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OPTIMAL MASSING LIQUID VOLUME DETERMINATION BY ENERGY CONSUMPTION MEASUREMENT : STUDY OF THE INFLUENCE OF SOME PHYSICAL PROPERTIES OF SOLVENTS AND PRODUCTS USED

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ABSTRACT

This study tried to investigate, by the power comsumption technique, the influence of the powder's and solvent's properties on wet granulation.

It could be shown that the required amount of granulation liquid decreases when the particle size of the powder to be granulated increases. This relationship is however only true when the particle size distribution of the powder to be granulated is rather narrow.

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Powders having the same solubility in different solvents require the same optimal liquid quantity for granulation, but the properties of resulting granules depend on surface tension and wetting properties of the solvent.

When the powder to be granulated contains crystallisation water, the temperature rising in the mixer can be sufficient to liberate this water, which must be taken into account in the optimal granulation liquid requirement.

The effect of a macromolecular binder (PVP, HPMC) has also been studied : the optimal liquid quantity required changes with the kind of binder used and the manufacturing process (binder used in solution or added as dry powder).

It was also shown that in the case of lactose, the optimal quantity of PVP or HPMC can be determined from the power consumption records and from the granules friability studies

INTRODUCTION

In a previous work (1), it has been shown that the optimal quantity of liquid required for granulation can be studied by the mixer's power comsumption technique even on a very small batch. It has also been shown that this quantity of liquid is rather independent of the technological factors during granulation : only the screen size modifies significantly the quantity of liquid required.

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In the present work, the influence of the type of powder to be granulated, and the kind of solvent used has been studied.

The granulation process is based on attractive forces between particles. Liquid bridges are formed, and the cohesive forces between particles can be described by the equation given by RUMPF and al. (2) :

$$H_F = \alpha . \pi . \sin\beta \; x . \; \sin(\beta + \delta) + \left(\frac{1}{R_1} - \frac{1}{R_2}\right) . \frac{x}{4} . \sin\beta$$

where - α is the surface tension of the granulation liquid

x the particle diameter

β the center angle

δ the wetting angle

R_1 the radius of the concaveness of the liquid bridge

R_2 the half length of the minimal width of the bridge.

This equation is based on the physical properties of the powder and the granulation liquid.

For these reasons, it seemed interesting to try to find a practical relationship between the powder's and liquid's properties, and the optimal quantity of liquid required, measured by the power consumption technique.

Among the factors which can be studied, the most easy to investigate are the particle size (x), wetting (δ) and surface tension (α).

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MATERIALS AND METHODS

In order to study the influence of the solubility and particle size, different crystalline powders have been used for granulation : lactose, available on the market in different particle size, boric acid, zinc sulphate and potassium citrate (table 1) : these products were chosen either to study the influence of particle size (lactose), or to study the influence of the solubility (zinc sulphate and potassium citrate show the same solubility in water), or to study the influence of the kind of solvent (boric acid has the same solubility in water and in alcohol).

Potassium citrate was used in a milled and unmilled form. In fact (table 1) milling does not change the mean particle size, but modifies only the particle size distribution, due to the shape of the original crystals.

As granulation liquids, the most common used solvents were studied : water and alcohol.

Binders wich are used in granule manufacturing are very numerous : natural macromolecules (gelatin, gums,....), semi-synthetic ones (cellulose derivatives, ...) or synthetic products (PVP,....). Among them, only two were studied : PVP and hydroxypropylmethylcellulose (Pharmacoat 606^R^).

The granulation process was studied by the power consumption technique and particle size analysis, as described

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Table I : Characteristics of the studied products.

Product	Mean particle size	Solubility		Supplier
		Water	Alcohol	
Lactose "impalpable"	20 µm(1)	0.200 g/ml		H.M.S. (N.L.)
"fine powder"	50 µm(1)			
"extra fine crystals"	115 µm(2)			
Boric acid	80 µm(2)	0.055 g/ml	0.055 g/ml	Lambert Riviere (F)
Zinc sulphate ($ZNSO_4,7H_2O$) milled	120 µm(2)	1.66 g/ml		Merck (D)
Potassium citrate ($C_6H_5K_3O_7,H_2O$) unmilled	85 µm(2)	1.66 g/ml		Merck (D)
milled	85 µm(2)			

(1) particle size measured by microscopy

(2) particle size measured by screening

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in a previous work (1). Unless otherwise specified, the experiments were made on 1000 g batches, with a mixer speed of 170 rpm and a liquid flow rate of 10 ml/min. The wet mass was screened through a 630 µm screen to obtain granules, and the properties of the resulting granules were studied :

Particle size analysis was made by screening on an Erweka vibratory screen serie. Friability of the granules was analysed by shaking on a Turbula mixer during 15 minutes at 90 r.p.m. 10 g of granules having a size between 500 and 1000 µm. After this mechanical stress, the resulting granules were softly handscreened on a 500 µm screen, and the percentage of friability P_f was calculated.

