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RESEARCH PAPER

Emulsion/Solvent Evaporation as an Alternative Technique in Pellet Preparation

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ABSTRACT

Paracetamol/Eudragit RS, paracetamol/ethylcellulose, and paracetamol/cellulose acetate pellets of different drug/polymer ratios (w/w) were prepared by the dissolution/solvent evaporation technique. These pellets were then characterized by particle size distribution analysis, ultraviolet (UV) spectroscopy, differential thermal analysis, and scanning electron microscopy (SEM). Hard gelatin capsules were filled with each particle size fraction of these pellets, and in vitro dissolution studies were performed to verify the capability of each series of pellets to control drug release. Pellets were spherical, presented a polynucleated microcapsule structure, and under certain experimental conditions, the yield of the preparation process reached very high values. The dissolution studies pointed out the slow paracetamol release from these pellets.

Key Words: *Cellulose acetate; Controlled release; Eudragit RS; Ethylcellulose; Pellets.*

INTRODUCTION

Pelletization is a technique that enables the formation of spherical beads with a mean diameter usually ranging between 0.5 and 2 mm. They eventually can be film coated and are very often used in controlled-release delivery systems (1–10). Pellets are prepared on industrial scale by extrusion-spheronization (11–23), high-speed share mixers (24–30), rotoprocessors (31–34), and modified tablet machines. All these methods require specific and expensive instruments, qualified staff, and high maintenance cost, and the optimization of the process is

not so easy. Furthermore, if these pellets have to be coated for controlling drug release, an additional cost is needed because a fluid bed is necessary.

An alternative and more simple technique that allows the formation of pellets of a certain and narrow particle size that are directly utilizable for controlled-release systems and transposable on an industrial scale is not simple to find. To obtain pellets for controlled drug release, we tried to apply the emulsion/solvent evaporation technique usually used in the microsphere preparation (35–42). For this purpose, paracetamol was used as a model drug and Eudragit RS, ethylcellulose, and cellulose acetate were used as drug release controlling polymers.

In this paper, we only report about the possibility of pellet formation and controlling drug release.

