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EVALUATION OF SPRAY-DRYING AS A METHOD TO PREPARE MICROPARTICLES FOR CONTROLLED DRUG RELEASE

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ABSTRACT

The possibility to obtain microcapsules or microspheres for controlled release by spray-drying is evaluated. Drugs of different solubilities like theophylline and sodium sulfamethazine, with Eudragit RS as coating polymer, are chosen.
The polymer is used, either dissolved in an hydroalcoholic solution or suspended (pseudolatex) in water, in different weight ratios with the drug. The obtained solution or suspension is spray-dried.
Scanning electron microscope analysis of the powders reveals no sign of microencapsulation. Moreover, only a fraction of the particles has a spherical shape.
For each spray-dried powder, a part of the obtained particles is compressed into tablets, and the rest is stored.
Dissolution studies in distilled water at 37 C are performed on powders and tablets.

While the uncompressed microparticles do not give any controlled release, the tablets show an ability in slowing down drug delivery greater than the one obtained with the traditional methods.

INTRODUCTION

Spray-drying is a technique widely used in the pharmaceutical field to dry materials sensible to heat, to improve the drug solubility or the flowability of particular excipients, and several other applications[1,2].

Recently this technique has received considerable interest as a microincapsulation process to obtain a controlled delivery system. The method may offer, in comparison with the usual coating techniques, the advantage of realizing the microencapsulation process in one step.

Cellulose derivatives (such as cellulose acetate phthalate[2,3] ,sodium carboxymethyl cellulose[4,6], hydroxypropyl methyl cellulose[5,7], methylcellulose and hydroxypropyl methylcellulose acetate succinate[6]), biodegradable polymers (such as poly(±)lactide[7,8] and polylactide-co-glycolide[8]), polyacrylic acid[4] and methacrylic polymers (such as Eudragit L 100-55, Eudragit L 30D and Eudragit NE 30D[9]) have been used to obtain microcapsules by spray-drying. Anyway, sometimes it is not clear if the obtained particles are microcapsules, microspheres or just simple microparticles[5,6]. Besides, the practical experiments are generally carried out with laboratory minispray-dryers, without considering the final powder yield of the process and without taking into account a possible industrial application of the method.

The aim of this work is to verify if by spray-drying it is possible to obtain an effective encapsulation using a pilot spray-dryer. So, Eudragit RS in hydroalcoholic solution or in water suspension (Eudragit RS 30D pseudolatex) is spray-dried, with or without plasticizer, respectively with theophylline or sodium sulphamethazine.

Eudragit RS is chosen among the various Eudragits because of its very low water permeability which enables this polymer to be employed for controlled release systems.

Theophylline and sulfamethazine are chosen as model drug for their different water solubility: respectively 1/120 and 1/2 part of water[10].

The spray-dried powders are compressed into tablets and the dissolution studies are performed on either the powders or the tablets. Tablets are also prepared by direct compression with Eudragit RS PO, and with the solid dispersion powders previously prepared from an Eudragit RS-theophylline solution; by comparing these tablets with the others firstly described, the

real necessity of the spray-drying process can be verified. Besides, the influence of the drug solubility, the hardness of the tablets, the different ratio between polymer and drug in the formulation, and the presence of the plasticizer, on the rate of drug release, is pointed out.

MATERIALS

Eudragit RS PO and Eudragit RS 30D: Röhm Pharma (Germany).
Dibuthyl phthalate (plasticizer): Interchimie (France).
Anhydrous theophylline: Boehringer Ingelheim (Germany).
Sodium sulfamethazine: I.V.F.C. (France).
The spray-drying process is carried out with a Niro Atomizer (Denmark).
The dissolution studies are performed in distilled water at 37 C with a Prolabo Dissolutest (France), a UV-2101 PC scanning spectrophotometer Shimadzu (Japan) connected to a 486 DX 60 mhz computer.
The scanning electron microscopy is performed with a Jeol microscope (Japan).
The tablets are made with a Korsch EK0 press (Germany).

METHODS

The weight ratios polymer-theophylline 3:1, 2:1, 1:1, 1:2, are considered for preparing the following samples.

1) Eudragit RS-theophylline

Eudragit RS is dissolved, with or without the 20% of dibuthyl phthalate (calculated on the dry weight of polymer) as plasticizer, in a volume of ethanol necessary to obtain a final polymer concentration of 1,5% w/v, and theophylline is dissolved in water with the 1% ammonium hydroxide; after this the solutions are mixed together to give a unique 71% v/v ethanol solution, which is spray-dried with a centrifugal wheel under the following conditions: inlet temperature 110 C, outlet temperature 75 C, feed rate 15 ml/min. and pressure 6 kg/cm^2.

2) Eudragit RS 30D-theophylline

The theophylline is first dissolved in a volume of water, containing the 1% of ammonium hydroxide, necessary to dilute the Eudragit pseudolatex to a

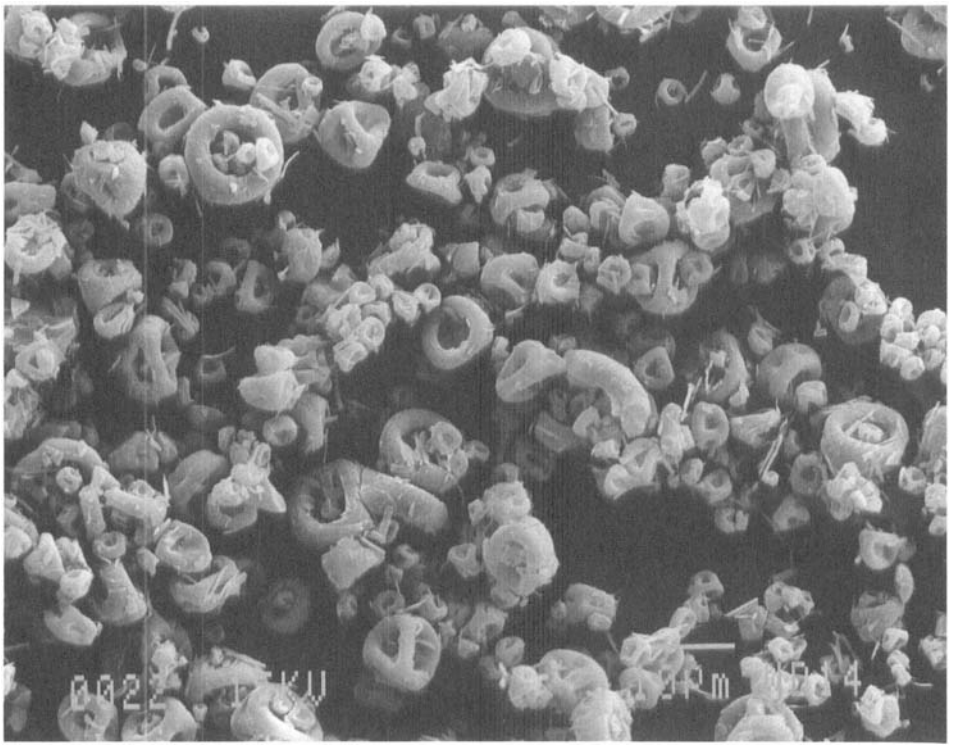

FIGURE 1 A
Powder from the hydroalcoholic solution.
Formulation without plasticizer (S.E.M. x 1000).

polymer concentration of 1,5% w/v; then, when used, the plasticizer is emulsified, and finally the Eudragit is joint. The suspension is next spray-dried with a centrifugal wheel under the following conditions: inlet temperature 120°C, outlet temperature 75°C, feed rate 15 ml/min. and pressure 6 kg/cm^2. During the spray-drying process, the suspension is continuously stirred.