Particule size analysis and friability tests were repeated 3 times on each batch.

RESULTS

3.1. Influence of particle size

Lactose of different particle sizes has been granulated with water. The power consumption records as a function of the quantity of water added show some differences with particle size increase (Figure 1) : The first peak becomes lower, and a second plateau appears. The optimal liquid quantity, calculated from these recordings are also modified (Table 2) : this quantity of liquid diminishes when the particle size increases. The obtained

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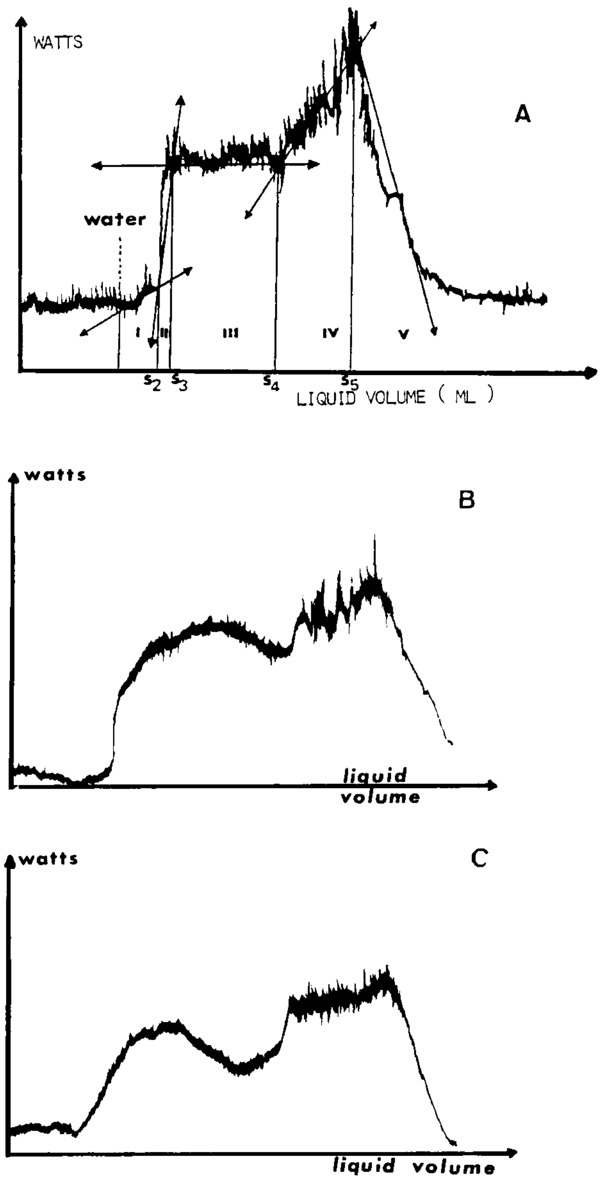

Figure 1 : Power consumption records of lactoses of various particle sizes (A = "impalpable" - B = "fine powder" - C = "extra fine crystals")

Table 2 : Optimal liquid quantities as a function of powder particule size.

Lactose (1000 g)	"impalpable"	"fine powder"	"extra fine crystals"
Optimal liquid quantity	135 ml	105 ml	98 ml

Potassium citrate 1000 g	milled	unmilled
Optimal liquid quantity	28 ml	35 ml

results seem in good fit with the Rumpf's cohesive force equation : the cohesive force increases when the particle size increases, so the quantity of liquid needed diminishes. An other explanation can be related to the total surface area of the powder : with the particle size increase, the surface area

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decreases, so the quantity of liquid needed to create bonds between particles is also less.

The quantity of liquid required for granulation is a straight line function of the reverse of particle size. Figure 2 indicates the relationship between particle size and optimal liquid quantity (measured either by the power consumption record or by the granule size analysis). This kind of relationship could be interesting for the calculation of the quantity of liquid required to granulate a lactose of any particle size.

In order to have a second example of the influence of particle size, the same experiment has been undertaken with potassium citrate before and after milling of this compound. The results obtained with the power consumption records show only a slight difference between the milled and unmilled product (table 2). Surprizingly this difference was not in the same way than this observed with lactose ; here less liquid was needed for the milled product. Furthermore, the values obtained with the power consumption record could not be related with those resulting from the granule size analysis.

