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GRANULATION SURFACE AREA AS BASIS FOR MAGNESIUM STEARATE CONCENTRATION IN TABLET FORMULATIONS

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ABSTRACT

Tablets provide drug delivery in a convenient and uncomplicated manner. Despite this apparent simplicity, they must comply with a formidable number of physico-chemical compendial requirements defined by specifications and test methods. What these specifications indirectly control is that each dosage form or each lot of dosage form may vary but the variance is held within stated limits.

This communication focuses on the weight variation of formulation ingredients that may be allowed in general and for magnesium stearate in particular and to define a relationship between the lubricant level and granulation

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surface area of a calcium phosphate matrix to obtain optimal tablet properties.

INTRODUCTION

Magnesium Stearate is widely used as a lubricant in tablet formulations. It minimizes inter-particulate friction during compression and the friction between the tablet and metallic surfaces during ejection. Nevertheless, there have always been concerns with respect to lubricant levels, since excessive quantities or extended mixing times can produce a hydrophobic matrix which retards tablet disintegration and dissolution. At the other extreme is the recognition that insufficient lubricant results in tabletting problems.

Several studies have focussed on the effects of lubricant levels. Mlodezeniec et al[1], derived a mathematical expression for relating tablet hardness to lubricant mixing times by considering the increases in surface coverage with prolonged mixing time. Holzer[2] observed a direct relationship between the specific surface area and the disintegration time of tablets. More recently, Frattini and Simioni[3] studied the effect of surface area of magnesium stearate on such tablet properties as hardness,

disintegration time, and dissolution. They found that different batches of this lubricant, differing in surface area, when used in such amounts so as to develop equivalent lubricating areas, the final characteristics of the tablets were almost identical. They concluded that magnesium stearate can be declared by weight only if well-defined specifications of its surface area are set. Otherwise constant weight of the lubricant may not necessarily mean constant quality of the product.

In reality, the problem has always been how to manufacture material with consistent properties from raw materials whose properties indeed vary. A possible solution might be to determine the specific surface area for each lot of the lubricant then use a factor to specifiy lubricant quantity for a particular unit dose. This approach should be easily applied to a composition whose bulking excipient is a water-soluble material, like lactose, which undergoes densification to the same extent irrespective of the length and intensity of agitation applied during wet granulation and this situation has been addressed by Simioni[3] et al, as discussed above. It may be more complex, however, when the bulking excipient is a water-insoluble material like calcium phosphate, particularly since it is very sensitive to the length and intensity of agitation during wet

granulation. This property has been the subject of several studies[4-8], where granulations of dicalcium phosphate prepared in a high intensity mixer were shown to have intragranular porosities of 20% while similar formulations prepared in the conventional pan method had intragranular porosities of 60%. These differences may be resolved by relating the granulation surface area to the lubricant concentration.

Thus the objective of this study was to optimize a drug formulation of a calcium phosphate matrix made in a high intensity mixer and to define a relationship between lubricant level and granulation surface area.

EXPERIMENTAL

Optimization of the formulation, shown in Table I, employed a commonly used five factor, orthogonal, central, composite, second order design. The modified design of five independent variables, which involves 27 experiments with zero as the base line and the experimental ranges varying from -1.547 to +1.547 experimental units, (e.u.) has been employed many times in these laboratories and has been thoroughly described in the literature[9]. The experiments were performed in random order. The translation of the

Table I

Formulation

Ingredients	mg/Tablet
1) Drug	21.78
2) Mannitol, USP	41.00
3) Calcium Phosphate Dibasic Hydrous, USP	124.00
4) Red Ferric Oxide, NF	0.056
5) Yellow Ferric Oxide, NF	0.145
6) Starch, Corn, NF	22.00
7) Starch, Pregelatinized, NF	4.40
8) Starch, Corn, NF	11.00
9) Magnesium Stearate	1.70

statistical design into physical units for the five independent variables is presented in Table II. Each experiment consisted of a batch of 6000 tablets. Wet granulation was carried out in a high intensity granulator[1] at a low impeller, (500 rpm), and chopper, (1000 rpm) speed. Granulations were tabletted on a rotary press[2]. The responses, (dependent variables), measured included: geometric granulation surface area, mathematically calculated from the quantitative mesh profile and the tapped density[10], dissolution rate, disintegration

Table II

Experimental Design

Independent Variables	-1.547 eu	-1 eu	0 eu	+1 eu	+1.547 eu
X1=Quantity of Granulating Water (i.e. Water required for an equivalent starch paste); 1 eu = 0.5%	7.626%	7.90%	8.4%	8.9%	9.17%
X2=Time for Granulation 1 eu = 1 min	1.45 mins	2.0 mins	3.0 min	4.0 mins	4.55 min
X3=Screen Size for Dry Grinding; 1 eu = 0.015"	0.04" (No.1A)	0.05" (No.1B)	0.063" (No.2)	0.078" (No.2AA)	0.086" (No.2A=0.093")
X4 = Quantity of Magnesium Stearate; 1 eu = 0.55 mg	0.85 mg	1.15 mg	1.7 mg	2.25 mg	2.55 mg
X5=Magnitude Compression Pressure 1 eu = 0.5 tons	1.2 tons	1.5 tons	2 tons	2.5 tons	2.8 tons

time, tablet hardness, tablet friability, tablet weight variation, and tablet thickness variation.