3) Eudragit RS-sulfamethazine

Eudragit RS is dissolved in a volume of ethanol necessary to obtain a final polymer concentration of 1,5% w/v, and sulfamethazine is dissolved in water. After this, the solutions are mixed together to give a 71% v/v ethanol solution, which is spray-dried with a centrifugal wheel under the following

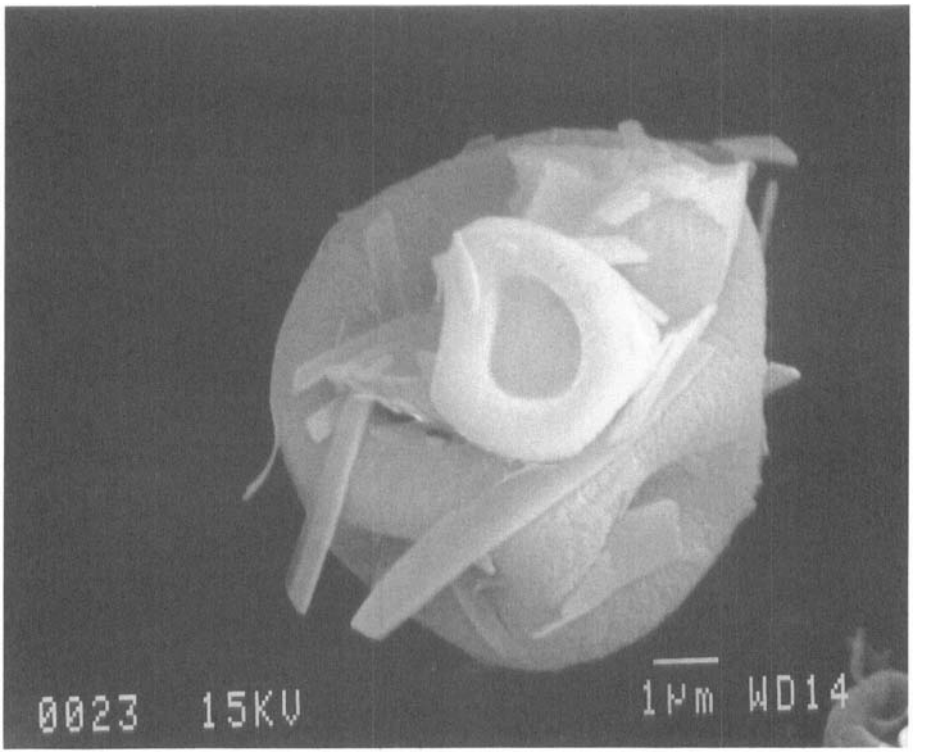

FIGURE 1 B
Powder from the hydroalcoholic solution.
Formulation without plasticizer (S.E.M. x 7500).

conditions: inlet temperature 110°C, outlet temperature 75°C, feed rate 15 ml/min. and pressure 6 kg/cm².

4) Eudragit RS-theophylline solid dispersions

Eudragit is dissolved in a volume of ethanol necessary to obtain a final polymer concentration of 1,5% w/v, and theophyllyne is dissolved in water with the 1% of ammonium hydroxide; after this, the solutions are mixed together to give a unique 71% v/v ethanol solution, which is evaporated under vacuum at 50°C.

5) Eudragit RS-theophylline direct compression

Eudragit RS PO and theophylline are directly compressed into tablets. The weight of each tablet is 450 mg, the hardness 8 kg/cm², the theophylline

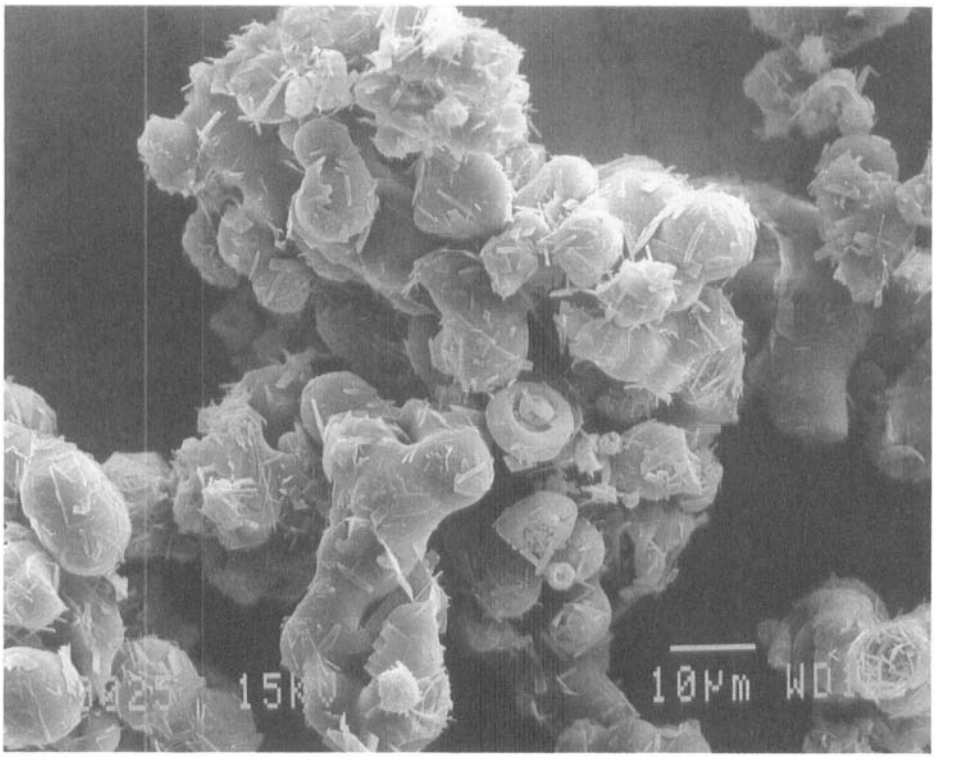

FIGURE 2 A
Powder from the hydroalcoholic solution.
Formulation with plasticizer (S.E.M. x 1000).

content 75 mg; avicel PH 101 is the filler used, and 1% magnesium stearate the lubricant.

6) Compression of spray-dried or solid dispersion powders

Each different powder is mixed with the necessary amount of avicel PH 101 and 1% magnesium stearate and compressed to have tablets of 450 mg and a theophylline content of 75 mg. For every polymer-theophylline ratio, the tablets are made in three different hardnesses: 4, 8, 12 kg/cm^2.

7) UV dosage of powders and tablets

The content and uniformity of the theophylline in the powders and tablets are controlled spectrophotometrically in ethanol at 288 nm.