This surprizing results could only be explained after a microscopic and screening particle size analysis of the potassium citrate before and after milling : in fact the original crystal size distribution is very wide, and, after milling in a blender, the mean particle size remains unchanged (table 1), but the particle size distribution is more uniform (table 3). The light

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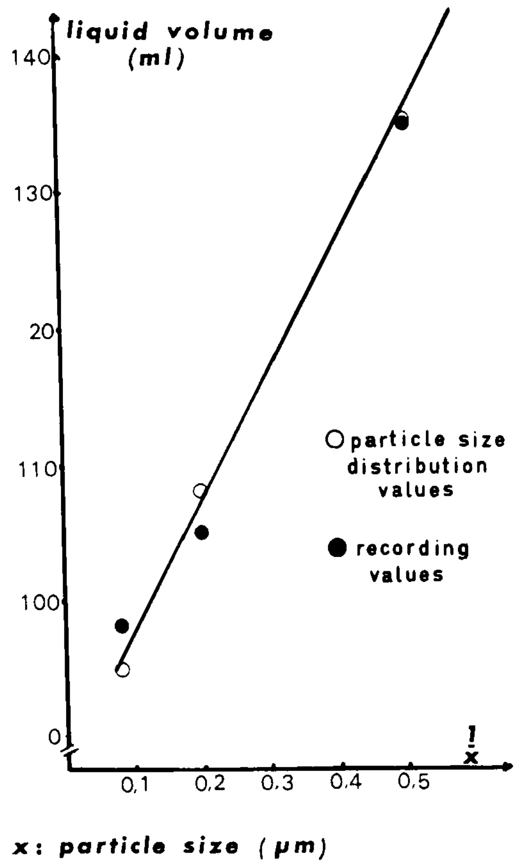

Figure 2 : Relationship between the particle size (x) and the optimal granulation liquid volume calculated from powder consumption records (●) and from granule size analysis (o).

difference between the values obtained with milled and unmilled potassium citrate can be considered as non significant, due to a variation in the particle size distribution homogeneity.

So it could be concluded that a relationship between the quantity of liquid required and particle size exists, but

Table 3 : Particle size distribution of unmilled and milled potassium citrate, calculated from screen analysis.

Percentage undersize	Particle size unmilled	milled
10 %	25 µm	38 µm
25 %	40 µm	60 µm
50 %	85 µm	85 µm
75 %	200 µm	125 µm
90 %	300 µm	180 µm

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only if the particle size distribution is regular, as for example in the various commercial grades of studied lactoses.

3.2. Influence of solubility

3.2.1. Study of boric acid

The first step of the study of influence of solubility has been made on batches of 500 g of boric acid, which shows the same solubility in water and in alcohol (Table 1). The power consumption records obtained with water or with alcohol have some similarities in general shape (figure 3). They are also close to those obtained with lactose (figure 1). The optimal quantity of liquid, calculated from these curves is 204 ml/kg for water granulation and 203 ml/kg for alcohol granulation : these two values are identical (table 4).

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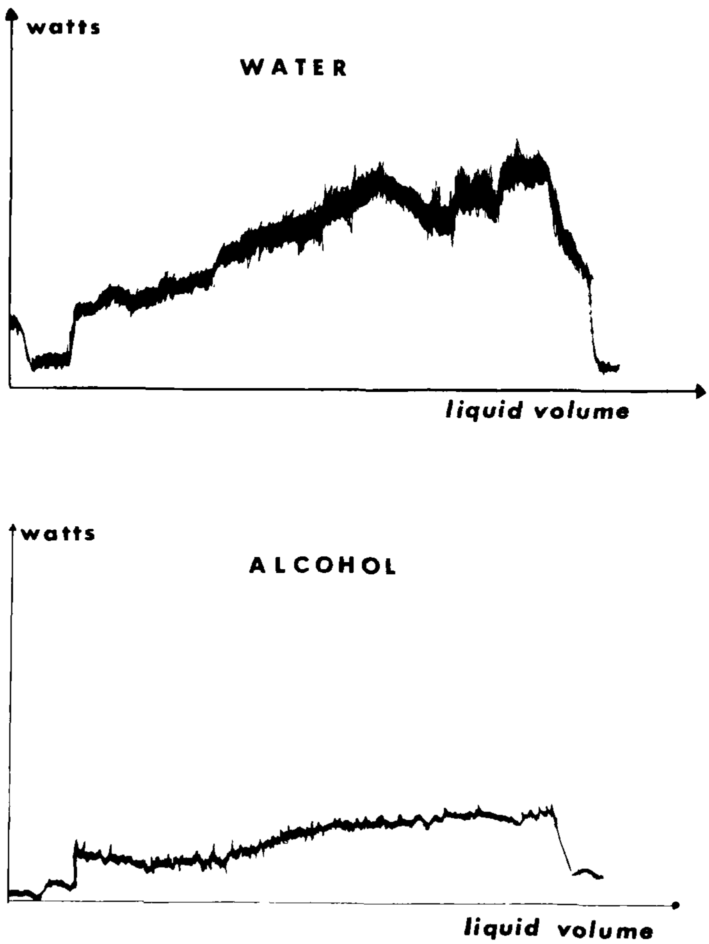

