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EVALUATION OF THE GRANULATION OF A HYDROPHILIC MATRIX SUSTAINED RELEASE TABLET

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ABSTRACT

Wet granulation of a hydrophilic sustained release matrix tablet formulation has been studied. A fractional factorial experimental design was employed to identify principal influences and interacting factors from the following : granulation fluid volume, mixing time, mixer speed and inclusion of a wet screening step. Fluid volume and mixing time were primary factors

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affecting mean granule size. Fines in the granulation were reduced at higher fluid levels and by inclusion of a wet screening operation. There were several interacting factors influencing the particle size properties of the granulation. The factors studied had little influence on the bulk density of the granulation.

The influence of granule mean particle size on flow, compressibility and drug release from finished tablets was evaluated. Flow and compressibility were influenced by granule properties and the data generated suggested that should final tablet properties deteriorate on scale up it may be possible to ameliorate the effect by modification of granulation fluid volume or mixing time or both.

The factors studies had no influence on release of drug from finished tablets.

INTRODUCTION

Sustained release oral dosage forms have become increasingly important in therapy as a means of reducing dosing frequency, hence potentially improving patient compliance and consequently efficacy. Side effects and therapeutic response may be beneficially modified by the reduction in peak to trough variation of drug plasma concentration resulting from therapy with a sustained release oral dosage form. Finally there is great impetus from within the pharmaceutical industry to develop

sustained release oral dosage forms as a means of product life cycle management in protecting market share for patent expiring drugs.

Hydrophilic polymer-based sustained release matrix tablets utilising cellulose ethers are well established as a means of providing prolonged drug delivery via the oral route. There have been a number of studies on the influence of formulation factors on in-vitro drug release and in-vivo performance of these systems which have been reviewed by Hogan (1), Ranga Rao et al (2) and Ranga Rao and Padmalathan Devi (3). Baveja and Ranga Rao (4) demonstrated that ionic and non-ionic cellulose ethers could be combined to provide zero order drug delivery from a hydrophilic matrix.

More recently the formulation of a novel dual polymer hydrophilic matrix system for the provision of a sustained release oral system based on sodium alginate and hydroxypropylmethylcellulose has been described, (5). This system can be optimised to provide pH-independent in-vitro release of basic drug substances (6).

Processing properties of sustained release systems based on hydrophilic matrices have not been reported previously. Excluding clinical and pharmacokinetic studies the majority of work reported in the literature for this type of formulation is on in-vitro evaluation of products prepared the laboratory scale where both wet granulation and direct compression processes have been employed. To ensure good content uniformity, and avoid flow

related inter-tablet weight variation problems, wet granulation may be a preferred processing route for hydrophilic sustained release matrix tablets in commercial production. The present work describes fractional factorial design experiments undertaken to evaluate wet granulation processing of the sodium alginate/hydroxypropylmethylcellulose pH-independent matrix system.

EXPERIMENTAL

Granule and Tablet Preparations

The formulation evaluated consisted of verapamil hydrochloride (Fermion, Finland) as model drug, with sodium alginate (Kelco, UK) and hydroxypropylmethylcellulose 4000cps (Colorcon, UK) as rate-controlling hydrophilic polymers. Microcrystalline cellulose (FMC, Belgium) and lactose monohydrate (Lactochem, UK) were included as compression aids and magnesium stearate (Durham Chemicals, UK) was employed as lubricant.

A model 2Z Winkworth Z-blade mixer was used for preparing granulations at the 0.2kg scale. All formulation components except magnesium stearate were dry blended and then granulated by addition of water at a fixed rate in all studies. Where a wet screen operation was utilised this employed a Jackson Crockatt oscillating granulator fitted with a 20 mesh screen. Granules were dried at 50°C for 15 hours to give a moisture content (by loss on drying at 105°C) of 2.5 - 5%. Lubrication was performed

by mixing the dried granules with magnesium stearate in a Turbula mixer for five minutes.

Tablets were prepared at a range of applied compression pressures on a Manesty F3 single punch tablet press, instrumented to collect compression and ejection data (7).

