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The preparation of orally disintegrating tablets using a hydrophilic waxy binder

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Abstract

The demand for rapidly disintegrating tablets (RDT) has been growing during the last decade especially for elderly and children who have swallowing difficulties. The problem of certain RDT is their low physical resistance and high friability. This work describes a new approach to prepare RDT with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37 °C and an HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. Granule size distributions of both wet and melt granules of crystallised Paracetamol and D-mannitol were compared using laser light diffractometer. Scanning electron microscopy (SEM) was used to examine their morphological characteristics. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of croscarmellose sodium. An improvement in tablet hardness and friability was observed with both granulation methods where we were able to obtain RDT with a disintegration time of 40 ± 2 s and a hardness of 47.9 ± 2.5N.

Keywords: Rapidly disintegrating tablets; Hydrophilic waxy binder; Wet granulation; Melt granulation; Croscarmellose sodium

1. Introduction

Many patients find difficulty to swallow tablets and hard gelatine capsules, consequently they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy (Seager, 1998; Dobetti, 2001). For this reason the development of an orally disintegrating or rapidly disintegrating tablet (RDT) have recently interested not only the pharmaceutical industry, but also academia (Sastry et al., 2000).

Actually RDT tablets are preferred by an increasing number of patients especially children and elderly, but also adult consumers who like to have their medication readily available at any time. Patients appreciate the convenience and the discreteness of these products which can be taken without water and which guaranty a rapid onset of action (Mallet, 1996; Cremer, 2001).

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Recently the European Pharmacopoeia (European Pharmacopoeia 4.1, 2002) adopted the term orodispersible tablet as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than 3 min. There was no specification concerning neither the hardness nor the friability of this kind of tablets. That is why we find certain RDT in the market that disintegrate in less than 1min or maybe 30 s. but are brittle and require specified peel able blister packaging and thus higher costs (Habib et al., 2000).

Commercially available RDT are prepared by various techniques (Chang et al., 2000), mainly lyophilisation (Laboratoire L.Lefon, 1985; Green and Kearney, 1999), molding (Myers et al., 1995) and direct compression (Bruna et al., 1995; Mizumoto et al., 1996). The lyophilisation and molding techniques produce RDT which disintegrate within about 30 s, but that have low physical resistance and high friability. On the other hand, tablets obtained by direct compression are less friable but disintegrate in a longer time (Dobetti, 2001).

Attempts were made in order to decrease the disintegration time of RDT that have sufficient hardness prepared by direct compression. Bi et al. (1996) and Watanabe et al. (1995) used microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC) as disintegrants to prepare RDT by direct compression. According to the authors the ratios of these two disintegrants MCC/L-HPC in the range of 8:2–9:1 resulted in tablets with the shortest disintegration times. While Bi et al. (1999) and Sunada and Bi (2002) used a wet compression method where wet granules of α-lactose monohydrate were compressed and then the formed wet tablets were dried at 60 °C and kept in a desiccator for 12 h at room temperature. Formed RDT showed a disintegration time of less than 30 s and a hardness of 0.5 MPa. But according to our trials the accomplishment of this technique was quite difficult because of the evaporation that takes place before compression and also compression problems like stickiness and adhesiveness due to the high moisture content of granules to be compressed.

In the present work, the feasibility of a RDT that have both sufficient hardness to withstand all manipulation during processing and a disintegration time of about 40–50 s, using a hydrophilic waxy binder was considered.

Generally, waxy binders are used in the preparation of conventional and sustained release tablets (Jones and Percel, 1994) and more recently in the preparation of fast-release tablets (Perissutti et al., 2003). This explains the importance of the choice of the waxy binder was in our study, as it should increase the tablet hardness and not affect the disintegration time. Superpolystate® (PEG-6-stearate) is a waxy material with a melting point of 33–37 °C and an HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues or grittiness.

Superpolystate® was incorporated in the formulation of RDT by two different methods. Firstly by a wet granulation method where an emulsion of this waxy material was used as a granulating liquid (Farah et al., 2001). And secondly by a melt granulation method where granules were formed by the molten form of this material (Passerini et al., 2002; Perissutti et al., 2003). Crystallised Paracetamol was used as model drug and in addition the formulation included D-mannitol as a water soluble excipient and sodium croscarmellose as disintegrant (Jin et al., 2001).

Thus the first part of our study consisted of the preparation of granules of the active principal and excipients by the two granulation methods and the evaluation of the size and shape characteristics of these granules by laser diffractometry and scanning electron microscopy (SEM). Thereafter, the second part of the study encompassed the preparation of tablets to evaluate the potential of compressing granules prepared using the waxy binder. The potential of the intragranular and the extragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated (Ferrero et al., 1997; Chebli and Cartilier, 1998). Finally, the technological characteristics of the prepared tablets were evaluated in order to find the formula with the least time of disintegration and friability and eventually the best hardness.

