

THE UTILIZATION OF A HYDROPHILIC WAXY BINDER IN THE PREPARATION OF ORALLY DISINTEGRATING TABLETS BY MEANS OF TWO DIFFERENT GRANULATION METHODS

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في الأونة الأخيرة قد زاد الطلب على أقراص سريعة التفنت وخاصة للمرضى كبار السن والأطفال غير القادرين على البلع. والمشكلة لتحضير هذه الأقراص هي قلة المقاومة الفيزيائية حيث تكون سريعة التفنت. وفي هذا البحث تم تحضير أقراص سريعة التفنت ولكن لها قوة تحمل فيزيائية وهذه الأقراص تعتمد على أنها تتصهر في الفم وتذوب بسرعة ولا تترك بقايا. ولتحضير مثل هذه الأقراص تم خلط مادة السوبربوليستات بواسطة طريقتين: الأولى تحضير الحبيبات بالطريقة الرطبة وذلك باستخدام مستحلبات المواد الشمعية كسائل لتحضير الحبيبات، الثانية طريقة الصهر حيث يستخدم الشكل المنصهر للمواد الشمعية في تحضير الحبيبات. وقد تم في هذا البحث تقييم حجم الحبيبات المحضرة بالطريقتين لعقار الباراسيتامول المبلور وكذلك للمانيتول. وقد استخدم جهاز الليزر الضوئي التشتتي وكذلك ميكروسكوب المسح الإلكتروني لفحص شكل الحبيبات بالإضافة إلى ذلك فقد أتبع خطوات متتالية لتحضير وتقييم الأقراص وتحسين درجة الصلابة وسرعة التفنت في كلا الطريقتين وقد أسفرت النتائج عن تحضير صياغة لها وقت تفنت = ± ثانية وصلابة = ± N.

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° and an HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but it will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues. The incorporation of Superpolystate[®] in the formulation of RDT was realized 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 granulates 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 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. 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±2.5 N.

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.^{1,2} 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.³

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 discreetness of these products which can be taken without water and which guaranty a rapid onset of action.^{4,5}

Recently the European Pharmacopoeia⁶ 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 1 min or may be 30 sec but are brittle and require specified peel able blister packaging and thus higher costs.⁷

Commercially available RDT are prepared by various techniques,⁸ mainly lyophilisation,^{9,10} molding¹¹ and direct compression.^{12,13} The lyophilisation and molding techniques produce RDT which disintegrate within about 30 sec, 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.²

Attempts were made in order to decrease the disintegration time of RDT that have sufficient hardness prepared by direct compression. Microcrystalline cellulose and low-substituted hydroxypropyl cellulose were used as disintegrants to prepare RDT by direct compression.^{14,15} Where ratios of these two disintegrants in the range of 8:2-9:1 resulted in tablets with the shortest disintegration times. A wet compression method^{16,17} where wet granules of α -lactose monohydrate were compressed and then the formed wet tablets were dried at 60° and kept in a desiccator for 12 h at room temperature. Formed RDT showed a disintegration time of less than 30 sec 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 sec, using a hydrophilic waxy binder was considered.

Generally, waxy binders are used in the preparation of conventional and sustained release tablets¹⁸ and more recently in the preparation of fast-release tablets.¹⁹ This explains the importance of the choice of the waxy binder 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° 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 solubilises 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.²⁰ And secondly by a melt granulation method where granules were formed by the molten form of this material.^{19,21} 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.²²

Thus the first part of our study consists of the preparation of granulates of the active principal and excipients by the two granulation methods and the evaluation of the size and shape characteristics of these granulates 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 granulates prepared using the waxy binder. 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.

MATERIALS AND METHODS

Materials

The following materials were used in the study: Crystallised Paracetamol (acetaminophen, Coop ration 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.

Methods

Wet granulation

Preparation and characterisation of the emulsions €wetting liquid•

An oil in water emulsion of Superpolystate[®] was used as granulating liquid. The emulsion was prepared according to a direct emulsification process.²³ Superpolystate[®] was heated in a water bath at 45° 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). Table 1 shows the characterisation of each one.

Table 1: Technological characterisation of the emulsions.