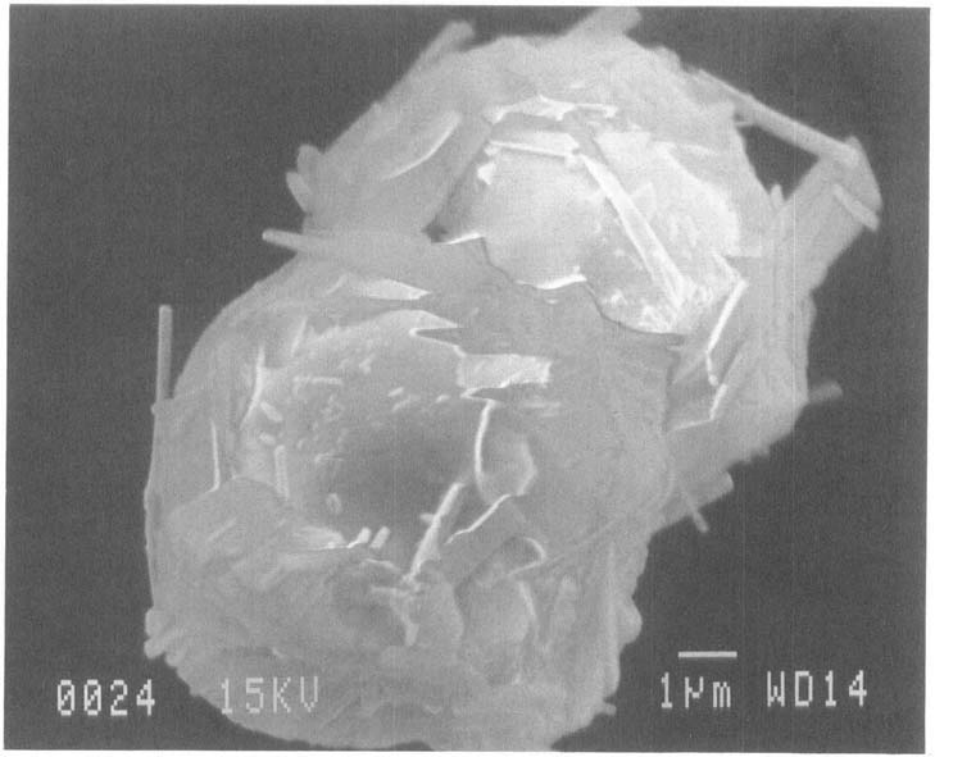

FIGURE 2 B
Powder from the hydroalcoholic solutions.
formulation with plasticizer (S.E.M. x 7000).

RESULTS AND DISCUSSION

1) Spray-drying process

Under the described operating conditions, it is possible to minimize the adhesion of the spray-dried powders onto the spray-dryer walls; so, the great drawback of the process, due to the presence of the polymer, can be avoided. In fact, for the formulations without plasticizer, nearly the 90% of the initial powder is collected in the final container. On the other hand, for the formulations including the plasticizer, the yield of powder is only the 25% and the tendency to stick can't be avoided. The use of additives, as talc or colloidal silica, which could reduce these unpleasant phenomena, has been voluntarily avoided because they affect the characteristics of the

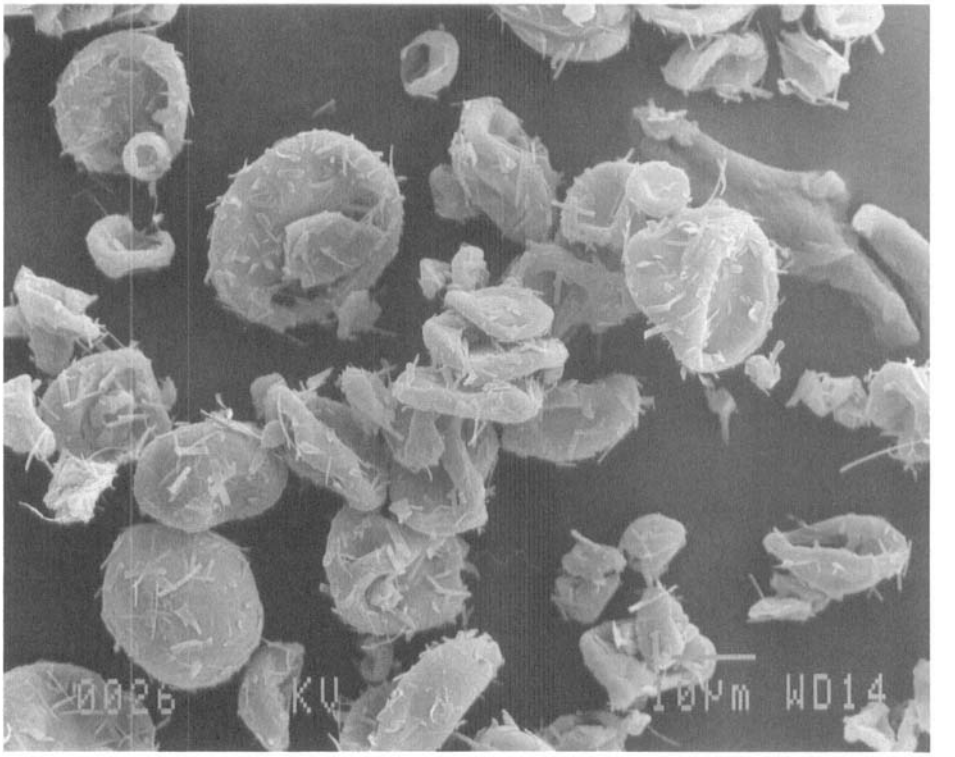

FIGURE 3 A
Powder from the aqueous Eudragit suspension.
Formulation without plasticizer (S.E.M. x 1000).

spray-dried particles and so, evaluating the effect of other parameters becomes more difficult.

2) Scanning electron microscope

Scanning electron microscope analysis of the spray-dried products gives some basic information (figure 1, 2, 3, 4, 5 and 6). Microparticles derived from the hydroalcoholic solutions present differences according to the presence or not of the plasticizer: without the plasticizer (figure 1A and 1B), the smallest particles with a mean size of 3µm are obtained, but we are in presence of rings instead of spheres; with the plasticizer (figure 2A and 2B), the particles are spherical with a mean size of 10µm, but these particles are not well separated from each other.

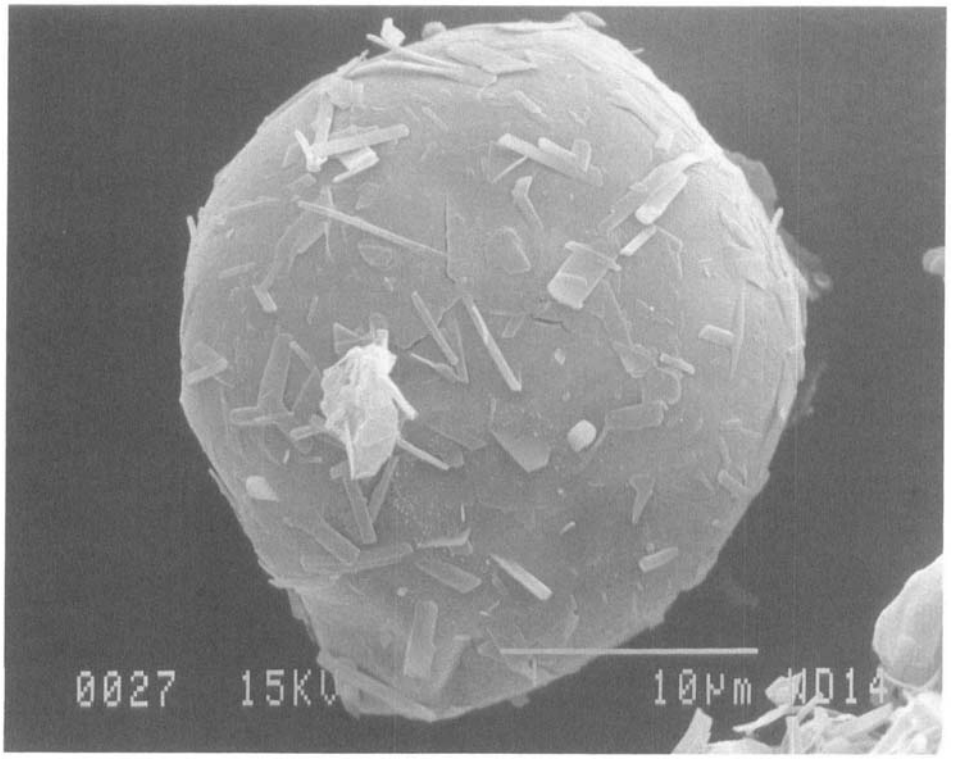

FIGURE 3 B
Powder from the aqueous Eudragit suspension.
Formulation without plasticizer (S.E.M. x 3000).

