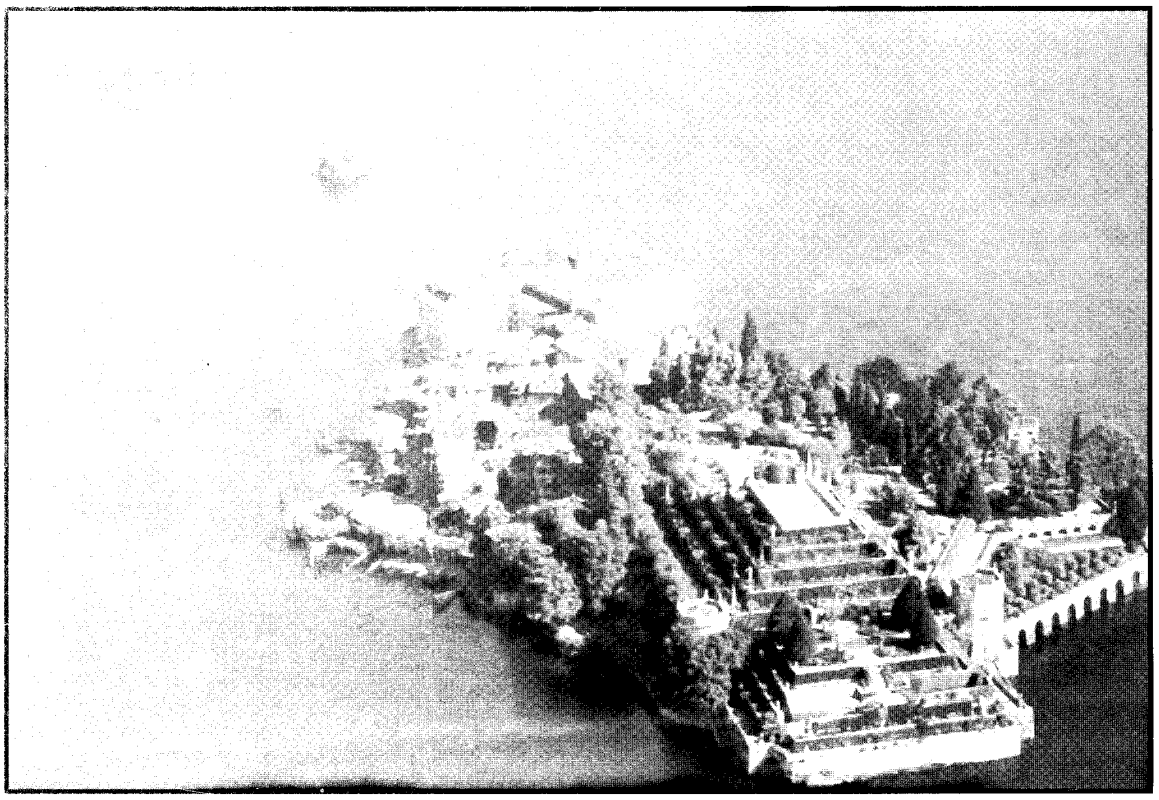
19th

Pharmaceutical Technology *Conference*

April 11th, 12th & 13th, 2000

Baveno-Stresa, Italy



Volume 3

Thursday April 13th, 2000

SPRAY-DRYING AS A METHOD FOR MICROPARTICULATE CONTROLLED RELEASE SYSTEMS PREPARATION: ADVANTAGES AND LIMITS. I. WATER SOLUBLE DRUGS.

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Keywords: Paracetamol, spray-drying, microspheres, tablets.

ABSTRACT

Spray-drying was used for the preparation of paracetamol/eudragit RS or RL or ethylcellulose microspheres in order to verify the possibility of their use in controlled release solid dosage forms formulation and try to set advantages and limits of the technique on this point of view. Microspheres were first characterized by scanning electron microscopy, differential scanning calorimetry, X-ray diffractometry and in vitro dissolution studies and then used for the preparation of tablets. During this step, the compressibility of the spray-dried powders was also evaluated.
In vitro dissolution studies were performed also on the tablets and their release control was pointed out.
While powders were unable to slow down drug release, tablets obtained from microspheres compression showed a good capability of controlling paracetamol release when eudragit RS or ethylcellulose were used, even at low polymer amounts.