Emulsion	PH	Conductivity (µg/cm)	Viscosity (mpa.s)
4%	5.86	111.2	208
8%	4.77	51.4	920
12%	4.69	49.5	3250

Preparation of granulates

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 granulates 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 A5, thus it would be possible to differentiate between the effect of the aqueous phase and that of the waxy binder on the granules€ size distribution.

Wet granulation took place in a planetary mixture (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 during stirring. The formed wet mass was then blended for 5 min at 90 rpm, and dried at 30° in a tray oven (Halvatia, France) for 90 min. Finally it was sieved through 1 mm mesh in an oscillating calibrator (Erweka-Type FGS).

Melt granulation

Table 2 reports the percent composition of melt granulates. Granules were prepared in a high speed blade mixer (Guedu, France), equipped with a heated jacket. The granulation temperature was maintained at 42±2° throughout the procedure. Firstly the mixture of

Table 2: Percent compositions of granulates 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	B1
A4	37.4	50.6	-	2.5	B2
	37.4	50.6		5	B3
A5	37.4	48.6	2	2.5	B4

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. 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.

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 18mm beam diameter collimated and spatially filtered to a single transverse mode. The active beam length was 10 mm, and a 1000mm lens was used for the measurements with a range of 4 μm -3500 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% fractions 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: $I_c = 100 * \frac{(\rho_t - \rho_b)}{\rho_t}$ and the

Hausner ratio was calculated according to the following equation: $R_H = \frac{(\rho_t)}{\rho_b}$.²⁴

Finally, to investigate the morphology of the formed granulates, scanning electron micrographs were taken using (JOEL JSM-35 CF) scanning electron microscope (SEM); where the samples were previously sputter-coated with gold.

Preparation of the tablets

Prior to compression, each sample of granulates 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. An alternative tableting 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.

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.⁶

The friability of 20 tablets from each lot was also determined using a friabilator (Erweka TAR, France) at 25 rpm for 4 min.

A hardness tester (Vanderkamp, Germany) was used to measure the crushing strength of tablets. Ten tablets from each lot were analysed.

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

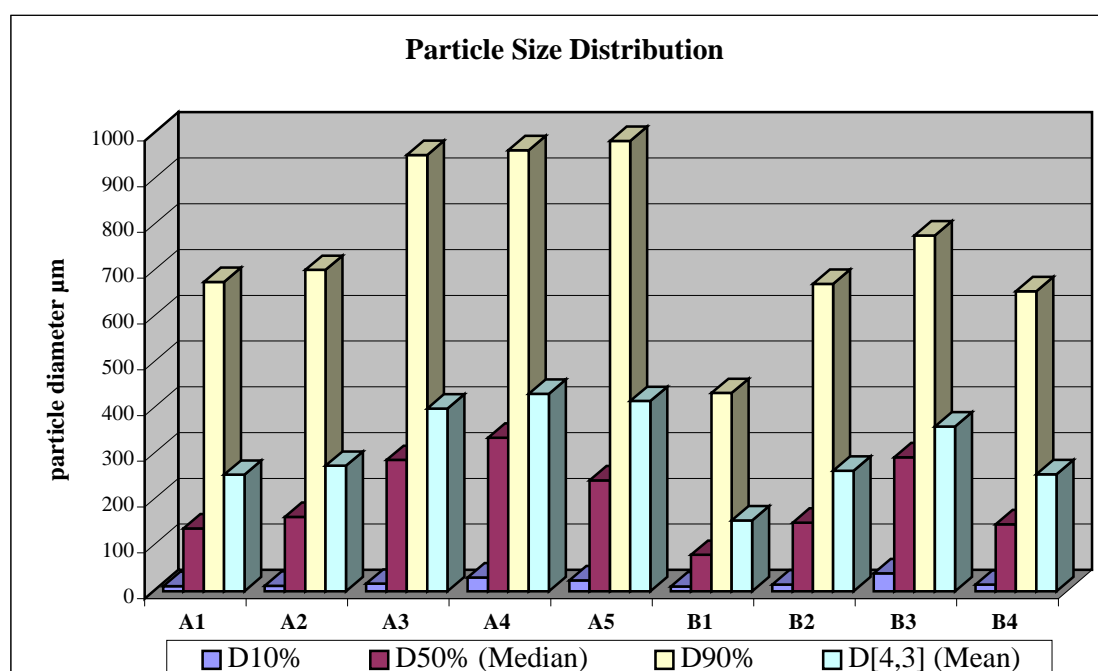
RESULTS AND DISCUSSION

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 granulates (A1, A2 and A3) prepared using 4%, 8%, and 12% emulsions respectively, where an increase in all granule size fractions 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 to that of the aqueous phase. In addition the residual humidity in these three samples was the same after drying.

