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INFLUENCE OF DRUG SOLUBILITY IN THE FORMULATION OF HYDROPHILIC MATRICES

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INTRODUCTION

Sustained release dosage forms are a convenient mean to obtain a reduction of daily administrations of drugs with fast absorption and/or elimination. By this way, observance for the treatment may be increased. In this study three different drugs are compared : one is slightly water soluble, and two are highly water soluble (table 1). Production of hydrophilic matrices is a well known technology, by direct compression as well as by wet granulation [1, 2]. A lot of research have been done and literature on this subject is plentiful. Different polymers may be used to control the diffusion of the drug across the tangle. Among them, hydroxypropylmethylcellulose (HPMC) seems to be the most employed. [3, 4, 5].

TABLE 1

	DRUG A	DRUG B	DRUG C
Sol. in water	about 0.5%	> 50%	> 50%
pKa	-	4.0, 9.0	8
Half-live (plasma)	12 h	< 6 h	< 8 h

MATERIALS

The following ingredients were used for the preparation of hydrophilic matrices : calcium hydrogenophosphate dihydrate, (SPCI, F-La Plaine Saint Denis), calcium hydrogenophosphate for direct compression (Emcompress, SPCI), lactose 150 Mesh (Sucre de Lait, F-Sains-du-Nord), lactose Fast Flo (SEPPIC, F-Paris), polyvinylpyrrolidone (PVP) (Luviscol K30, BASF, F-Levallois), HPMC (Methocel K4M and E4M CR, Colorcon, F-Bougival or Metolose 60SH4000 and 90SH4000 SEPPIC), hydroxyethylcellulose (HEC) (Natrosol, Aqualon, F-Rueil-Malmaison), magnesium stearate (Stéarinerie Dubois, F-Paris) and colloidal silicon dioxid (Aerosil 200, Degussa, F-Neuilly sur Seine).

Different grades of Methocel and Metolose may be supplied, with nominal viscosity of 4,000 mPa.s (measured with a Brookfield

TABLE 2

	Formulas (mg)				
	1	2	3	4	5
DRUG A	3.0	3.0	3.0	3.0	3.0
HPMC	40.0	50.0	60.0	70.0	82.0
Fast Flo Lactose	42.6	42.6	42.6	42.6	42.6
Emcompress	71.0	71.0	71.0	71.0	71.0
Aerosil 200	0.4	0.4	0.4	0.4	0.4
Magnesium stearate	1.0	1.0	1.0	1.0	1.0

viscosimeter on a 2 p.cent solution). Methocel 4M of types E and K are different in their hydratation speed, type K being the quickest. Metoloses SH4000 differ in their precipitation temperature. Grades 60 and 90 were used. Another polymer of 4,000 mPa.s viscosity was used : hydroxyethylcellulose, in order to observe possible modifications of the dissolution rate.

FORMULATION, PREPARATION AND TESTS

Drug A

With drug A, HPMC was used at different concentrations, from 25.3% to 41.0% (Table 2). Five 1 kg batches were prepared using direct

TABLE 3

	Formulas (mg)	
	6	7
DRUG A	2.5	2.5
Lactose	114.9	-
Calcium hydrogenophosphate	-	114.9
PVP	6.2	6.2
HPMC	74.0	74.0
Aerosil 200	0.4	0.4
Magnesium stearate	2.0	2.0

compression. Lactose and Emcompress were mixed together, using a rotary mixer, then drug was incorporated in three premixings. HPMC was mixed with Aerosil 200 in the same mixer, blended with the first mix, mixed and lubricated with magnesium stearate. Compression was conducted on a MR12 rotary press (Frogerais, F-Ivry sur Seine) equipped with 7 mm diameter punches with a 5 mm bending radius. Compression force was adjusted to obtain tablets with a hardness of about 7 daN.

Two batches were prepared by wet granulation, one with lactose as a diluent (table 3), the other with calcium hydrogenophosphate. Diluent, drug and PVP were mixed together 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 a 30/70 vol% water/alcohol solution. After drying (60°C under vacuum), the product was sized with an oscillating granulator, blended with HPMC in a rotary mixer, then lubricated with Aerosil and magnesium stearate in the same mixer. Compression was conducted on a rotary press (MR12) equipped with 8 mm diameter punches with a 7 mm bending radius.

