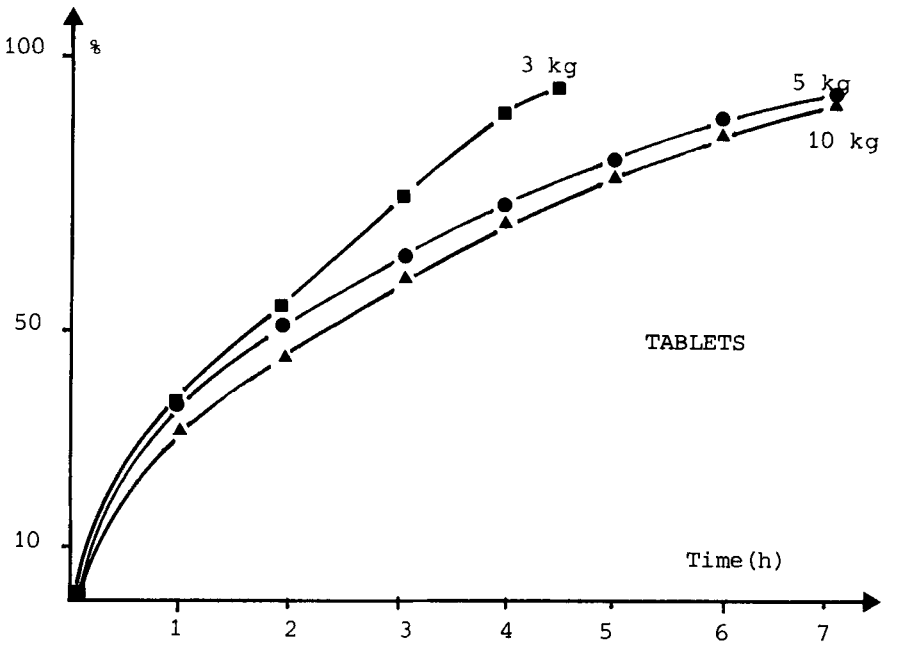

FIGURE 8

Dissolution of tetracycline - PRECIROL Tablets (method B).

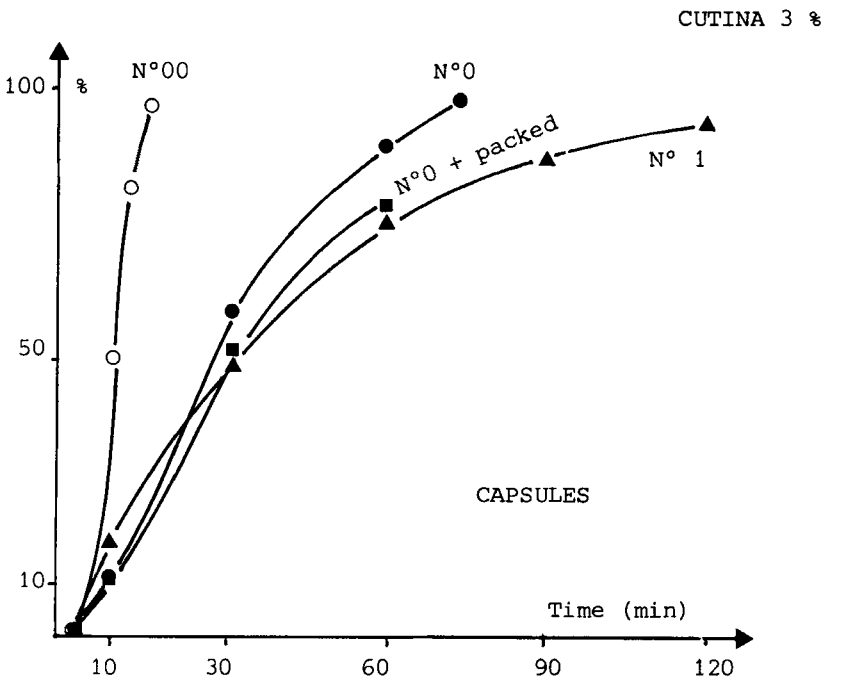

FIGURE 9

Dissolution of tetracycline - CUTINA Capsules (method A).