INTRODUCTION

Spray-drying is a technique allowing the instantaneous drying of solutions, suspensions or emulsions. Recently, the process received great attention in the field of microparticles, for the preparation of dried liposomes (1-2), amorphous drugs (3), mucoadhesive microspheres (4-5), drying of preformed microcapsules (6-8), gastroresistant microspheres (9-14) and controlled release systems (15-31). Despite the great number of works carried out on this last aspect, the limits of the method, concerning the possibility of formulating an oral controlled release system, have not been set yet. In fact, the success of this kind of formulation mostly depends on the equilibrium between the type of polymer used to retain the drug and the water solubility of the same drug. So, the authors tried to

find out what drug solubility is suitable for the formulation of a microparticulate oral controlled release system, using the most known and effective water insoluble polymers such as eudragit RL and RS or ethylcellulose.
In this first article, the attention is drawn on drugs having an intermediate water solubility. For this reason paracetamol (water solubility 1:70 w/w) was chosen to prepare microspheres with eudragit RL or RS or ethylcellulose, by the spray-drying method.
The obtained powders were then compressed to verify paracetamol release also from tablets and compare it with that obtained from tablets having the same composition but prepared by direct compression of drug and polymers powders.

MATERIALS AND METHODS

1) Microspheres preparation.
A certain amount of eudragit RS or RL (Röhm, Darmstadt, Germany) or ethylcellulose NF 50 (Aqualon) was first dissolved in the minimal quantity of ethanol 96% necessary to maintain the polymer in solution when diluted with water from 96% to 75%. This solution was diluted with water to obtain a 75% ethanol solution and then, a certain amount of paracetamol (ACEF, Fiorenzuola D'Arda, Italy) was added to obtain the following w/w drug/polymer ratios: 1:2, 1:1, 2:1, 3:1, 4:1, 6:1, 9:1 and 19:1.
This final solutions were spray-dried with a Büchi B-191 mini spray-dryer at the following conditions: feed rate 15 ml/min., inlet temperature 110°C, outlet temperature 85°C, pressure 4 bar and throughput of drying air 35 m^3/h. The collected powders were stored under vacuum in a dessiccator for 2 days and then analyzed.

2) Microspheres analysis.
A certain amount of all the different spray-dried powders were crushed in a mortar and assayed spectrophotometrically (Cary 1E UV-VIS, Varian) at 257 nm in distilled water to be sure that no loss of drug or variation in the composition occurred during their preparation.
Scanning electron microscopy analysis was carried out with a Stereoscan 360 (Cambridge Instruments Limited, Cambridge, UK) on all series of microspheres in order to obtain a visual image and evaluate their particle size, shape and surface.
Differential scanning calorimetry was performed on the microspheres with a Perkin-Elmer Pyris 1 differential scanning calorimeter connected to a personal computer. Each sample (3 mg of powder in aluminium pans) was heated at a heating rate of 10°C/min. between 100° and 200°C.
X-ray diffractograms of the prepared powders and of pure drug and polymers were carried out with a Philips PW 1730 X-ray generator using CuK_α radiation and a goniometer camera.

3) Tablets preparation.
All the series of microspheres, prepared as above described, were compressed by an instrumented 10 stations rotary press type "Piccola" (Ronchi, Cinisello Balsamo, Italy) to obtain 250mg tablets of 8 Kp crushing strength (Erweka TBH30 hardness tester).
Tablets, having the same composition and crushing strength of those above described but obtained by direct compression of drug and polymer powders, could not be prepared because the physical mixtures of paracetamol and each of the polymers in turn, were not compressible at all.

The addition of other excipients such as the lubricant was spontaneously avoided to study the effect on the drug release characteristics only due to the structure and composition of the microspheres.

4) Dissolution studies.
The dissolution studies were performed in triplicate on all the different series of tablets and spray-dried powders with an Erweka DT6 dissolution test, using the paddle method at the rotation speed of 75 rpm (USP XXIII Apparatus 2). One tablet of each series was put into a vessel with 1000 ml of HCl 0,1N. At 10 min. intervals, 3 ml of water were withdrawn, passed through a 0.45μm membrane filter (Millipore) and assayed spectrophotometrically at 257 nm to measure the concentration of drug present in the solution. The initial volume of the vessel was maintained by adding 3 ml of HCl 0,1N after each sampling.
After 2 hours, the tablet was recovered and immediately put into 1000 ml phosphate buffer (pH 7). At 10 min. intervals, 3 ml of water were withdrawn, passed through a 0.45μm membrane filter and assayed spectrophotometrically at 257 nm, for 6 hours. The initial volume of the vessel was maintained by adding 3 ml of phosphate buffer after each sampling.

RESULTS AND DISCUSSION

1) Microspheres analysis.
The UV analyses performed on the prepared powders show in all cases a 100 % drug content according to the theoretical composition.
Figures 1-2 show the SEM images of paracetamol/ethylcellulose 1:2 and 4:1 microspheres respectively.
Both types of microspheres have a similar mean diameter (25-30 μm) and are formed by clusters of smaller microparticles. The form of these smaller particles depends on the composition of the microspheres. They are not spherical when the amount of ethylcellulose exceeds that of drug (fig.1) and become gradually spherical as the quantity of paracetamol increases (fig. 2).