Product Evaluation

The particle size of the unlubricated granules was determined by sieve analysis and the mean particle size determined graphically. Bulk and tap density were evaluated in a measuring cylinder, carefully pouring in a known weight to calculate bulk density and using volume data obtained after fifty taps to obtain tap density. Carr's index (8) was calculated from the density data. Angle of repose was determined by passing unlubricated granules through a funnel at an even rate to form a stable cone of powder. The funnel was maintained at a fixed height in all experiments. The height and diameter of the cone was measured and the angle of repose calculated by trigonometry.

Drug release studies on compressed tablets were carried out on a USP XXII apparatus I at 50rpm (Pharmatest, UK). Dissolution tests were undertaken on six tablets for each test, and testing was conducted in both simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) to characterise the pH-independent nature of drug release. Dissolved drug was determined by spectrophotometry at 260nm on a LKB Ultrospec II spectrophotometer (LKB, UK).

Mean tablet crushing strength, mean weight and weight variation were determined on twenty tablets from each experiment on a Pharmatest WHT-1 tablet testing system.

Study Design

The effect of processing variables on the physical properties of granules and the resultant effects on compression and final product performance were investigated using a fractional factorial experimental design (9). Based on preliminary experiments, four variables were chosen for investigation at two levels.

Granulation fluid volume

Mixer speed

Mixing time

Use of wet screening stage

The factorial design is given in Table 1.

RESULTS AND DISCUSSION

The mean particle size, angle of repose and Carr index for granulations from each of the experiments are given in Table 2. The main effects and interactions for particle size were determined according to Davies (9), summing the particle sizes and applying the appropriate signs from Table 1. Sums of squares were determined from the square of the sum of particle sizes for each main effect and interaction divided by eight (9). The

TABLE 1

Experimental design for evaluating some variables in granulation of a hydrophilic matrix

Experiment Number	Factor			
	A	B	C	D
1	-	-	-	-
2	+	-	-	+
3	-	+	-	+
4	+	+	-	-
5	-	-	+	+
6	+	-	+	-
7	-	+	+	-
8	+	+	+	+

Factor	Level and Designation	
A. Fluid Level	+ = 50ml	- = 60ml
B. Mixing Time	+ = 60 mins	- = 45 mins
C. Wet Screening Stage	+ = Wet screen step	- = No wet screen step
D. Mixer Speed	+ = 75rpm	- = 50rpm

TABLE 2

Properties of Granules from Fractional Factorial Design Experiments

Experiment No. (see table 1)	Mean Particle Size (microns)	Standard Deviation of Particle Size Distribution	Angle of Repose (degrees)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index	Fines (% passing 90 micron aperture)
1	179	4.7	46	0.48	0.56	14.1	24.7
2	171	5.3	51	0.50	0.59	15.6	16.3
3	387	3.1	43	0.48	0.54	11.7	9.7
4	147	5.9	51	0.51	0.59	14.6	17.9
5	203	4.2	46	0.50	0.57	13.3	26.4
6	151	3.6	52	0.49	0.58	15.0	32.6
7	304	3.6	44	0.48	0.54	12.0	10.6
8	155	4.1	50	0.48	0.57	18.9	31.5

analysis of variance results obtained from this data handling is presented in Table 3.

By the inspection of sums of squares it can be seen that the most influential factors relating to particle size of the granulation are the level of water in the granulation (decreasing granulation fluid level depresses particle size) and mixing time (increasing mixing time yields increased mean granule size). The other process parameters studied, mixer speed and inclusion of a wet screening stage, have a lesser effect on mean granule size. From preliminary experiments with this formulation the system error variance was estimated as 9.0 and therefore the factors A (water level), B (mixing time) and the interaction (AB, CD) are of primary significance, having sums of squares in excess of this value.

For the interaction, factors CD are probably not significant as the analysis of variance suggests that inclusion of a wet screening stage and increase in mixing speed have little effect on the mean particle size. For factors A and B, fluid volume and mixing time, this interaction is probably real. Re-analysis of the data for these two interacting factors on a two way basis gives the averaged totals data in Table 4.