2. Materials and methods

2.1. Materials

The following materials were used in the study:

Crystallised Paracetamol (acetaminophen, Coopération pharmaceutique Française, France); D-Mannitol

powder 60 (Roquette, France) was used as a water soluble excipient; Sodium carboxymethyl cellulose (AC.DI.SOL.®, Seppic, France); croscarmellose sodium (Vivasol®, JRS, France) as disintegrants; PEG-6-stearate (Superpolystate®, Gattefossé, France) was used as a waxy binder; Aspartame (Quarrechin, France) as sweetening agent and Magnesium stearate (SPCI, France) as lubricant.

2.2. Methods

2.2.1. Wet granulation

2.2.1.1. Preparation and characterisation of the emulsions "wetting liquid". An oil in water emulsion of Superpolystate® was as used as granulating liquid. The emulsion was prepared according to a direct emulsification process (Roussos et al., 1983). Superpolystate® was heated in a water bath at 45 °C until it completely melted, distilled water heated to the same temperature was then slowly added, and finally the mixture was stirred using a paddle stirrer mixer (RW 20DZM, Kika labortechnik, Germany) at 500 rpm until it reached room temperature. Three different concentrations of the emulsion were prepared (4, 8 and 12% (w/v)). The pH, viscosity and conductivity of each emulsion were measured using a pH meter (Hanna instruments, France), a viscosimeter (Brookfield, Engineering Laboratories Inc.) and a conductivity meter (TDS, Hanna Instruments, France), respectively.

2.2.1.2. Preparation of granules. Throughout the formulation study the Paracetamol concentration was kept constant at 37.4% (w/w). The remaining part of the formulation consisted of D-mannitol and/or AC.DI.SOL. Table 2 gives an overview of the percent composition of the granules prepared by wet granulation. Where the 4% emulsion was used to prepare sample A1, the 8% emulsion was used to prepare sample A2 and the 12% emulsion was used to prepare samples A3, A4 and A6, thus it would be possible to differentiate between the effect of the aqueous phase and that of the waxy binder present in the emulsion, on the granules' size distribution.

Wet granulation took place in a planetary mixer (Kenwood, UK), which operates with a planetary action to ensure that all parts of the mixture are thoroughly mixed. The granulation process was standardised on basis of preliminary trials. Paracetamol, D-mannitol and/or croscarmellose were firstly dry blended for 2 min at 60 rpm then the granulating liquid (emulsion) was added in small quantities under stirring. The formed wet mass was then blended for 5 min at 90 rpm, and dried at 30 °C in a tray oven (Halvatia, France) for 90 min, finally it was sieved through 1 mm mesh in an oscillating calibrator (Erweka-Type FGS).

2.2.2. Melt granulation

Table 2 reports the percent composition of melt granules. Granules were prepared in a high speed blade mixer (Guedu, France), equipped with a heated jacket. The granulation temperature was maintained at 42 ± 2 °C throughout the procedure. Firstly the mixture of powders was blended for 3 min at 330 rpm, then the appropriate quantity of Superpolystate® (cf. Table 2) was added and the mixing phase was continued for further 10 min at 480 rpm. The granulation takes place once the waxy binder melts inside the mixer. At the end of the granulation process the granules were allowed to cool, at room temperature, by spreading them out in thin layers on trays. The sieving process was the same as wet granulation.

All wet and melt samples were prepared in triplets in order to verify the reproducibility of the method.

2.2.3. Granule characterisation and evaluation

Granule size distribution were determined by laser diffraction method. A Malvern Mastersizer S (Malvern Instruments, UK) was used to measure granule size distribution. The diffractometer is equipped with a He–Ne laser with 18 mm beam diameter collimated and spatially filtered to a single transverse mode. The active beam length was 10 mm, and a 1000 mm lens was used for the measurements with a range of 4–500 μm. The samples were introduced using a dry powder feeder (Malvern Instruments, UK) at a feed rate of 3.0 G and a jet pressure of 2.4 Bar. All measurements were made in triplets to assure the reproducibility of the method. The mass or the volume moment mean diameter (or the Brouckere mean, $D[4,3]$) and the 10, 50 (median) and 90% fractiles were also determined using the Mastersizer software version 2.18 (Malvern Instruments, UK). Particle diameter versus the volume in % curves (frequency curves) were also traced for each sample.