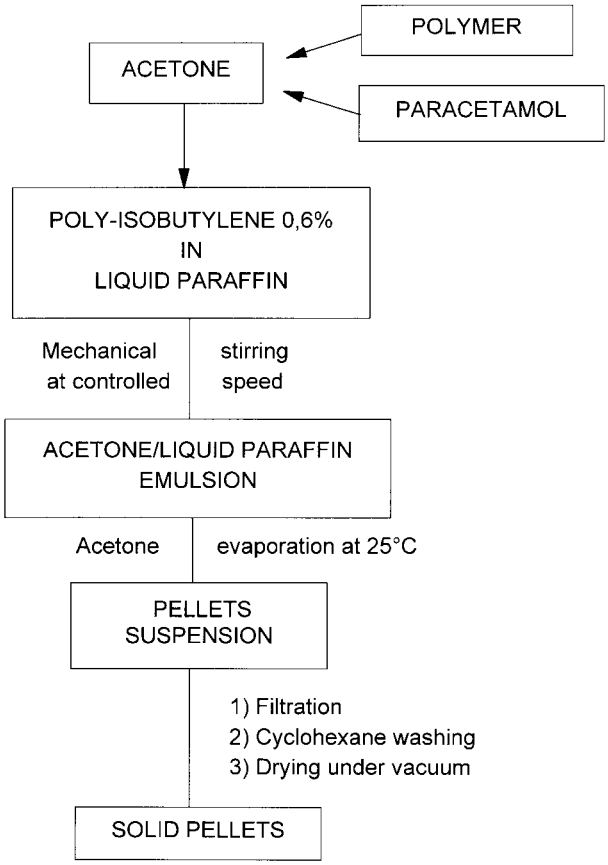
EXPERIMENTAL

Preparation of Paracetamol/Polymer Pellets

Paracetamol (ACEF, Fiorenzuola d'Arda, Italy) and Eudragit RS (Röhm Pharma, Darmstadt, Germany) or ethylcellulose NF50 (Aqualon) or cellulose acetate (Eastman, Milan, Italy) in the 2:1 and 1:1 w/w ratios were first dissolved in the lowest volume of acetone necessary to obtain a solution (Scheme 1). This solution was then added to an amount of liquid paraffin containing 0.6% w/v polyisobutylene necessary to give a 7:20 v/v acetone: liquid paraffin ratio. The system was then stirred by a mechanical stirrer with a paddle at a controlled speed (Ika Labortechnik, Staufen, Germany) ranging from 150 to 350 rpm; an acetone in liquid paraffin emulsion formed. This emulsion was maintained under mechanical stirring for 3–4 hr until complete evaporation of the internal phase. The obtained pellets were filtered under vacuum, washed three times with cyclohexane to eliminate the residual liquid paraffin, and stored 3 days under vacuum in a desiccator before being analyzed. Since paracetamol solubility in acetone is by far lower than the solubility of polymers, pellets formed as described above are suspected of possessing the structure of a polynucleated microcapsule.

Pellets Analyses

Granulometric distribution analysis was performed using a Retsch apparatus (Germany) and 0.106-, 0.425-, 1-, and 1.4-mm sieves. Pellet fractions having a mean diameter higher than 1.4 mm were characterized by a micrometer. All the recovered fractions were separately used for further analyses.



Scheme 1. Preparation of the pellets.

A certain amount of all the different pellet fractions was crushed in a mortar and assayed spectrophotometrically (Cary 1E UV-Vis, Varian) at 257 nm in distilled water to be sure that there was no loss of drug or variation in the composition during preparation.

Scanning electron microscopy (SEM) analysis was carried out with a Stereoscan 360 (Cambridge Instruments Ltd., Cambridge, England) on all series of pellets to obtain a visual image and evaluate their particle size, shape, and surface.

Differential scanning calorimetry (DSC) was performed on the pellets with a Perkin-Elmer DSC-2C differential scanning calorimeter connected to a personal computer (PC) data station. Each sample (10 mg of powder in aluminum pans) was heated at a heating rate of 5°C/min between 27°C and 227°C.

Hard Gelatin Capsule Preparation

An amount of each fraction of pellets corresponding to 100 mg of paracetamol was put into hard gelatin cap-

sules to study the in vitro dissolution kinetics of drug from a final pharmaceutical form.

Dissolution Studies

Dissolution studies were performed in triplicate with an Erweka DT6 dissolution test (Heusenstamm, Germany) in distilled water at 37°C using the paddle method at a rotation speed of 75 rpm (USP 23 apparatus 2). A hard gelatin capsule containing 100 mg of paracetamol was put into a vessel with 1000 ml water. At 5-min intervals, 3 ml of liquid were withdrawn, passed through a 0.45-μm membrane filter (Millipore), and assayed spectrophotometrically with a Cary 1E UV-Vis spectrophotometer (Varian) at 257 nm to measure the concentration of paracetamol present in solution. The initial volume of the vessel was maintained by adding 3 ml of water after each sampling.

RESULTS AND DISCUSSION

Pellets Characterization

Tables 1–5 show the yield of pellets and the percentages (w/w) of the different fractions obtained at the different mechanical stirrer speeds for the paracetamol/Eudragit RS 2:1 and 1:1, paracetamol/ethylcellulose 2:1, paracetamol/cellulose acetate 2:1 and 1:1 pellets, respectively. As the speed of the mechanical stirrer increased, the yield of pellets always increased, even if not linearly.

On the other hand, there was no correspondence between stirrer speed and the percentages of the different granulometric fractions. Particularly, when paracetamol and Eudragit RS were used in the 2:1 w/w ratio (Table 1), except at the maximum speed (350 rpm), which gives a considerable amount of 1200-μm pellet fractions, the same two-dimensional classes were obtained: 712 and >1400 μm.

Table 1

Yield of Paracetamol/Eudragit RS 2:1 Pellets

rpm	Mean Diameter (μm)	%	Yield
150	2653	40.7	60.2
	1200	13.3	
	712	46	
200	2431	62.9	69.2
	200	1.8	
	712	35.3	
250	2741	32	77.8
	1200	6	
	712	62	
300	2563	44.5	78
	1200	5	
	712	50.5	
350	1200	49.7	88.3
	712	53.3	

Table 2

Yield of Paracetamol/Eudragit RS 1:1 Pellets

rpm	Mean Diameter (μm)	%	Yield
150	Clusters >1400	100	31.8
	1200	—	
	712	—	
200	Clusters >1400	25.31	46
	1200	49.1	
	712	25.6	
250	2800	27.25	78.58
	1200	72.75	
300	2280	29	82.76
	1200	71	
350	Clusters >1400	5	92
	1200	58.5	
	712	36.55	