Figure 3 : Power consumption records of boric acid granulated with water and with alcohol.

The study of the granule size distribution curves as a function of liquid quantity (figure 4) indicates that the optimal liquid quantity is 205 ml/kg for water granulation, and 204 ml/kg for alcohol granulation. These different values are in good fit with those obtained by power consumption.

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Table 4 : Optimal liquid quantities for granulation of boric acid, zinc sulphate and potassium citrate calculated from power consumption records and from granules size distribution curves.

	Optimal liquid quantities (ml) for 1000 g of powder, calculated from	
	Power consumption records	Granule size distribution curves
Boric acid		
- water	204	205
- alcohol	203	204
Zinc sulfate	30	30
Potassium citrate	28	45

The granule size distribution curves also show that the area under the curves 500-1000 µm is larger in the case of water granulation than in the case of alcohol granulation (figure 4) : these areas are respectively 4896 %.ml with water and 2715 %.ml with alcohol. This result means that water can be considered as a more efficient solvent for granulation of boric acid than alcohol.

To explain this difference, the wetting of the crystalline powder by the two solvents has been studied in a very simple, non quantitative, manner : 100 mg of boric has been gently put at the

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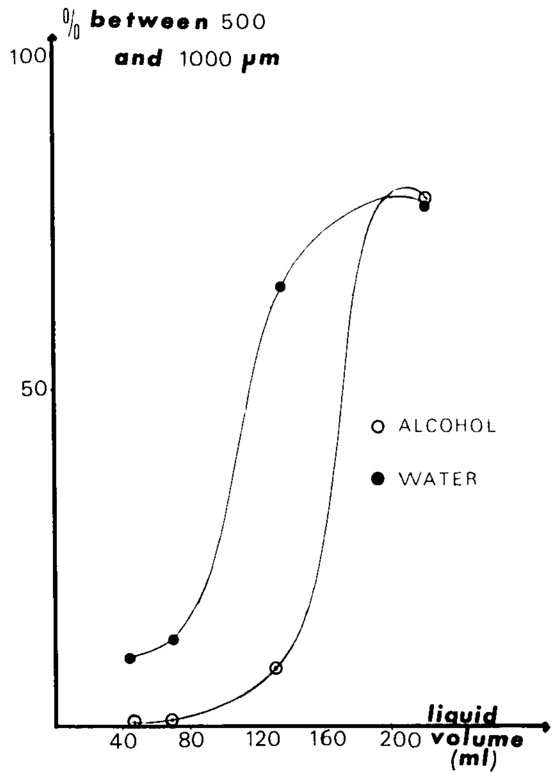

Figure 4 : Granule size distribution curves (granules between 500 and 1000 µm) as a function of liquid volume.

surface of 50 ml of water or alcohol. In the first case total immersion of the powder needs some seconds. In the second case, wetting and immersion are immediate.

So the wetting angle (δ) of boric acid with water is higher than this of boric acid with alcohol.

As the surface tension of water is also higher than this of alcohol (water : approx.73 dynes/cm ; alcohol : aprox.23 dynes/cm at 20°C (3), both factors act, according to the Rumpf's

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equation, to produce higher cohesion forces with water than with alcohol.

Furthermore, it seems that with water, a saturated solution is produced around the particles to be granulated (this phenomenon can clearly be seen during the immersion test), and the saturated solution is very propitious for the bonding during granulation. The quick formation of a solution around the boric acid particles can be demonstrated by the study of the speed of dissolution of boric acid : 100 mg of boric acid has been put into 500 ml of solvent, alcohol or water, and the variation of the resulting pH values has been followed, under stirring during 24 hours. The results of this experiment (figure 5) indicates that the dissolution in water, during the first minutes of the experiment, occurs faster than in alcohol.

The two factors (wetting and speed of dissolution) can explain the difference observed in the granule size distribution curves.