Table 3: Granules size fractions, 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
A5	24.02 ± 0.49	242.73 ± 4.26	984.53 ± 14.7	415.89 ± 5.22
B1	10.74 ± 0.64	79.7 ± 4.1	433.5 ± 26.77	154.75 ± 9.5
B2	14.69 ± 0.33	150.01 ± 2.75	672.09 ± 11.33	263.44 ± 5.11
B3	39.44 ± 1.12	293.19 ± 6.82	778 ± 17.01	360.12 ± 7.4
B4	14.55 ± 0.27	146.6 ± 2.01	656.08 ± 8.69	256.04 ± 3.72

**Fig. 1:** Granule size fractions prepared by wet and melt granulation.

Concerning wet granulation, the binder concentration that gave the best granulates was the 2.5%, where the mean diameter and the granule size fractions were 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 A5 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 granulates (B1, B2, B3 and B4) an increase in granule size fractions and mean diameter was also observed with increasing binder concentration where the highest values were obtained with the 5% concentration.

Fig. 2 (a) and (b) represent granule size distributions curves of wet and melt granulates 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.²⁵

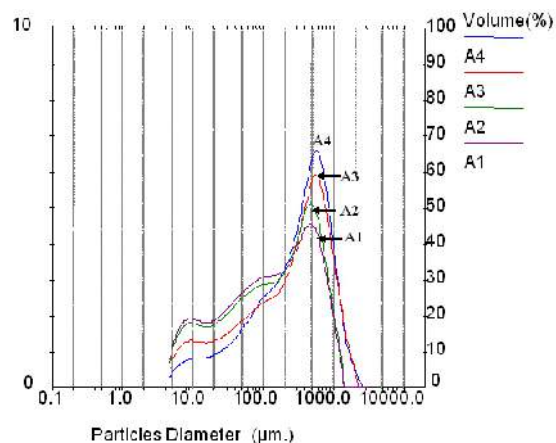


Fig. 2a: Granule size distribution curves or frequency curves of granules prepared by wet granulation.

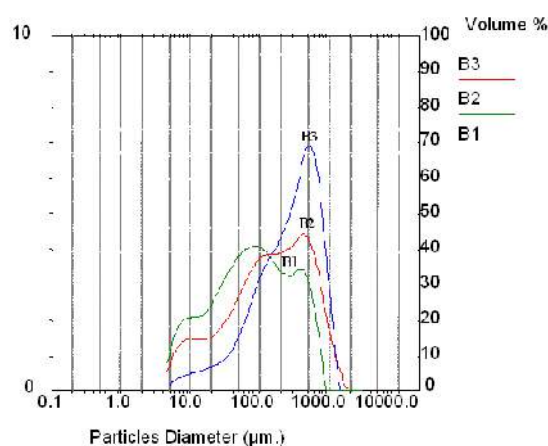


Fig. 2b: Granule size distribution curves prepared by melt granulation.

From these results we can deduce that wet granulations show higher granule size and mean diameter values, for the same binder concentration, than melt granulates (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 granulates.²⁶

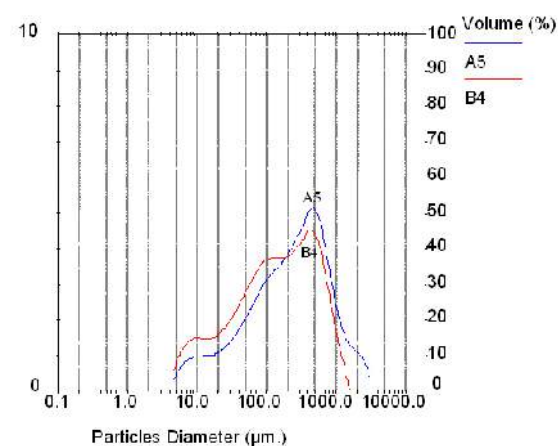


Fig. 3: Granule size distribution curves of batches A5 and B4. Comparison between wet and melt granulates containing the same concentration of Superpolystate®.