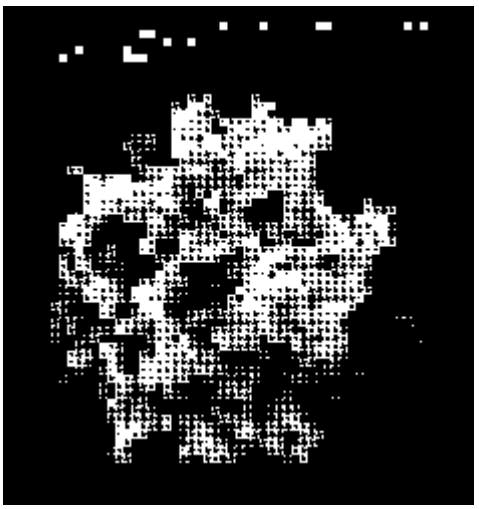

Figure 1
SEM image of paracetamol/ethylcellulose 1:2 microspheres.

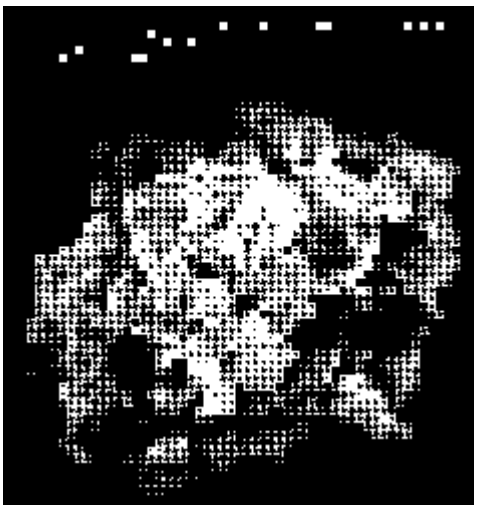

Figure 2
SEM image of paracetamol/ethylcellulose 4:1 microspheres.

Figures 3-4 show the SEM images of paracetamol/eudragit RS 1:2 and 4:1 microspheres respectively. In this case, microspheres having a higher polymer amount are a little bigger (55 μm mean diameter) than those with more paracetamol (25 μm mean diameter) but both are formed by clusters of smaller particles. Differently from the ethylcellulose-containing microparticles, these smaller particles forming clusters are quite spherical even at the 1:2 drug/polymer ratio.

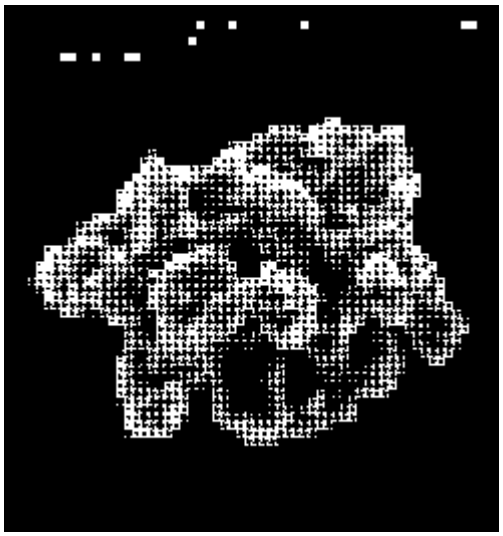

Figure 3
SEM image of paracetamol/eudragit RS 1:2 microspheres.

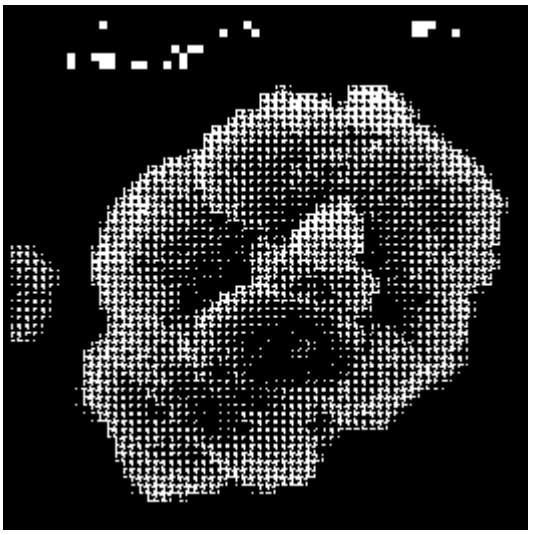

Figure 4
SEM image of paracetamol/eudragit RS 4:1 microspheres.

Figures 5-6 show the SEM images of paracetamol/eudragit RL 1:2 and 4:1 microspheres respectively. There is a considerable difference between paracetamol/eudragit RS and paracetamol/eudragit RL 1:2 particles. In fact, these last ones are not spherical. Paracetamol/eudragit RL particles begin to resemble to those containing eudragit RS when the amount of drug increases, as both the 4:1 particles are clusters of smaller microspheres.