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3.2.2. Study of zinc sulphate and potassium citrate

Zinc sulphate and potassium citrate were choosen as model substances because they have the same solubility in water (table 1).

The optimal liquid requirement (table 4) are, according to the power consumption technique, 30 ml/kg for zinc sulphate and 28 ml/kg for potassium citrate. The study of granule size

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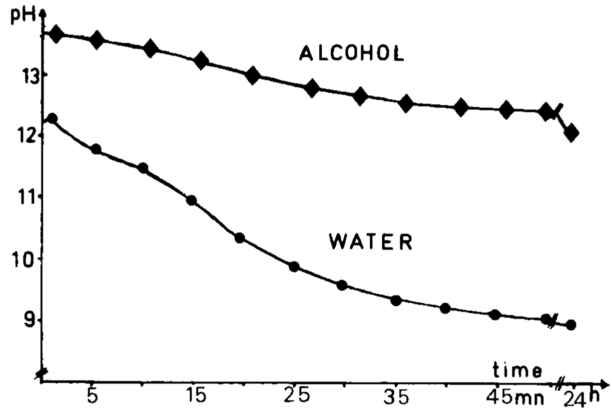

Figure 5 : pH variations during dissolution of boric acid in water and in alcohol.

distribution indicates that the optimal water quantity is respectively 30 ml/kg for zinc sulphate and 45 ml/kg for potassium citrate.

So, these two compounds, having the same solubility, need approximatively the same amount of water to produce good granules. The study of the granule size distribution of zinc sulphate (figure 6) indicates that the granulates contain a great amount of particles over 1000 μm, as if a kind of over-wetting could have taken place. As the liquid addition has been made very slowly, and in a regular manner, such an over-wetting cannot be related to the water added for granulation. But the crystals of zinc sulphate contain 7 molecules of water (see formula table 1), and a simple experiment of storing the crystalline powder in an oven indicates that this crystallisation water is liberated at a temperature of 50°C.

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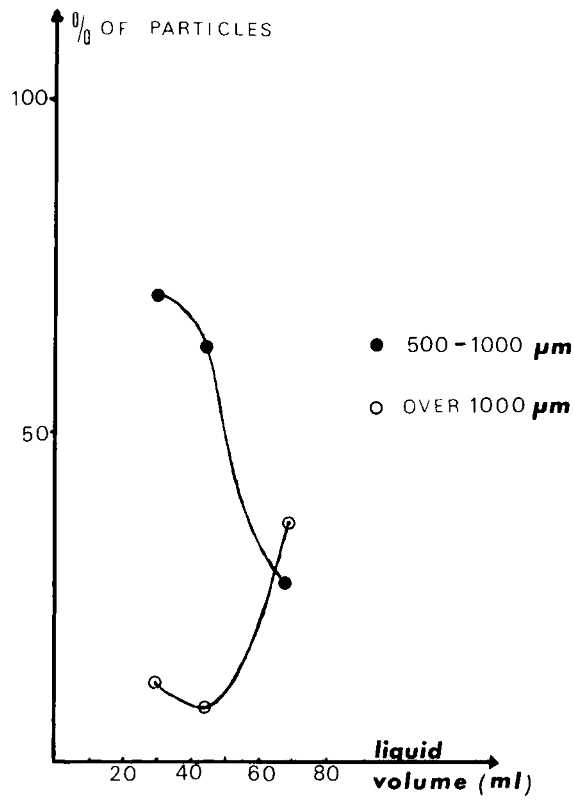

Figure 6 : Granule size distribution of zinc sulphate granules.

A control of the temperature increase in the small mixer used for this study showed that a non negligible temperature increase results for the frictions between particles and the mixer (after 15 minutes mixing, the temperature at the top of the powder in the mixer is 30°C - the temperature at the bottom is higher, but could not be recorded accurately in the powder under mixture).

This temperature increase can liberate some crystallisation water, and have an influence on the granulation process.

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The water liberation could also be noticed in the power consumption records : after addition of the optimal quantity of liquid, and additional mixing, the base line changed as if liquid had been added.

If the granulation liquid is added quickly, and in greater amount than the theoretical optimum, this phenomenon disappears : the added liquid avoids a part of the frictions, and picks up the free set heat. In this case even additional mixing does not change the baseline drawing.

3.3. Effect of a binder

A binding agent can be used for granulation either in solution, or added in powder form. In the case of solution, the binder is in the "internal phase" ; in the case of powder addition, it can be called in "external phase". Both were studied for ganulation of lactose "impalpable powder".