Table 3

Yield of Paracetamol/Ethylcellulose 2:1 Pellets

rpm	Mean Diameter (μm)	%	Yield
150	Clusters >1400	53	46.1
	1200	34	
	712	13	
200	Clusters >1400	36.7	58.8
	1200	24.3	
	712	39	
250	1200	3	81.4
	712	86	
	265	11	
300	Clusters >1400	72.3	86.04
	1200	20.8	
	712	6.9	
350	Clusters >1400	38.2	96
	1200	51	
	712	10.8	

Table 4

Yield of Paracetamol/Cellulose Acetate 2:1 Pellets

rpm	Mean Diameter (μm)	%	Yield
150	1200	35	29.4
	712	65	
200	Clusters >1400	14.5	50.2
	1200	17.5	
	712	68	
250	3000	7	50.5
	—		
	712	93	
300	2893	11.3	68.6
	1200	3.8	
	712	74.7	
	212	10.2	
350	1947	12.5	74.13
	Clusters >1400	13.2	
	1200	13.3	
	712	35.1	
	212	25.9	

The use of paracetamol and Eudragit RS in the 1:1 ratio (Table 2) makes pellets more tacky during their preparation, particularly when, at the end of the process, acetone is almost completely evaporated. This increased tackiness influences negatively the yield and size of the pellets. In fact, at 150 rpm, pellets aggregate, forming only big clusters that cannot be used. A considerable quantity of these clusters is still obtained at 200 rpm, even if other fractions (1200 and 712 μm) can be recovered at this stirrer speed. The increase of the stirring speed (250–350 rpm) avoids cluster formation, but a fraction of pellets having a diameter larger than 1400 μm forms.

The use of ethylcellulose instead of Eudragit RS (Table 3) gave worse results. Pellets of paracetamol/ethylcellulose in the 1:1 ratio could not be obtained, but even in the 2:1 ratio, many big clusters were always obtained. Besides, the yield of the other fractions was not reproducible because it changed without specific order when the stirring speed changed.

All these phenomena are probably related to the higher tackiness of ethylcellulose than Eudragit RS under this preparation process.

Pellets of paracetamol/cellulose acetate in the 2:1 ratio (Table 4) formed easier than pellets of paracetamol/ethylcellulose, and the yield increased proportionate to the stirring speed. The number of particle size fractions recovered also increased with the increase of the stirring speed. In fact, at 300 and 350 rpm, the 212-μm mean diameter fraction appeared.

Pellets of paracetamol/cellulose acetate in the 1:1 ratio (Table 5) could be formed, but without correspondence between stirring speed and yield and particle size. Clusters or big particles were always present, but the quantity of these fractions was not constant and did not depend on the stirring speed.

In conclusion, pellet formation was easier when the amount of polymer was low. When the polymer quantity reached 50% of the pellet composition, particles became sticky, the yield was reduced, and clusters or fractions of

Table 5

Yield of Paracetamol/Cellulose Acetate 1:1 Pellets

rpm	Mean Diameter (μm)	%	Yield
150	Clusters >1400	48.7	49.76
	1200	30.9	
	712	20.4	
200	Clusters >1400	2.8	68.22
	1200	20	
	712	77.2	
250	2318	6.2	75.24
	1200	3.8	
	712	90	
300	Clusters >1400	6	81.88
	1200	50.5	
	712	43.5	
350	Clusters >1400	77	81.4
	1200	23	

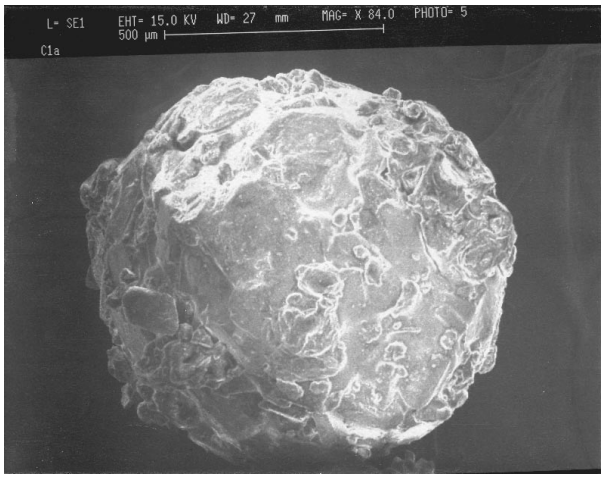


Figure 1. SEM image of the 712-μm mean diameter fraction of paracetamol/Eudragit RS 2:1 pellets.