The bulk density (ρ_t) and the tap density (ρ_b) were determined with a volume presser (Stampf volumeter, StAV2003, Germany) that dropped 10 and 2000 times, respectively. For each sample, the compactability index or Carr index was calculated according to the following equation: $I_c = 100(\rho_t - \rho_b)/\rho_t$ and the Hausner ratio was calculated according to the following equation: $R_H = (\rho_t)/\rho_b$ (Moneghini et al., 2000). Finally, to investigate the morphology of the formed granules, scanning electron micrographs were taken using (JOEL JSM-35 CF) scanning electron microscope; where the samples were previously sputter-coated with gold.

2.2.4. Preparation of the tablets

Prior to compression, each sample of granules was dry blended with 8.6% croscarmellose (Vivasol®) as an external phase disintegrant, 2.9% Aspartame and 0.5% Magnesium stearate, using a flexible mixer (Turbula T2C, Switzerland) for 10 min at 40 rpm. A single punch tabletting machine (Korsch KO, France), equipped with flat faced punches with a die diameter of 11 mm, was employed to prepare tablets with an average weight of 600 mg and at a rate of 54 tablets per minute.

2.2.5. Tablet properties

The mean weight of 20 tablets of each batch was determined using an electronic balance (Mark, Italy), in order to verify the uniformity and conformity of the tablets within each batch (European Pharmacopoeia, 2002). The mean weight is expressed in mg ± S.D.

The friability of 20 tablets from each lot was determined using a friabilator (Erweka TAR, France) at 25 rpm for 4 min. The friability is expressed in terms of weight loss and is calculated in percentage (% ± S.D.) of the initial weight.

A hardness tester (Vanderkamp, Germany) was used to measure the crushing strength of tablets. Ten tablets from each lot were analysed. The mean hardness was calculated and expressed in Newton (N ± S.D.).

Finally the mean disintegration time of six tablets from each lot was determined in seconds (±S.D.) using the disintegration test apparatus (Sotax, DT3, France). Distilled water kept at 37 °C was used as a medium and the basket was raised and lowered at a constant frequency of 30 cycles/min.

3. Results and discussion

3.1. Evaluation of prepared emulsion

Table 1 shows the pH, viscosity and conductivity of prepared emulsions containing 4, 8 and 12% Superpolystate®. We note that the viscosity of the emulsion increases with increasing the Superpolystate® concentration, where an increase from 208 MPa s with the 4% emulsion to 3250 MPa s with the 12% emulsion is observed. While for the pH and conductivity, we notice that after a certain concentration of Superpolystate®, their values slightly varied, as we can see with the 8 and 12% emulsions.

3.2. Granule size distribution and granule compactability

The results obtained from the laser diffractometer for both wet and melt granules are shown in Table 3 and Fig. 1. The effect of the concentration of Superpolystate® is clearly observed in wet granules A1, A2 and A3, prepared using 4, 8, and 12% emulsions, respectively, where an increase in all granule size fractiles and mean diameter is noted. Since the same quantity of emulsion or granulating liquid was used to prepare these three samples, this increase in granule size could be attributed to the binder concentration and not that of the aqueous phase. In addition the residual humidity in these three samples was the same after drying. The 12% emulsion was used to prepare samples A3, A4 and A6. The quantity of the emulsion added to each sample was varied in order to obtain the desired percentage of the waxy binder in the final granules, which was 1.2% for A3 and 2.5% for A4 and A6 (cf. Table 2).

Concerning wet granulation, the binder concentration that gave the best granules was the 2.5%, where the mean diameter and the granule size fractiles were

Table 1
Technological characterisation of the emulsions

Emulsion (%)	pH	Conductivity (μs/cm)	Viscosity (MPa s)
4	5.86	111.2	208
8	4.77	51.4	920
12	4.69	49.5	3250

