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The evaluation of formulation and processing conditions of a melt granulation process

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Summary

A melt granulation process for the manufacture of divided unit, sustained release dosage forms is described. Formulation and processing variables were investigated and results presented demonstrate that the product is not adversely affected by minor changes in the processing conditions. A linear relationship was established between percent dissolved and log time and the required dissolution profile can be achieved by selection of wax type and concentration and granule size. The process is shown to be rapid and reproducible and behaviour on scale-up can be predicted from small scale laboratory equipment.

Introduction

Slow-release dose forms are now widely used in the presentation of pharmaceutical products and they may be classified into non-disintegrating matrix dose forms and disintegrating or divided dose units. There is an increasing trend away from non-disintegrating matrix tablets to divided dose units because of the following advantages: (i) there is less risk of local high concentration of the drug in the gastrointestinal tract and thus less risk of irritation (Beckett, 1978); (ii) retention of small particles in the villi tends to prolong gastrointestinal transit time and so

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provide a more sustained action; and (iii) gastric emptying and influence of food tend to be less variable (Bechgaard and Nielsen, 1978).

These factors in combination indicate that divided unit dose forms are more suitable for sustained release products and are more likely to provide a consistent in vivo response. There are several methods of manufacture of dispersible sustained release dose forms including pelletization, microencapsulation and the use of ion-exchange resins (Kawashima et al., 1981; Morse, 1971; Raghunathan et al., 1981). However, these processes tend to be time consuming and subject to processing variables.

We have evaluated a melt granulation process as a means of manufacture of divided unit dose forms. A melt granulation method previously reported was conducted in small scale modified equipment using stearic acid as the binder to give a product with rapid dissolution (Rubinstein and Musikabhuma, 1980). In our method sustained release matrix granules are produced which can be further processed into single disintegrating unit dose forms by incorporating suitable excipients and then filling into capsules or compressing into tablets. The ability to compress them into tablets confers on the matrix granules which we describe considerable advantages over alternative sustained release units such as microcapsules or coated pellets and granules. The outer wall or coating of these other units tends to rupture on compression thereby reducing their sustained release properties (Walker et al., 1977; Juslin and Puumalainen, 1977).

The following factors have been investigated: drug–wax ratio, wax type, batch size and regranulation. Their effects on the processing properties, particle size and dissolution of the melt granulate have been determined. Tablets prepared from the granulate have been characterized.

Materials and Methods

We have used as our model drug substance a non-steroidal anti-inflammatory compound, Isoxepac, which has a solubility of 0.025 mg/ml in the unionized form and a pK_a of 4.5. Hence the solubility and dissolution are highly pH dependent. The drug was used as a fine powder of mass median diameter approximately 5 μm. The high speed Henschel mixer (F.R.G.) was used for the melt granulation process with bowl capacities of 15 litres and 75 litres enabling batches of approximately 2 kg and 12 kg to be manufactured. The granulate was prepared by the addition of powdered drug and wax to the bowl and the two were mixed at high speed, 3800 rpm and 1200 rpm in the 15 litre and 75 litre machines, respectively. The temperature of the mix was raised by friction and granulation occurred by sintering of the wax near its melting point. Alternatively, a low melting point wax was added in a molten form directly to the warm drug in the mixer, in which case granulation occurred immediately. Table 1 gives details of the waxes used. The hot granulation process was evaluated by the time taken to achieve granulation, the temperature at which granulation occurred, the granule size of the end product, determined by sieve

TABLE 1

PROPERTIES OF WAXES USED

Wax type	Trade name	Supplier	Melting range (°C)	Particle size (μm)
Paraffin wax J.P.	–	Nikkol (Japan)	56– 58	NA
Partially hydrogenated castor oil	Castorwax MP 80	N.L. Chemicals (U.K.)	80– 81	Flakes
Organic derivative of castor oil	Thixcin R	N.L. Chemicals (U.K.)	86– 90	> 20
Paraffin wax	Specialwachs 4900	H. Lux (F.R.G.)	93–108	> 50

NA = not applicable; wax supplied in blocks and used when molten.

analysis after crushing the cooled granulate through a 1-mm screen, and the dissolution properties of the granulate.