3.3.1. Study of P.V.P.

P.V.P. has been used in form of solutions of 1 %, 3 % and 5 % (w/v). When 1 % or 3 % solution were used, no significant difference in the power consumption recording could be noticed. The optimal liquid quantity remained unchanged (table 5).

After a correction due to the densities of the various solutions, the optimal quantity of water needed for granulation

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Table 5 : Optimal liquid quantities for 1 kg lactose granulations with different binders

Binder	1 %	3 %	5 %
PVP solution "internal phase"	135 ml	135 ml	134 ml
PVP Powder "external phase"	145 ml	120 ml	110 ml
HPMC solution "internal phase"	130 ml	111 ml	103 ml
HPMC Powder "external phase"	129 ml	129 ml	115 ml

has been plotted as a function of the binder quantity (figure 7). This figure shows a straight line relationship between the optimal quantity of water and the quantity of dry powder (w/w ratio to the quantity of lactose granulated). By plotting the optimal quantity of liquid as a function of the reverse of binder concentration, an asymptotical curve is obtained : this

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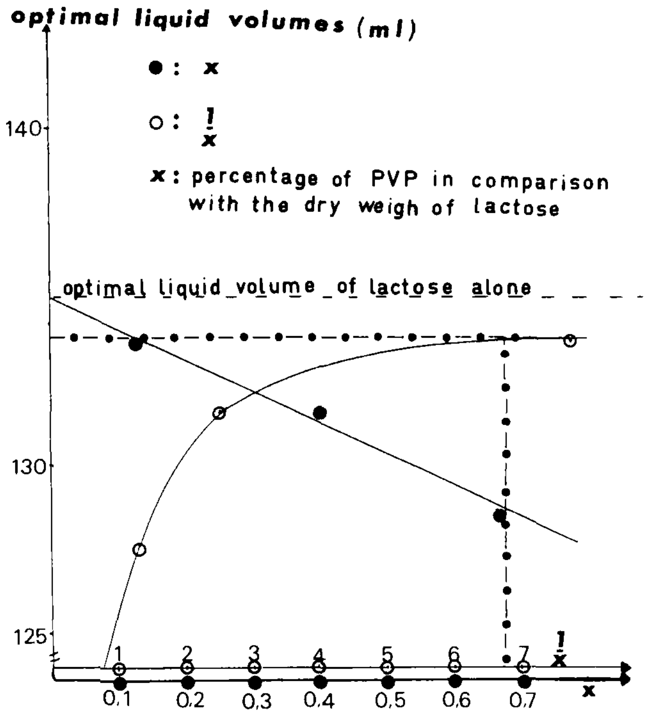

Figure 7 : Optimal water volumes as a function of the percentage of PVP used for lactose granulation.

curve could show that the minimum quantity of PVP needed to realize a granulate with lactose is 1/6.75 = 0.148 %.

A study of the granules friability (figure 8) shows that with a 1 % PVP solution, the friability curve is changed. This quantity corresponds to 0.135 % dry powder addition to lactose.

The friability curves also show that with such a small quantity of PVP the strength of granules is increased, and an use of higher quantities of binder has only few effects on granule strength increase.

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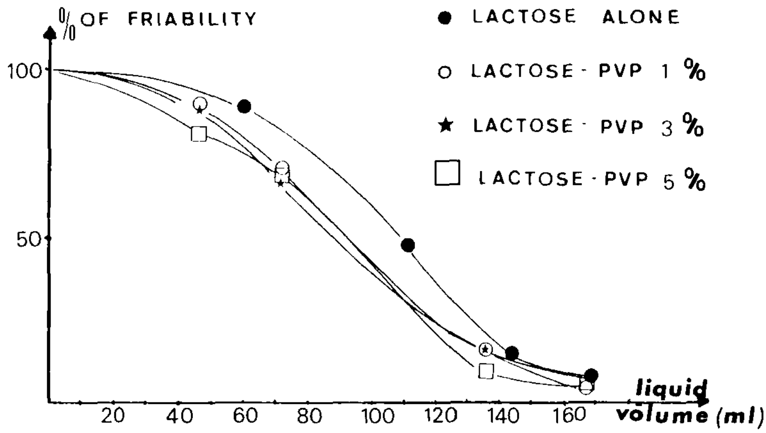

Figure 8 : Fraility of lactose granules prepared with PVP solutions of various concentration.

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So it seems that the plotting of the optimal quantity of liquid as a function of the PVP concentration (figure 7) as well as the friability measurement gives similar results, and the optimal quantity of PVP needed to produce good lactose granules is in the range 0.135 - 0.148 % (w/w - dry powders).