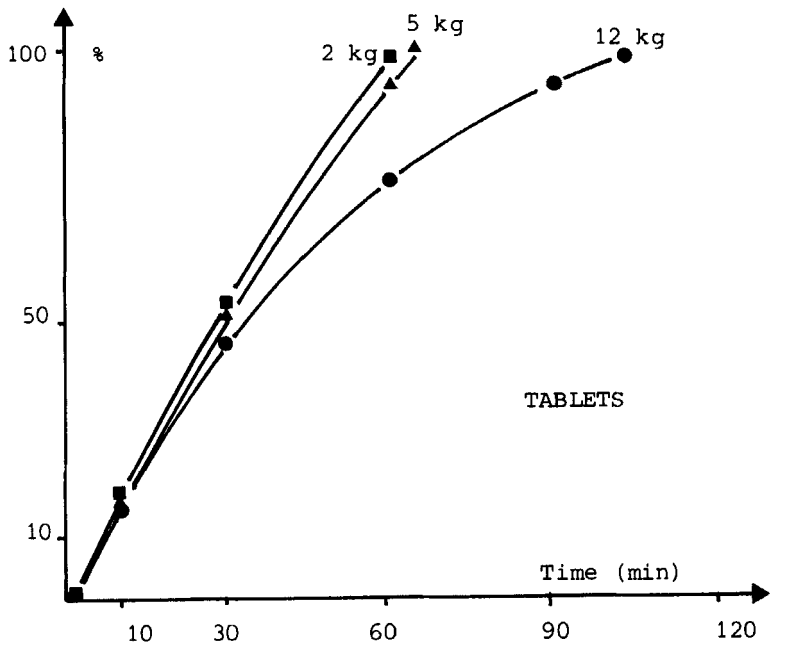

FIGURE 10

Dissolution of tetracycline - CUTINA Tablets (method A).

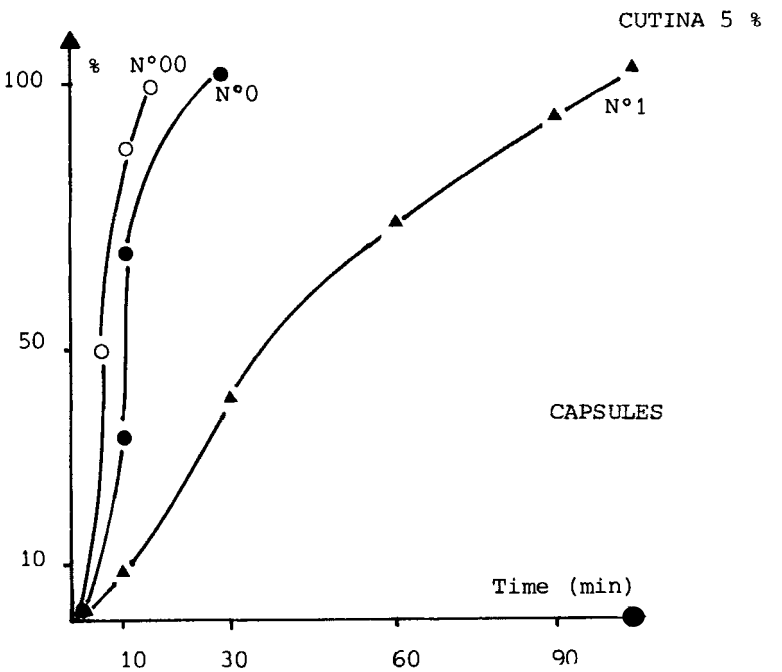

FIGURE 11

Dissolution of tetracycline - CUTINA Capsules (method B).