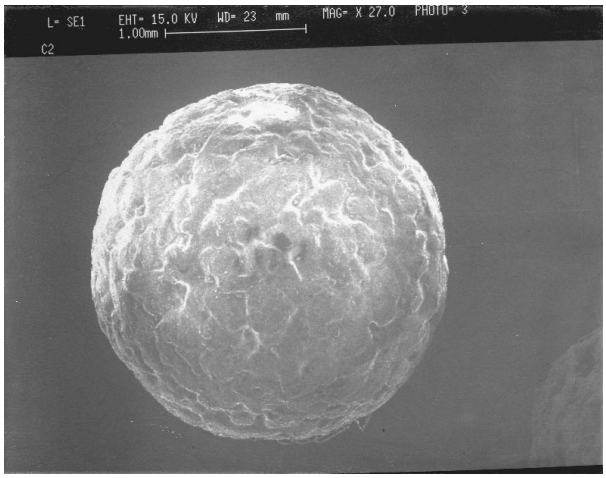


Figure 2. SEM image of the 2560-μm mean diameter fraction of paracetamol/Eudragit RS 2:1 pellets.

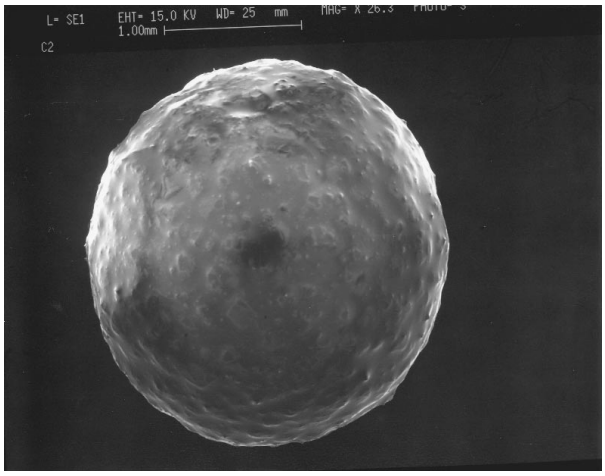


Figure 4. SEM image of the 2800-μm mean diameter fraction of paracetamol/Eudragit RS 1:1 pellets.

pellets with a mean diameter more than 1400 μm increased.

On the other hand, pellets of drug/polymer in the 2:1 ratio could be formed with all the polymers tested even if cellulosic polymers gave a certain percentage of clusters.

The UV analyses confirm the presence of 64–66% drug in the 2:1 pellets and 49–52% in the 1:1 pellets with no substantial variation among the different fractions.

Figures 1 and 2 show the SEM images of 712 μm and 2560 μm mean diameter paracetamol/Eudragit RS 2:1 pellets. Both types of particles are spherical, but bigger

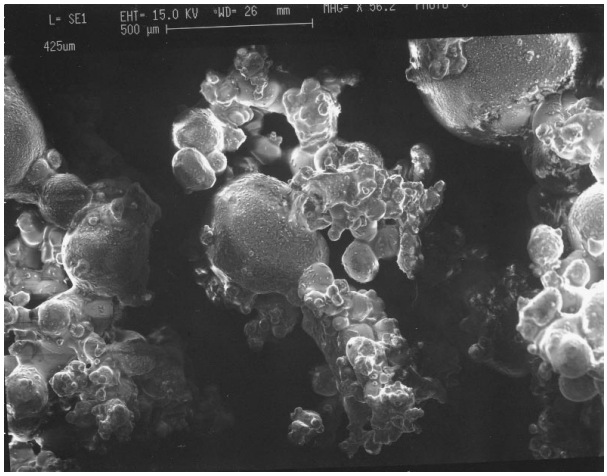


Figure 3. SEM image of the 712-μm mean diameter fraction of paracetamol/Eudragit RS 1:1 pellets.