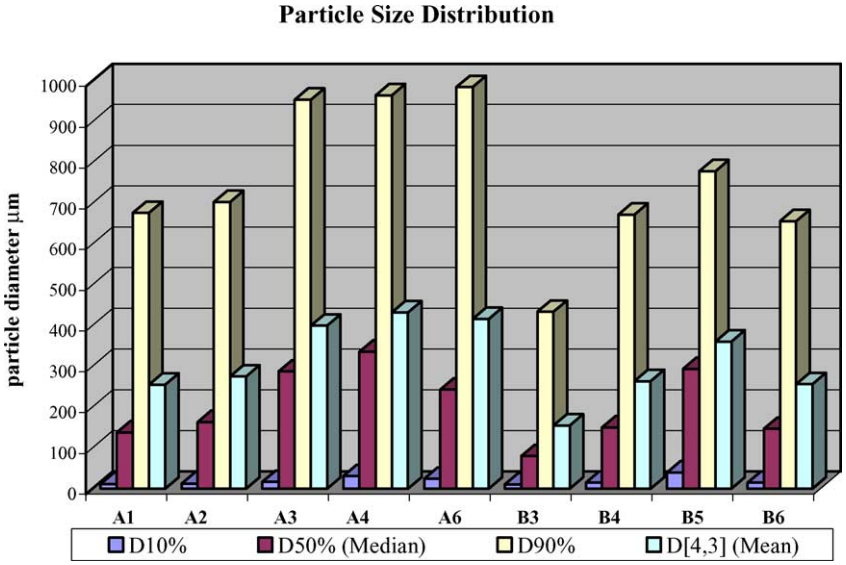

Fig. 1. Granule size fractiles prepared by wet and melt granulation.

the highest. Further increase in the concentration of Superpolystate® was not possible due to the formation of a pasty mass. We also note differences in the granule size values between A4 and A6, which have the same binder concentration. This could be explained by the presence of intragranular croscarmellose (AC.DI.SOL.) which is a powerful disintegrant that absorbs a quantity of the disintegrating liquid.

In the case of melt granules B3, B4, B5 and B6 (cf. Table 2) an increase in granule size fractiles and mean diameter was also observed with increasing binder concentration where the highest values were obtained with the 5% concentration B6 (cf. Fig. 1).

Fig. 2a and b represent granule size distributions curves of wet and melt granules, respectively. We can notice that none of these curves show a Gaussian distribution, which explains the differences in the mean and median diameter values. Nevertheless, as the concentration of Superpolystate® increases the curves become more regular in form and show higher mode values, where the mode is the most common value of the frequency distribution represented by the highest point in the frequency curve (Rawle, 1993).

From these results we can deduce that wet granules show higher granule size and mean diameter values, for the same binder concentration, than melt granules (see Table 3 and Fig. 3). This could be explained by the fact that using an emulsion of Superpolystate® as a granulating liquid enables a better distribution of the binder over the particles as it is already in the form of fine droplets which improves its binder effect, and also the presence of the aqueous phase (distilled water) enhances the formation of granules (Murakami et al., 2001).

Table 2
Percent compositions of granules prepared by wet and melt granulation

Samples wet granulation	Paracetamol	Mannitol	AC.DI.SOL.	Superpolystate®	Samples melt granulation
A1	37.4	50.6	–	0.4	
A2	37.4	50.6	–	0.8	
A3	37.4	50.6	–	1.2	B3
A4	37.4	50.6	–	2.5	B4
	37.4	50.6		5	B5
A6	37.4	48.6	2	2.5	B6

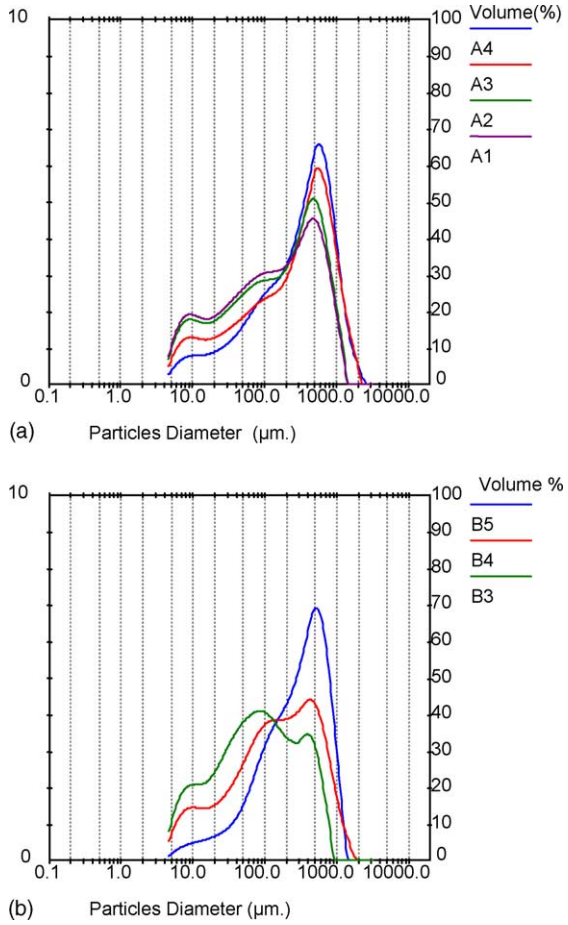

Fig. 2. (a) Granule size distribution curves or frequency curves of granules prepared by wet granulation. (b) Granule size distribution curves prepared by melt granulation.