Dissolution properties were determined over 6 h using the USP paddle method at 100 rpm with 900 ml of pH 6.0 phosphate buffer containing 0.025% polysorbate 80 as the dissolution fluid. This dissolution method was developed and refined in the light of results obtained in bioavailability studies in human volunteers with several batches of tablets. The conditions above were selected after modifications to dissolution methodology, involving the equipment used, (USP methods 1, 2 and 3 and a flow-through system), the degree of agitation and the pH and surface tension of the dissolution fluid, to optimise correlation of dissolution results with in vivo performance.

Although the dissolution profile of the finished tablets is the final in vitro criterion of acceptability, the use of tablet dissolution results to evaluate a granulation procedure is complicated and interpretation is difficult. Inter-related factors such as the effects of granule size distribution and of compression and other post-granulation processes are difficult to separate. Therefore, we evaluated granulation by performing the dissolution test on granules rather than tablets. The granule size fractions obtained by sieve analysis of the bulk granulates were tested to minimize granule size effects and to facilitate comparison of dissolution from the same sized granules prepared to different formulations or under different processing conditions.

The effect of granule size is similar in all batches with, as expected, dissolution becoming slower as granule size increases, this is illustrated in Fig. 1 for a wax content of 22.5% of the drug using Specialwachs 4900. The effects of processing and formulation were similar for all the granule size ranges and for ease of comparison only the results of the granule size fraction 500–710 μm are reported.

To further simplify comparisons a linear relationship was sought between the

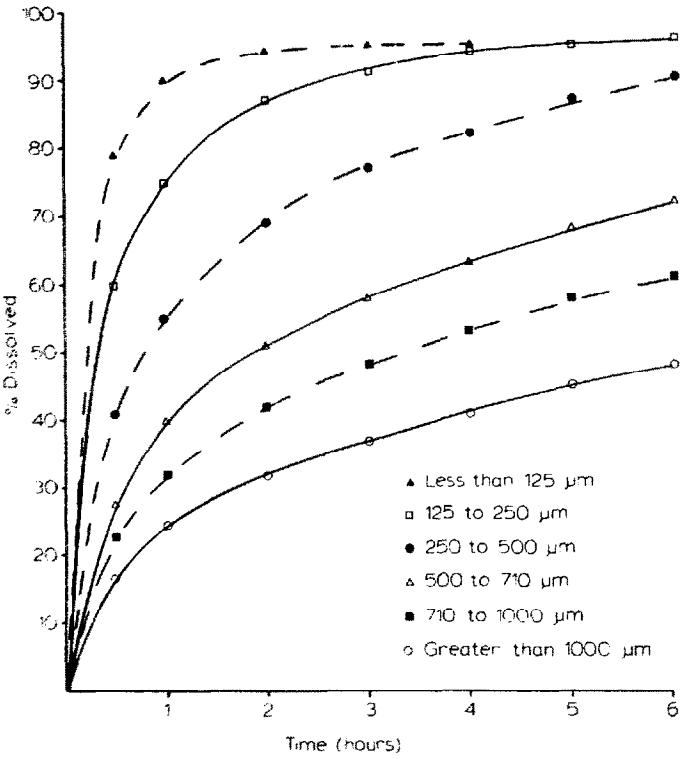

Fig. 1. In vitro dissolution profiles of different granule size fractions. Wax content—22.5% of the drug, Specialwachs 4900.