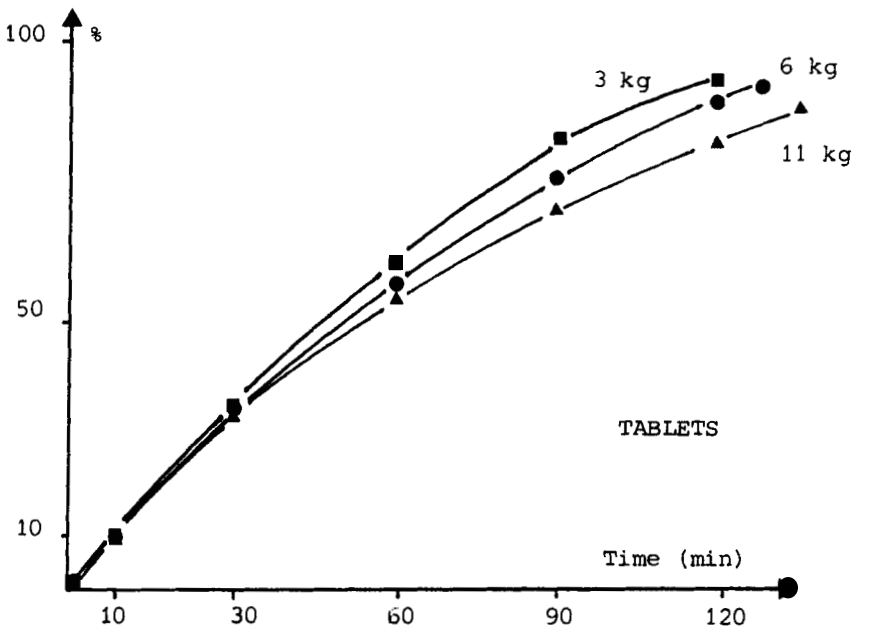

FIGURE 12

Dissolution of tetracycline - CUTINA Tablets (method B).

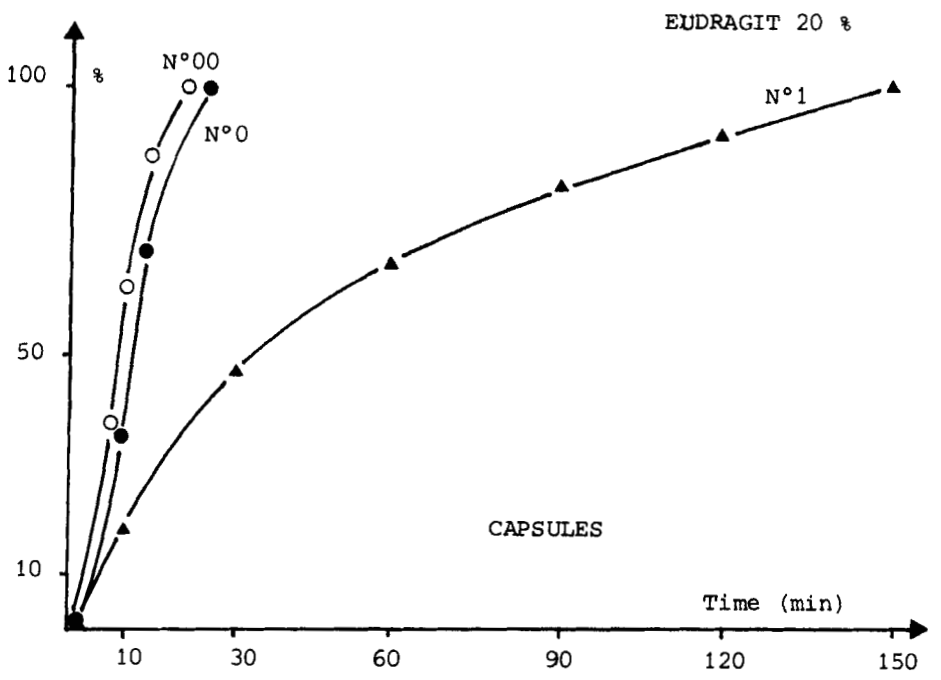

FIGURE 13

Dissolution of tetracycline - EUDRAGIT RL Capsules.