A third batch was prepared with formula number 6, using a planetary mixer for the granulation. It was dried in a ventilated oven.

Drug B

Formulas are described in table 4. 6 kg batches of formulas 8 to 13 were prepared. Calcium hydrogenophosphate was mixed during 5 min with drug and PVP at 200 rpm in a Moritz TS10. The mixture was granulated at the same speed during 5 min, after addition of a 30/70 vol% water/alcohol solution. After drying (60°C under vacuum) product was sized with an oscillating granulator, blended for 10 min with HPMC or HEC in a rotary mixer, then lubricants were added and mixed for 10 min in the same mixer. Compression was conducted on a rotary press (MR12).

Drug C

Formulations are described in table 5. Mixing and granulation were done in a planetary mixer. After drying (60°C in a

TABLE 4

	Formulas (mg)					
	8	9	10	11	12	13
DRUG B	80.00	40.00	40.00	40.00	80.00	80.00
Calcium hydrogeno-phosphate	92.00	46.00	46.00	112.00	92.00	221.00
PVP	13.30	6.65	6.65	13.30	13.30	16.20
HPMC	112.00	56.00	115.45	112.00	-	325.00
HEC	-	-	-	-	112.00	-
Aerosil 200	0.50	0.25	0.40	0.50	0.50	1.30
Magnesium stearate	2.20	1.10	1.50	2.20	2.20	6.50
Total	300.00	150.00	210.00	280.00	300.00	650.00
Punch Ø (mm)	9	7	8	9	9	12.5
Bending radius (mm)	7	5	7	7	7	11

TABLE 5

	Formulas (mg)		
	14	15	16
DRUG C	100.0	100.0	100.0
Calcium hydrogenophosphate	72.0	72.0	72.0
PVP	13.3	13.3	13.3
HPMC	112.0	161.5	211.0
Aerosil 200	0.5	0.6	0.7
Magnesium stearate	2.2	2.6	3.0
Total	300.0	350.0	400.0

ventilated oven), the granulates were sized with an oscillating granulator, blended with HPMC and lubricants and compressed in order to obtain tablets of about 6 daN.

Dissolution Test

The dissolution test was carried out using the 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. A study was conducted to assess the dependency of the dissolution rate on the pH :tests were conducted comparatively at pH = 2, 5 and 7.4 with drug A and at pH = 1.6 and 6.8 with drug B.

For non-linear dissolutions, values were fitted with equation 1 using non-linear regression with RS/1 software (BBN Software Product 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 calculated with these equations (t50 represents the 50% drug released time).

RESULTS AND DISCUSSION

DRUG A

Using direct compression, dissolution rate is relatively dependent of the amount of HPMC. t50 varies from 4.75 h with 29.8% of HPMC

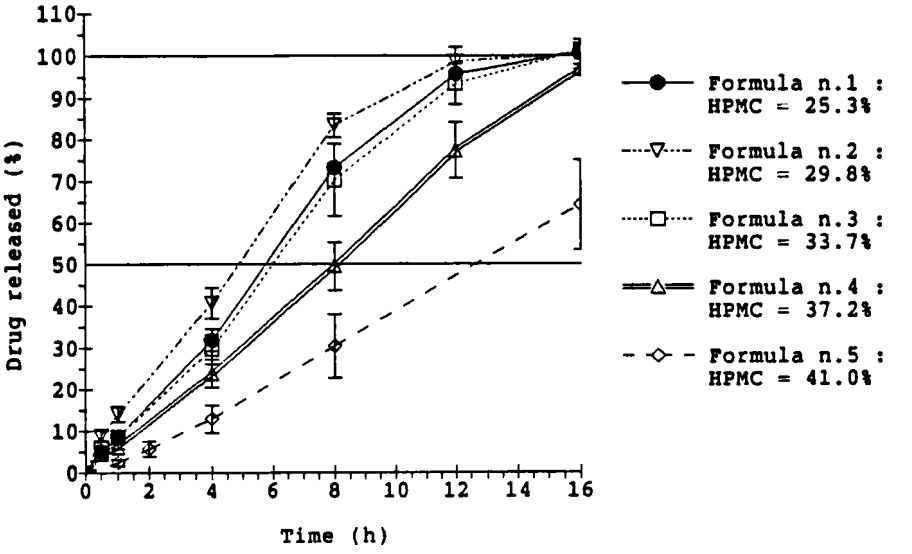

FIGURE 1

to 12.25 h with 41.0% (figure 1). Dissolution rate follows zero-order release from 0 to 70 per cent. In this case, dissolution is limited by the solubility of the drug in the matrix.