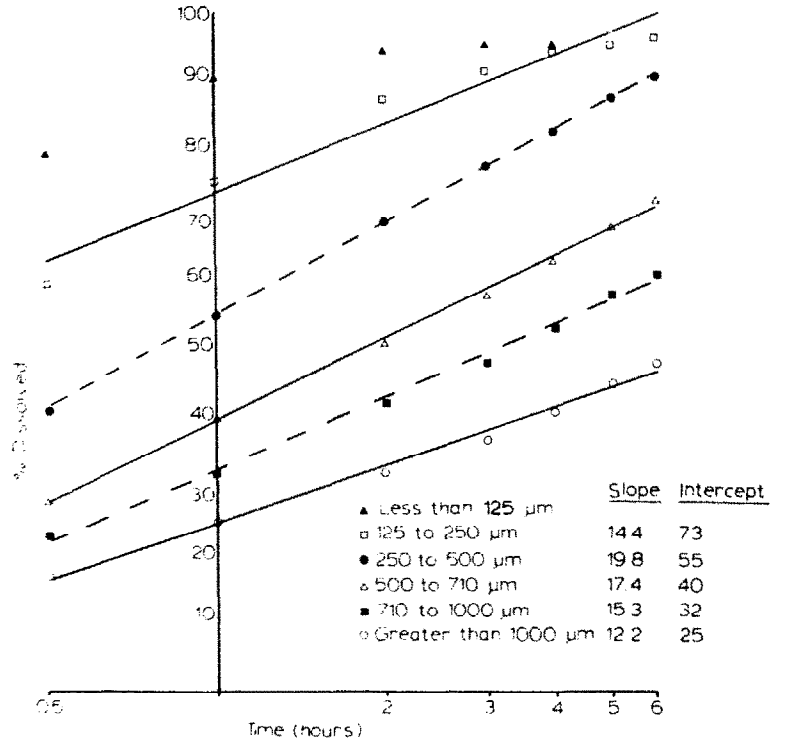

Fig. 2. Linearized dissolution graphs of different granule size fractions. Wax content—22.5% of the drug, Specialwachs 4900.

amount dissolved and time. This would enable the complete dissolution profile to be specified by two figures: the slope and intercept of the linearized graph. It was found empirically that the graph of percent dissolved against log time approximated to a straight line in all cases except where dissolution was very rapid. Slope and intercept were thus determined by linear regression analysis. Fitting the data to the equation:

$$\% \text{ dissolved} = \text{slope} \times \log \text{time} + \text{intercept}$$

Fig. 2 illustrates the linearized dissolution graphs of the various granule size fractions from Fig. 1. Where dissolution is not extremely rapid (size fractions above 250 μm) the figures fit the straight line graph with a correlation coefficient better than 0.99. Even the 125 μm to 250 μm fraction, where dissolution is 75% after 1 h, gives a correlation coefficient of 0.98.

The slope of the linearized graph is dependent on the rate of dissolution at the later time periods and indicates how well release is sustained. Samples with a slow dissolution have a low value for the slope as do samples with a very fast dissolution when insufficient drug remains undissolved at later time periods to maintain release. The in vitro release after 1 h gives an indication of initial release rate and is in fact represented by the intercept of our linearized graph.

The two values obtained by linear regression analysis of the dissolution data completely specify the dissolution profile. Results are therefore reported in terms of the slope and intercept of the linearized graph. In comparisons of sets of data for the linearized graph any differences were tested for statistical significance at the 5% confidence level by the method of Dixon and Massey (1969).

Results and Discussion

(1) Wax content

Wax contents of 50, 37.5, 25, 22.5 and 18.75 (expressed as % w/w of drug) were examined using Specialwachs 4900.

Processing properties are illustrated in Table 2. With decreasing wax content of the granule the following effects are observed: (i) the time taken to reach the granulation end-point increases; (ii) the granule size decreases; and (iii) the slope and intercept of the linearized dissolution graph increase indicating a greater initial release and more rapid release rate.

Granulation occurs by a sintering process in which local melting on the surface of the wax particles causes aggregation and granulation. With reducing wax content the time and temperature at which the end-point of granulation occurs will tend to increase due to the dilution of wax by the drug particles. Granules produced with low wax contents will have a more porous structure and thus be more friable, giving rise to the dissolution and particle size changes.

(2) Wax type

The versatility of the process with different waxes (see Table 1) ranging in melting

TABLE 2

INFLUENCE OF WAX CONTENT ON PROCESSING AND DISSOLUTION PROPERTIES. BATCH SIZE 2 kg. 15 LITRE MIXER USING SPECIALWACHS 4900

Wax content (% w/w of drug)	End point		MMD (μm)	Dissolution parameters Granule size 500–710 μm	
	Time (min)	Temp. (°C)		Slope	Intercept
50	4.25	68	910	10.8	24.9
37.5	ND	72	730	10.0	19.9
25	4.5	87	450	17.0	33.8
22.5	5.0	83	400	19.7	42.5
18.75	5.5	78	235	19.1	42.8

ND = not determined. MMD = mass median diameter: that diameter above which 50% by weight of granules lies

point from 56°C to 108°C is demonstrated in Table 3. The waxes were added to the drug in powder form (Thixcin R and Specialwachs 4900), as flakes (Castorwax MP 80) which were reduced to a powder at a low temperature in the mixer, or in a molten form (paraffin wax J.P.). Granulation occurred in under 5 min when the wax was added as powder or flakes, or immediately when molten wax was added to the prewarmed drug. The granulation mechanism for the molten wax may differ from that for the powdered waxes and is possibly similar to that occurring in conventional wet granulation during which drug particles are aggregated by a film of liquid. However, as this occurs immediately there is insufficient time for thorough mixing of the drug and wax and therefore dissolution is rapid— as shown by the high values for the slope and intercept of the linearized graph.