When PVP is added in powder form instead of solution, the optimal quantity of liquid required for granulation is different (table 5). The plotting of the optimal liquid quantity as a function of the PVP concentration (figure 9) can be drawn either from the power consumption measurements or from the granule size distribution. Both show that with 5 % of PVP, the maximum quantity of powder which can be added is not reached.

The friability plot of PVP - lactose granules as a function of the quantities of water added (figure 10) shows that

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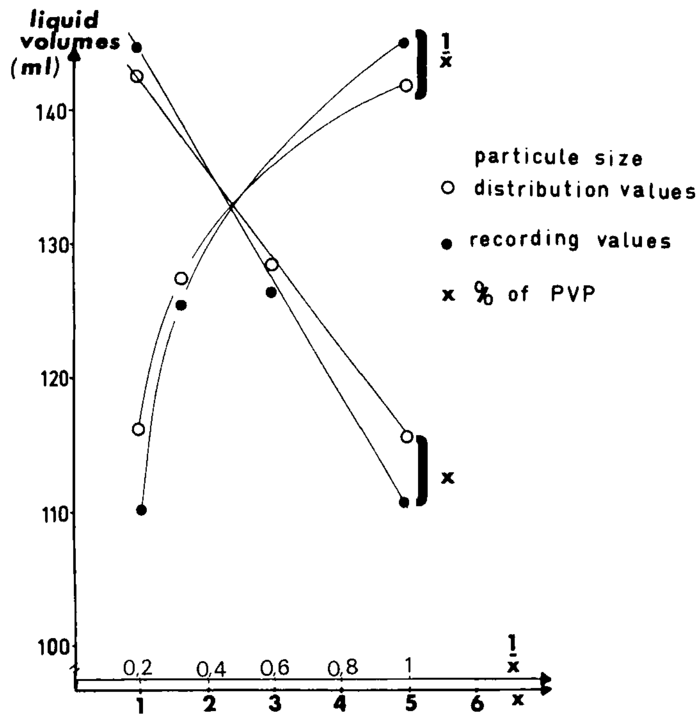

Figure 9 : Optimal liquid quantities as a function of the PVP concentration (PVP added in powder form).

with 1 % of PVP added in powder form, some effect on friability can be observed, but a reel efficiency of the binder is only reached with 3 % or 5 %. With this concentration of 5 %, the friability is decreased by approximately 50 % in a large range of wetting liquid quantities (40 - 80 ml/Kg).

3.2.2. Study of hydroxypropylmethylcellulose

With the use of HPCM solutions (Pharmacoat 606^R), the results are different from those observed with PVP (table 5) :

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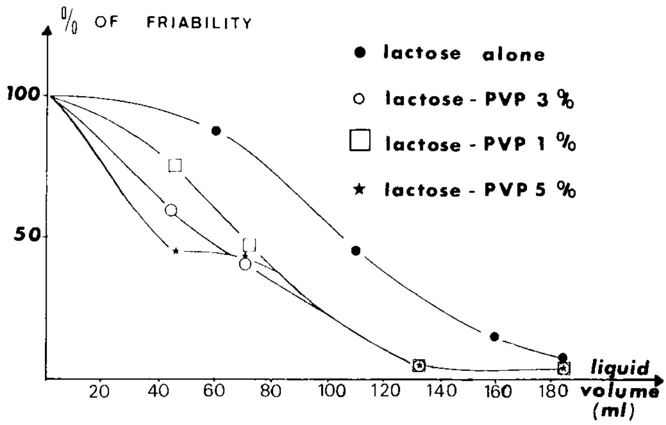

Figure 10 : Friability of lactose with PVP (PVP added in dry powder form) as a function of the quantity of water used for granulation.

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even with a 1 % solution of HPCM, the quantity of liquid required to prepare granules is diminished, compared to the requirement for lactose granulated with water. It seems for this reason that HPCM is more efficient than PVP.

By plotting the optimal quantity of water as a function of binder percentage (figure 11), it seems that the maximum quantity of HPMC which can be usefull is 5 %. This conclusion is the same wether the plotting is made from power consumption records, or from granule size distribution curves.

