Laboratoire de Pharmacie Galénique et Industrielle[1], Faculté de Pharmacie de Marseille, and Gattefossé. S. A.[2], Saint-Priest, France

Hot melt coating technology: influence of Compritol® 888 Ato and granule size on chloroquine release

A. Faham[1], P. Prinderre[1], P. Piccerelle[1], N. Farah[2] and J. Joachim[1]

The tangential spray technique was used to coat chloroquine granules with Compritol® 888 Ato in a fluidized bed (Glatt GPCG-1,1). After validation of the assay method for chloroquine, dissolution tests were carried out on four size fractions obtained from the same batch of granules. The dissolution profiles obtained showed differences in the rate of release between one fraction and another, despite the fact that each of these fractions had been coated with the same quantity of wax. This suggests that the rate of release of the chloroquine may be adjusted by controlling the size of the granules. Furthermore these dissolution profiles were characterized by a rapid release phase followed by a slow release phase. Examination of the surfaces of the granules from the various size fractions under a scanning electron microscope revealed that Compritol® did not form a continuous film but existed rather as a lipid environment around the granule. This lipid environment was made up of solidified droplets of the wax which had become piled up on the surface of the granule. Compression of the granules produced tablets which remained intact until chloroquine dissolution was complete. This undicated that the active substance diffused across the Compritol matrix generated during compression. Determination of the dissolution kinetics using the Higuchi model demonstrated the diffusion release mechanism.

1. Introduction

Sustained release oral solid dosage forms are specifically designed to maintain appropriate therapeutic concentrations over long periods [1]. These forms may be produced by coating techniques involving a fluidized bed equipment. Coating in a fluidized bed is generally carried out with polymers soluble in aqueous or organic solvents. In the prevailing environment of the pharmaceutical industry which is economy-based and highly competitive, it is evident that new coating procedures need to be developed – these should be simple, efficient, accurate, less costly and quality control of the coated drugs should present no difficulty. Under such conditions, the possibilities offered by coating methods involving melted waxes are attractive and research into the pharmaceutical applications of lipids agent is constantly increasing [2].

Hot melt coating does indeed offer numerous advantages over conventional coating techniques [3]. It does not require the use of solvents (neither organic nor aqueous) and is thus an environment – friendly coating technique. Moreover, for the same end result, the concentration of wax employed is not more than that of the commonly used polymers.

One of the techniques used to produce sustained release forms is the coating of a granules containing active drug with molten wax. This coating controls the rate of release of the active drug from granules and from tablets.

This article describes the influence of the size of coated chloroquine granules on the rate of release of this drug from granules and from tablets.

2. Investigations and results

The calibration curve plotted for chloroquine showed the response of the active drug to be perfectly linear, thus validating the assay method for the remainder of the study.

The formula used for manufacture of the granules was as follows: 10% chloroquine, 87% dibasic calcium phosphate dihydrate and 3% PVP K30.

Following preliminary tests using the tangential spray system during which optimal process conditions were defined, i.e. enabling hot melt coating to take place without clogging the filter and without solidification of the coating agent, the parameters listed in Table 1 were chosen. The experimental assembly is illustrated in Fig. 1.

2.1. Particle analysis

This analysis gave the particle size distribution in each batch. This test is very important for the optimization of the process because it is used to change the parameters which affect the homogeneity of the size of the granules.

The values displayed in Table 2 show the particle size profile, the proportions of which remain the same whatever the percentage of Compritol® 888 Ato deposited. A low proportion of fines (F1 and F2) is obtained, which decreases as the percentage of wax increases and as the fluidization rate is reduced (this decreased from 2.9 m/s for batch 1 to 2.2–2.4 m/s for batches 2 and 3 respectively).

Decreasing the fluidization rate leads to a smaller volume of fluidization air which reduces the passage of fines into the filter. They are thus subjected to optimal coating. In contrast, high percentages of fractions F3 and F4 are produced.