With increasing melting point of the powdered wax, the time taken to achieve granulation remains constant, the end-point temperature increases, granule size shows no trend and the dissolution parameters decrease. This decrease in the

TABLE 3

THE INFLUENCE OF WAX TYPE ON PROCESSING AND DISSOLUTION PROPERTIES. BATCH SIZE 1.5 kg. 15 LITRE MIXER. 25% WAX CONTENT

Wax type	End point		MMD (μm)	Dissolution parameters Granule size 500–710 μm	
	Time (min)	Temp. (°C)		Slope	Intercept
Paraffin wax J.P.	Immediate	Molten wax added at 76	730	24.7	47.7
Castorwax MP 80	4.0	63	460	19.8	54.2
Thixcin R	4.6	65	410	18.4	46.5
Specialwachs 4900	4.5	87	450	16.9	33.8

dissolution parameters with increasing melting point of the wax could be related to the increasing melting range of the powdered waxes as their melting point increases (see Table 1). The major proportion of the processing time is taken by mixing prior to the commencement of the granulation. The actual granulation process is relatively short. Melting occurs over an increasingly wide temperature range for the 3 waxes (1°C Castorwax, 4°C Thixcin and 15°C Specialwachs) which will give rise to increasing duration of the granulation stage and this in turn will result in more efficient wax distribution and a slower dissolution rate.

(3) Batch size

The effect of different batch sizes within the same capacity mixer (15 litre) was examined as was the effect of scale-up from a 2 kg batch size in the 15 litre mixer to a 12 kg batch size in the 75 litre mixer. The granule size and dissolution properties using Specialwachs 4900 are presented in Table 4.

In the 15 litre mixer, at the 25% wax level, as the batch size is increased from 1.25 kg to 2.75 kg there is no significant change in the overall dissolution rate as indicated by the slope of the linearized graph but there is a trend for the initial dissolution rate to increase. This could be explained by the faster heat build-up (and slower heat loss) in the larger batches giving rise to faster granulation and a less uniform distribution of drug and wax and consequently a slightly increased dissolution rate. When the wax content is decreased to 22.5% the effect of increasing the batch size is similar, i.e. only the initial dissolution changes.

Scale-up properties of batch sizes of 2 kg and 12 kg were evaluated in 15 litre and 75 litre capacity mixers (see Table 4.2). The dissolution properties are similar for granules prepared in the two sizes of mixer indicating that the small scale mixer can be used to predict performance at the larger scale.

TABLE 4

EFFECT OF BATCH SIZE AND WAX CONTENT ON PROCESSING AND DISSOLUTION PROPERTIES USING SPECIALWACHS 4900

Batch size (kg)	Wax content (%)	MMD (μm)	Dissolution parameters Granule size 500–710 μm	
			Slope	Intercept
4.1. 15 litre mixer				
1.25	25	570	16.3	30.2
1.85	25	480	16.9	31.1
2.0	25	450	16.9	33.8
2.75	25	380	17.1	33.6
1.5	22.5	400	18.0	36.0
2.0	22.5	400	19.7	42.5
4.2. 75 litre mixer				
12	25	ND	15.3	39.6
12	22.5	550	18.9	43.3

(4) Regranulation

The regranulation process was investigated as a means of evaluating whether a re-work procedure could be used to recover a batch whose dissolution properties do not comply with the desired specifications and also to determine if unwanted size fractions from one batch could be incorporated into subsequent batches. Batches of 25% Specialwachs content were regranulated. Table 5 illustrates the properties of the original and regranulated materials from two different batches.

Granulation of batch A was terminated prior to its end point and the dissolution was rapid. On regranulation the dissolution rate decreased to give a profile similar to that obtained when initial granulations are taken to the end point. Although not a practical proposition, the mix was repeatedly regranulated and the dissolution rate was shown to increase slightly. A possible explanation is that on regranulation, which was always started from ambient temperature, the granulate is initially milled and granule size reduction occurs. However, size reduction is inefficient and as the temperature rises, sintering begins and granules are formed from a number of smaller particles and have a more porous structure, and therefore more rapid dissolution rate, than granules formed from fine powders. Hence, the effect of regranulation is a combination of improved wax distribution resulting in a decreased dissolution rate and increased porosity which gives an increased dissolution rate. The former mechanism predominates initially when wax distribution is less uniform and granules are probably more friable.