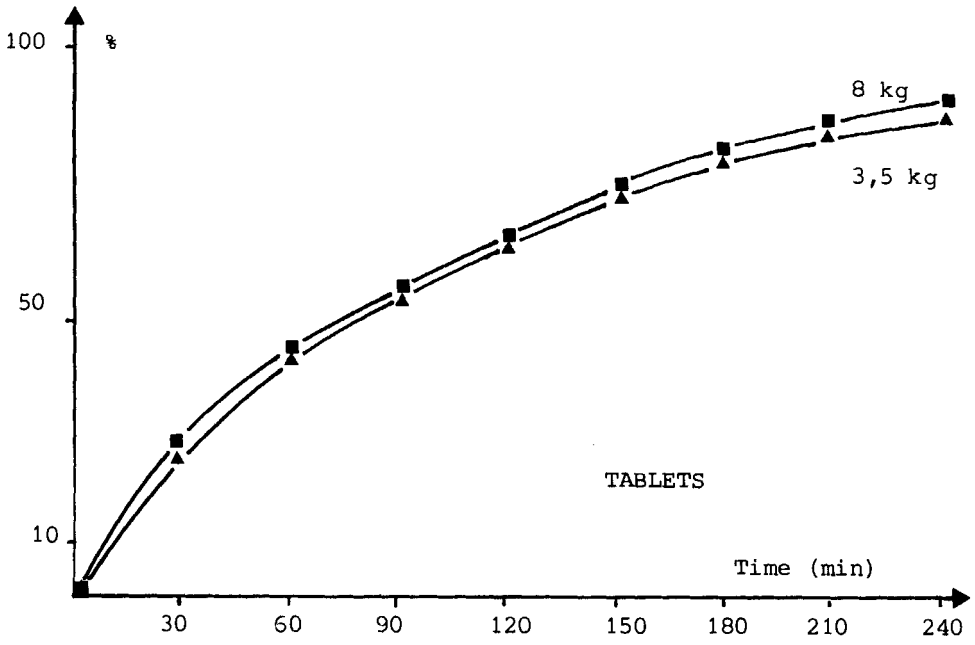

FIGURE 14

Dissolution of tetracycline - EUDRAGIT Tablets.

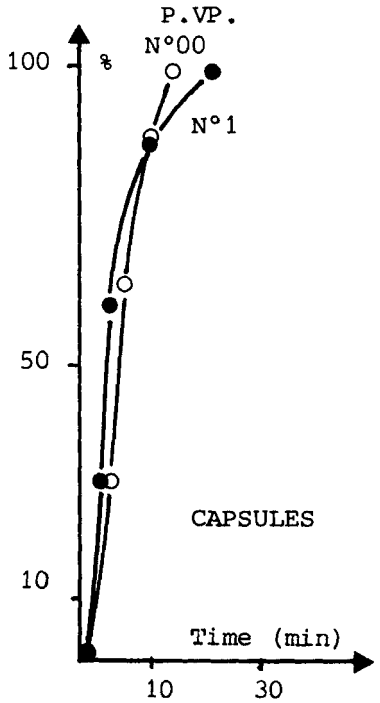

FIGURE 15

Dissolution of tetracycline - P.V.P. Capsules.

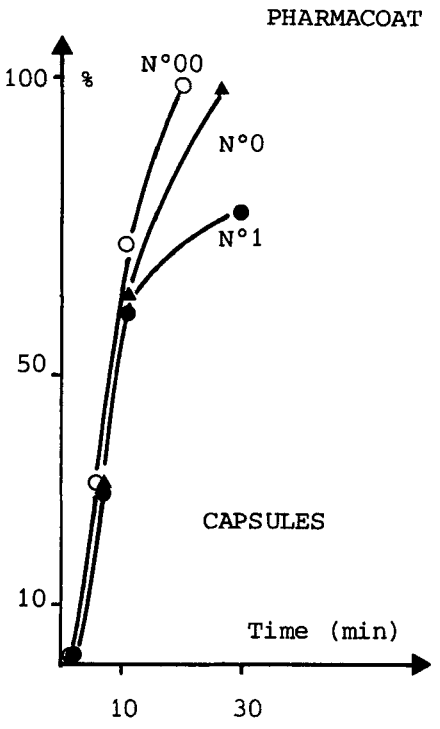

FIGURE 16

Dissolution of tetracycline - PHARMACOAT Capsules.

range (figure 11) than those of PRECIROL 20 % (method B). When these granulates are packed in a capsule size 1, the liberation can be prolonged during 90 minutes.