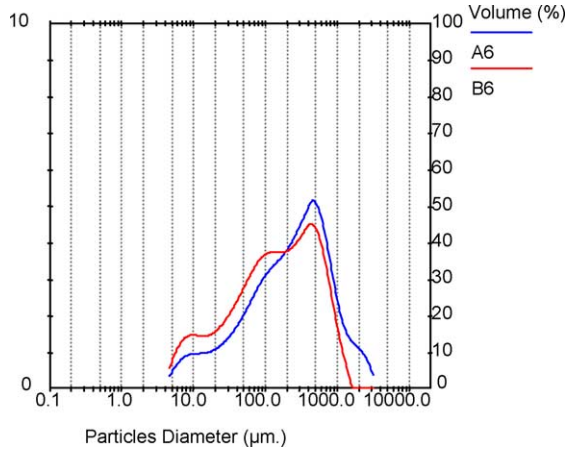

Fig. 3. Granule size distribution curves of batches A5 and B4. Comparison between wet and melt granules containing the same concentration of Superpolystate®.

Table 4 reports the bulk density, tap density, compactability index CI and Hausner ratio for all studied batches. According to the literature data (Wells, 1997), powders with a CI between 5 and 18% are suitable for producing tablets, and those with a Hausner ratio below 1.25 are of good flowability. All studied formulations, except B5 granules, had a CI between 8.707 and 16.203 and a Hausner ratio below 1.25. For B5 granules, both CI and Hausner ratio exceeded these values, thus only melt granules containing 5% Superpolystate® were not suitable for compression.

3.3. Scanning electron microscopy

The morphology and surface properties of certain wet and melt granules were visualised using scanning electron microscopy.

Table 3
Granules size fractiles, $n = 3$

Samples	$D_{10\%}$ (μm) ± S.D.	$D_{50\%}$ (μm) ± S.D.	$D_{90\%}$ (μm) ± S.D.	Mean diameter (μm) ± S.D.
A1	11.21 ± 0.79	137.7 ± 9.54	676.23 ± 40.09	254.77 ± 19.98
A2	11.95 ± 0.61	162.73 ± 10.72	702.51 ± 38.8	274.41 ± 18.82
A3	16.67 ± 0.35	287.02 ± 7.59	953.58 ± 21.39	399.34 ± 10.57
A4	30.36 ± 0.58	335.64 ± 6.67	964.01 ± 15.22	431.83 ± 8.05
A6	24.02 ± 0.49	242.73 ± 4.26	984.53 ± 14.7	415.89 ± 5.22
B3	10.74 ± 0.64	79.7 ± 4.1	433.5 ± 26.77	154.75 ± 9.5
B4	14.69 ± 0.33	150.01 ± 2.75	672.09 ± 11.33	263.44 ± 5.11
B5	39.44 ± 1.12	293.19 ± 6.82	778 ± 17.01	360.12 ± 7.4
B6	14.55 ± 0.27	146.6 ± 2.01	656.08 ± 8.69	256.04 ± 3.72

Table 4
Compactability of granules, $n = 3$

Samples	ρ_{10} (g/ml) ± S.D.	ρ_{2000} (g/ml) ± S.D.	CI (Carr Index) ± S.D.	Hausner ratio ± S.D.
A1	0.685 ± 0.004	0.781 ± 0.009	12.291 ± 0.533	1.140 ± 0.007
A2	0.681 ± 0.003	0.751 ± 0.006	9.320 ± 0.399	1.102 ± 0.005
A3	0.671 ± 0.003	0.735 ± 0.004	8.707 ± 0.245	1.095 ± 0.003
A4	0.579 ± 0.002	0.666 ± 0.003	13.063 ± 0.116	1.150 ± 0.002
A6	0.581 ± 0.003	0.639 ± 0.002	9.077 ± 0.173	1.099 ± 0.002
B3	0.693 ± 0.005	0.827 ± 0.007	16.203 ± 0.324	1.193 ± 0.005
B4	0.606 ± 0.003	0.711 ± 0.004	14.768 ± 0.236	1.173 ± 0.003
B5	0.512 ± 0.004	0.638 ± 0.003	19.749 ± 0.369	1.246 ± 0.006
B6	0.597 ± 0.004	0.707 ± 0.004	15.559 ± 0.202	1.184 ± 0.003

Wet granules of batches A3 and A4 are presented at three magnifications in Figs. 4a–c and 5a–c, respectively. We observe that as the concentration of the binder increases from 1.2 to 2.5%, the granules appear slightly larger, more circular and show different surface properties. Figs. 6a–c and 7a–c show melt granules B4 and B5, respectively, where granules of B4 appear typically acicular and smaller in size than those of B5.