At a high fluid level the increased mixing time has a marked positive effect on mean particle size whilst at the lower fluid level there is little effect or perhaps a negative effect. The negative effect may be related to increase in attrition at

TABLE 3

Analysis of Variance Table for Granule Size Process Effects and Interactions

Comparison of Factors[a]	Magnitude of Effect	Sum of Squares $x10^3$
A	-112.2	25.18
B	71.7	10.28
C	-17.9	0.64
D	-33.6	2.26
(AB, CD)	-82.2	13.51
(AC, BD)	11.8	0.28
(AD, BC)	-19.7	0.78

a = For key to factors see Table 1

TABLE 4

Interaction of fluid volume and mixing time influencing particle size of granules

	Shorter Mixing Time	Longer Mixing Time
Higher Fluid Volume	191.0	345.5
Lower Fluid Volume	161.0	149.0

extended mixing times. At either mixing time the increase in fluid level has a positive effect on mean particle size.

These observations are in accord with published data on the influence of the employed variables on properties of conventional granules derived by wet granulation. Although there is no specific literature on the wet granulation of hydrophilic matrix sustained release formulations, the literature on wet granulation of conventional formulations indicates the possible influences of granulation fluid volume and mixing time on mean granule size. Hunter and Ganderton (10) showed increases in mean granule size for granulation of single component systems on increase in granulation fluid volume. These observations were extended to binary systems by Selkirk (11) and Opakunle and Spring (12). The latter authors explained their observations on the basis of increases in the amount of soluble components in the mass being

dissolved and crystallising on drying. This would result in larger, stronger granules.

In the case of the binary mixture studies by Opakunle and Spring (12) the effect of mixing time on mean granule size was dependent upon the powder mixture composition. In general, increased mixing time produced granules with increased mean granule size. Some formulations which yielded less robust granules showed the possible breakdown of granules on increased mixing time, resulting overall in a reduction in mean granule size on increased mixing time. Carstensen et al (13) and Zoglio et al (14) examined the effect of extending mixing times for prototype granulations and concluded that a maximum or even equilibrium granule size may be achieved and increasing mixing time would result in an approach to the equilibrium or maximum value, or possibly passing the maximum value.

For the sustained release matrix studied here, the influence of granulation fluid level and mixing time can be interpreted as arising as the hydrophilic polymers present in the blend are hydrating during the granulation stage. Both the increase in fluid available and the extending of mixing time might enable hydration to occur more fully which will result in enhanced interparticulate bonding. The result is an increase in mean granule size. The water soluble drug present, verapamil hydrochloride, could also dissolve to a greater extent on increasing granulating fluid level and result in enhanced granule

growth. The hydrophilic polymers present may however compete with dissolving components for granulating fluid as they hydrate and a complex dynamic system may be present. This may manifest as a marked sensitivity to scale and mixer type on scale-up perhaps demanding a rapid and even distribution of granulating fluid into the essentially binder-rich system.

Bulk density is a factor critical to die fill on high speed tablet machines. A granulate dense enough to provide the volumetric fill of the die for final tablet weight at a level not too close to maximum punch stroke is desirable. All granulations were considered of acceptable bulk density for tabletting, being in the range 0.48 - 0.51g/cc (Table 2). As there was no marked variation in this parameter the data was not analysed further.

Fines in a granulation impact on bulk density, compressibility and flow of granules in addition to contributing to sticking and picking problems. Therefore controlling the level of fines in a granulation by identifying factors responsible for their generation is desirable. In the present work fines have been defined as that portion of the granulate that will pass through a 90 micron aperture mesh sieve. The fines data in Table 2 was subjected to analysis of variance and the results are presented in Table 5.

Inclusion of the wet screening stage (factor C) and increasing the granulating fluid level (factor A) appear to be important factors in controlling the level of fines in the granulate.