Table 1: Operating parameters used during coating in a FBD

	Batch 1	Batch 2	Batch 3
Tangential spray system	GPCG-1,1	GPCG-1,1	GPCG-1,1
Disk	smooth	smooth	smooth
Load in tangential spray (g)	1500	1500	1500
Nozzle port size (mm)	1.2	1.2	1.2
T° fluidization air (°C)	62	63	64
Rate of fluidization (m/s)	2.9	2.2	2.4
T° of pulverization air (°C)	140	140	140
Bed T° (°C)	55	55	56
Atomization air pressure (bar)	2	2	2
Percentage of coating agent (%)	6	10	15
Spray rate (g/min)	15	15	15
Rotor position (%)	30	30	30
Speed of rotation (rpm)	600	600	600
Shaking of filters (s)	8	8	8
Interval between shaking filters (s)	40	40	40
Drying time (min)	10	10	10

All the granules, irrespective of their size and the percentage of wax deposited, exhibited good rheological properties. However, the unlubricated fines (F1) of the uncoated granules exhibited a rather long flow time, which was improved after coating and lubrication.

Study of the results obtained and reported in Table 3, reveals that the tangential spray technique does not affect the distribution of the chloroquine in the various size fractions of the various batches. In addition, the calculated percentages of chloroquine were very close to the theoretical percentage of 10%.

Table 4 shows that efficient coating with a molten wax was achieved in a FBD using the tangential spray technique and that the distribution of the coating agent among the various size fractions was relatively similar. For example, for batch 3 and its fractions, for a theoretical coating percentage of 15%, the concentrations of Compritol® 888 Ato actually deposited ranged from a maximum of 16.35% for fraction F1 to a minimum of 15.31% for fraction F4. The authors consider this to be due to the spraying system and the mode of fluidization of the granules. As the nozzle is located below the bed and parallel to the disk, the coating substance is always in contact with the granules which are fluidized in the same direction as the direction of the spray.

2.2. Dissolution

A study of the dissolution kinetics of batches 1, 2 and 3 showed that coating with increasing quantities of wax substantially modified the release kinetics of chloroquine (Fig. 2). For all three batches, a large quantity of active drug was released during the first minutes. Over 50% was released after 60 min dissolution. Beyond this time, the principal release mechanism was diffusion of the active drug which occurred progressively over at least 12 h.

Coating with molten wax does not form a continuous film; the droplets are deposited on the core and solidify, becoming piled up in several layers the thickness of which depends on the quantity deposited. It is thus a lipid environment in which the less well-coated granule surfaces rapidly release the chloroquine in the first minutes of contact with the dissolution medium.

The surface of the granules of the uncoated batch (Fig. 3) and that of batch 3 (15% wax) (Fig. 4) were observed under a scanning electron microscope. These two photographs clearly show the piles of wax droplets on the surface of the coated granule which cause the effect of the prolonged release of chloroquine from the coated batch.

The individual release profiles of each size fractions differ from that of the total batch. The results in Table 4, which shows the actual percentages of wax deposited, coupled with the curves displayed in Fig. 5, clearly demonstrate

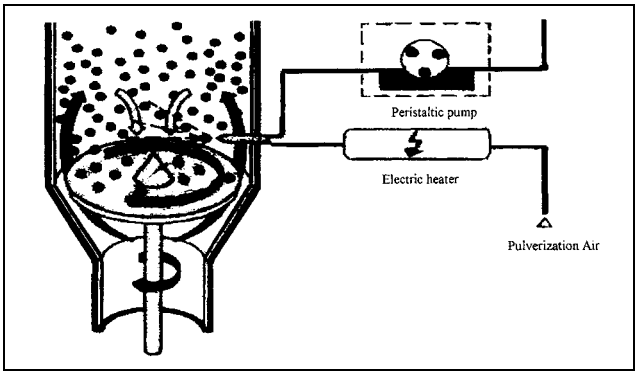

Fig. 1: Experimental assembly for coating in a tangential spray system (Glatt GPCG 1.1)