From these micrographs we deduce that the granule size increased with increasing binder concentration for each granulation method separately. But if we compare wet and melt granules we observe the clear difference in their size and surface, where wet granules appear larger in size and more circular than melt granules even with higher concentration of Superpolystate®. The small dimension of melt granules could be attributed to the shearing action of the granulating mixer (Guedu), as well as the unequal or coarse distribution of the waxy binder on the particles (Fig. 7c). This coarse distribution could be explained by the type of mixer (Guedu) used in melt granulation, which requires a higher quantity of the binder in order to obtain a homogenous distribution.

3.4. Evaluation of prepared tablets

The subsequent step consisted in the preparation of tablets. Although granules A1, A2 and B3 had good compactability and flowability, they were not subjected to compression as preliminary trials with similar concentrations showed that the positive effect of Superpolystate® on tablet hardness is observed in a concentration higher than that contained in these samples.

Hence after addition of the external phase (composed of croscarmellose, aspartame and magnesium stearate) to the granules, following the procedure reported earlier, samples A3, A4, A6, B4, B5 and B6 were tabletted. For sample B5 the compression process was difficult as the granules showed bad compactability and flowability (cf. Table 4), in addition the high concentration of the waxy binder caused compression problems like stickiness to the punches of the compression machine. Nevertheless we were able to produce tablets in order to verify the effect of this high binder concentration over tablet's disintegration time.

Table 5 shows the technological characterisation of compressed tablets. All tablets were acceptable

Table 5
Technological characterisation of tablets, $n = 3$

Samples	Mean weight (mg) ± S.D.	Friability (%) ± S.D.	Hardness (N) ± S.D.	Disintegration time (s) ± S.D.
A3	618 ± 4.6	2.059 ± 0.023	27.8 ± 0.4	37 ± 1
A4	614 ± 7.2	0.879 ± 0.01	41.2 ± 1.3	58 ± 2
A6	615 ± 5.7	0.556 ± 0.005	47.9 ± 2.5	40 ± 2
B4	611 ± 9	0.523 ± 0.009	53.6 ± 2.7	91 ± 3.6
B5	622 ± 6.2	1.447 ± 0.011	30.8 ± 2.1	135 ± 6
B6	620 ± 8	0.482 ± 0.019	54.3 ± 1.8	67 ± 2.6

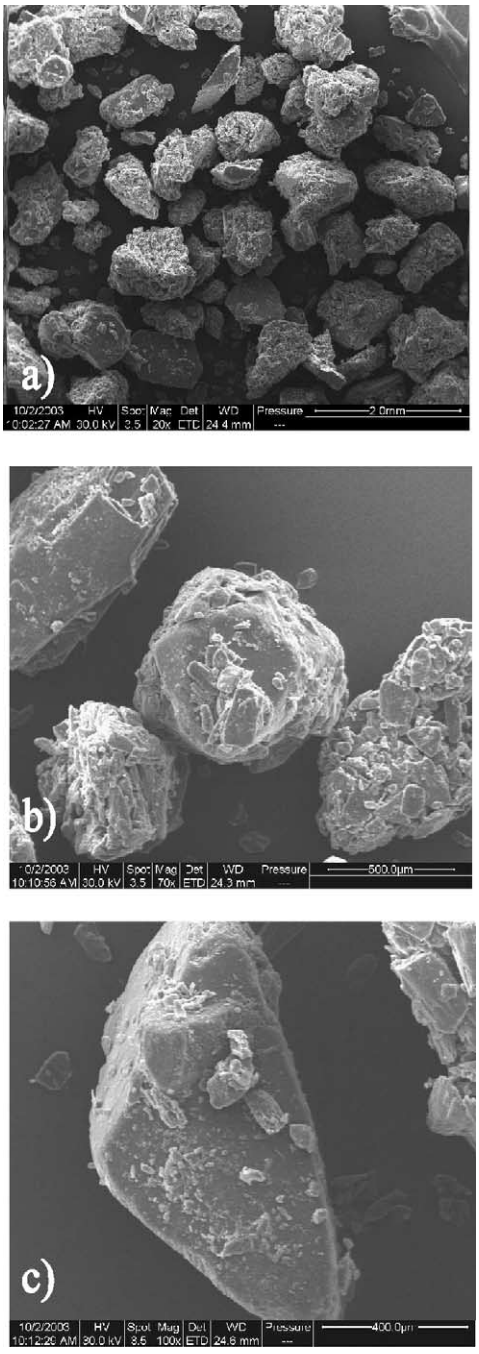

Fig. 4. (a–c) Scanning electron micrographs of A3 at three magnifications.

