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ORAL SUSTAINED RELEASE DOSAGE FORMS
COMPARISON BETWEEN MATRICES AND RESERVOIR DEVICES

B. Huet de Barochez, F. Lapeyre, A. Cuiné

Ardix, 25, rue E. Vignat, F-45000 Orléans

Biopharmacie SERVIER

ABSTRACT

For the formulation of a monolithic controlled release form for oral use, containing 80 mg of a highly soluble drug, different systems have been compared.

At first, matrices where prepared containing 37.3 percent of a water soluble polymer : HPMC (Methocel or Metolose) and HEC (Natrosol). With such swelling agents, it is quite difficult to reach a zero order release. But industrial scale-up is easy, because the process uses only classical machines. Variations intra and between batches have beeen found very small and stability is good.

An other possibility is a lipophilic matrix. Hard gelatin capsules were filled with a drug dispersion in Gélucire of

different grades. The fabrication process is quite easy but at this time, few informations about stability are available.

A third convenient way is a reservoir device, a tablet coated with an insoluble polymer film (Aquacoat ECD 30). A zero order release was obtained until 80 percent of drug released after 12 hours. But the coating is a very critical phase of the process : disturbances affect the drug dissolution rate. The film may also be altered by the patient, who can break or crunch the tablet. In this case, all the drug is dissolved quasi instantaneously.

For all these reasons, the hydrophilic matrix was preferred, especially if a zero order is obtained.

INTRODUCTION

Sustained-release dosage forms are of great interest for the formulation of an oral drug containing an active ingredient with short half-live in plasma. They offer a way to reduce the number of administrations. Another interest is to avoid plasma peak concentration due to quick absorption.

The aim of the work described in this paper was to formulate an oral dosage form containing 80 mg of drug and releasing 80% of this drug in about 10 hours. Characteristics of the drug are summarized in table 1.

With such a drug, the frequency of administration of a classical form must be every 6 hours, in order to obtain constant plasma concentration during the treatment's period [1].

TABLE 1

Molecular weight	266.33 (base)
Solubility in water	more than 50% (w/v)
pH of an 1% solution in water	3.15
pKa	4 and 9
Partition coefficient of a 150 ng/ml solution in water at pH = 7.1	around 0.25
Half-live in human plasma	less than 6 hours.

This is drawn in figure 1. Curve 1 represents the plasma concentration of a drug administered every 6 hours, curve 2, what happens if the patient takes four tablets together and curve 3, the plasma concentration obtained with a sustained release dosage form containing the same quantity of drug as 4 tablets of conventional form and releasing 80% of drug in 20 hours. Theoretical representations are computerized according to the formulae proposed by Leeson and coll. [2].

Many classifications of sustained release dosage forms have been published. SEGOT-CHICQ et al. [3] propose a classification in four great classes (table 2). Many of these systems are not yet ready for easy industrial production. For this study, we restricted ourselves to formulations based on classical fabrication processes. By this way, choice was reduced to three forms : two matrices, one hydrophilic, the other lipophilic, and a reservoir device.