Batch B was granulated in the first instance to its optimum end-point and on regranulation there was no change in the dissolution rate although the amount dissolved in the early time periods decreased slightly. This may be attributed to improved wax distribution as described above.

(5) Tablet properties

As emphasized previously the dissolution performance of the finished dosage

TABLE 5

INFLUENCE OF REGRANULATION ON PROCESSING AND DISSOLUTION PROPERTIES. BATCH SIZE 2 kg, 15 LITRE MIXER, 25% SPECIALWACHS 4900

Batch	Granulation step	Granulation end-point		Dissolution parameters Granule size 500–710 μm	
		Time (min)	Temp. (°C)	Slope	Intercept
A	Original	ND	101	21.0	43.0
	Regranulation 1	4.8	78	17.1	30.4
	Regranulation 2	11.0	82	ND	ND
	Regranulation 3	8.8	91	ND	ND
	Regranulation 4	7.5	81	ND	ND
	Regranulation 5	7.5	81	20.6	31.1
B	Original	4.5	81	16.9	31.1
	Regranulation	5.5	74	15.7	24.5

form is the final in vitro criterion of acceptability. If the granules are filled into capsules, post-granulation processing should have little effect on dissolution but compression into tablets can affect both granule structure and size distribution. The effect of compression will be dependent on pre-existing granule structure and size distribution and also on the nature and quantity of extra-granular excipients. However, in practical terms the important factor is whether the process is reproducible or if variation in performance is introduced by compression.

Using Specialwachs 4900 the reproducibility of the dissolution properties of tablets prepared from 3 separate batches of granulate of each of two wax contents was investigated. The results in Table 6 demonstrate that, with the exception of a high intercept value for batch D, there is no statistically significant difference between the batches. Therefore, with the granules produced by the Henschel process, compression into tablets gives a reproducible product in terms of physical properties and dissolution performance.

(6) Conclusion

The melt granulation process starts with mixing of the ingredients at ambient temperature and as mixing at high speed continues, friction causes a rapid rise in temperature. When the sintering point of the wax is achieved aggregation of the particles occurs and the process is stopped when granulation is complete. Alternatively, the addition of molten wax to a prewarmed drug results in immediate granulation. The granules produced using the powdered wax are aggregates of drug and wax particles in a matrix whereas it is possible that those produced by addition of a molten wax are structurally different. The structure of granules was investigated by differential staining, light microscopy, electron microscopy, densitometry and porosimetry but no clear differences were demonstrated.

The process itself is carried out within a single machine and has been shown to be simple and rapid, involving only a direct fill and mixing operation of the drug and

TABLE 6

PROPERTIES OF TABLETS COMPRESSED FROM GRANULATES PREPARED WITH SPECIAL WACHS 4900

Batch	Wax content (% w/w of drug)	Hardness [a] (kg)	Disintegration time [b] (min)	Dissolution parameters	
				Slope	Intercept
C	25	7.5	1.0	15.3	51.3
D	25	8.1	2.0	15.6	57.8
E	25	8.4	1.75	16.0	52.0
F	22.5	10.4	1.5	17.6	57.1
G	22.5	7.4	2.0	17.9	55.3
H	22.5	7.6	1.0	18.3	55.6

[a] Schleuniger Hardness Tester.

[b] B.P. Method.

wax in powder or molten form. A granule suitable for compression or capsule filling can then be produced by a single-stage crushing process and admixture with suitable disintegrants and flow aids.

The process is reproducible with standard conditions producing a granulate with consistent physical properties and dissolution profile. Minor processing changes such as end-point temperature and fill capacity have little effect on the product and material can be reworked by incorporation into another batch. The process can be applied to a variety of drugs and the desired dissolution properties of the final dosage form, capsule or tablet, can be obtained by appropriate selection of the wax content, type of wax or granule size. The sustained release properties of the product depend on leaching of the drug through the granule matrix and are therefore less likely to be susceptible to changes on compression or physical and chemical changes on aging than systems where release is controlled by an outer coat, e.g. microcapsules or coated granules and pellets. A satisfactory retard profile can be achieved with a low wax content and the process is therefore applicable to high dose drugs.

Performance at large batch sizes can be predicted from laboratory scale batches which is of considerable value in the scale-up to manufacture and a high production output can be achieved with this process.

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