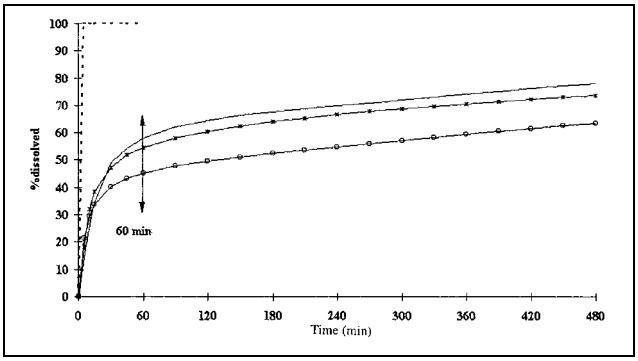

Fig. 2: *In vitro* dissolution profiles of the coated granules (batches 1, 2 and 3) —— Batch 1 (6%), —∗— Batch 2 (10%), —⊖— Batch 3 (15%), - - - - Uncoated granules

Table 2: Particle size distribution of the uncoated batch and the coated batches

Fractions	Uncoated granules	Batch 1 (6%)	Batch 2 (10%)	Batch 3 (15%)
F1 (0–200 μm)	21.00%	13.35%	9.03%	7.88%
F2 (200–400 μm)	25.89%	21.89%	19.05%	15.03%
F3 (400–600 μm)	18.55%	26.87%	27.95%	30.44%
F4 (>600 μm)	34.56%	37.89%	43.97%	46.65%

Table 3: Chloroquine content in each size fraction of the three coated batches 1, 2 and 3

	% active drug in coated granules	% active drug in uncoated granules
Batch 1 (6%)	8.19%	9.88%
F1 (0–200 μm)	7.35%	9.75%
F2 (200–400 μm)	7.77%	9.82%
F3 (400–600 μm)	7.91%	9.85%
F4 (>600 μm)	8.14%	9.88%
Batch 2 (10%)	7.06%	9.71%
F1 (0–200 μm)	6.50%	9.79%
F2 (200–400 μm)	6.73%	9.61%
F3 (400–600 μm)	6.81%	9.66%
F4 (>600 μm)	7.03%	9.70%
Batch 3 (15%)	5.50%	9.42%
F1 (0–200 μm)	5.09%	9.19%
F2 (200–400 μm)	5.22%	9.24%
F3 (400–600 μm)	5.35%	9.27%
F4 (>600 μm)	5.40%	9.29%

Table 4: Percentage of Compritol® 888 Ato actually deposited on each size fraction

	% Compritol® 888 Ato
	% actual
Batch 1 (6%)	6.00%
F1 (0–200 μm)	8.80%
F2 (200–400 μm)	7.40%
F3 (400–600 μm)	6.95%
F4 (>600 μm)	6.20%
Batch 2 (10%)	9.77%
F1 (0–200 μm)	12.40%
F2 (200–400 μm)	10.80%
F3 (400–600 μm)	10.62%
F4 (>600 μm)	9.87%
Batch 3 (15%)	15.40%
F1 (0–200 μm)	16.35%
F2 (200–400 μm)	15.93%
F3 (400–600 μm)	15.50%
F4 (>600 μm)	15.31%

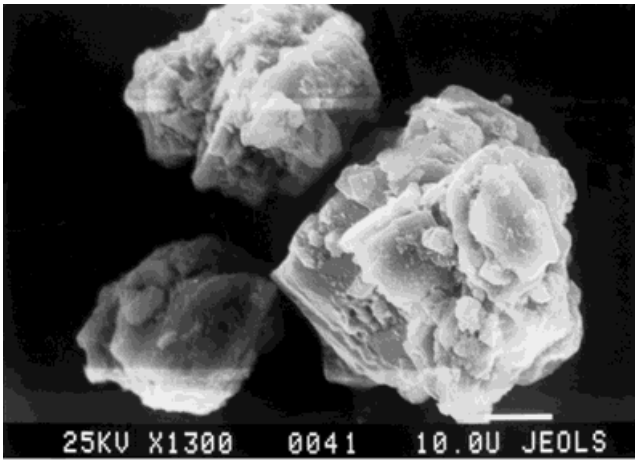

Fig. 3: Scanning electron micrograph of an uncoated granule (×1300)