For microparticles derived from aqueous Eudragit suspensions, according to the presence or not of the plasticizer, differences are also observed: without the plasticizer (figure 3A and 3B), a mixture of rings and spherical particles with a mean size of 11µm is obtained; with the plasticizer (figure 4A and 4B), the spray-dried product is characterized by rings and holed particles with a mean size of 5µm. These particles are not well separated from each other and are covered all around with small sticks.

All these described powders are obtained with a w/w ratio polymer/theophylline of 3:1.

The powders with ratio 1:1, showed in figures 5 and 6, confirm that no changes in dimension are detectable changing the proportion of polymer or drug, and prove that the sticks present on the surface of the particles are

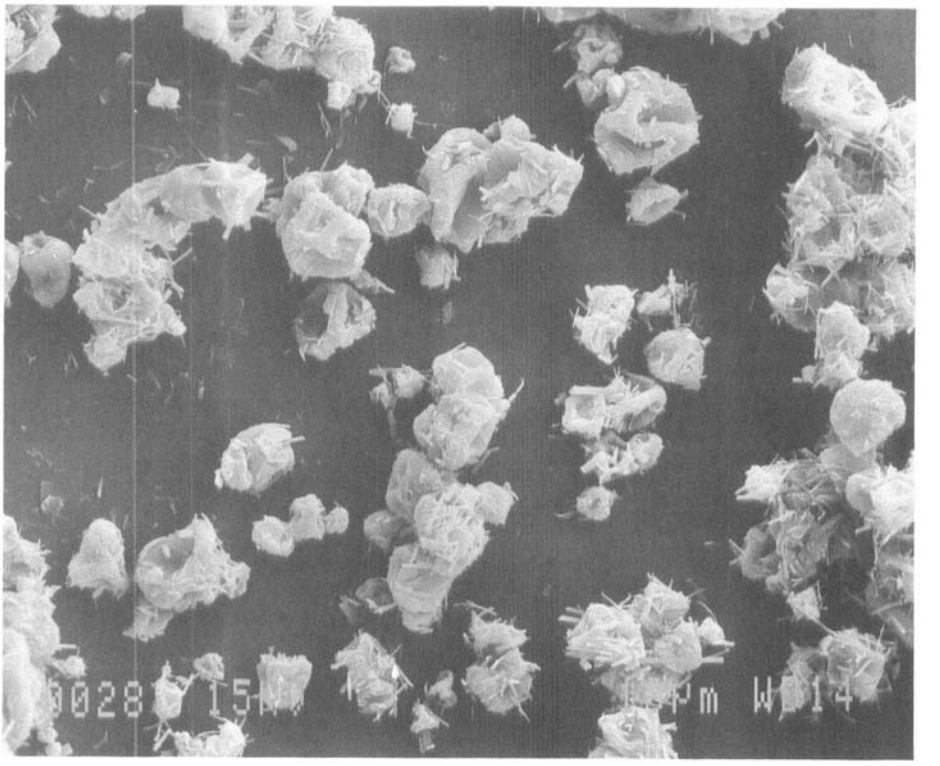

FIGURE 4 A
Powder from the aqueous Eudragit suspension.
Formulation with plasticizer (S.E.M. x 1000).

composed of theophylline, because increasing the amount of drug in the formulation, the quantity of sticks covering the particles is increased too. Figures 5A and 5B show the microparticles of ratio 1:1 derived from hydroalcoholic solutions without plasticizer; figures 6A and 6B show the microparticles of ratio 1:1 derived from aqueous Eudragit suspensions with plasticizer.

Finally, there is no detectable sign of the presumable tendency of the polymer to surround the drug core in order to give a microencapsulation process; the microparticles look like microspheres or irregular shaped particles rather than microcapsules.

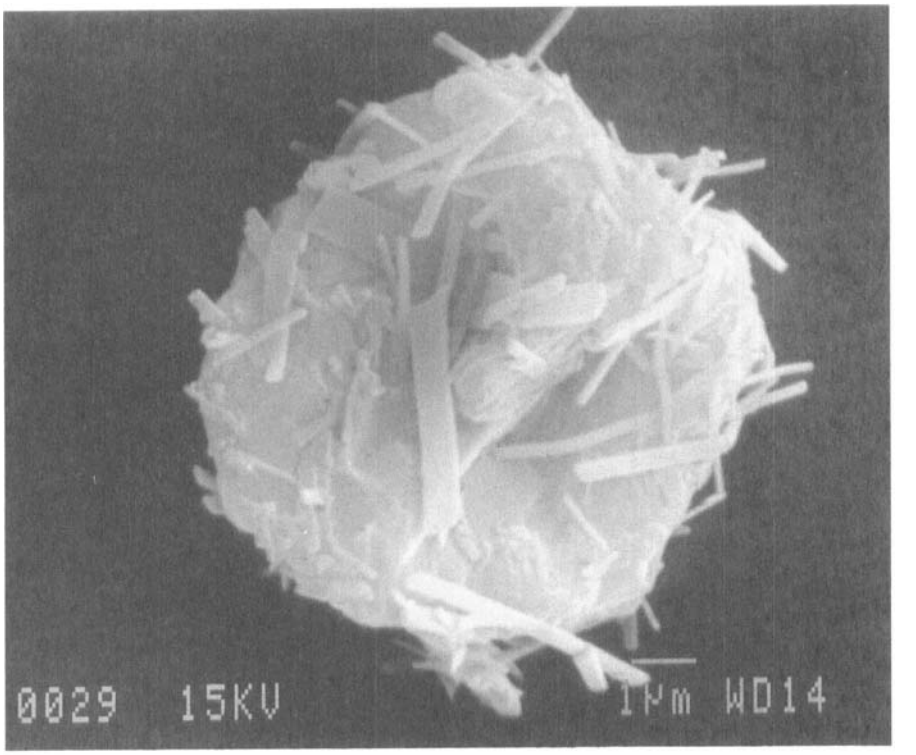

FIGURE 4 B
Powder from the aqueous Eudragit suspension.
Formulation with plasticizer (S.E.M. x 7500).

3) Dissolution studies of the spray-dried powders

Every powder releases immediately the drug, even when the polymer-theophylline ratio is 3:1. This complete ineffectiveness in controlling drug release is probably due to the wide release surface (as the particles are very small) and to the high porosity of the very light powder. This a rather clear confirmation to the weakness of spray-drying as a microincapsulation process when the drug is dissolved in the solvent.

4) Dissolution studies of the tablets

Figures 7 and 8 show the theophylline release curves of the tablets derived from the compression of Eudragit RS microparticles respectively obtained in absence or in presence of the plasticizer.