The tablets (figures 10 and 12) show a liberation during two hours, and the applied pressure has less influence.

Similar resultas were observed with EUDRAGIT RL granulates : in capsules (figure 13) the liberation is quick if the capsule content is not strongly packed (in capsules 00, $\varepsilon = 0.65$; in capsules O, $\varepsilon = 0.60$), but a good packing gives a liberation during 150 minutes (in capsule size 1, $\varepsilon = 0.51$). The tablets prepared in the same conditions (figure 14) show a liberation during four hours, and the applied pressure has no effect.

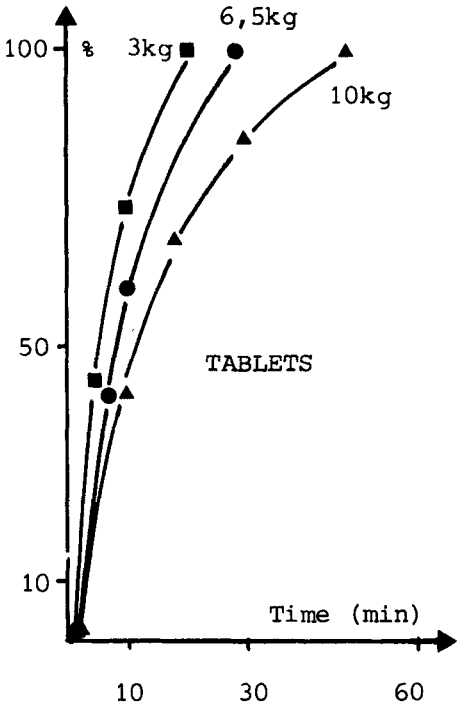

FIGURE 17

Dissolution of tetracycline - P.V.P. Tablets.

As could be supposed, hydrophilic matrixes (PVP and HPMC) do not allow to lengthen the drug liberation time, neither in capsules nor in tablets (figure 15 to 18).

This first part of the study showed how it is possible to have a prolonged action with capsules, but a very long action as in the case of tablets, could not be reached by the only treatment of capsules content. This is probably due to the high porosity of the capsules content.

3) Example of a poor water soluble drug

The second example choosen is griseofulvin, an antibiotic which is well known for its bad water solubility (15µg/ml at 37°C) (1). It is bette soluble

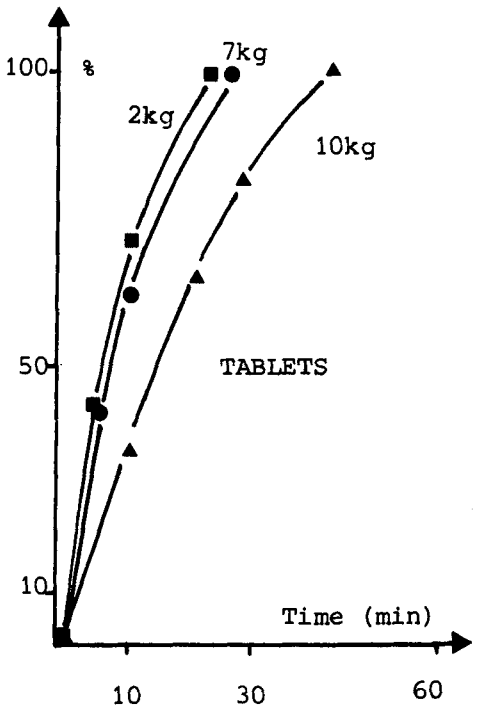

FIGURE 18
Dissolution of tetracycline - PHARMACOAT Tablets.

in chloroform (1 part in 25) or in aceton (1 in 20).

The therapeutic use of this drug needs high dosages, because of its bad solubility and fast metabolisation.