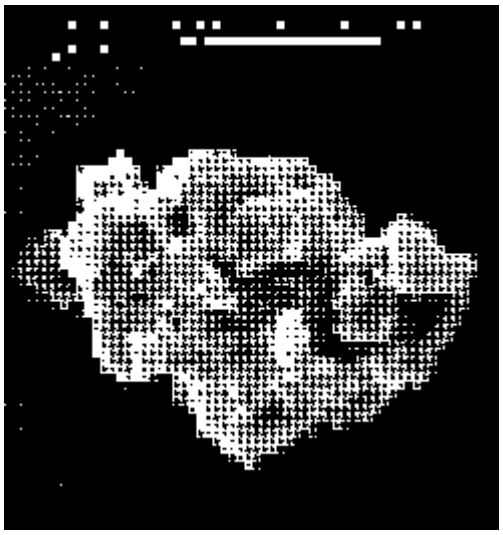

Figure 5
SEM image of paracetamol/eudragit RL 1:2 microspheres.

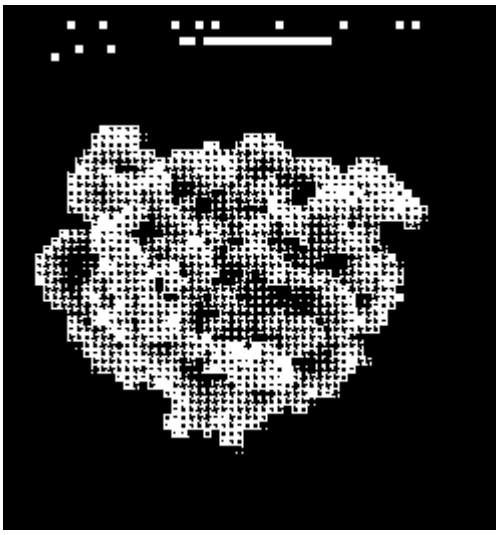

Figure 6
SEM image of paracetamol/eudragit RL 4:1 microspheres.

Figures 7-9 show the thermograms of paracetamol/ethylcellulose, paracetamol/eudragit RS and paracetamol/eudragit RL microspheres respectively, at different dug/polymer ratios.
In all cases, solid solubility of the paracetamol in the polymers is less than 30% as a very flat and large drug melting peak can be detected even in the drug/polymer 1:2 ratio.

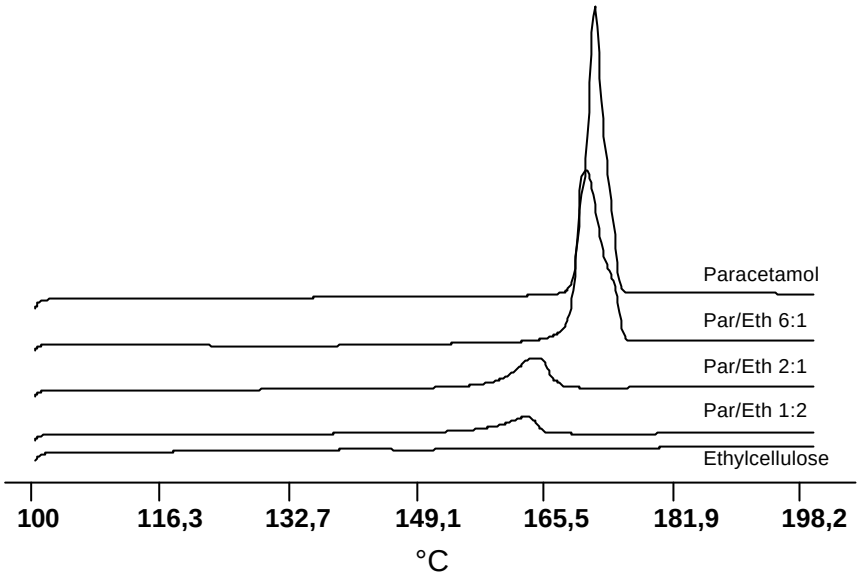

Figure 7
DSC curves of paracetamol/ethylcellulose microspheres.