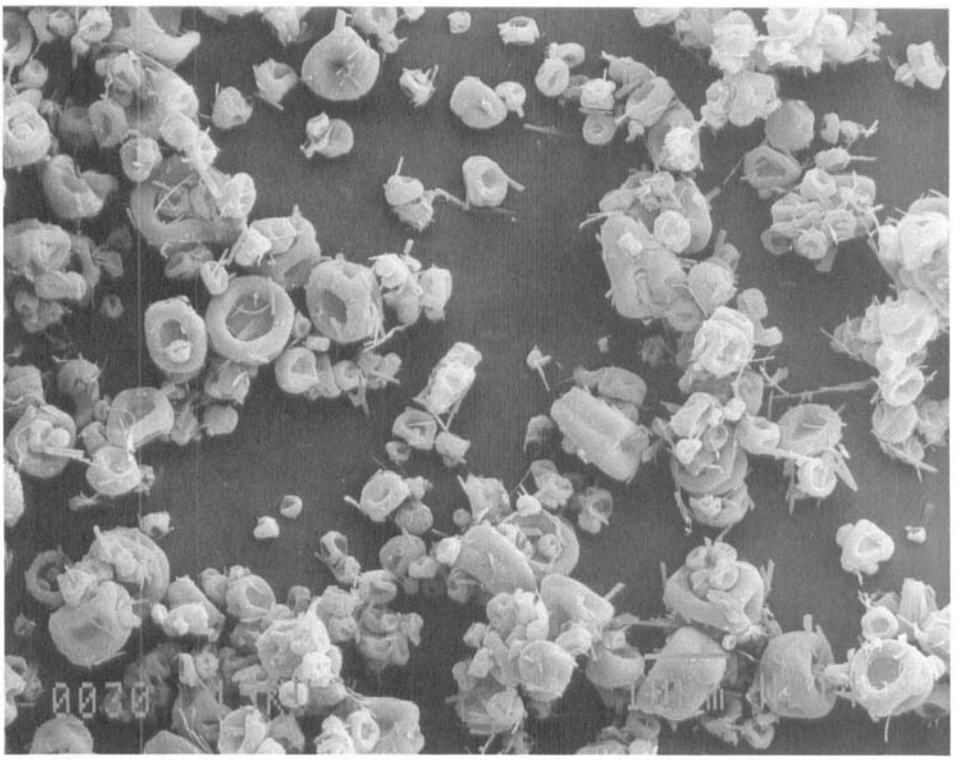

FIGURE 5 A
Powder from hydroalcoholic solution, with an 1:1 ratio polymer-drug; formulation without plasticizer. S.E.M. x 1000.

Figures 9 and 10 show the theophylline release curves of the tablets derived from the compression of Eudragit RS 30D microspheres obtained respectively in absence or in presence of the plasticizer.

Figures 11 and 12 show the theophylline release respectively of the tablets obtained by direct compression of Eudragit RS PO and of the tablets obtained by compression of the solid dispersion powders.

Provided that each series of tablets has an hardness of 8 kg/cm^2, as expected, the release of theophylline decreases with the increasing of the amount of polymer in the formulation. More interesting is, however, the comparison between the compressed microparticles and the tablets produced with Eudragit RS PO which is a specific Eudragit formulation for

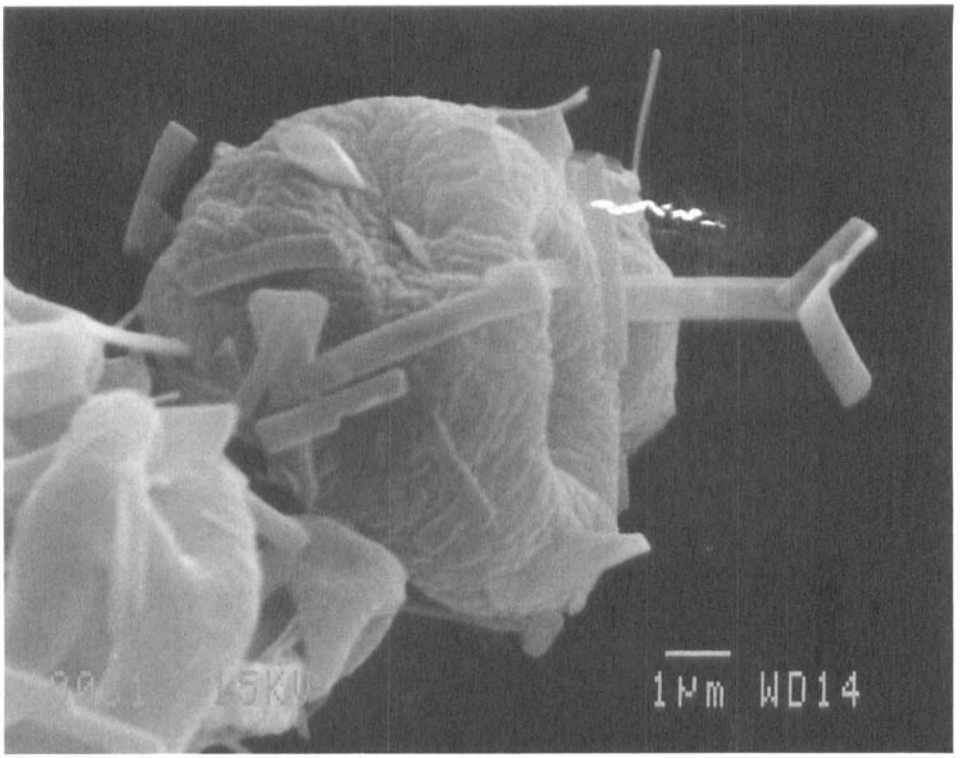

FIGURE 5 B
Powder from hydroalcoholic solution, with an 1:1 ratio polymer drug; formulation without plasticizer. S.E.M. x 7500.

direct compression giving the possibility to realize in only one step a matrix controlled release tablet.

In the reality, both the types of formulation are matrix tablets, but the dissolution profiles are very different. While the direct compressed tablets of Eudragit RS PO, at the hardness of 8 kg/cm^2, have not got the capability to control the drug release, the tablet formulations of Eudragit RS microparticles (from the hydroalcoholic solution) without plasticizer and Eudragit RS 30D microparticles (from the aqueous suspension) with plasticizer are very effective; particularly, for the polymer-theophylline ratio of 3:1, the curve is practically linear after the first portion; this means that, excluding the first minutes, the system follows a zero-order release kinetics.

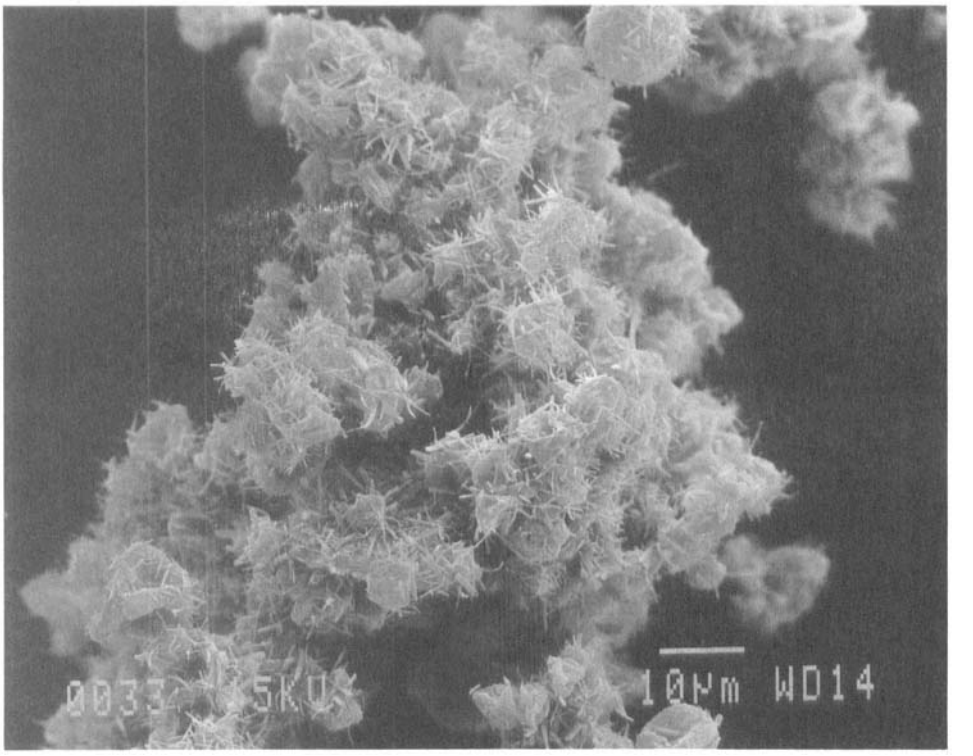

FIGURE 6 A
Powder from aqueous Eudragit suspension, with an 1:1 ratio polymer-drug; formulation with plasticizer S.E.M. x 1000.