It is well known from the litterature that a particle size reduction of the drug allows a better solubility (2) and ATKINSON and al. (1) have reported that the plasma level is in direct relation with the specific surface area of griseofulvin. CHIOU and RIEGELMAN (2) have shown that griseofulvin can be completely absorbed in the G.I. Tract when given in form of a solid dispersion in P.E.G.. NURNBERG and KRIEGER (4) have studied different methods for the preparation of solid dispersion of griseofulvin in various macromolecules like

Table 4 : Composition of the mixture griseofulvin hydrophilic macromolecules

L-HPC[9] (low viscosity HPMC)	0.25
Griseofulvin	4.75
Alcohol	
PHARMACOAT 606[9]	0.3
L-HPC	0.7
Griseofulvin	4.0
Alcohol	
Arabic Gum	1.0
Griseofulvin.....	1.0
water	
Gelatine	1.0
Griseofulvin	1.0
water	

(9) Shin Etsu

P.V.P., methylcellulose, P.E.G. or polypropyleneglycol. They reported that interesting results can be given by these kind of dispersions.

The first experiences were made without dissolution of the active drug : Griseofulvin was simply mixed with various hydrophilic excipients, and the mixture granulated with alcohol or water (see table 4). The granulates were dried at 37°C, and screened. Only the fraction between 250 and 500 µm was used to fill capsules of various sizes.

None of these formulas gave a significant increase in the dissoltuion of griseofulin :

When a sample of 50 mg of pure griseofulvin is put in the dissolution apparatus, the dissolution is about 6 % after one hour, and 10 % after 2 hours.

In order to make the comparisons between results easier, the dissolution test were all realised on such a quantity of material that 50 mg of griseofulvin is in the dissolution medium.

The results obtained with simple mixtures of griseofulvin with hydrophilic macromolecule used in small amount were all in the same range, and did not allow a significant increase of the quantity of drug dissolved.

The second serial of experiments were tried by dissolution of griseofulvin in a solvent. Two hydrophilic macromolecules were used : P.V.P. and P.E.G.

With P.V.P. the first kind of studied formula was :

Griseofulvin.....1
P.V.P.....10
Chloroform

Griseofulvin was mixed with P.V.P. and the mixture dissolved in chloroform under stirring. The solvent was then evaporated, and the residue milled, and filled into capsules. This method is long and tedious. The mixture is not homogeneous, so this methods seems not to be sa-