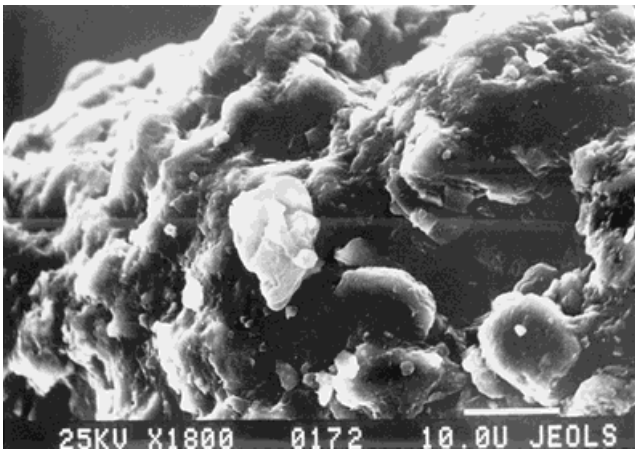

Fig. 4: Scanning electron micrograph of a wax-coated granule (×1800); total batch 3 (15%)

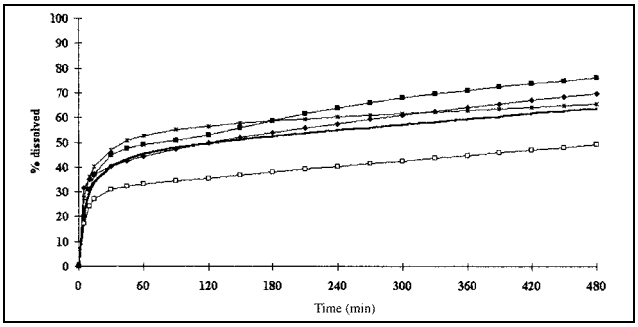

Fig. 5: *In vitro* dissolution profile of the various granule size fractions (batch 3)
—□— Fraction 1, —◆— Fraction 2, —■— Fraction 3, —*— Fraction 4 —— Total batch

the influence of particle size on chloroquine release kinetics; this is notably clear with this batch. The difference in dissolution profiles of the 4 fractions of batch 3 reflects the relationship which exists between granule size and the percentage of Compritol® 888 Ato. Thus, despite the same actual percentages deposited on the four fractions, the smaller the granule, the better the coating and also the dissolution profile. Indeed for a same diameter of wax droplets, the lipid environment formed on a small granule is better than that on a larger granule.

Following these results the authors examined the surface of the total batch 3 and each of the fractions under the scanning electron microscope.

Figs. 6 and 7 show fraction F1 and fraction F4 granules respectively. Compritol® 888 Ato is deposited as droplets

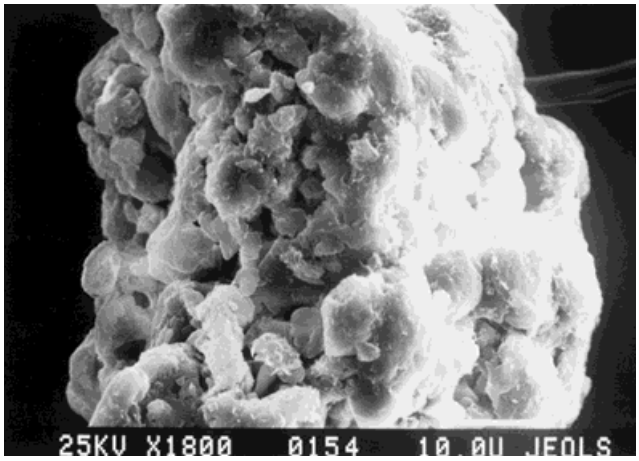

Fig. 6: Scanning electron micrograph of a wax coated granule (×1800); fraction F1 (16.35%) of batch 3