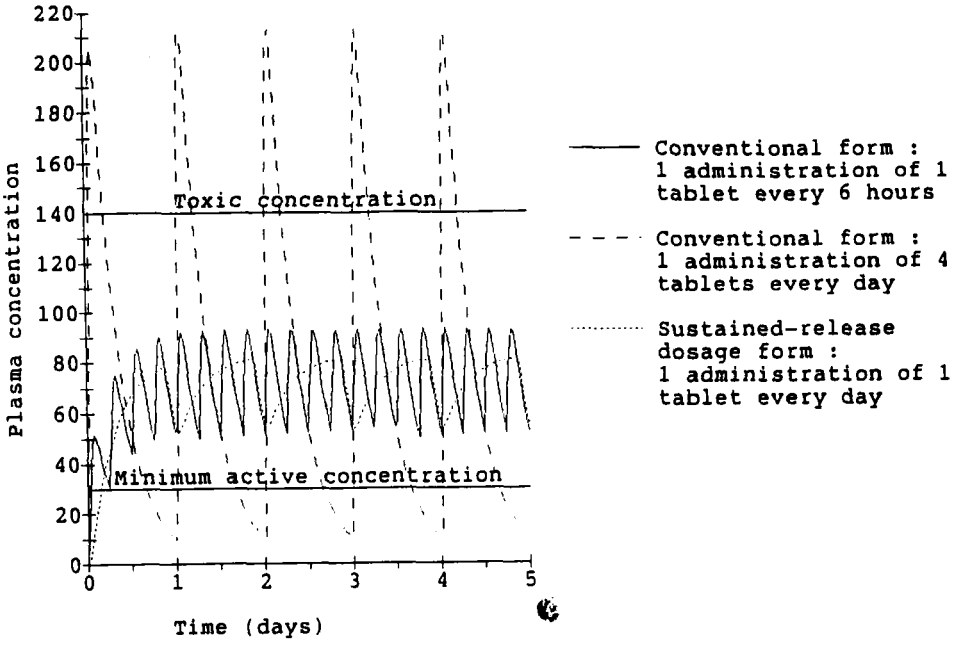

FIGURE 1

TABLE 2

1. Controlled diffusion systems
   - Reservoir devices
   - Matrices
2. Chimically controlled systems
   - Biodegradable systems
   - Systems with grafted chains
3. Solvent activated systems
   - Swelling systems
   - Systems controlled by osmotic pressure
4. Magnetic or ultrasonic waves activated systems

In the matrices, drug diffuses through the polymer, after swelling for hydrophilic matrices, diffusion being controlled by the tangling of the polymer's molecule. Diffusion through lipophilic matrices is controlled by the hydrophilicity of the polymer (assessed by the Hydrophile Lipophile Balance or H.L.B.). In reservoir devices thickness and porosity of the membrane control drug diffusion.

THE DIFFERENT CHOICES

Hydrophilic Matrix was choosen because of its well known production technology, by direct compression as well as by wet granulation. Many works have been done, and litterature on this subject is plentiful. Hydroxypropylmethylcellulose (HPMC) seems to be the most employed polymer, especially the qualities with nominal viscosity of 4,000 mPa.s (measured with a Brookfield viscosimeter on a 2 p.cent solution) [4,5,6].

Hard Gelatin Capsule Filled With Liquid Product is a quite new form of interest. Formulation of lipophilic matrices may be done with only the drug and a diluent. This excipient may be solid or semi-solid at room temperature [7].

Besides matrices, another way is a Reservoir Device. Its major advantage is to permit theoretically zero-order release [5,6]. Insoluble polymer films may be used for coating conventional tablets. These films may be organic solvent-based, but because of environmental regulations and necessity for using

special production facilities, aqueous dispersions have been developed, especially with acrylic polymers or ethylcellulose [8,9].

MATERIALS

The following ingredients were used for the preparation of hydrophilic matrices : calcium hydrogenophosphate (SPCI, F-La Plaine Saint Denis), polyvinylpyrrolidone (Luviscol K30, BASF, F-Levallois), hydroxypropylmethylcellulose (Methocel K4M and E4M CR, Colorcon, F-Bougival or Metolose 60SH4000 and 90SH4000 SEPPIC, F-Paris), hydroxyethylcellulose (Natrosol, Aqualon, F-Rueil-Malmaison), magnesium stearate (Stéarinerie Dubois, F-Paris) and colloidal silicon dioxid (Aerosil 200, Degussa, F-Neuilly sur Seine).

The same ingredients, except HPMC, were employed for tablets to be coated (reservoir devices). The coating film is composed of Aquacoat ECD 30, dibutylsebacate and hydroxypropylmethylcellulose (Pharmacoat 606), all supplied by SEPPIC.