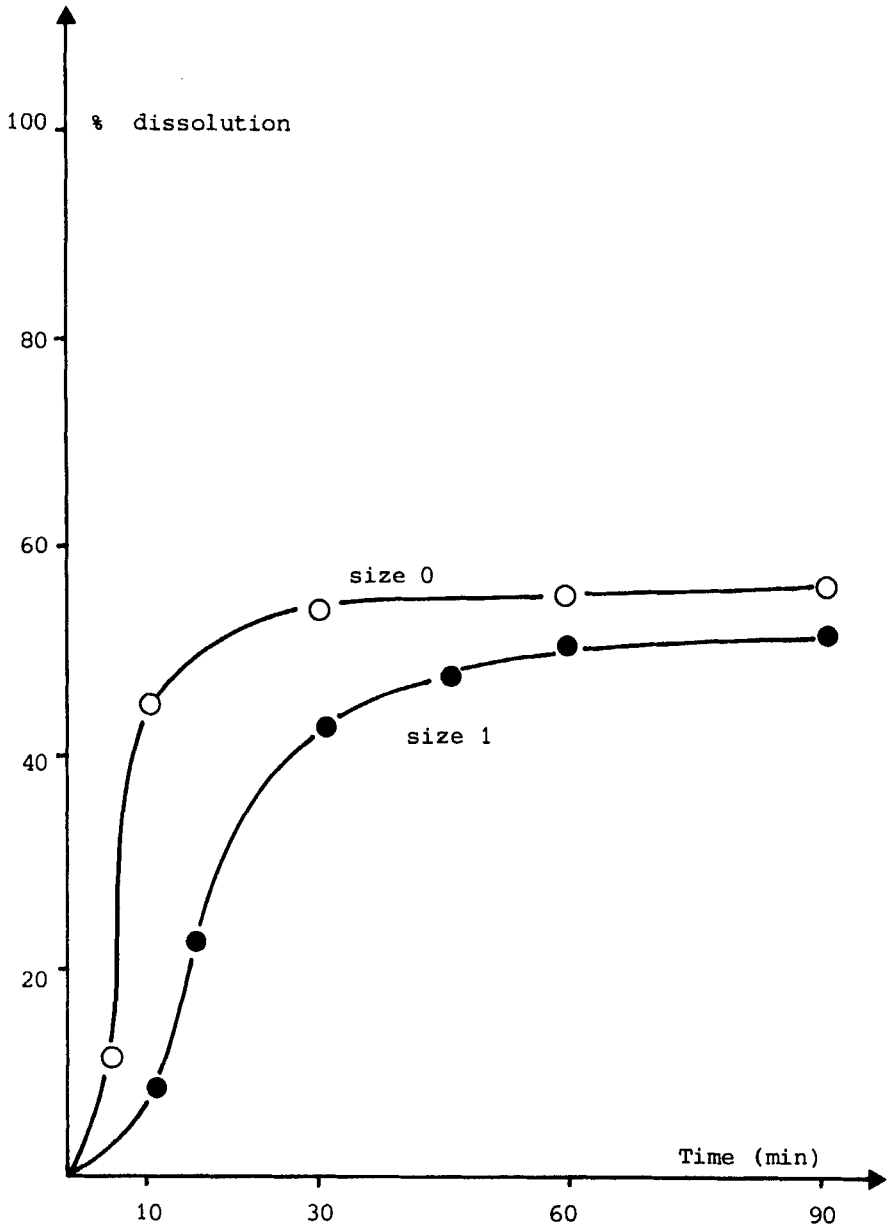

FIGURE 19

Dissolution rate of griseofulvin - P.V.P. dispersions.