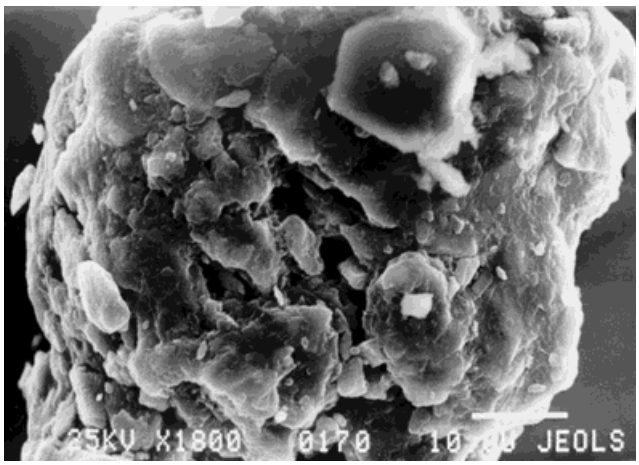

Fig. 7: Scanning electron micrograph of a wax coated granule (×1800); fraction F4 (15.31%) of batch 3

which solidify on the surface of the particles. The Fraction F1 granule surface is heavily loaded (Fig. 6), the quantity of wax being sufficient to cover a large part of the particle. This multilayer covering is, however, insufficient to adequately cover a larger granule (Fig. 7).

As the same percentage of wax was deposited on the 4 fractions of batch 3, it would be logical to expect that the dissolution of chloroquine from tablets manufactured from the various fractions would exhibit the same profile. That would be due to the matrix effect of Compritol® 888 Ato generated during compression.

2.3. Compression

The pharmacotechnical characteristics of the tablets were acceptable, complying with the requirements of the European Pharmacopoeia 3rd edition. Moreover, each fraction of the granules was compressed with the forces necessary to produce tablets of the same hardness each time.

The matrix effect of Compritol® 888 Ato generated during compression steadied and prolonged the release kinetics of chloroquine from the tablets (Fig. 8). As expected, all fractions (F1, F2, F3 & F4) gave dissolution profiles which were almost identical to that of the total batch. Curves were linearised, due to matrix effect.

After 12 h dissolution, and after the chloroquine release was complete, only the tablet ghosts remained. The drug was released by diffusion from the lipid matrix after penetration of the dissolution liquid which dissolved the active drug.

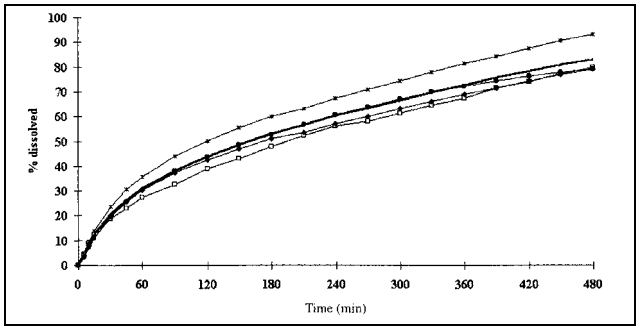

Fig. 8: *In vitro* dissolution profiles of tablets from different sieve fractions (batch 3)
—□— Fraction 1, —◆— Fraction 2, —●— Fraction 3, —*— Fraction 4 —— Total batch

A sample of batch 3 (15%) tablets were placed on stability for 6 months at 40 °C and 75% RH. Other tablets of the same batch were matured for 24 h and 48 h at 55 °C and then placed on stability for 6 months at 40 °C and 75% RH. Fig. 9 reveals a slight drift of the dissolution profiles over time. It was observed that tablets manufactured from batch 3 granules showed stability over time.

The dissolution test results obtained show that the tablet form is stable after 6 months' storage, irrespective of the fraction compressed. These findings were identical to that observed for the tablets from the total batch.