The same conclusion can be drawn comparing these formulations with the tablets obtained by compressing the solid dispersion powders. Probably, the spray-drying method gives a finer solid dispersion, but this point should be better studied to prove this explanation and to find out why the other formulations of compressed microspheres are not able to give any controlled release.

To study the effect of hardness on drug release, the spray-dried powders of Eudragit RS without plasticizer and Eudragit RS 30D with plasticizer are compressed in three different hardnesses: 4, 8, 12 kg/cm². In figure 13 is presented the Eudragit RS formulation and in figure 14 the Eudragit RS 30D formulation with polymer-drug ratios 3:1.

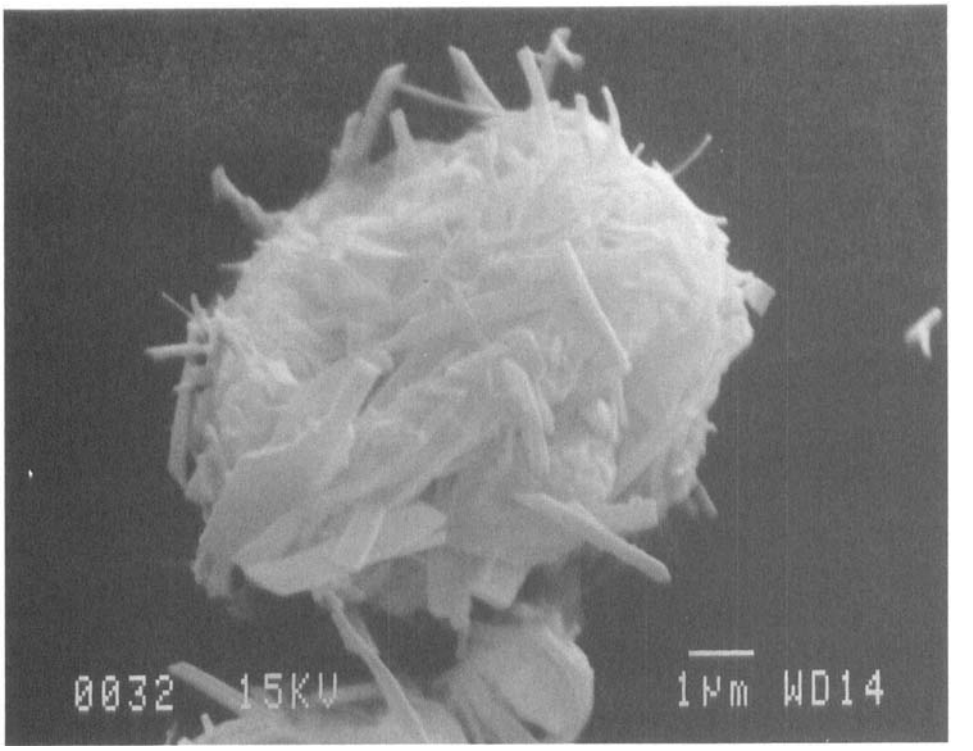

FIGURE 6 B
Powder from aqueous Eudragit suspension, with an 1:1 ratio polymer-drug; formulation with plasticizer S.E.M. x 7500.

As expected, an increasing of hardness causes a reduction of drug release, but not always this reduction is proportional to the compression force applied. This phenomenon is probably due to the inner structure of the microparticles, their porosity and water permeability.

Finally, the effect of water drug solubility is defined using sodium sulfamethazine as model drug. Figure 15 shows the release of the spray-dried microparticles of Eudragit RS-sodium sulfamethazine compressed into tablets of 8 kg/cm² hardness. As it can be observed, under the same conditions, this release is faster than the theophylline one, and to reach the same controlled release it is clearly necessary to increase the hardness of the tablet or the amount of Eudragit or both of them.

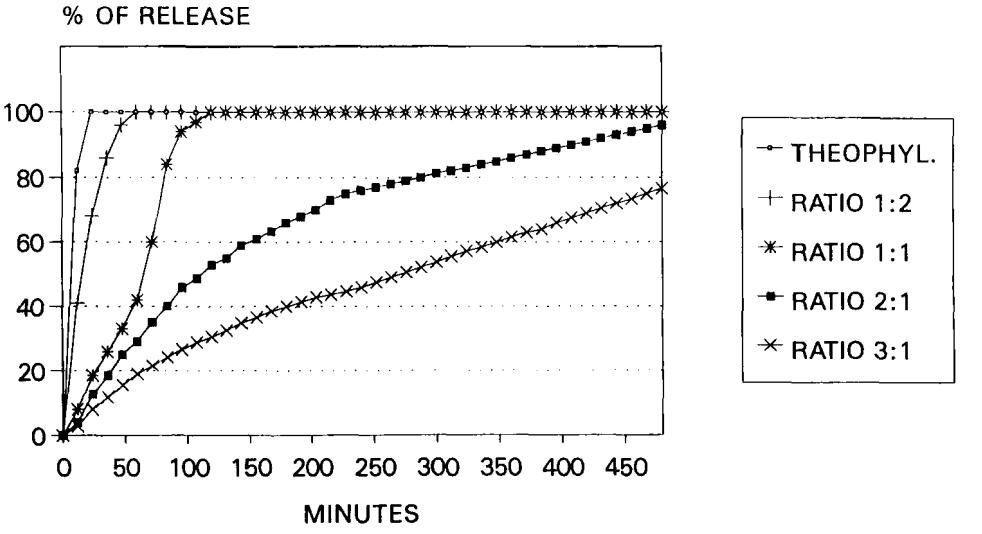

FIGURE 7
Theophylline release curves of the tablets derived from Eudragit RS microparticles without plasticizer, at different polymer-drug ratios.

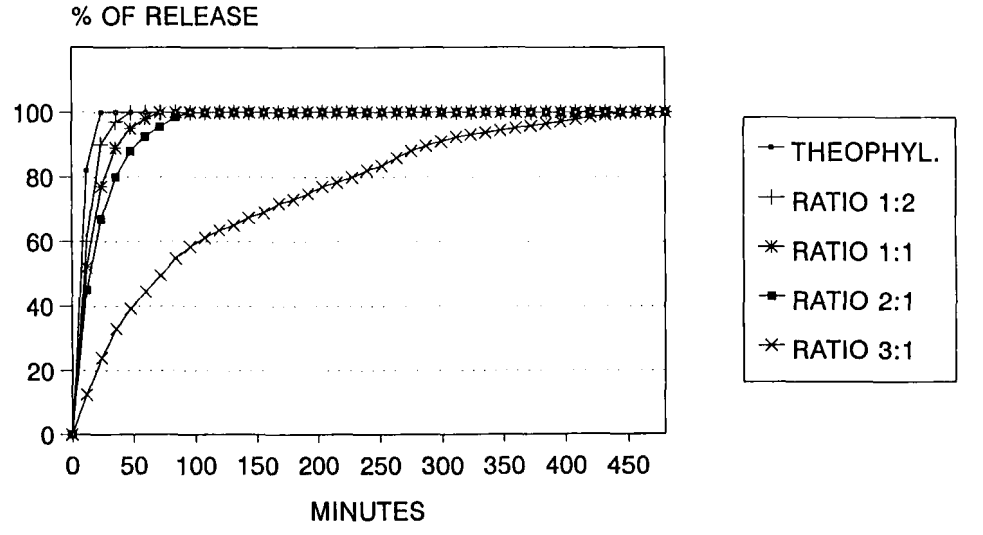

FIGURE 8
Theophylline release curves of the tablets derived from Eudragit RS microparticles without plasticizer, at different polymer-drug ratios.