Table 4 represents the bulk density, tap density, compactability index CI and Hausner ratio for all studied batches. According to the literature data,²⁷ powders with a CI between 5% and 18% are suitable for producing tablets, and those with a Hausner ratio below 1.25 are of

Table 4: Compactability of granulates, n = 3.

Samples	ρ_{10} (g/ml) \pm S.D.	ρ_{2000} (g/ml) \pm S.D.	CI (Carr Index) \pm S.D.	Hausner ratio \pm S.D.
A1	0.685 \pm 0.004	0.781 \pm 0.009	12.291 \pm 0.533	1.140 \pm 0.007
A2	0.681 \pm 0.003	0.751 \pm 0.006	9.320 \pm 0.399	1.102 \pm 0.005
A3	0.671 \pm 0.003	0.735 \pm 0.004	8.707 \pm 0.245	1.095 \pm 0.003
A4	0.579 \pm 0.002	0.666 \pm 0.003	13.063 \pm 0.116	1.150 \pm 0.002
A5	0.581 \pm 0.003	0.639 \pm 0.002	9.077 \pm 0.173	1.099 \pm 0.002
B1	0.693 \pm 0.005	0.827 \pm 0.007	16.203 \pm 0.324	1.193 \pm 0.005
B2	0.606 \pm 0.003	0.711 \pm 0.004	14.768 \pm 0.236	1.173 \pm 0.003
B3	0.512 \pm 0.004	0.638 \pm 0.003	19.749 \pm 0.369	1.246 \pm 0.006
B4	0.597 \pm 0.004	0.707 \pm 0.004	15.559 \pm 0.202	1.184 \pm 0.003

good flowability. All studied formulations, except B3 granulates, had a CI between 8.707 and 16.203 and a Hausner ratio below 1.25. For B3 granulates, both CI and Hausner ratio exceeded these values, thus only melt granulates containing 5% Superpolystate[®] were not suitable for compression into tablets.

Scanning electron microscopy

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

Wet granulates of batches A3 and A4 are presented at three magnifications in Fig. 4a,b,c and Fig. 5a,b,c respectively. We observe that as the concentration of the binder increases from 1.2% to 2.5%, the granulates appear slightly larger, more circular and show different surface properties. Fig. 6a,b,c and Fig. 7a,b,c show melt granulates B2 and B3 respectively, where granulates of B2 appear typically acicular and smaller in size than those of B3.

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 granulates we observe the clear differences in their size and surface, where wet granulates appear larger in size and more circular than melt granulates even with higher concentration of Superpolystate[®]. The small dimension of melt granulates could be attributed to the shearing action of the granulating mixer (Guedu). In spite of the binder fusion in melt granulation, it is not well distributed on the particles (Fig. 7c), thus it would be necessary to have a higher concentration of the binder in order to produce granulates equivalent to those prepared by wet granulation.

Evaluation of the prepared tablets

The subsequent step consisted in the preparation of tablets. Although granulates A1, A2 and B1 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 granulates, following the procedure reported earlier, samples A3, A4, A5, B2, B3 and B4 were tableted. For sample B3 the compression process was difficult as the granulates showed bad compactability and bad 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 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 in terms of uniformity of mass.²⁸ The hardness of wet granulation tablets increased and their friability decreased as the Superpolystate[®] content increased whilst in melt granulation tablets this effect was inverted. In addition, B3 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 B2 and B3. This could be explained by the formation of a binder matrix in melt granulates upon compression which could not be destroyed by extragranular disintegrant as what has been reported.²⁹

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.

Wet granulation tablets gave better disintegration results than melt granulation tablets, where we note the best formula obtained was A5 with a hardness of 47.9 ± 2.5 N and a disintegration time of 40 ± 2 s.

Fig. 4 (a,b,c): Scanning Electron micrographs of A3 at 3 magnifications.