Given the dissolution results obtained with tablets from various fractions of batch 3, it was decided to mature only tablets manufactured from the total batch in order to determine if maturing could be used to predict stability. After 24 h of maturing at 55 °C, chloroquine release kinetics were prolonged, and decreased by at least 10% compared with the profile obtained with tablets tested immediately after manufacture. However, these release kinetics remained steady after 48 h of maturing (Fig. 10).

Furthermore, storage for 6 months after maturing did not modify dissolution kinetics. On the other hand, it was noted that the dissolution profile of tablets sored for 6 months without maturing tended to be similar to that obtained with the agend tablets. In conclusion 24 h maturation (55 °C) appears to be equivalent to 6 months' storage (40 °C/75% RH).

The dissolution kinetics obtained with batch 3 tablets, after manufacture, after 6 months' storage and after maturing, were modelized and found to follow the Higuchi model (Table 5).

3. Discussion

The coated granules obtained with the tangential spray technique are characterized by good rheological properties. The particle size distribution revealed low levels of fines and of coarse particles, which decreased as the concentration of the wax increased. Moreover, the coated granules exhibited good flow and settling properties with a uniform distribution of the active drug in the various fractions of a given batch.

As the nozzle is immersed in the expansion chamber, the droplets of coating solution traverse a short distance before meeting the granule for coating. The tangential spray deposits a same quantity irrespective of the particle size of the fraction.

Analysis of the dissolution profiles provided a wealth of data on the subject of the coating process and enabled the authors to draw the following conclusions:

Firstly, the dissolution profiles of the active drug are characterized by a massive release in the first 60 min, followed by diffusion. The magnitude of this massive release diminished as the concentration of wax increased. This type of profile may be explained by the fact that the wax spray is deposited as solidified in the form of a multilayer structure thus forming a lipid environment and not a continuous film as in the case of polymers.

In addition, Fig. 5 shows that the dissolution kinetics of chloroquine differ in the various fractions of granules, despite the same percentage of wax deposited. This rate of release is thus also dependent on the size of the granule and not only on the concentration of wax deposited.

Analysis of the surface of the granules of batch 3 using the scanning electron microscope confirms this comment and shows that a given quantity of Compritol® 888 Ato, sufficient to cover a large part of the surface of fraction F1 ($< 200\ \mu m$) is insufficient to protect the granule of fraction F4 ($> 600\ \mu m$).

Chloroquine release kinetics become linear after compression when the active drug is released by diffusion through the matrix. The interpretation of the dissolution kinetics in accordance with the Higuchi model demonstrated that the release mechanism was diffusion and confirmed that the matrix was formed after compression only.

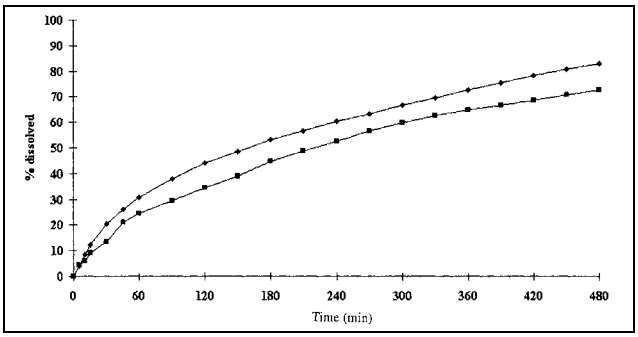

Fig. 9: *In vitro* dissolution profiles of tablets prepared total batch 3 (before and after stability testing)
—*— Total batch (before stability), —◆— Total batch 24 h, —◆— Total batch 48 h, —■— Total batch (stability after ageing), —●— Total batch (after stability)

Table 5: K and R^2 values from Higuchi model from batch 3

	After compression		Stability samples		Aged samples			
					48 h		Stability study	
	K	R^2	K	R^2	K	R^2	K	R^2
Total batch	3.916	0.996	4.079	0.997	3.157	0.999	3.362	0.997
Fraction 1	3.707	0.995	3.407	0.997				
Fraction 2	3.706	0.999	3.778	0.997				
Fraction 3	3.884	0.993	3.663	0.994				
Fraction 4	4.369	0.995	4.153	0.992				