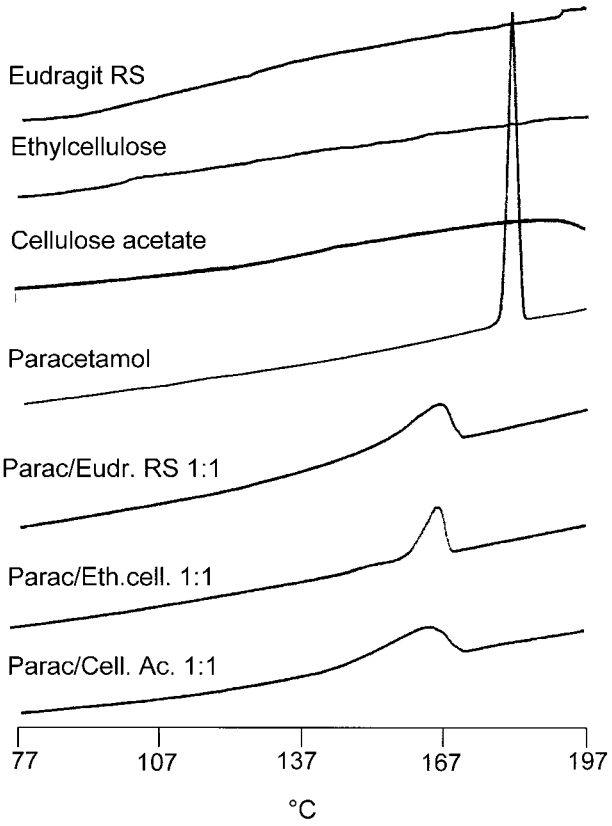


Figure 5. DSC analysis of paracetamol/polymer 1:1 pellets.

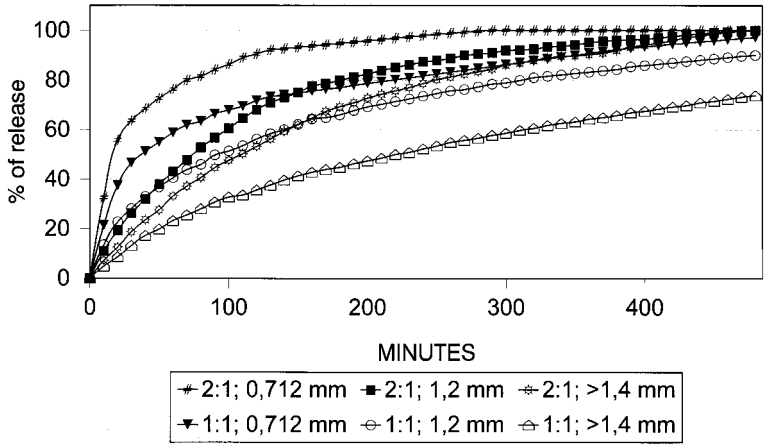


Figure 6. Drug release kinetics of paracetamol/Eudragit RS pellets.

pellets present a smoother surface than the smaller ones, even if pores are visible.

Figures 3 and 4 show the SEM images of 712 μm and 2800 μm mean diameter paracetamol/Eudragit RS 1:1 pellets. While big particles (2800 μm) are very smooth and perfectly spherical, pellets of the 712-μm fraction have clusters of smaller and quasi-spherical particles with a wide dimensional range. Probably, the increased amount of polymer present in the pellet composition makes them stickier when their dimension is small, but at the same time, big particles are more smooth than the corresponding 2:1 pellets.

Images of paracetamol/ethylcellulose and paracetamol/cellulose acetate pellets are similar to those described above and are not shown.

Figure 5 shows the thermograms of the paracetamol/polymer 1:1 pellets compared with those of pure drug and the same polymers. The plots reveal the presence of drug crystals inside the pellet structure. This result indicates that the prepared pellets possess a polynucleated microcapsule structure rather than a matrix structure, even if a partial drug solid solubility in the polymers can be deduced by comparing the enthalpy of fusion data (not shown) of the pure paracetamol with the data for paracetamol/polymer 1:1 peaks.