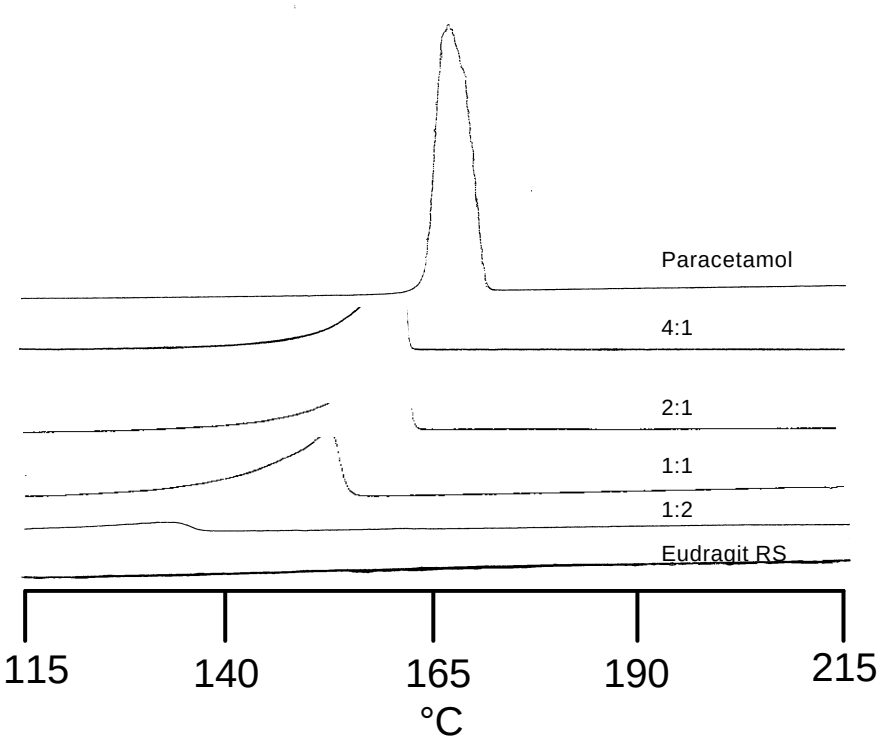

Figure 8
DSC curves of paracetamol/eudragit RS microspheres.

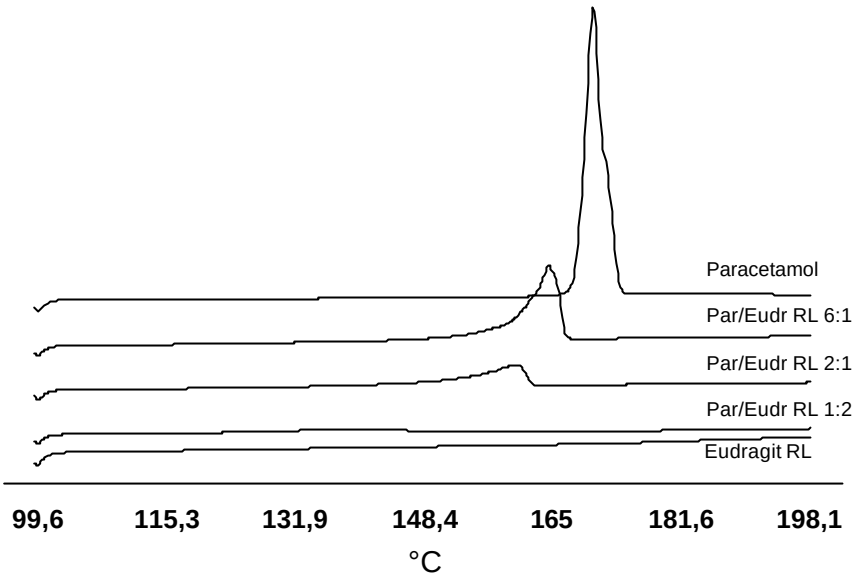

Figure 9
DSC curves of paracetamol/eudragit RL microspheres.

Figure 10 shows the values of the enthalpy of fusion of the peaks visible in fig. 7-9, reported against the percentage of paracetamol in the powder. In this way, the limit of solid solubility can be extrapolated as the intercept between the line, obtained from the experimental points, and the X axis. The calculated limits are 30% for eudragit RS and RL and 17% for ethylcellulose. So, the two acrylic polymers are more effective to disperse monomolecularly the drug in their own solid matrix.

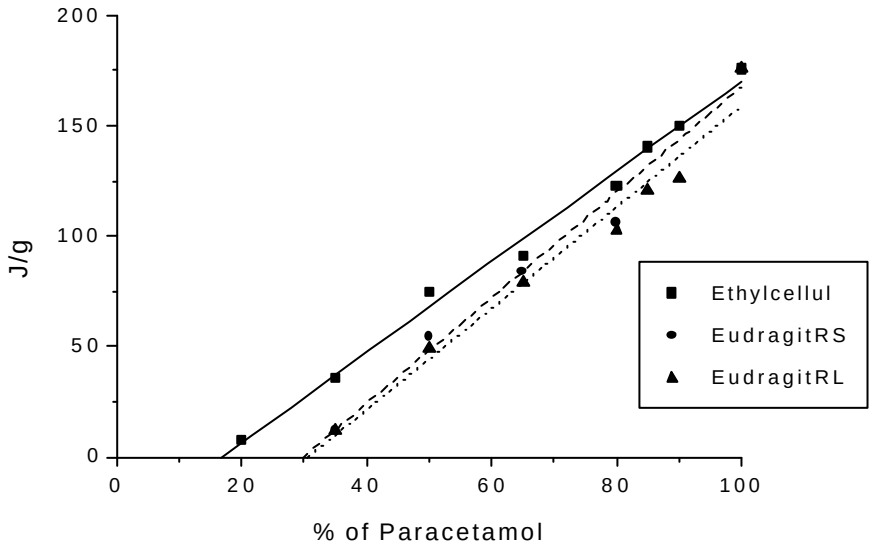

Figure 10
Paracetamol solid solubility in ethylcellulose, Eudragit RS and RL.