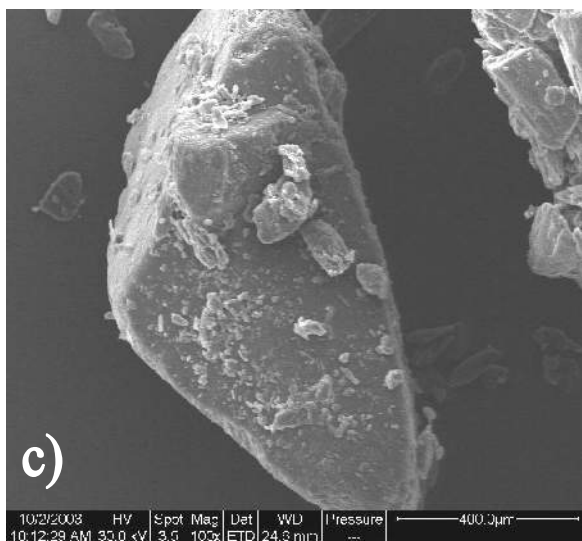
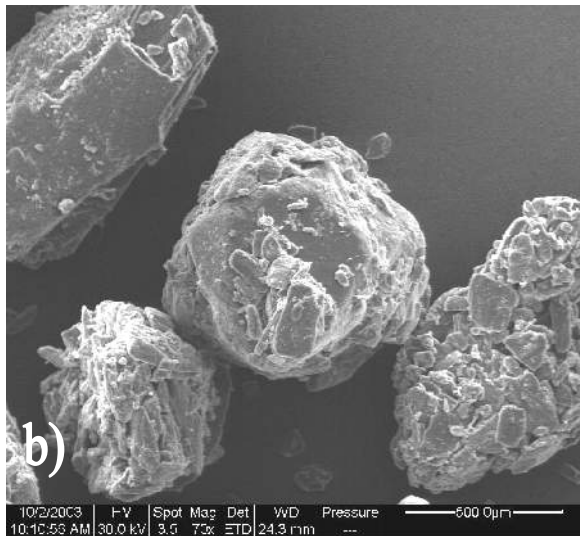
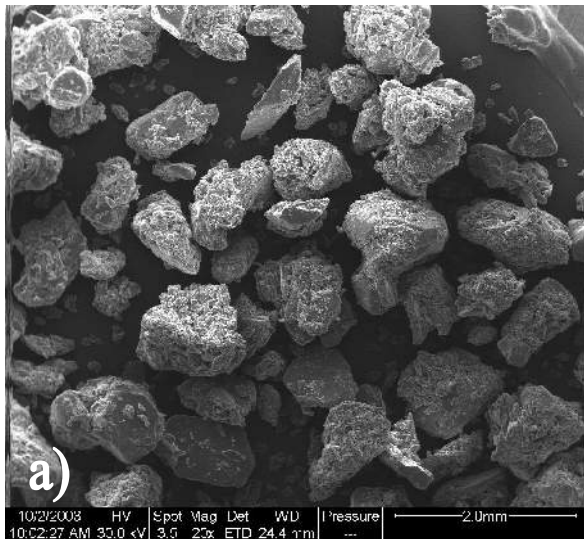


Fig. 5 (a,b,c): Scanning Electron micrographs of A4 at 3 magnifications.