Gattefossé Company (F-Saint Priest) produces a range of waxy polymers with various H.L.B. and melting points (Gélucire). The higher is the H.L.B., the higher is hydrophilicity. These products were employed for the lipophilic matrices.

FORMULATIONS

For the hydrophilic matrices, different grades of Methocel and Metolose may be supplied. Methocel 4M of types E and K are

TABLE 3

Drug	80.0 mg
Calcium hydrogenophosphate	92.0 mg
Hydroxypropylmethylcellulose or Hydroxyethylcellulose	112.0 mg
Polyvinylpyrrolidone	13.3 mg
Magnesium stearate	2.2 mg
Colloidal silicon dioxid	0.5 mg
Weight of tablet	300.0 mg

different by their hydratation speed, type K being the quickest. Metoloses SH4000 differentiate by their precipitation temperature. Grades 60 and 90 were used. Another polymer with nominal viscosity of 4,000 mPa.s was used : hydroxyethylcellulose, in order to observe possible modifications of the dissolution rate (table 3).

For the tablets to be coated (reservoir devices), the formula was the same for all trials (table 4).

Ethylcellulose dispersion was choosen for coating the tablets. Aquacoat ECD 30 is a ready-to-employ suspension containing 30% of ethylcellulose. Dibutylsebacate was used as a plasticizer. According to the manufacturer of Aquacoat (F.M.C.), dissolution rate can be controlled by the quantity of ethyl-cellulose sprayed on the tablet, and also by a percentage of a

TABLE 4

Drug	80.0 mg
Calcium hydrogenophosphate	80.0 mg
Polyvinylpyrrolidone	8.0 mg
Magnesium stearate	1.7 mg
Colloidal silicon dioxid	0.3 mg

Weight of tablet	170.0 mg

soluble polymer dispersed in the insoluble film. The soluble polymer choosen was low viscosity hydroxypropylmethylcellulose (6 mPa.s) : Pharmacoat 606. Quantities of Aquacoat used ranged from 4 to 10 percent of the total tablet weight. Quantities of Pharmacoat 606 ranged from 0.5 to 5 percent of dry matter in the final suspension. The quantity of dibutylsebacate was maintained constant : 20 percent of the quantity of Aquacoat.

The grades of Gélucire used for formulation of hard gelatin capsules (lipophilic matrices) were 50/02 and 50/13, in order to see the effect of H.L.B., and 62/05, in order to observe the effect of melting point on the dissolution rate. Trials were conducted with capsules of 2 different sizes (1 and 3) with different quantities of Gélucire (table 5).

TABLE 5

Drug	80.0 mg
Gélucire	140.0 or 320.0 mg, according to the capsule's size

METHODS

Preparation of Hydrophilic Matrices

6 kg batches were prepared to obtain 300 mg tablets containing 80 mg of drug. Calcium hydrogenophosphate was mixed during 5 min with drug and polyvinylpyrrolidone at 200 rpm in a high-speed-granulator dryer "Turbo-sphère" TS10 (Moritz, F-Chatou). The mixture was granulated at the same speed during 5 min, after addition of 220 ml of a 30/70 vol% water/alcohol solution. Drying was achieved at 60°C under vacuum with a rotation speed of 10 rpm. The product was sized with an oscillating granulator fitted with a 750/500 µm screen. The sized granulate had 2.0% loss on drying. The granulate was mixed for 10 min with HPMC or HEC in the 20 l barrel of a rotary mixer, then lubricants were added and mixed for 10 min in the same mixer. Compression was conducted on a MR12 rotary press (Frogerais, F-Ivry sur Seine) equipped with 9 mm diameter punches with a 7 mm bending radius. Compression force was about 700 daN in order to obtain tablets with a hardness of 8 daN. Production speed was 28,800 tablets.h-1.