Dissolution rate is very dependent on pH variations : with formula 5 (41.0% of HPMC), t50 increases from 10.0 h (pH = 2.0) to 22.2 h (pH = 7.4) (figure 2).

When tablets are prepared by wet granulation, the standard deviation of dissolution rates seems to be dependent on the grain size distribution (figure 3). Mean diameters of batches prepared with Moritz TS10 are 166 µm (formula 6) and 152 µm (formula 7). Repartition is unimodal, centered around the mean diameter (80% between 90 and 250 µm). For the granulate prepared with a

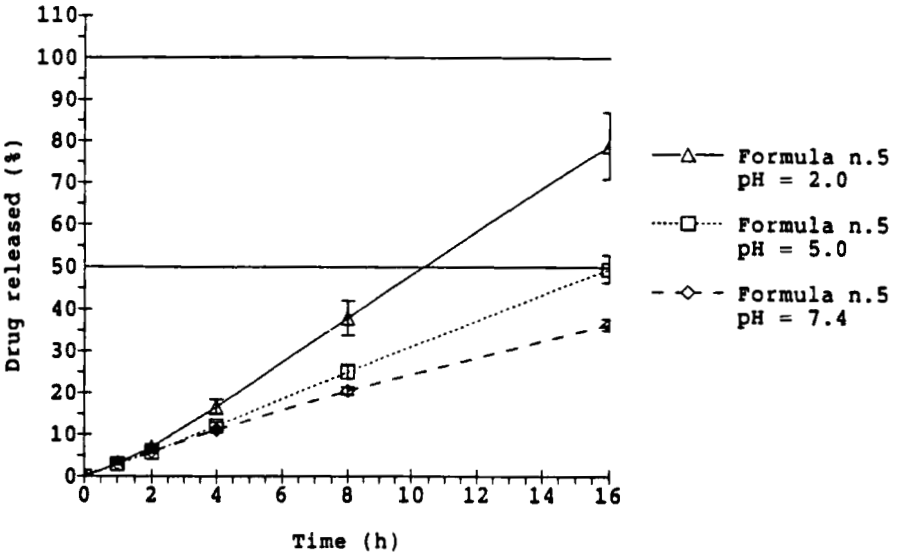

FIGURE 2

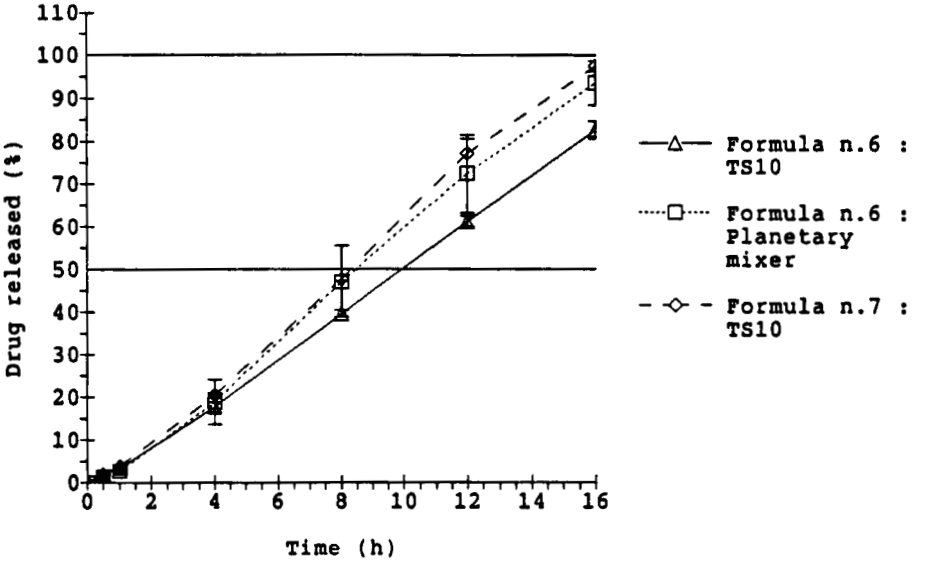

FIGURE 3

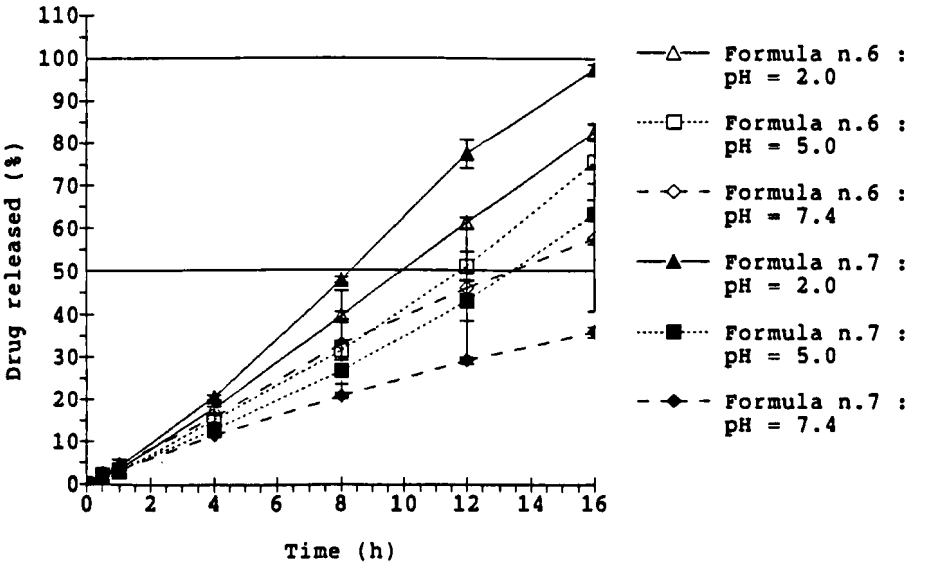

FIGURE 4

planetary mixer, mean diameter is 326 µm and distribution is wider (80% between 180 and 500 µm).

