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ALUMINIUM-MAGNESIUM HYDROXIDE TABLETS : EFFECT OF PROCESSING AND COMPOSITION OF GRANULATING SOLUTION ON THE GRANULE PROPERTIES AND IN VITRO ANTACID PERFORMANCE

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ABSTRACT

Wet granulation experiments on aluminium-;magnesium hydroxide;mannitol blends were carried out, in order to produce chewable antacid tablets.

The influence of binder solvent, of type and concentration of polyvinylpyrrolidone as a binder and of granulating and drying equipment on the granule and tablet characteristics was investigated.

Water as a binder solvent offered several advantages over the use of alcohol. The use of high molecular weight polyvinylpyrrolidone reduced the antacid capacity and caused some manufacturing problems.

The granulating equipment (high shear granulator or planetary mixer) and the drying technique (oven or fluidized bed) had no major influence on the granule and tablet characteristics.

INTRODUCTION

Most chewable antacid tablets are composed of aluminium hydroxide, magnesium hydroxide and mannitol. Magnesium hydroxide is added to counteract the constipation effect of aluminium hydroxide and is a relative potent antacid. Mannitol is added as a sweetening agent and has an additional cooling effect in the mouth.

Because the active ingredients as aluminium- and magnesium hydroxide show unfavorable compression characteristics, granulation is advisable prior to compression but is very difficult (1). Different parameters of the granulation and tabletting process may influence the performance of antacid tablets.

The purpose of this study is to evaluate the influence of the concentration and type of polyvinylpyrrolidone (binder), of the granulation solvent and of the granulating and drying equipment on the characteristics of the granules.

The antacid capacity is determined for granules and tablets.

MATERIALS AND METHODS

Granulation and granule characterisation

Granules were prepared, containing aluminium hydroxide, magnesium hydroxide and mannitol (all chemicals were of B.P. quality), in a ratio 4:2:1 (w/w) respecticely, using an aqueous or alcoholic polyvinylpyrrolidone (Kollidon 12 PF, Kollidon 30, or Kollidon 90; BASF, Ludwigshafen, W. Germany) solution.

All powders were sieved through a 350 µm sieve and dry blended in a planetary mixer for ten minutes at 90 rpm (Kenwood, Model A 907) or in a high shear granulator (Grall, Collette, Wommelgem, Belgium) for 1 min at 600 rpm for the mixing arm and 3000 rpm for the shopper. The granulating liquid (125 ml water or 150 ml alcohol per 175 g dry material) is added and granulation proceeded for 7 minutes using the planetary mixer or for less than 1 minute using the high shear granulator.

The mass was wet milled through a 1 mm oscillating sieve (Erweka, Frankfurt, W-Germany). The batches were oven dried or fluidised bed dried (Glatt, Uni-Glatt, Bilzen, W-Germany) at 50 °C

The drying time, optimised in function of minimal fine formation, was fixed at 20 minutes when alcohol was used as a solvent and at 45 minutes for aqueous solutions.

The granule properties investigated include tendency to fine formation, size distribution, friability, bulk and tap density expressed in percent of volume reduction after 100 taps. The tendency to fine formation in function of residual humidity levels was determined by passing 100 g oven dried granules through a 1000 µm oscillating sieve. The fraction of a 20 g sample, passing a 150 µm sieve was considerated as fines. This value was used to determine the optimal residual humidity level (related to the drying time) for final granule sizing. Sieve analysis and tapped volume (100 taps) were determined by standard methods.

Granule friability was determined by subjecting 10 g granules (710-250 µm fraction) together with 200 glass beeds (2 mm diameter) to falling shocks in an Erweka friabilator for 10 minutes at 25 rpm. The friability was calculated as the loss of weight on the 250 µm sieve and expressed in percentage. The composition of the different granules investigated is indicated in Table 1.

TABLE 1

Composition of the Formulas

Formula number	1	2	3	4	5	6	7	8	9
Type P.V.P. (Kollidon®)	12	12	12	30	30	30	90	90	90
% P.V.P.	2.5	5.0	10.0	2.5	5.0	10.0	2.5	5.0	10.0

Tabletting

Silicium dioxide (0.05 %, particle size < 180 µm (Aerosil 200, Pharmachemic, Antwerp, Belgium) was added to each batch of granules and blended in a Turbula mixer (Type T2A, Basel, Switserland) for eight minutes. Next, magnesium stearate (0.01 % particle size < 180 µm) was added as a lubricant and blended for an additional two minutes. The mixture was compressed on a single punch press (Korsch, W-Germany), fitted with 18 mm flat punches, at a 78 $kg.cm^{-2}$ pressure.

Tablet friability was determined using the Roche friabilator and a Heberlein hardness tester was used to measure the hardness of the tablets.

Antacid capacity

The antacid capacity of granules and crushed tablets was determined on 400 mg material (710 µm - 250 µm sieve fraction) following the USP XXI method.

RESULTS AND DISCUSSION

Effect of the binder solvent and type of P.V.P. on the physical characteristics of the granules.