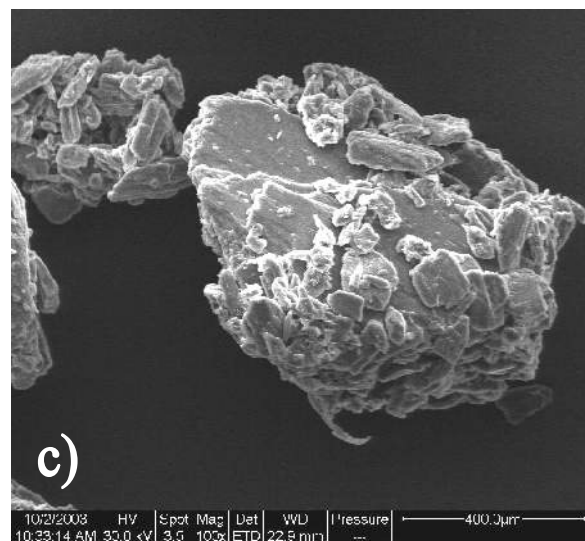
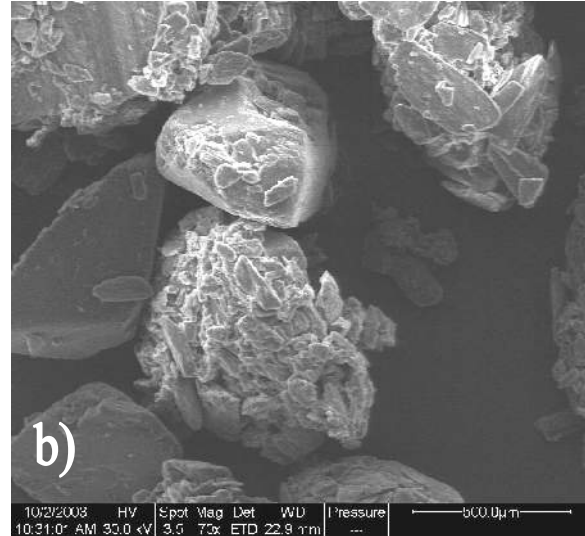
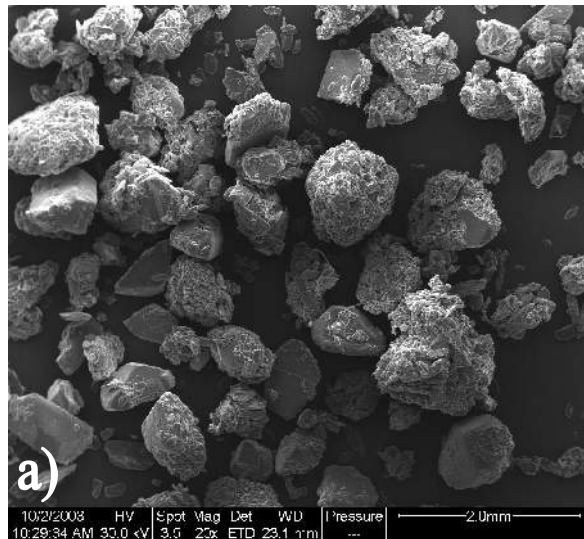


Fig. 6 (a,b,c): Scanning Electron micrographs of B2 at 3 magnifications.

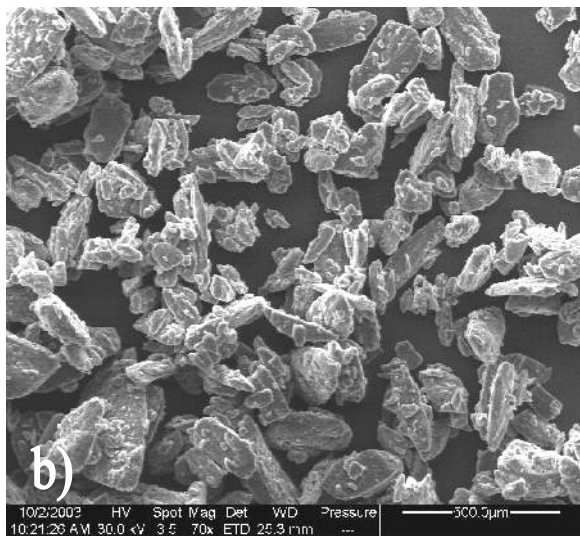
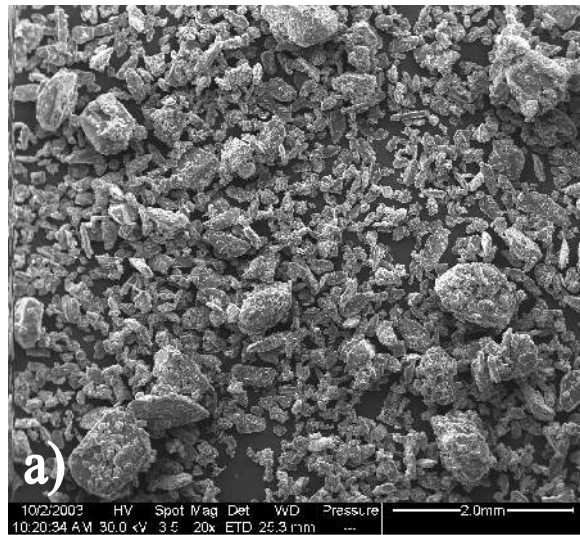


Fig. 7 (a,b,c): Scanning Electron micrographs of B3 at 3 magnifications.