If calcium hydrogenophosphate is the only diluent, dissolution rate is more dependent on pH variations (figure 4) than with lactose : t50 increase from 8.0 h (pH = 2.0) to 22.1 h (pH =7.4) with calcium hydrogenophosphate, and from 9.7 h (pH = 2.0) to 13.7 h (pH =7.4) with lactose.

DRUG B

Dissolution rate does not show significant differences between Methocel E4M CR, Methocel K4M and Metolose 60SH4000 (formula 8) :

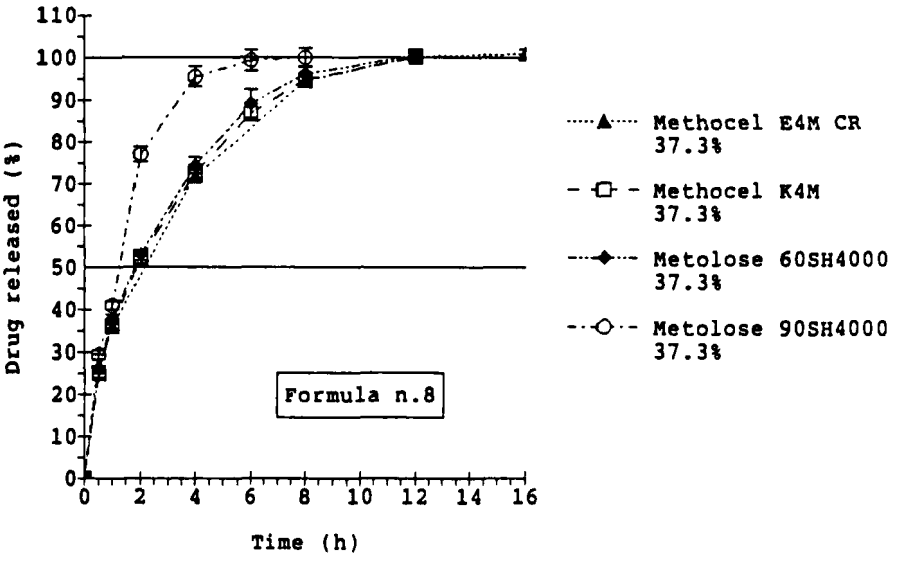

FIGURE 5

respective t50 values are 1.78h, 1.86h, and 1.75h. Dissolution speed is higher with Metolose 90SH4000 (t50=1.06h) (figure 5) and Natrosol (formula 12 : t50=1.18h) (figure 6). Standard deviations are very low in all tests (<2%).

pH variation has no effect on dissolution rate (figure 7).