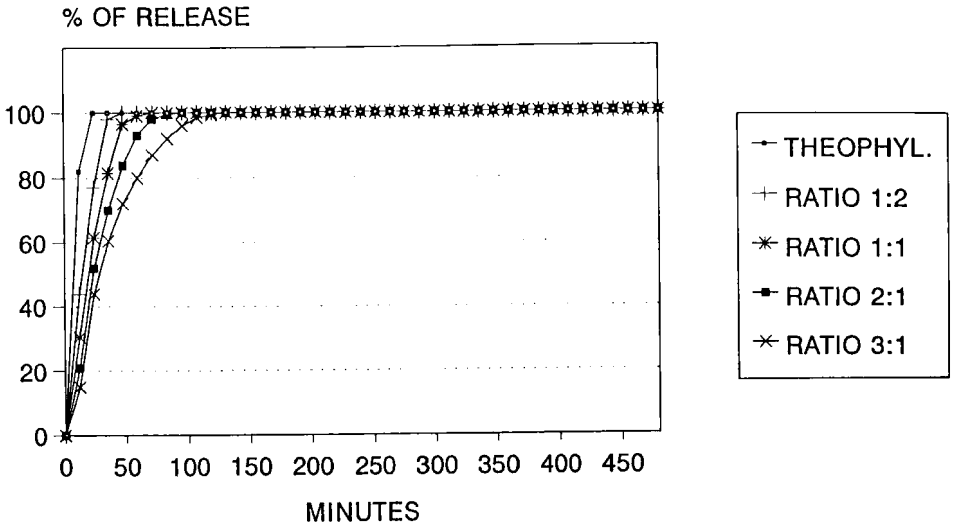

FIGURE 9

Theophylline release curves of tablets derived from Eudragit RS 30D microparticles without plasticizer, at different polymer-drug ratios.

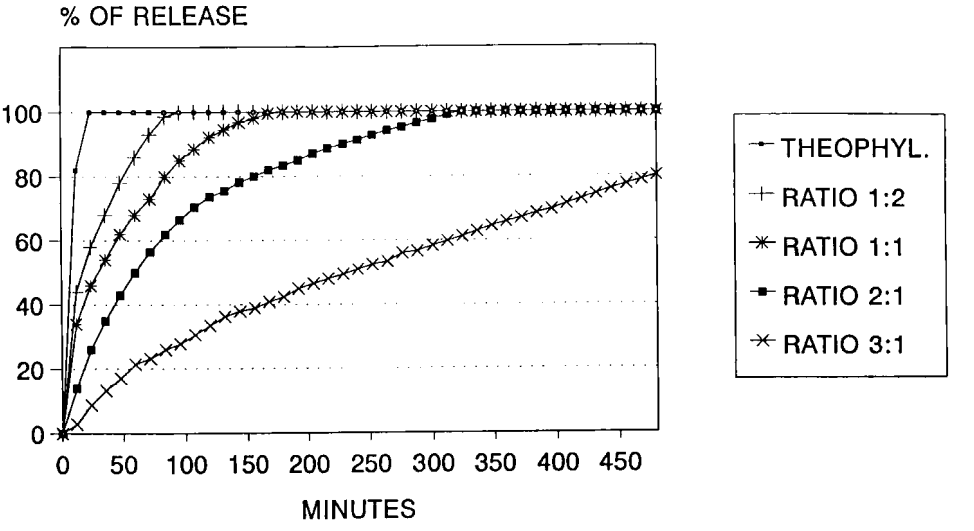

FIGURE 10

Theophylline release curves of the tablets derived from Eudragit RS 30D microparticles with plasticizer, at different polymer-drug ratios.

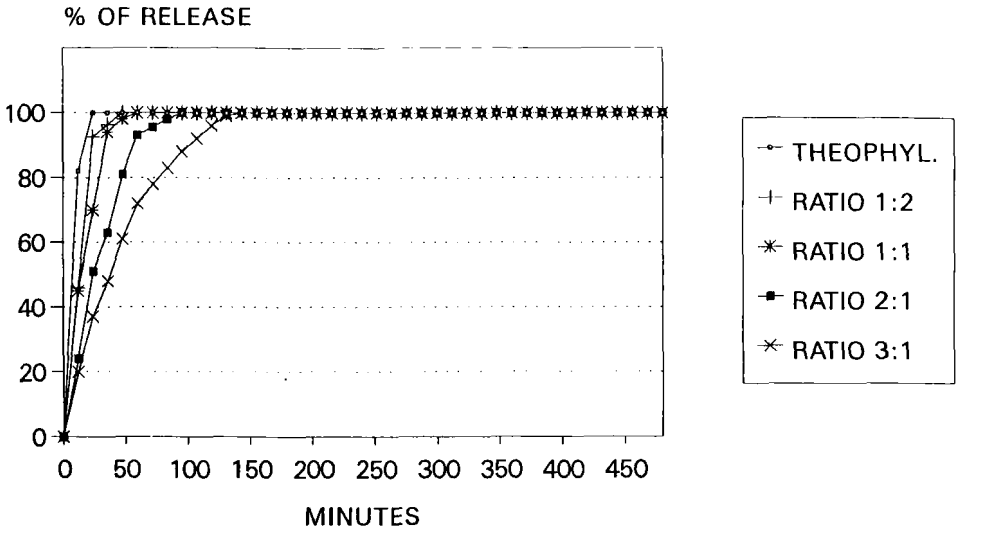

FIGURE 11

Theophylline release curves of the tablets obtained by direct compression of Eudragit RS PO.

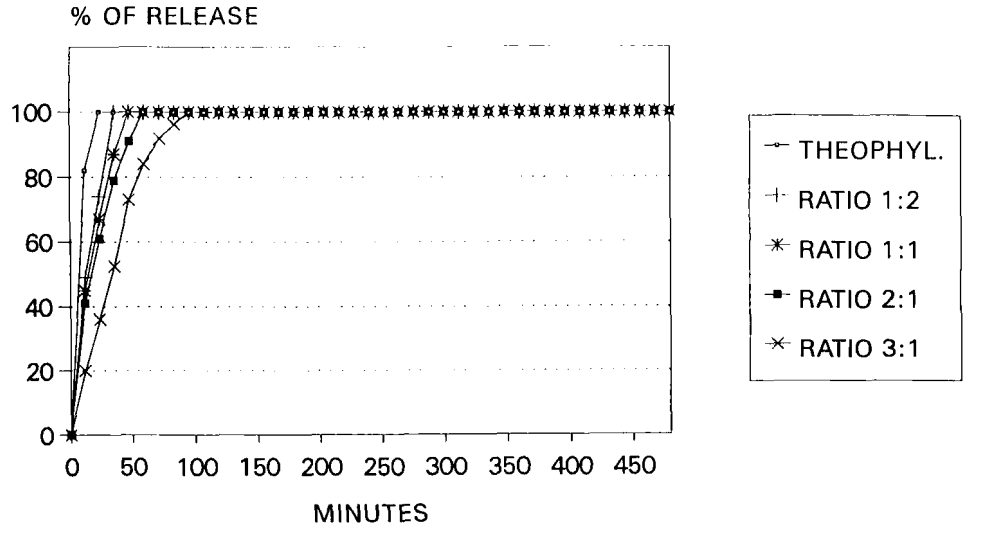

FIGURE 12

Theophylline release curves of the tablets obtained by compression of the solid dispersions.