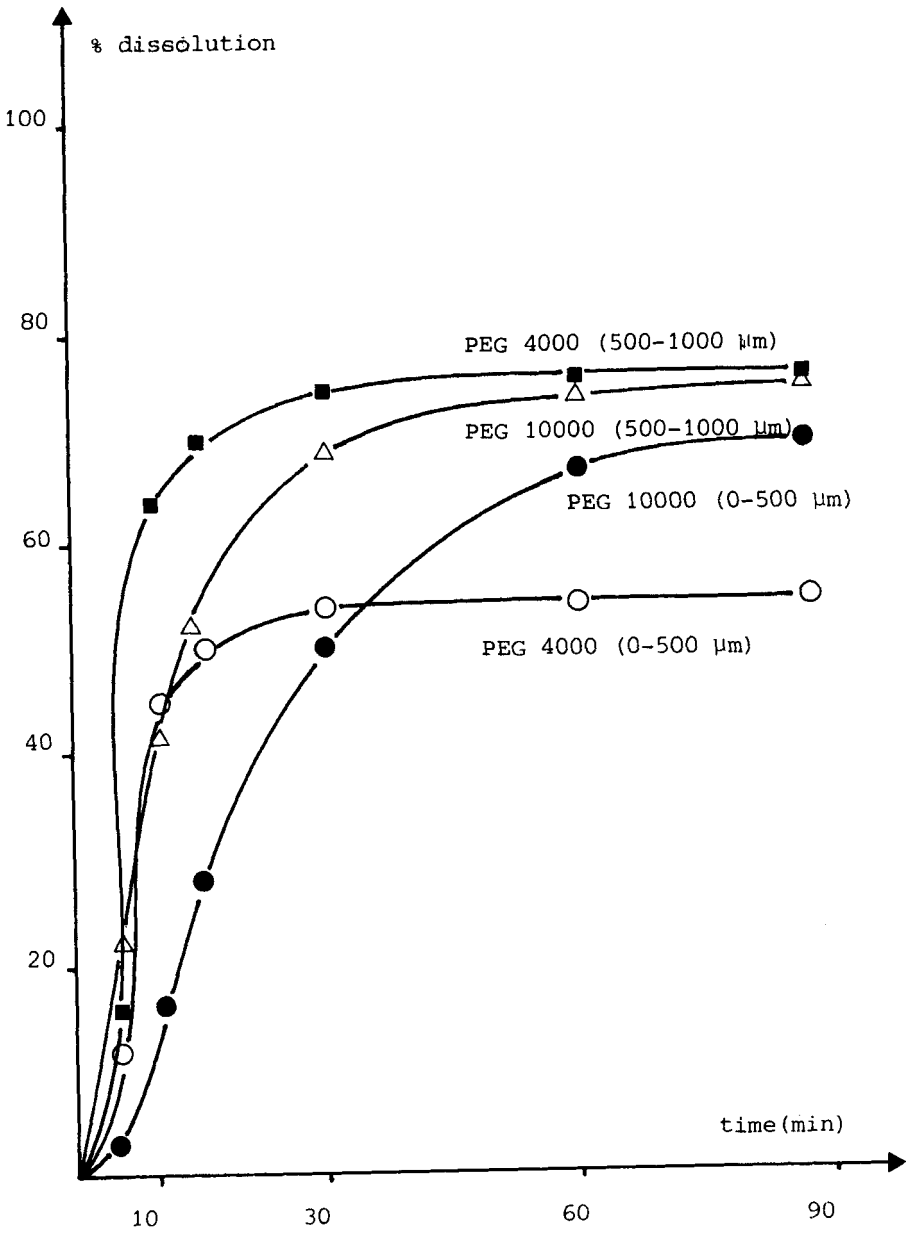

FIGURE 20

Dissolution rate of griseofulvin - P.E.G. dispersions.

tisfactory. In order to shorten the preparation, a second formula was tried :

Griseofulvin	1
Silicon dioxide (AEROSIL 200)[10]	4
P.V.P.....	10
Chloroform	

Here again griseofulvin was mixed with P.V.P. and the mixture dissolved under stirring in chloroform. But immediately after dissolution, silicon dioxide was added to the solution in order to give a paste. The solvent evaporated faster, and more regulary. The evaporation residue was milled, and filled into capsules. The results of the disssolution tests of these capsules are given in figure 19.

These formula gave interesting results : a dissolution of about 50 % could be reached after one hour. The capsule size 0, where the porosity is greater, allows a faster dissolution of the active ingredient than the capsule size 1, but the total dissolved amount is in the same range.

It was also tried to prepare a dispersion of griseofulvin in P.E.G.. Two polymers were used : PEG 10000 and PEG 4000, according to the formula :

Griseofulvin.....	5
PEG.....	80

P.E.G. was melt at 70°C, and griseofulvin dissolved in chloroform. Under stirring the griseofulvin solution was pourred in the melt P.E.G. The solvent evaporation was quickly achieved and an homogeneous dispersion was obtained. It was cooled to solidify, and then milled. The solid dispersion was screened, and two size

(10) Degussa

fractions were taken : less than 500 µ m and between 500 µm and 1000 µm. Capsules were filled with these dispersions and their dissolution studied (figure 20).

The formulas with P.E.G. allow a dissolution of 70 to 75 % of the drug after one hour, exepted with the small fractions of P.E.G. 4000 dispersions, where the dissolution is only 50 %.

In order to compare the results with those which can be obtained with the same formulas in tablets, the P.E.G. 10000 and the P.V.P. dispersions were added with 0.75 % of magnesium stearate, and tabletted.

In these cases, only 20 to 25 % dissolution could be reached after five hours.

This experiment shows that in some cases, it is more interesting to fill an active drug into hard gelatin capsules then to compress in into tablets. The use of solid dispersions could be of great interest with the new possibility of filling liquids and pastes into hard capsules.

CONCLUSION

The present paper only aimed to show, with two examples, some possibilities and limits of the hard gelatin capsules. It indicates that it is not indifferent to present drugs in capsules or in tablets. With tablets, it is possible to reach prolonged action ; with hard gelatin capsules, a quicker liberation of poor water solution drugs cans in some cases be achieved.

ACKNOWLEDGMENTS

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