TABLE 5

Analysis of variance table for level of fines in granulation

Comparison of factors	Magnitude of effect	Sum of squares
A	6.7	89.8
B	-3.8	28.9
C	8.2	132.9
D	-0.5	0.5
AB,CD	7.9	123.3
AC,BD	6.9	93.9
AD,BC	-0.9	1.5

System variance was not known in the case of evaluation of fines. However, the sum of squares data suggest that in addition to the two significant factors already identified, the interactions (AB, CD) and (AC, BD) might also be important. Interaction AB, granulation fluid volume x mixing time, represents individual factors already identified as influencing mean granule size which could impact the level of fines and this interaction is therefore probably real. Interaction CD, wet screening x mixer speed may also be a real effect, as wet screening has been identified as an individual factor influencing the level of fines. However, the situation may be complex as the interacting factor of increasing mixer speed may have an opposite effect to including wet

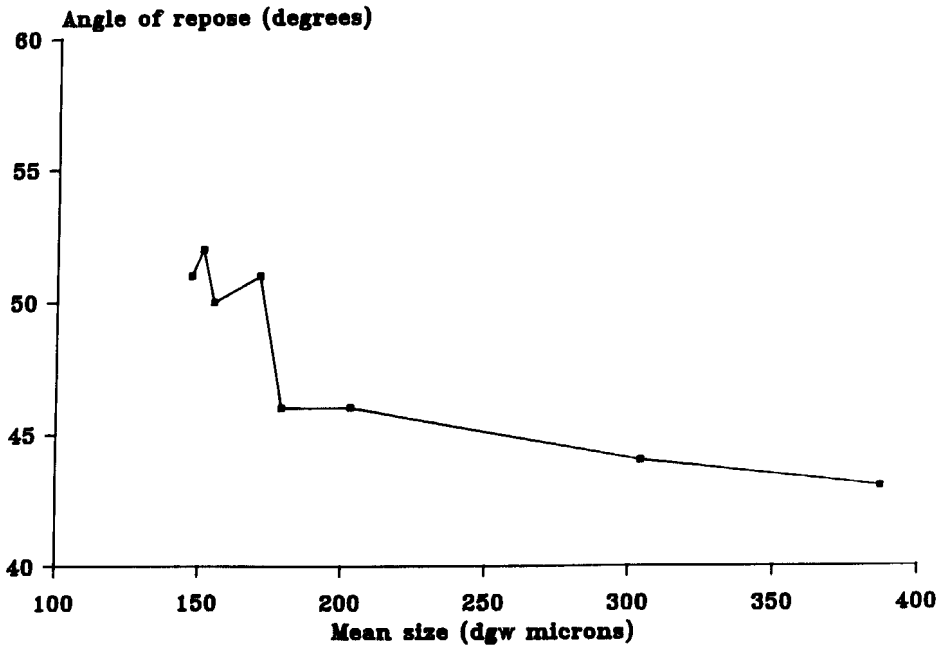

FIGURE 1

Variation in angle of repose with geometric mean granule size

screening as the increased mixing speed may induce generation of fines by attrition.

For the second interaction identified (AC, BD), granulation fluid level x wet screen inclusion (AC) is probably real as both factors have been identified as individual factors influencing the level of fines. The possible interaction BD is complex. The identified positive effect of mixing time on overall particle size distribution might be expected to reduce fines, but this could be negated by the potential for increased mixer speed to produce attrition, enhancing the level of fines. Furthermore,

TABLE 6

Granulation process Studies : Tablet Physical Properties

Experiment	Mean Tablet Weight (% COV)(a)	Crushing Strength at 2000kg top punch load (b)	Dissolution T50% hrs	
			pH1.2	(c)pH7.4
1	485 (1.33)	14.7	6.03	6.08
2	485 (1.25)	N.D.	5.46	6.86
3	529 (0.57)	21.2	5.78	5.33
4	461 (0.26)	13.8	5.46	6.79
5	485 (1.26)	17.0	6.19	5.78
6	467 (1.08)	13.0	N.D.	N.D.
7	487 (1.26)	15.7	5.17	6.03
8	484 (0.68)	16.8	6.08	5.68

a coefficient of variation

b interpolated from compression force/crushing strength plots

c determined by interpolation from log percent undissolved versus time plots

N.D. not determined

the particle size data analysed as in Table 4 suggests that at lower granulation fluid levels, increased mixing time itself may depress mean particle size which could contribute to increase in level of fines.