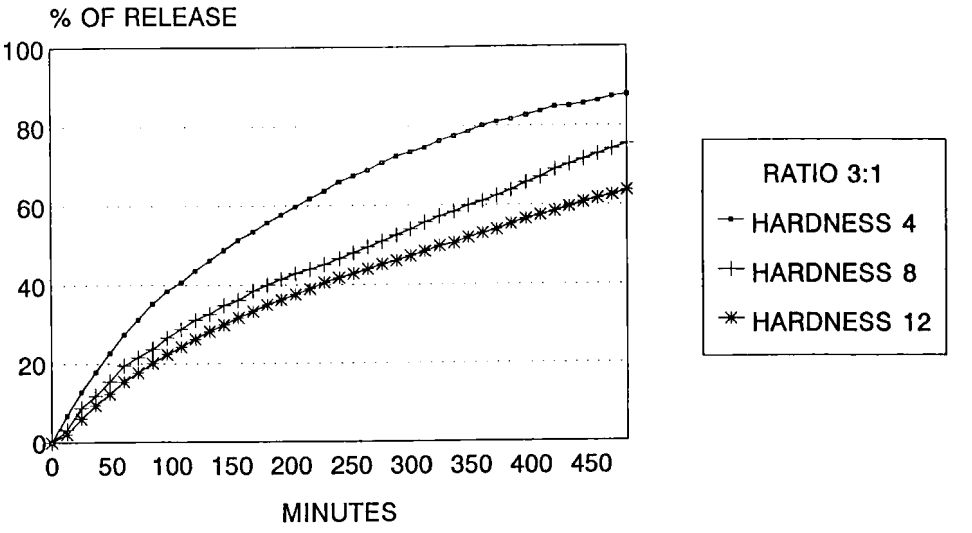

FIGURE 13
Theophylline release curves of the tablets from Eudragit RS without plasticizer; polymer-drug ratio 3:1.

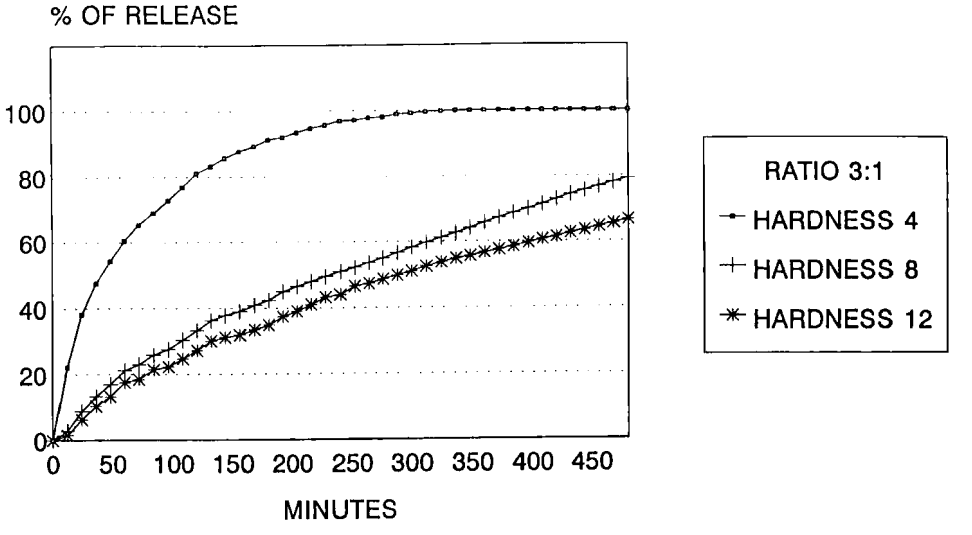

FIGURE 14
Theophylline release curves of the tablets from Eudragit RS 30D with plasticizer; polymer-drug ratio 3:1.

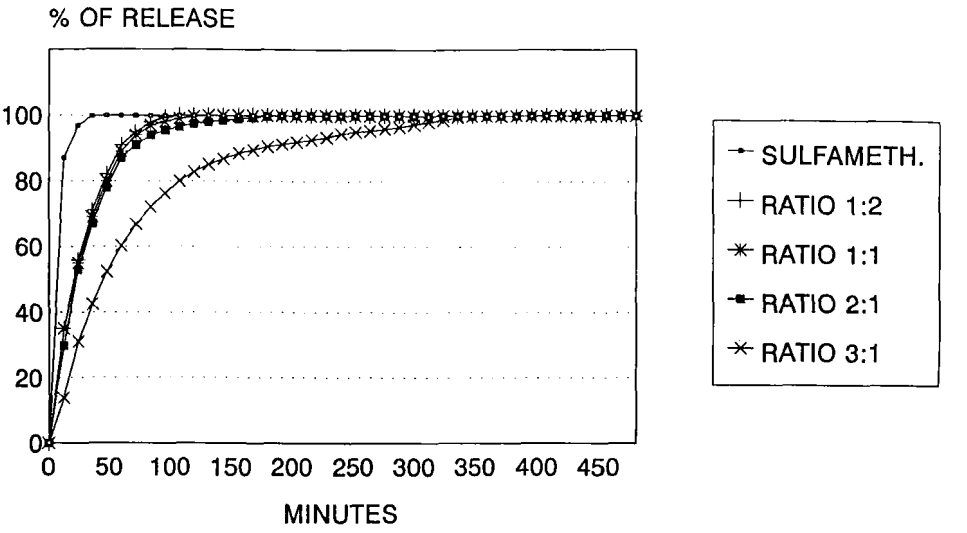

FIGURE 15
Sodium sulfamethazine release curves of tablets derived from Eudragit RS microparticles without plasticizer.

CONCLUSION

No microencapsulation occurs by spray-drying a drug and polymer solution; the spray-dried particles are simple minimatrixes, that is, a fine drug dispersion in the polymer network. Even if these microparticles are not able to reduce the rate of drug release, the tablets, derived from their compression, are very effective as controlled release system and offer a real advantage compared with the matrix-tablets obtained by direct compression of the polymer powder or by compression of the solid dispersion powders realized by evaporation under vacuum. So, spray-drying is a useful step in the formulation of controlled release matrix tablets.

The drug solubility, the hardness of the tablets, the polymer-drug ratio and the presence of a plasticizer are the main parameters to take into account in the realization of the optimal ormulation.

REFERENCES

1. P. Wehrlé, Ph. Nobelis, A. Stamm, **S.T.P. Pharma**, 4, 202 (1988)
2. J. L. Wells, M. H. Rubinstein, " Tableting technology: Volume 2 ", chapter 8.

3. H. Takenaka, Y. Kawashima, and Shan-Yang Lin, **J. Pharm. Sci.**, 69, 1388 (1980).
4. P. Vidgren, M. Vidgren, J. Arppe, T. Hakuli, E. Laine, P. Paronen, **Drug Dev. Ind. Pharm.**, 18, 581 (1992).
5. Lucy S. C. Wan, Paul W.S. Heng, and Cecilia G.H. Chia, **Int. J. Pharm.**, 77, 183 (1991).
6. Lucy S.C. Wan, Paul W.S. Heng, and Cecilia G.H. Chia, **Drug Dev. Ind. Pharm.**, 18, 997 (1992).
7. Roland Bodmeier and Huagang Chen, **J. Pharm. Pharmacol.**, 40, 754 (1988).
8. F. Pavanetto, I. Genta, P. Giunchedi and B. Conti, "**6th International Conference on Pharmaceutical Technology**", Paris 2-4 June 1992.
9. H. Takeuki, T. Handa and Y. Kawashima, **Drug Dev. Ind. Pharm.**, 15, 1999 (1989).
10. Martindale, " The Extra Pharmacopeia", London 1982.