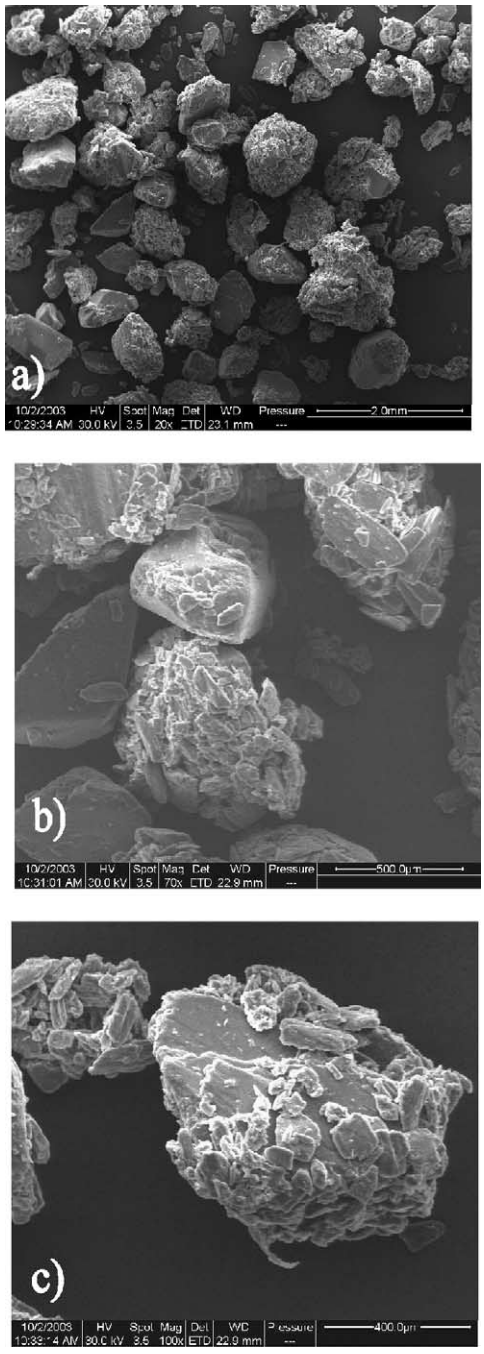

Fig. 5. (a–c) Scanning electron micrographs of A4 at three magnifications.

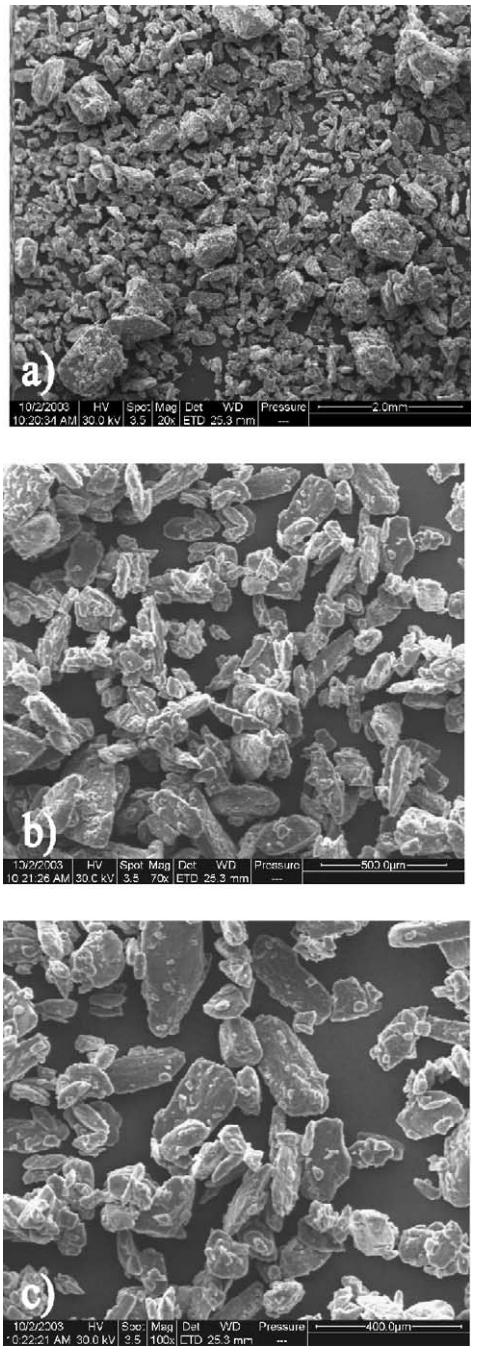

Fig. 6. (a–c) Scanning electron micrographs of B4 at three magnifications.