If a same formula is compressed to obtain a reduction by half of the weight (formula 9 vs formula 8), dissolution rate increases (t50=1.78 h for formula 8, t50=1.15 h for formula 9). There are two ways to reduce this dissolution rate : increasing the amount of HPMC by about 100% (formula 10, t50=1.46 h), but with such an augmentation, dissolution rate does not increase very much, and

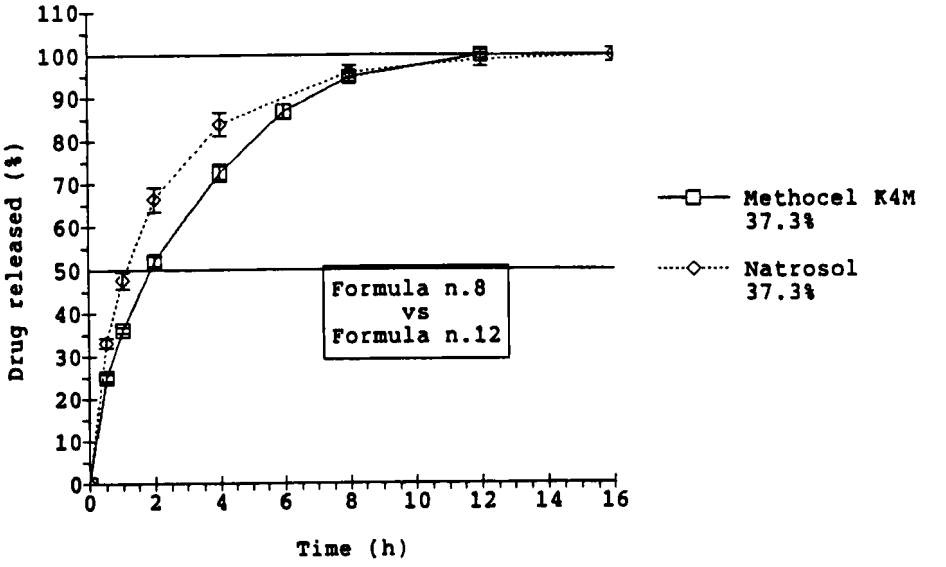

FIGURE 6

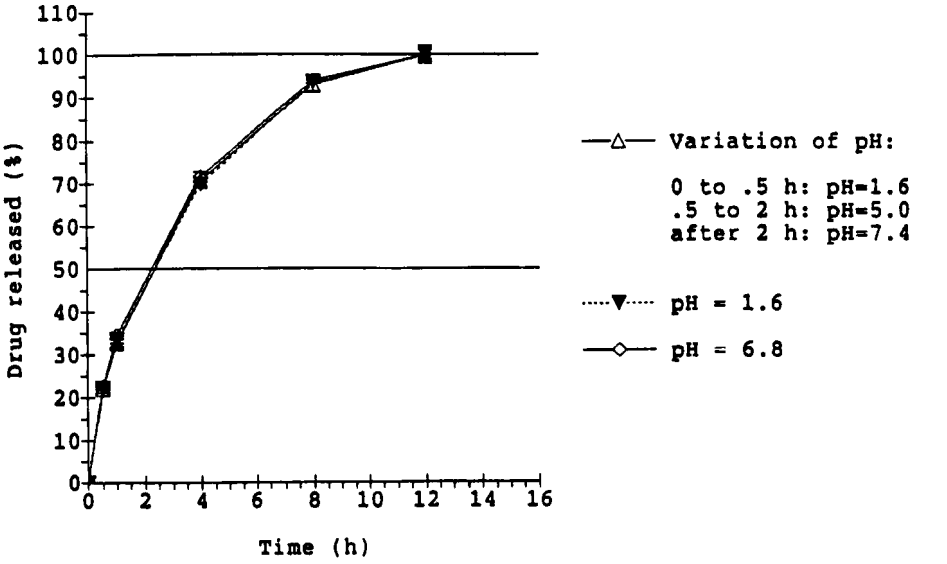

FIGURE 7

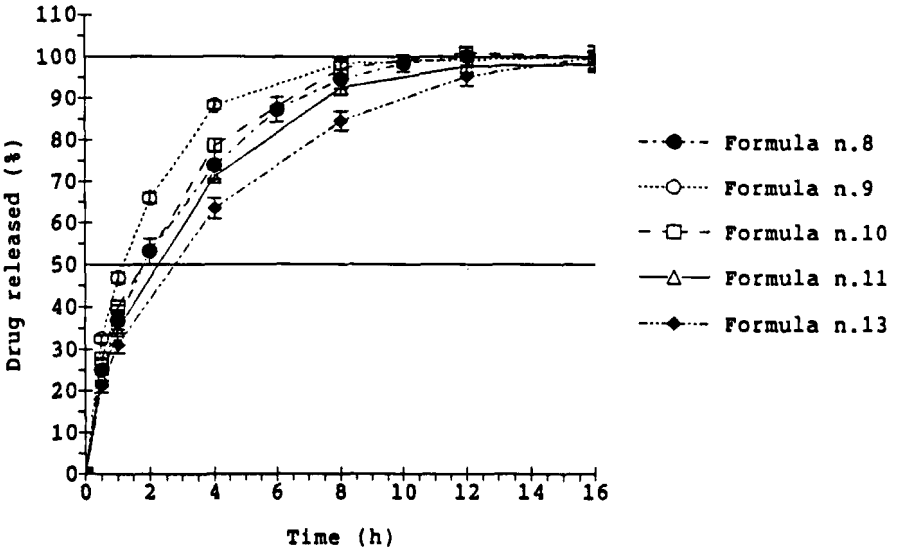

FIGURE 8

compression is more difficult, or increasing the amount of calcium hydrogenophosphate in the granulate, before addition of HPMC and lubricants (formula 11, t50=1.93 h).

If the quantity of HPMC is increased by about 300% (formula 13), the quantity of calcium hydrogenophosphate must be augmented to obtain a compressible granulate. In this case, dissolution is only slightly reduced (t50=2.50 h, figure 8).