Preparation Of Tablets For Coating

A 20 kg batch was prepared to obtain 170 mg tablets for coating. Calcium hydrogenophosphate, polyvinylpyrrolidone and drug were mixed during 10 min at 120 rpm in a high-speed-granulator dryer TS50. The mixture was granulated at the same speed during 5 min, after addition of 1410 ml of a 30/70 vol% water/alcohol solution. Drying was achieved at 60°C under vacuum with a rotation speed of 10 rpm. The product was sized with an oscillating granulator fitted with a 750/500 µm screen. The sized granulate had 1.9% loss on drying. Lubricants were admixed to the granulate in the 50 l barrel of a rotary mixer. Compression was conducted on a RLS15 rotary press (KILIAN, D-Köln) equipped with 7 mm diameter punches with a 5 mm bending radius. Compression force was about 400 daN in order to obtain tablets with a hardness of 7.5 daN. Production speed was 50,000 tablets.h-1.

Coating Of Tablets (Reservoir Devices)

Aquacoat was mixed with dibutylsebacate during 30 min with a magnetic stirrer. Pharmacoat 606 was dispersed in water with an electric stirrer during 30 min. The Pharmacoat solution was incorporated with the Aquacoat suspension and mixed for 30 min with the same magnetic stirrer. Coating of 3 kg tablets batches was achieved in a Driacoater 500 pan (DRIAM, D-Eriskirch). Pan

rotation speed was 14 rpm. After 15 min of preheating with 3 $m^3.h-1$ of air at 78°C, Aquacoat suspension was sprayed with a spray gun equipped with a 0.8 mm diameter nozzle, at the same speed and temperature.

Preparation of Lipophilic Matrices

First trials were processed with a little quantity of drug and various grades of Gélucire. Gélucire was melted with a heating magnetic stirrer and drug was dispersed in the liquid. Capsules were hand filled at the right weight, on a precise scale.

As a pilot production, 12,000 hard gelatin capsules were filled with a mixture of 80 mg of drug and 140 mg of Gélucire 50/02. Gélucire was melted at 55°C in the feeding hopper of a GKF400 capsules filling machine (Höflinger and Karg, D-Waiblingen). Then drug was dispersed in the melted Gélucire and stirred at 750 rpm during 45 min at 51-52°C. Capsules were filled at a production speed of 9,300 capsules.h-1.

Dissolution Test

Dissolution test was carried out using European Pharmacopoeia apparatus at a paddle speed of 100 rpm. The dissolution medium was 900 ml of hydrochloric acid 0.05 N (pH=1.6). Temperature was maintained at 37°C (± 0.5°C). Samples of 10 ml were automatically withdrawn, filtered and analysed by UV spectophotometry. 4 or 6

samples were analysed for each test to assess dispersion of the dissolution rate.

Non-dependence of the dissolution rate on the pH was verified with hydrophilic matrices : tests were conducted comparatively in variable pH dissolution medium and at pH=6.8.

For non-linear dissolutions, values were fitted with equation 1 using non-linear regression with RS/1 software (BBN Corporation, MA-Cambridge).

$$y = 100 \times (1-\exp(-k \times t)) \qquad \text{(eq.1)}$$

In case of linear dissolution, the dissolution follows equation 2.

$$y = k \times t \qquad \text{(eq. 2)}$$

y = percentage of drug released at time t

k = constant, characterizing the dissolution

t = time.

The t50 value was computerized with these equations (t50 represents the 50% drug released time).

RESULTS AND DISCUSSION

Hydrophilic Matrices

Dissolution rate does not show significant differences between Methocel E4M CR, Methocel K4M and Metolose 60SH4000 : respective t50 are 1.78h, 1.86h, and 1.75h. Dissolution speed is greater with Metolose 90SH4000 (t50=1.06h) (figure 2) and Natrosol (t50=1.18h) (figure 3). Standard deviations were very low on all tests (<2%).