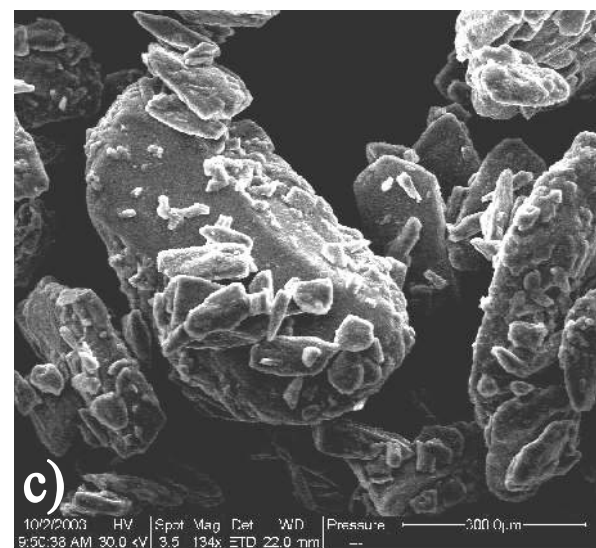
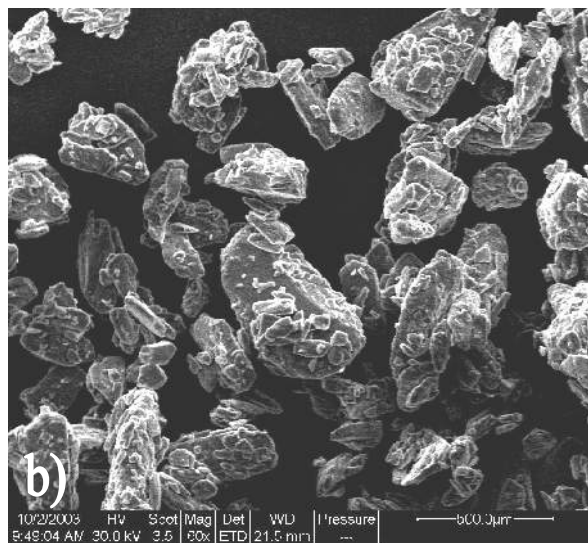
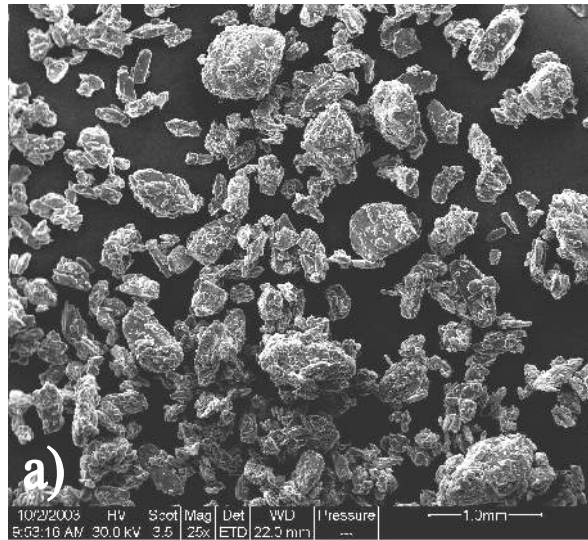


Table 5: Technological characterisation of tablets, n = 3.

Samples	Mean weight (mg) ± S.D.	Friability (%) ± S.D.	Hardness (N) ± S.D.	Disintegration time (sec) ± 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
A5	615 ± 5.7	0.556 ± 0.005	47.9 ± 2.5	40 ± 2
B2	611 ± 9	0.523 ± 0.009	53.6 ± 2.7	91 ± 3.6
B3	622 ± 6.2	1.447 ± 0.011	30.8 ± 2.1	135 ± 6
B4	620 ± 8	0.482 ± 0.019	54.3 ± 1.8	67 ± 2.6

Conclusions

Although RDT is a dosage form that is appreciated by patients because of their convenience and discreetness, 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 pharmacopoeia⁶ 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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