Increase in mean granule size produces, with respect to the prediction of improved flow, a beneficial effect on angle of

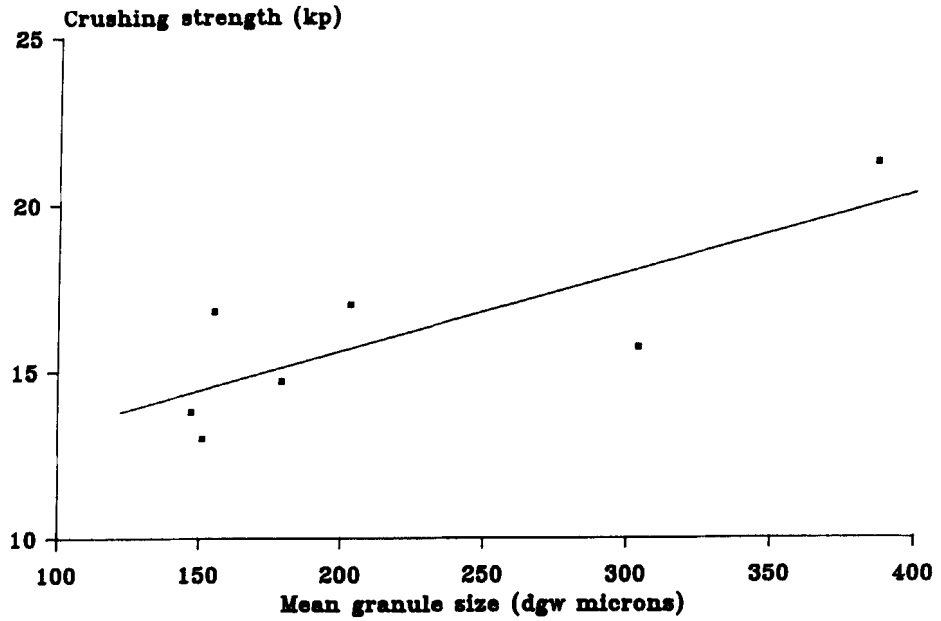

FIGURE 2

Relationship between tablet crushing strength (2000kg applied compression force) and geometric mean granule size

repose (Figure 1). The angle of repose increases sharply as mean particle size decreases below 170 microns. A granulate with mean particle size below 170 microns may show flow related problems, such as high inter-tablet weight variation, on tabletting machines. The current experiments have shown that this may be controlled by means of varying mixing time and granulation fluid level. It should be noted that in spite of the caution given, granules with mean sizes below 170 microns did give tablets with acceptable weight and uniformity on a single punch tablet press as indicated in Table 6. The weight variation on a more

demanding rotary tablet press was not evaluated in the present study.

Although the data is somewhat variable, there appears to be no correlation between granule properties, hence the variables studied, and dissolution rate (Table 6). There is a trend however that on increasing granule size, the compression properties of the granules improve. Tablet crushing strengths at a 200kg applied force (taken from compression force/crushing strength profiles) show a weakly positive correlation with mean granule size (correlation coefficient by linear regression 0.79, Fig. 2). This observation would be of value should compression characteristics of the product deteriorate on scale up and transfer to a rotary tablet press, as it would appear to be possible to ameliorate this effect by increasing mean granule size by increasing mixing time or granulation fluid level or both.

CONCLUSION

The present study has demonstrated that mixing time and volume of granulating fluid were primary factors in controlling particle size of the granulation for a dual polymer hydrophilic sustained release matrix tablet.

Analysis of data from a fractional factorial design experiment has also indicated some interacting factors that can affect mean particle size and level of fines. Particle size has implications

on granule flow and compressibility and it may be possible to address problems of product flow and compression by adjusting these granulation parameters. The process variables studied, within the range studied, had no impact on drug release properties.

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