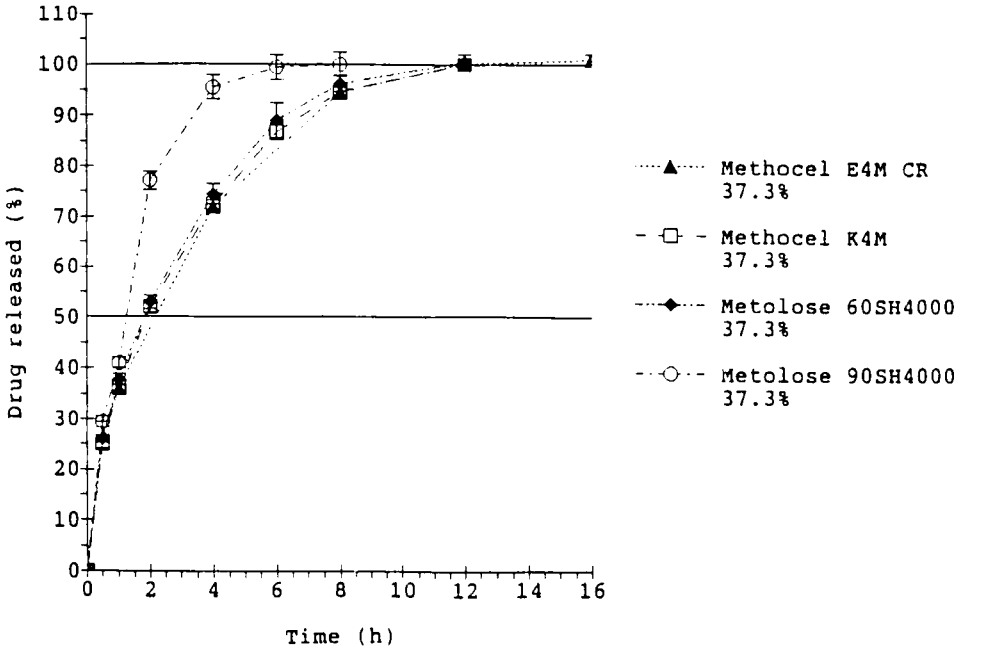

FIGURE 2

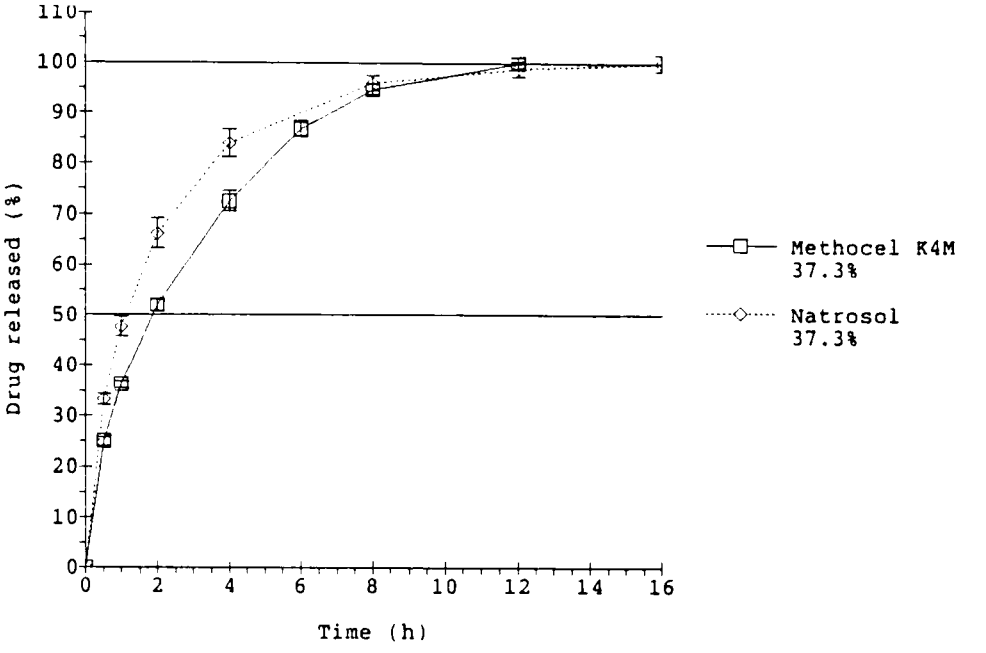

FIGURE 3

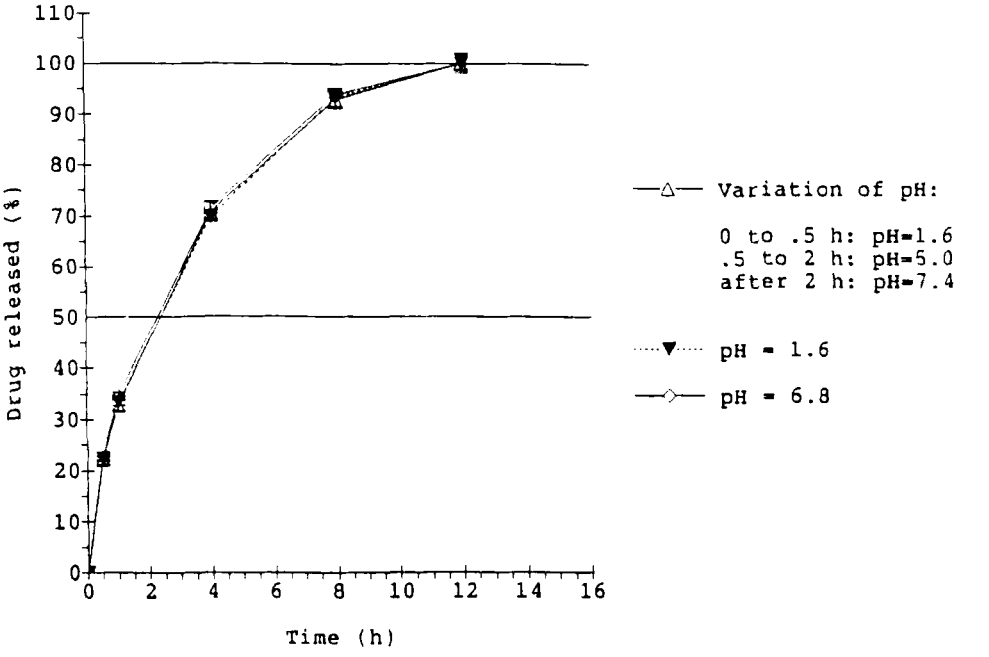

FIGURE 4

pH variation has no effect on dissolution rate of hydrophilic matrices (figure 4).

Lipophilic Matrices

Dissolution rate is lower with Gélucire 50/02 than with Gélucire 50/13 (figure 5). This may be explained by the higher hydrophilicity of Gélucire 50/13 which allows water to dissolve easily the drug. With Gélucire 62/05, the medium dissolution rate was expected to be intermediate between Gélucire 50/02 and Gélucire 50/13. The dissolution rate is lower, this may be due to the higher melting point.