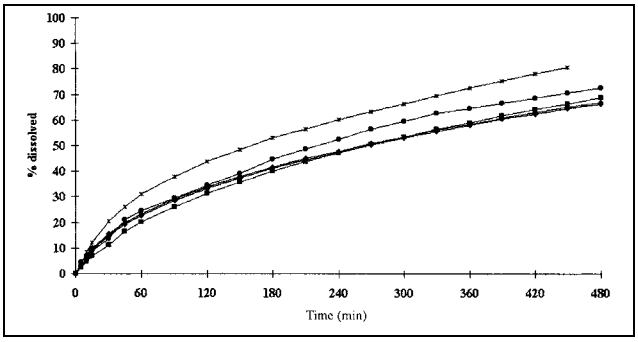

Fig. 10: *In vitro* dissolution profiles of tablets prepared total batch 3 (before and after ageing)
—◆— Total batch (before stability), —■— Total batch (after stability)

The stability study showed the pharmaceutical form to be unstable. In fact, maturing for 24 h at 55 °C modified the relase kinetics, reducing them by at least 10%. This rate of release remained steady after 48 h maturing and after 6 months' stability storage. It thus appears that 24 h maturation (55 °C) were equivalent to 6 months' storage (40 °C/ 75% RH).

4. Experimental

4.1. Materials

Chloroquine phosphate was used as a tracer for the granules manufacture (Cooper, France); Dibasic calcium phosphate, dihydrate was used as diluent (SPCI, France); Polyvinylpyrrolidone K30 (PVP) was used as binder (Sigma, France); Compritol® 888 Ato was used as coating agent (Gattefosse, France).

4.2. Apparatus

Lôdige MR 20 high-shear mixer (France); Ventilated tray oven (Lequeux, France); Oscillating sieve (Erweka type FGS, France); Flexible mixer (Turbula T2C, Switzerland); Granular-pellicular fluidized bed (Glatt GPCG1,1 Binzen, Germany); Sieve shaker (Retsch type 3D, Germany); Bulk volumeter (Stav 203 Engelsmann, Germany); Alternating tablet press (Frogerais OA, France); Hardness tester (Erweka TBT/S Vankel, Germany); Friability apparatus (Erweka TAR, France); Dissolution apparatus: (Prolabo, France); Spectrophotometer UV (CAM-SPEC M330 Cambridge, U.K.); Scanning electron microscope (JOEL JSM-35 CF, Japan).

4.3. Methods

4.3.1. Manufacture of the granules

A total amount of 5 kg powder was mixed for 5 min in an 10 l capacity high-shear mixer (Lôdige MR 20) at 250 rpm. The granulation liquid (765 ml) was added gradually to the powder mixture over a period of 10 min. The wet mass thus obtained was passed through a 1 mm mesh screen of an oscillating sieve (Frewitt GM 263) and the resulting granules was dried in an oven at 60 °C for 2 h.

4.3.2. Coating process

An amount of 1.5 kg uncoated granules were fluidized with an air volume of 110 m^3/h, known to produce good fluidization patterns, on a Glatt GPCG-1,1 fluidized bed adjusted for tangential-spray technique. A bottom screen of 50 μm pore size was used (Glatt® International). A binary type nozzle with a port size of 1 mm and an air dome setting of 60° provided a good spray pattern with the molten agent at an atomization pressure of 3 bar.
The atomization air was heated with an electric heater and maintained at a temperature slightly higher than the melting point of the wax. Alternate halves of the filter were shaken at 40 s intervals for 8 s without interruption of fluidization or spraying.
Inlet air temperature was 60 °C and was increased to maintain the temperature of the granules at 67 °C, just below the melting point of Compritol 888 Ato (between 69 °C and 74 °C). Molten wax was maintained at constant temperature (120 °C) by means of a hot plate. A spray rate of 20 g/min was achieved with a peristaltic pump. The quantities of coating applied were 6%, 10% and 15% and the coated granules were cooled for 15 min.