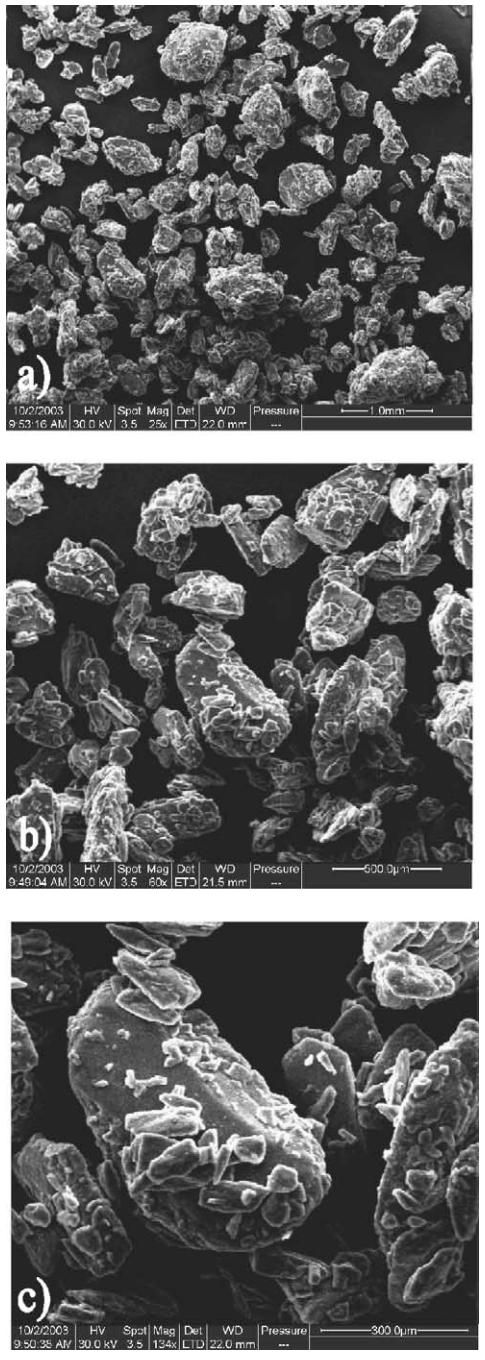

Fig. 7. (a–c) Scanning electron micrographs of B5 at three magnifications.

in terms of uniformity of mass (European Pharmacopoeia, 1997). The hardness of wet granulation tablets increased and their friability decreased as the Superpolystate® content increased whilst in melt granulation tablets this effect was inversed. In addition, B5 tablets had cleaving problems. For wet granulation and melt granulation tablets we notice an increase in the disintegration time, which was more significant for batches B4 and B5. This could be explained by the formation of a binder matrix in melt granules upon compression which could not be destroyed by extragranular disintegrant as reported by Abberger (2001).

Although the obtained disintegration times did not exceed the limit reported by the European Pharmacopoeia for RDT, we were able to decrease this time by the addition of 2% intragranular croscarmellose. This enabled a considerable decrease in the disintegration time, without affecting neither the hardness nor the friability of the tablets, as observed for tablets A6 and B6 (cf. Table 5).

Wet granulation tablets gave better disintegration results than melt granulation tablets, where we note the best formula obtained was A6 with a hardness of 47.9 ± 2.5 N and a disintegration time of 40 ± 2 s.

4. Conclusions

Although RDT is a dosage form that is appreciated by patients because of their convenience and discreteness, it represents some disadvantages notably their high friability and low physical resistance, which causes manipulation problems not only during their processing but also with patients. We were able to prove through this work that the utilisation of a waxy hydrophilic binder Superpolystate® is an innovating and a viable means in the preparation of RDT as it enables an increase in the physical resistance without exceeding the disintegration time limitations specified in the European Pharmacopoeia 4.1 (2002), for this type of tablets.

In fact, waxy binders are essentially used in the preparation of conventional and prolonged release tablets, but the hydrophilic and melting point properties of the studied binder enabled the formulation of RDT using two different methods: wet and melt granulation. The melt granulation tablets gave better hardness results whilst the disintegration times of wet granulation tablets were more favourable.

However, the intragranular addition of a powerful disintegrant as croscarmellose was proved efficient in decreasing the disintegration time of melt and wet granulation tablets, where we were able to obtain RDT with a disintegration time of 40 ± 2 s and a hardness of 47.9 ± 2.5 N.

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