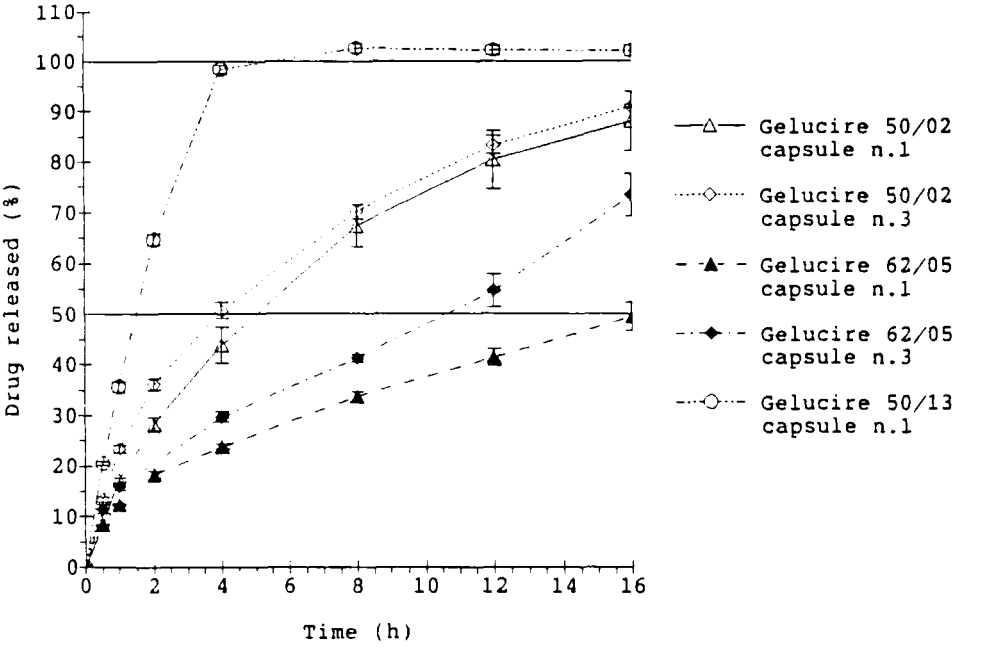

FIGURE 5

At 37°C, Gélucire 50/x are partially melted and dissolution rate may be increased. With a lower ratio of Gélucire, i.e. in capsules n.3, the dissolution rate is higher than in capsules n.1. The difference is greater with Gélucire 62/05 than with Gélucire 50/02. Standard deviations are slightly higher than with hydrophilic matrices, but still low (<6%).

Reservoir Devices

A first set of 5 experiments, build on a centered factorial design had been carried out to observe the variations of

TABLE 6

Experiment number	Aquacoat (%)	Pharmacoat (%)	t50 (h)
1	6	1	2.88
2	6	5	0.48
3	10	1	>16
4	10	5	1.81
5	8	3	2.73

dissolution rate with the quantities of Aquacoat and Pharmacoat (table 6).

Aquacoat decreases the dissolution rate and Pharmacoat increases it. Experiments number 1 and 5 are quite similar, but number 1 is preferred to number 5 because of the smaller quantities of raw material used. Standard deviations are very high (15-20%) for certain points (figure 6).

Three other formulations have been tried successively (table 7). These last three experiments are of great interest because dissolution profile tends to be linear for 10 hours. But standard deviations on experiment 7 are the higher measured during this study (figure 7).