Figure 11 shows the X-ray diffractograms of the raw paracetamol and polymers powders compared with the spray-dried drug/polymer 1:2 powders.
Peaks of paracetamol crystals are always present in all the 1:2 spray-dried powders, even if very reduced in intensity. This result is in agreement with DSC data and confirms the presence of paracetamol crystals in the powders.
The peaks of paracetamol increase their intensity as the amount of paracetamol in the spray-dried powders increases too (not shown results).

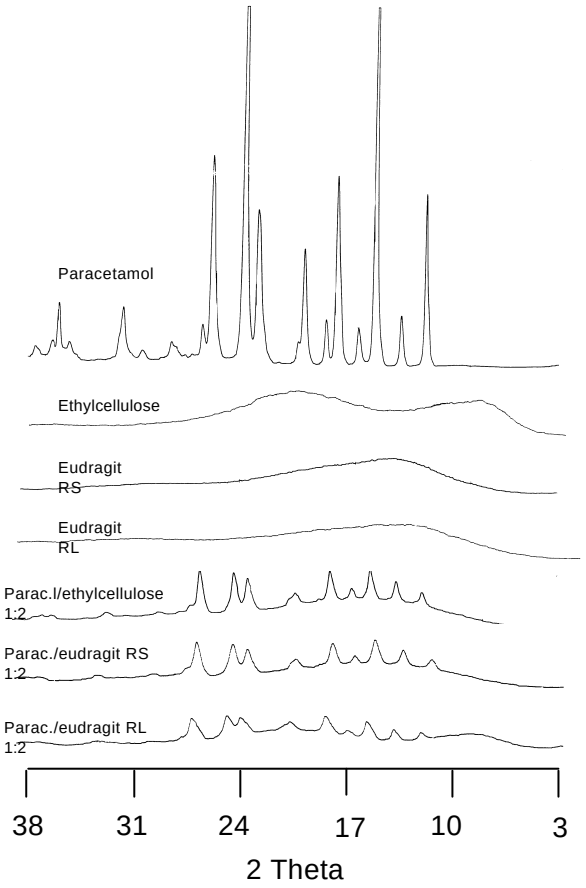

Figure 11
X-ray diffractograms of the raw paracetamol and polymers powders compared with the spray-dried drug/polymer 1:2 powders.

2) Compression studies.
The compressibility of paracetamol/ethylcellulose, paracetamol/eudragit RS and paracetamol/eudragit RL spray-dried powders is shown in figures 12-14 respectively, where there are reported their crushing strength/compression force curves.
Independently from the type of polymer present in the microspheres, as the amount of polymer increases, the compaction properties are gradually improved too.
The compressibility is still acceptable when the amount of drug present does not exceed the 80%, except for the paracetamol/eudragit RL microspheres which seem to be less compressible at a low polymer content. In fact, in this case, when microparticles contain the 50% of polymer, the crushing strength/compression force curve is similar to that obtained from microparticles containing only the 20% of ethylcellulose or eudragit RS.

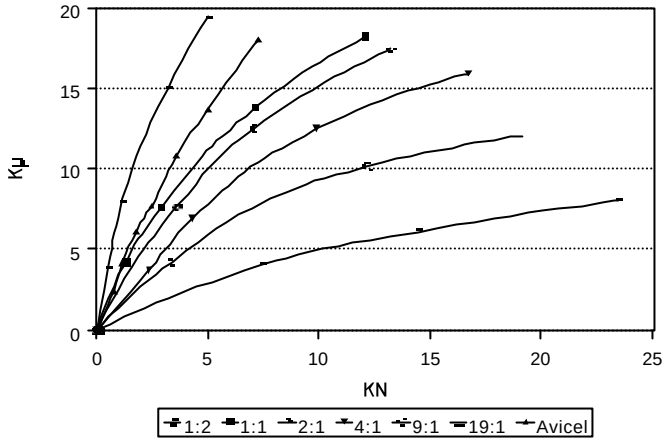

Figure 12
Crushing strength/compression force curves of the paracetamol/ethylcellulose microspheres.