Dissolution Kinetics

Figures 6–8 show the dissolution profiles of the 0.712-, 1.2-, >1.4-mm fractions of the paracetamol/Eudragit RS, paracetamol/ethylcellulose, and paracetamol/cellulose acetate 2:1 and 1:1 pellets, respectively. Every

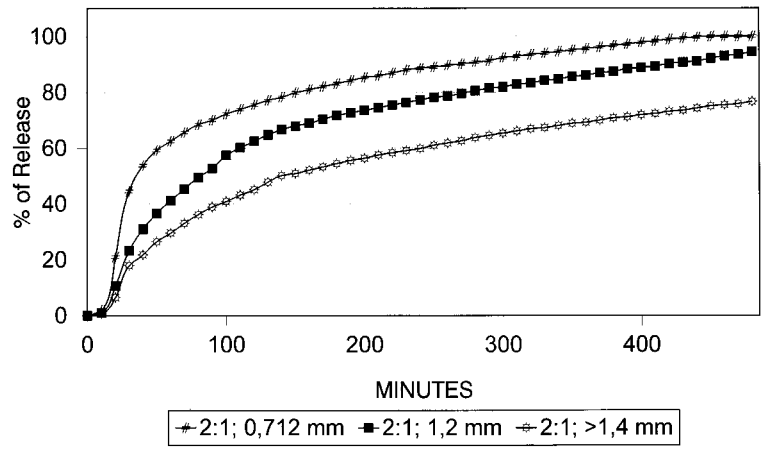


Figure 7. Drug release kinetics of paracetamol/ethylcellulose pellets.

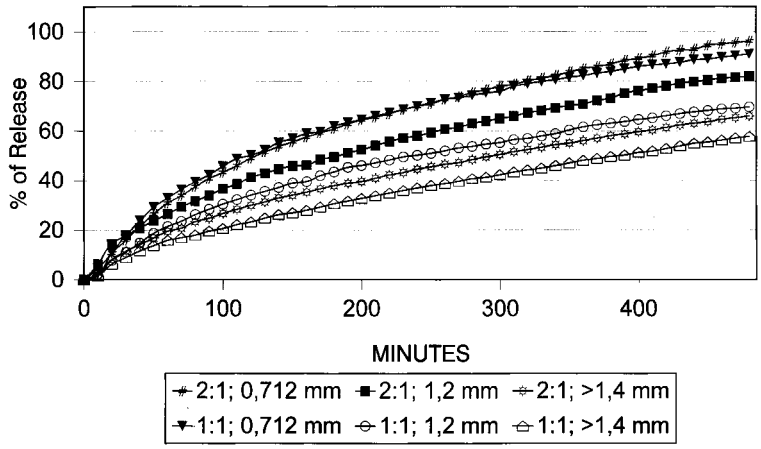


Figure 8. Drug release kinetics of paracetamol/cellulose acetate pellets.

value of the curves is the mean of three experiments, and standard deviation bars are omitted to avoid overlapping.

Some main points can be drawn looking at Figs. 6–8. Pellets always presented a certain capability to slow drug release, but the importance of this phenomenon differed according to the polymer amount and size of the pellets. As expected, paracetamol release was slower in the drug/polymer 1:1 ratio than in the 2:1 ratio pellets of the same size and decreased from the 0.712 mm to the fraction larger than 1.4 mm of certain drug/polymer ratio pellets.

Paracetamol/Eudragit RS pellets (Fig. 6) showed dissolution profiles typical for first-order release kinetics and with considerable drug released in the first 30 min, except for the fractions larger than 1.4 mm, which had a release that was almost linear after 200 min and less drug was released in the first 30 min. The profiles of paracetamol/ethylcellulose pellets (Fig. 7) are very similar to these.

Drug release from paracetamol/cellulose acetate pellets (Fig. 8) was quite gradual, even in the very first minutes, and curves are quasi linear after 100–150 min.

Among pellets having the same drug/polymer ratio and the same size, those containing cellulose acetate were the most effective in paracetamol release control, whereas those containing Eudragit RS were the least effective.

CONCLUSION

Pellets having the structure of a polynucleated microcapsule can be obtained using the method described above. Considerable yields were reached (88% without clusters), particularly at the highest tested stirring speed and at a low polymer content. A better yield was obtained in the pellet preparations with Eudragit RS than with cellulosic polymers.

An optimization of the experimental parameters should be performed to find an exact relationship among particle size, yield, and stirring speed.

All the particle size fractions were spherical, but the biggest ones were smoother, particularly at the higher polymer content.

Pellets possess good capability to slow drug release, particularly when their mean diameter is 1.2 mm or more than 1.4 mm and cellulose acetate is present in the composition.

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