4.3.3. Production of sieve fractions

A 100 g sample was sieved using 600-, 600–400, 200–400 μm sieves in order to separate them into 4 sieve fractions. The sieves were placed on a Retsch sieve shaker for 10 min at 40% of the maximal vibrational capacity. The fraction retained on each screen was weighed and expressed as percentage of the total weight.
Fraction 1 (F1): (< 200 μm), Fraction 2 (F2): (200–400 μm), Fraction 3 (F3): (400–600 μm), Fraction 4 (F4): (> 600 μm).
This particle size analysis was performed on the uncoated granules and on the coated batches (batches 1, 2 and 3)

4.3.4. Rheological testing

The flowability test was performed using a standard funnel. Granules were considered to possess good compression characteristics when the time taken for 100 g of test substance to flow through was less than or equal to 10 s. The test was carried out three times and the result is expressed as the mean of the three determinations.
The apparent volume test was performed using a standard setting apparatus (Stav 2003). Place a 100 g sample in a 250 ml graduated cylinder (2 ml intervals) and read the unsettled apparent volume (V0). Carry out 10 and 500 taps and read the corresponding volumes: V10 and V500. If the difference between V10 and V500 is less than 20 ml, the granules are considered acceptable. Again, the result is expressed as the mean of 3 determinations.
These two tests were repeated on the libricated granules. The results of these tests enabled the authors to predict the behaviour of the granules during filling of the die before compression and were used to select the types and quantities of lubricants.

4.3.5. Chloroquine assay

A chloroquine calibration range was prepared from a stock solution containing 1 g/l in a pH 6.8 medium. The absorbences of the various solutions were read on a single beam UV spectrophotometer CAM-SPEC M330 in 10 mm quartz cells at the absorption maximum of chloroquine $\lambda_{max} = 343$ nm.

$$C_{(mg/l)} = 29.32 \times Abs - 0.758\,. \qquad R^2 = 0.999$$

The concentration of active drug in each total batch and in the corresponding size fractions was determined. A 500 mg sample was dissolved in 1000 ml of medium. The absorbances determined by UV spectrophotometry at 343 nm were used to calculate the concentration of active drug in each total batch and in each of its size fractions.
Coating efficiency is reflected by the percentage of Compritol® 888 Ato actually deposited on the granules. 500 mg samples of coated (total batch and its size fractions) and uncoated granules were each placed in a beaker containing 1 l of pH 6.8 medium and stirred with a magnetic stirring bar until chloroquine release was complete. The concentration of the active drug present in the granules before and after coating was used to calculate the actual percentage deposited on the substrate.

4.3.6. Experiments using scanning electron microscopy

The granules were gold coated and photographed using a JOEL JSM-35 CF scanning electron microscope (SEM).

4.3.7. Compression

The coated granules were lubricated with 1% talc and 1% magnesium stearate and mixed for 5 min in a Turbula T2C at 40 rpm. Tablets containing 50 mg of chloroquine were manufactured using an alternating tablet press Frogerais type OA.
Tablets thus prepared were subjected to the tests for uniformity of mass, hardness, friability, drug content and drug content uniformity (European Pharmacopoeia 3rd edition).

4.3.8. Stability and maturing

With the aim of improving the stability of the pharmaceutical preparation, that is, to minimize changes in the release of the active drug with time, the tablets were placed in a well-closed container and subjected to an maturing step by heating in an oven for 24 and/or 48 h at 55 °C and to stability testing by storage in a controlled temperature and humidity oven for at least 6 months at 40 °C and 75% relative humidity.

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Prof. Joseph Joachim
Pharmacie Galenique
Université d'Aix-Marseile II
27, boulevard Jean Moulin
13385 Marseille Cedex 5
France
prinder@rousseau.timone.univ-mrs.fr