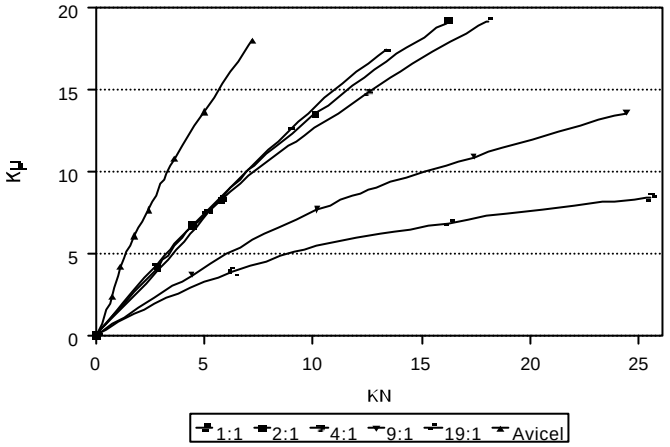

Figure 13
Crushing strength/compression force curves of the paracetamol/eudragit RS microspheres.

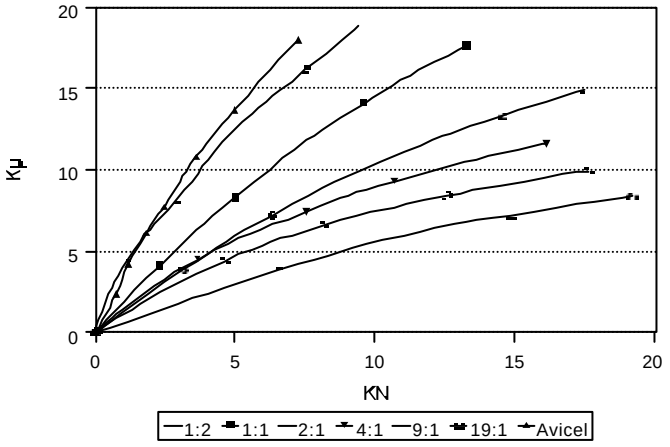

Figure 14

Crushing strength/compression force curves of the paracetamol/eudragit RL microspheres.

Another very interesting result is represented by the increased compaction abilities of the spray-dried powders in comparison with those of the corresponding physical mixtures which turned out impossible to convert into tablets because of their very poor compaction properties. Moreover, the compaction ability of drug/eudragit RL 1:2 and drug/ethylcellulose 1:1 microspheres is very similar to that of Avicel, known to be a very compressible filler in tablets preparation. Besides, the drug/ethylcellulose 1:2 microspheres are even more compressible than Avicel. This could depend on their morphological characteristics, on the variation of the physical structure of the solid spray-dried powders respecting a drug/polymer simple physical mixture, or could depend on both these two effects.

Anyway, even if the spray-drying process often improves the compressibility of materials, the improvement level reached by the microspheres powders in comparison with the raw materials was quite unexpected. For this reason, this aspect will be further investigated using more refined techniques such as F-D or Hekel plots.

3) Dissolution studies.

The reported values are the arithmetical mean of three measurements, and standard deviation bars are omitted to avoid overlapping.

Dissolution profiles of microspheres are not shown because they are very similar to that of the pure drug, with no evidence of slow release. This is probably due to the porosity of the spray-dried particles which is responsible for the fast water penetration inside microspheres.

A very different result is achieved once the microspheres are converted into tablets. In fact, as shown by figures 15-17, in which the release kinetics of tablets obtained from drug/ethylcellulose or eudragit RS or eudragit RL microspheres are presented, the compression process sensibly slows down the drug release. This phenomenom depends on the strong reduction of particles porosity.

Anyway, differences in the release kinetics can be found between tablets containing ethylcellulose or eudragit RS and those containing eudragit RL.

As one should expect, these last ones are less effective in paracetamol release rate slowing down because eudragit RL is more permeable and swellable in water than the other two polymers.

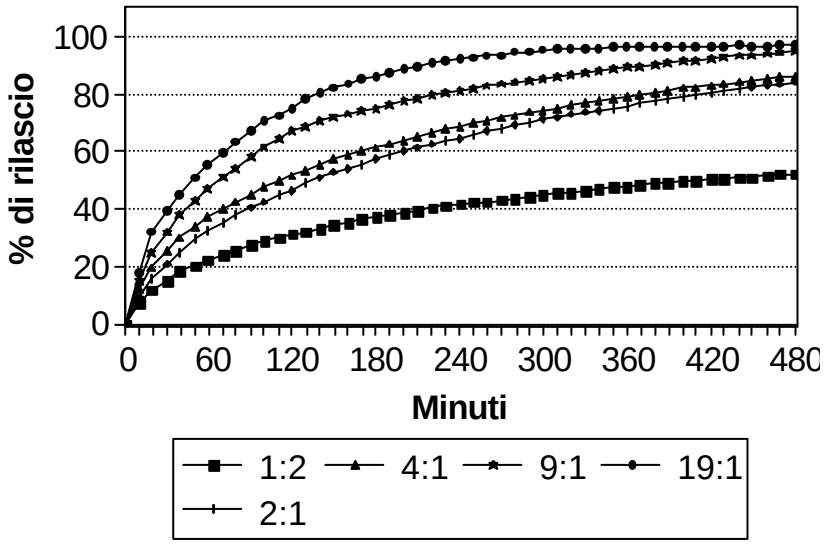

Figure 15

Release kinetics of tablets obtained from paracetamol/ethylcellulose microspheres.