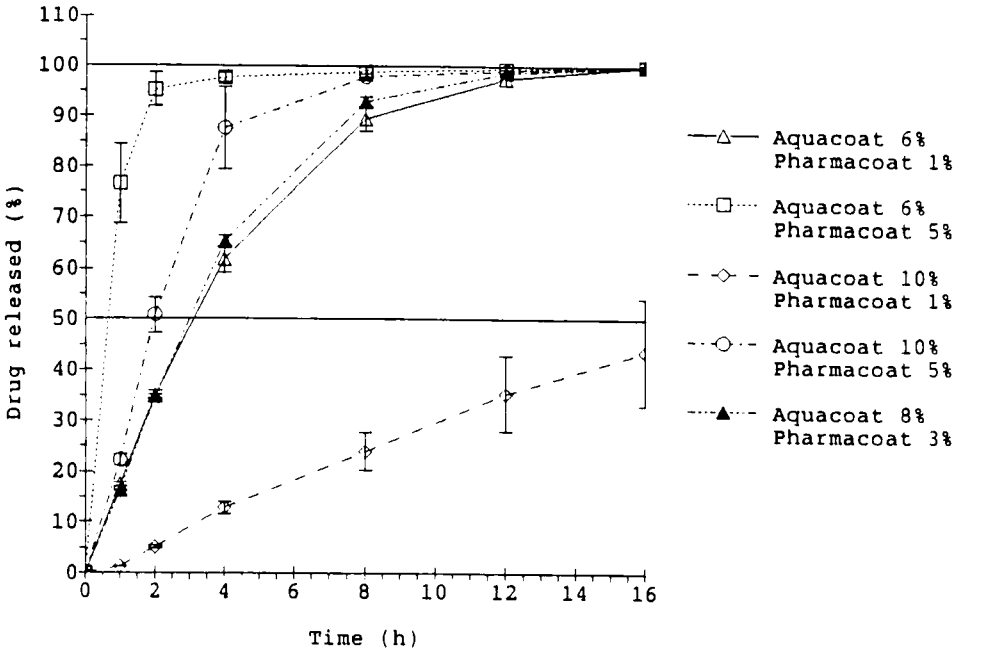

FIGURE 6

TABLE 7

Experiment number	Aquacoat (%)	Pharmacoat (%)	t50 (h)
6	6	0.5	>16
7	5	0.5	7.5
8	4	0.5	5.25

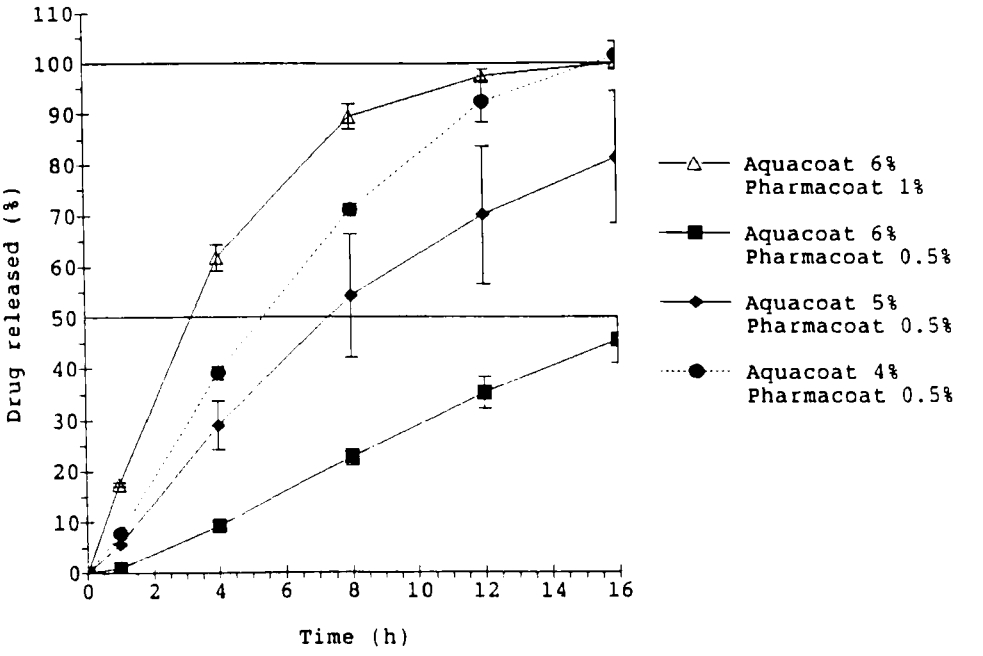

FIGURE 7

CONCLUSION

Hydrophilic matrix is a very interesting way to formulate oral sustained release dosage forms. Fabrication process is easy and does not require special production equipment. They are slight variations between different samples of a same batch and dissolution curves are easily reproductible, even with different polymers qualities : no difference has been found between Methocel K4M, Methocel E4M CR, and Metolose 60SH4000. Natrosol may be used, but dissolution rate is quicker than with HPMC.

Lipophilic matrix is a interesting alternative to hydrophilic matrix. But fabrication process for big batches is a little more critical than for classical tablets : for example, temperature has to be rigorously controlled to avoid sedimentation of drug in capsules.

The only advantage found to reservoir device is the possibility to obtain in vitro zero order release. But for some formulations, there were great variations between different samples of a same batch. This is a bad point when a rigorous dissolution profile is searched for.

Finally, hydrophilic matrix seems to be a good choice for formulation of an oral sustained release dosage form.

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