DRUG C

The physical characteristics of this drugs are similar to those of drug B, dissolution rates are also similar with the same quantity

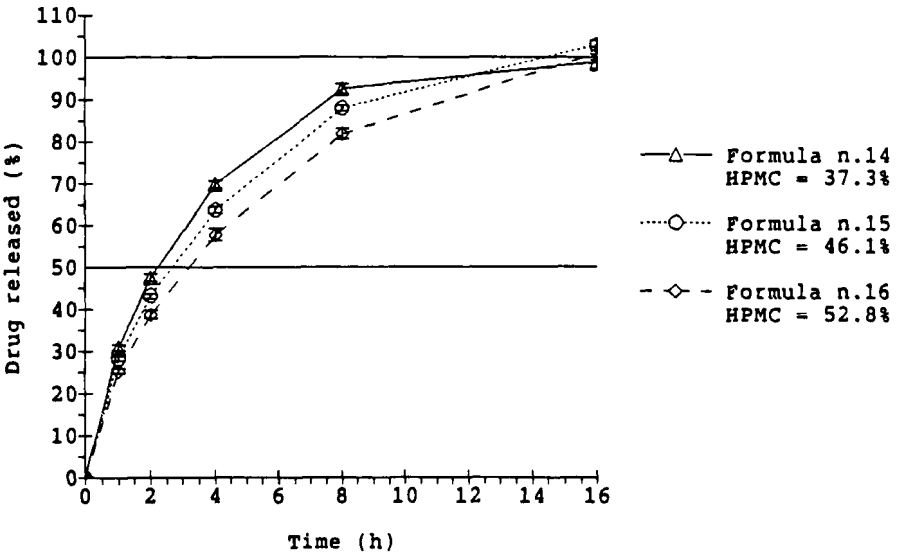

FIGURE 9

of HMPC (formula 14 : t50=2.16 h). When the amount of HPMC is increased, dissolution rate decreased, but slowly (figure 9).

CONCLUSION

Formulation of hydrophilic matrices with release time longer than 8 hours is difficult with drug B and C, due to the high solubility of the substances. Contrary to what is possible with slightly soluble drug (e.g. A), zero-order release cannot be obtained by classical means. But, in this case, dissolution rate is more sensitive to quantities of hydrophilic polymer present, fabrication process, nature of the diluent and/or pH variations in the dissolution medium.

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