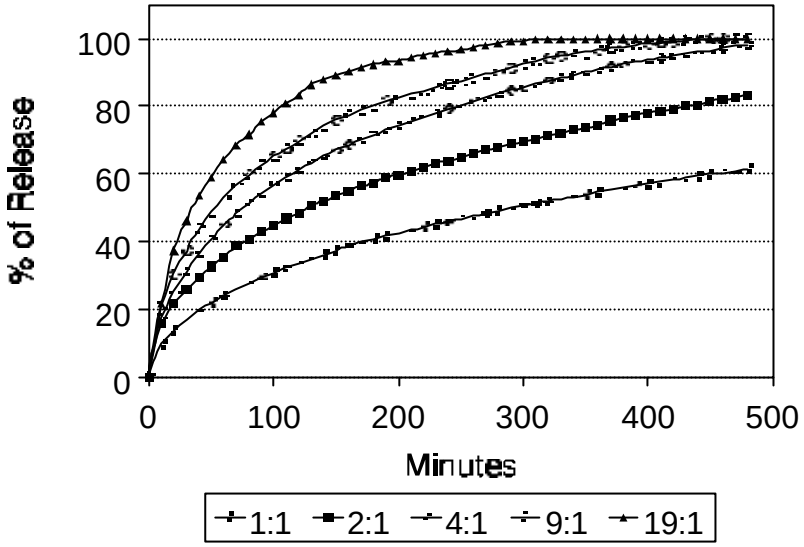

Figure 16
Release kinetics of tablets obtained from paracetamol/eudragit RS microspheres.

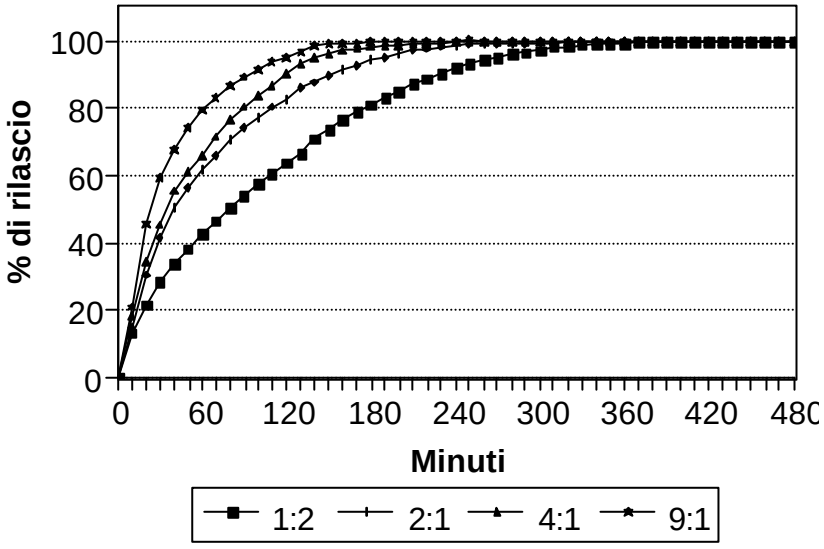

Figure 17
Release kinetics of tablets obtained from paracetamol/eudragit RL microspheres.

Besides, independently from the type of polymer present in the tablets, differences on drug release rate are related to the amount or paracetamol contained into the tablets. As drug content increases, its release from tablet becomes faster.
Finally, if ethylcellulose or eudragit RS are used, the presence in the tablet of just a little amount of polymer is enough to guarantee drug release control. In fact, the drug/polymer 9:1 and even 19:1 tablets are still able to retard drug release.

CONCLUSION

Microspheres paracetamol/polymer can be easily prepared by spray-drying. Even if they are not spherical, they are in most cases clusters of smaller and spherical microparticles, as shown by the scanning electron microscope.
Differential scanning calorimetry and X-ray diffractometry gave no evidence of eutectics or complexes formation between paracetamol and the used polymers. On the other hand, these two techniques evidenced the very good paracetamol solid solubility in the three polymers.
The compaction abilities of the spray-dried microspheres are by far higher than the corresponding physical mixtures which could not be transformed into tablets. Besides, microspheres containing 50% or more of eudragit RS or ethylcellulose possess compaction abilities similar or even better than the Avicel one.
In vitro dissolution studies pointed out the impossibility of formulating, by spray-drying, a microparticulate oral controlled release system of a drug having a water solubility of 1:70, such as paracetamol, or similar. Despite this result, very effective oral controlled release systems can be obtained if the spray-dried microspheres are converted into tablets even when the content of polymer is low.

Acknowledgements
The authors gratefully acknowledge the financial support of Italian MURST (40% Funds, national project "Tecnologie farmaceutiche").

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