The friaility plot (figure 12) indicates that a 1 % solution is not sufficient to decrease the friability of granules. With 3 and 5 % solutions, the mechanical properties of granules are significantly improved. These results are in good fit with the power consumption records : a significant change

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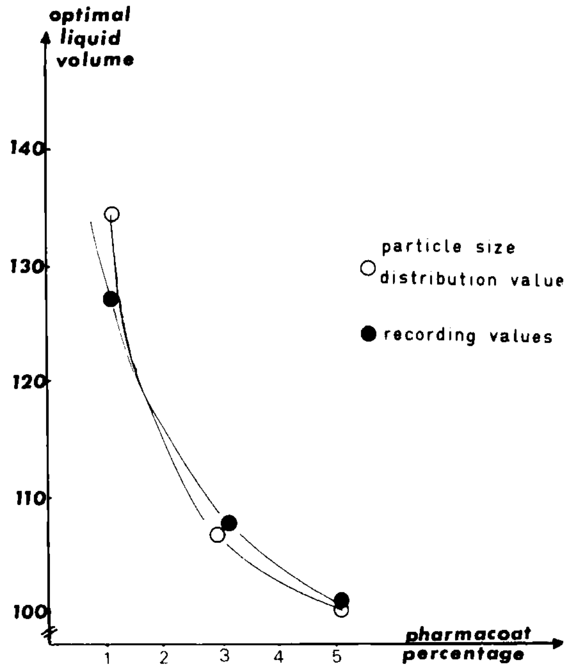

Figure 11 : Optimal quantity of water needed for granulation of lactose as a function of the percentage of HPMC.

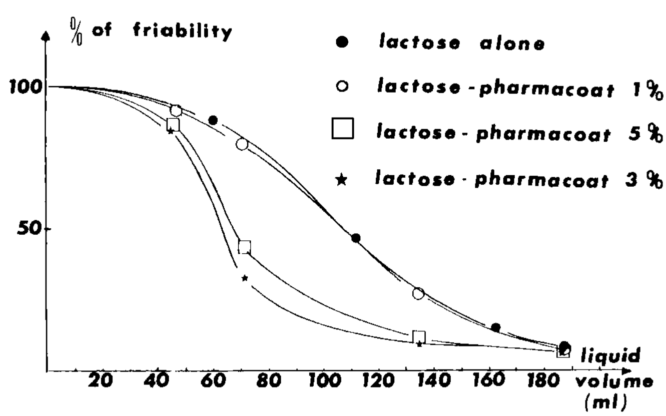

Figure 12 : Friability of lactose - HPMC granules as a function of the volume of liquid used.

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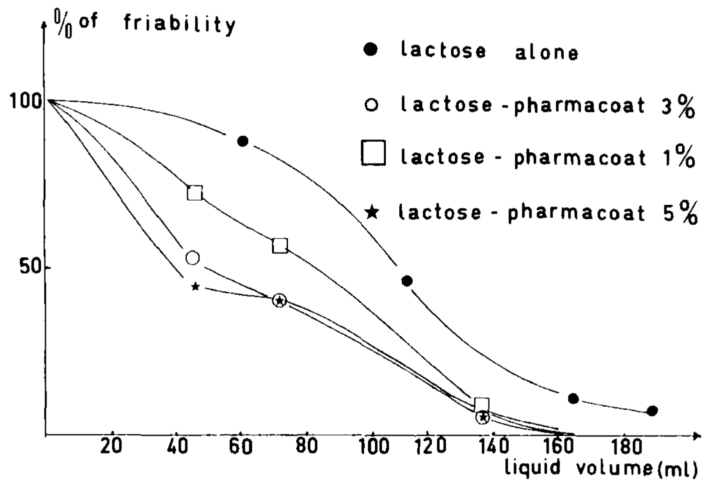

Figure 13 : Friability of lactose - HPMC granules as a function of liquid volume used for granulation (HPMC added in powder form).

in the general shape of the records could be seen from a concentration of 3 % HPCM.

The use of HPCM in external phase (dry powder) leads to results which are very close to those observed with PVP, but a binding effect can be seen with lower concentrations : the friability curves (figure 13) indicate that the friability can be decreased with 1 % of powder addition, and the binder seems really efficient at 3 %. The use of 5 % does not give better results than 3 %.

In both cases of binders added as powder (table 5), it is clear that the quantity of liquid required for optimal granulation is higher than with corresponding solutions. This phenomenon could be due to the solvatation of the macromolecu-

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lar binders, which need some liquid before any bonding between lactose particles is possible.

CONCLUSION

This study tried to investigate the influence of the powder and solvent properties on the granulation process.

It could be shown that the optimal liquid requirement depends on numerous factors such as solubility of the powder to be granulated, surface tension and wetting properties of the granulation solvent, particle size of the powder, crystallisation water.

The quantity of liquid required also depends on the kind of bridges formed during granulation, with or without the use of macromolecular binders.

Although the study has only be made on a small laboratory scale, the influence of many factors could be illustrated.

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