Dissolution rates were determined in 900 ml, 0.1N hydrochloric acid with USPXXI apparatus 2 at 50 rpm. Tablet disintegration time, breaking strength and friability were measured with commonly employed equipment.

RESULTS AND DISCUSSION

All stated responses from the 27 experiments were measured. A routine multivariate statistical optimization analysis was then carried out. Data reduction included calculation of means and correlation coefficients of the dependent variable measurements. Each response was examined as to fit in a second order polynomial equation, as described before. R-square values indicated good linearity for all variables.

The optimum solution was obtained through traditional optimization analysis, i.e., feasibility and grid searches and then verified in the laboratory. The values of the response variables from the batch closely paralleled those predicted by the regression equation.

Data from the 27 experiments indicated that:

a) an increase in the amount of granulating water to -1.547 eu increased densification and hence resulted in a smaller granulation surface area (329 cm^2/g) than the base, (X1 = 0 eu), surface area (570 cm^2/g). A decrease in the amount of granulating water to +1.547 eu, in contrast, resulted in an increase in this value to 1146 cm^2/g.

b) This trend was also observed with variations in the granulation mixing time, i.e., densification and hence size of the granules is directly proportional to time.

These results support literature reports which indicate that matrices of dicalcium phosphate are extremely sensitive to the volume of the granulating liquid and the length of time for granulation prepared in a high intensity mixer. Lactose matrices, in contrast, were found insensitive to these variables.

c) Effect of Lubricant: With the other variables maintained constant and, hence, at about an equivalent granulation surface area, a decrease in the lubricant level from 1.7 mg, (0 eu), to 0.85 mg, (-1.547 eu), decreased the disintegration time from about 10 min to 4 1/2 min, indicating decreased hydrophobicity. A corresponding increase in this level to 2.55 mg increased the disintegration time to about 15 min.

To define a relationship between granulation surface area and level of the lubricant, the following data normalized to correct for the influence of the 4 other independent variables was examined.

Expt.No.	Lubricant level, mg/CT	Granulation Surface area, m^2/g	Tablet, DT mins.
16	1.15 (-1.0 eu)	0.428	8-10
2	1.7 (0 eu)	0.571	9-11
4	1.7 (0 eu)	0.599	10-11
17	1.7 (0 eu)	0.615	9-11
19	2.25 (+1.eu)	0.849	10-11

A least squares linear regression analysis related the lubricant level (y) to the granulation surface area (x) producing the expressing:

$$Y = 2.5\ x + 0.157$$

with a correlation coefficient of 0.982.

The highly significant correlation coefficient indicates the linear dependence of this independent variable and the response variable.

CONCLUSION

This study provides an excellent predictor of the optimum lubricant concentration for any granulation.

The optimum lubricant concentration for a new granulation (g_2) can be calculated from that known for an adequately lubricated granulation, (g_1), of the same material, through simple arithmetic,

$$\text{i.e. } L_2 = \frac{Sg_2}{Sg_1} \times \frac{SL_1}{SL_2} \times L_1$$

where Sg = surface area of the granulation, $cm^2/100$ g

SL = surface area of the lubricants (m^2/g),

used in batch 1 and 2, respectively

L = concentration of the lubricant in grams.

If the same lubricant batch is used, then

$SL_1 = SL_2$ and so

$$L_2 = \frac{Sg_2}{Sg_1} \times L_1$$

The above calculation also accounts for the surface area of magnesium stearate, which can significantly affect lubricity and hydrophobicity, more so since magnesium stearate shows considerable batch-to-batch variation with regard to lubricating properties. Therefore, no only the initial physico-chemical characteristics of magnesium stearate are important but also its amount.

Magnesium stearate can be declared by an absolute quantity only if, a) well defined physico-chemical specifications are set for it, b) the formulation where-in it is used is made insensitive to the method of densification, i.e., approximately the same granulation surface area is obtained each time. If these constraints cannot be met then an absolute quantity of the lubricant will contribute to variable product quality. The acceptable approach then is to have ranges for lubricant weight,

especially since Part 314.7 Title 21 since Part 314.7 Title 21 of the Code of Federal Regulations indicates that reasonable variations of ingredients may be specified in the full statement of the composition of the drug. Presumably adjustments within this weight range may be made but only if the finished product meets specifications regarding dissolution.

FOOTNOTES

[1]BPMC 10 Liter Granulator - Baker Perkins Chemical Machinery

Limited, Stoke-on-Trent, England.

[2]Manesty Betapress - Manesty Machines Limited, Liverpool, England

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