As can be seen from Table 2, the particle size distribution seems not really influenced by the type of P.V.P. used. An increase in binder concentration increases moderately the particle size. The particle size distribution was not really influenced by the choice of solvent (Table 3). The same findings were confirmed when using K 30 as well as K 12 or K 90 as a binder.

In most cases granule friability was inversely related to the concentration and molecular weight of all P.V.P. types used (Table 2). In all cases where alcohol was the solvent, the friability nearly doubles except for the 10 % K 30 and 10 % K 90 where a low friability, ranging from 20 - 30 % is observed (Table 3).

This may indicate that the role of mannitol as a binder is not negligible and influences the friability of the granules. The solubility of mannitol is about 15 times higher in water than in alcohol. Nevertheles it was impossible to obtain granules without using a specific binder, indica-

TABLE 2

Effect of Type and Amount of P.V.P. using Water as the binder solvent on the granule properties. The granulation was performed in a planetary mixer and the granules were oven dried.

P.V.P.type	K 12			K 30			K 90		
P.V.P.conc.(w/w)	2.5	5.0	10.0	2.5	5.0	10.0	2.5	5.0	10.0
Particle size (µm)	% weight								
≤ 250	13.4	9.2	9.8	13.9	14.5	11.3	14.7	13.9	5.4
250 - 500	29.4	20.1	25.2	29.7	26.4	25.1	27.4	25.6	15.7
500 - 710	22.8	18.1	25.9	24.0	19.9	18.9	18.9	17.4	16.0
710 - 1000	28.0	42.0	25.7	24.3	33.6	26.0	22.7	28.4	27.7
> 1000	5.9	10.1	13.1	7.8	5.3	18.3	15.8	14.5	34.8
Volume reduction (%)	10	10	9	10	9	10	12	10	8
Friability (%)	43	38	36	43	35	28	37	26	24

ting the impossibility to use only mannitol as a binder.

Bulk volume reduction was in all cases very similar and nor the type or concentration of P.V.P., neither the binder solvent had a marked influence on the bulk or tapped volume.

TABLE 3

Influence of binder solvent on the granule properties. The granulation was performed with K-30 as a binder in a planetary mixer and the granules were oven dried. Granules prepared with other types of P.V.P. revealed similar results.

P.V.P.conc. (w/w)	2.5	5.0	10.0	2.5	5.0	10.0
Solvent	water			alcohol		
Particle size (µm)						
≤ 250	13.9	14.5	11.3	16.1	16.0	10.6
250 - 500	26.4	16.4	25.3	22.3	22.5	14.6
500 - 710	19.9	19.9	18.9	17.2	16.5	12.1
710 - 1000	33.6	33.6	26.0	34.4	28.2	15.4
> 1000	5.3	15.3	18.3	9.7	16.4	46.9
Volume reduction (%)	10	10	10	11	11	11
Friability (%)	43	35	28	95	84	21

The influence of granulating and drying equipment on granule properties

Because of the high friability of granules produced with an alcoholic solution, water was used as a solvent in the comparative study between the planetary mixer and the high shear granulator. All the granules in this part of the study were oven dried. The influence of the granulating equipment on the particle size distribution was negligible.

friability. A higher amount of fine production should have influenced the bulk volume reduction and the particle size distribution.

Influences on the antacid capacity

Table 4 shows the antacid capacity, expressed as meq.g^{-1} for the granules produced in a planetary mixer or a high shear granulator with different concentrations of all types of P.V.P. and alcohol or water as the binder solvent.

A small reduction of the antacid capacity was observed between the different batches when alcohol was the binder solvent. A pronounced negative influence on the antacid capacity of granules, was seen when granulation was performed with a high shear granulator and a high concentration of the high molecular weight P.V.P. (Kollidon 90). The antacid capacity of granules prepared with a planetary mixer is less influenced by the type and concentration of P.V.P.

Oven dried granules revealed slightly higher antacid capacities than fluidized bed dried granules, except for the granules prepared with 10 % K 90 as a binder.

TABLE 4

The influence of the type of binder solution, type and concentration of binder, granulating and drying equipment on the antacid capacity (meq. g^{-1}), n = 3, $SD_{max} = \pm 0.5$

Type of binder			K 12			K 30			K 90		
conc.binder(w/w)			2.5	5.0	10.0	2.5	5.0	10.0	2.5	5.0	10.0
Process definition											
A	Pl	O	14.0	16.0	13.5	14.3	15.0	14.0	15.2	15.9	14.0
W	Pl	O	15.1	16.0	13.8	15.5	15.8	15.6	15.5	15.9	15.4
W	H	O	16.4	16.0	15.7	15.5	15.0	16.1	14.5	14.9	10.9
W	H	Fl	16.4	15.2	15.6	15.3	14.9	15.5	14.1	13.8	13.6

A = alcohol
W = water
Pl = Planetary mixer
H = High shear mixer
O = Oven dried
Fl = Fluidized bed dried

Fig. 1 compares the friability of granules produced with the high shear granulator and the planetary mixer. In nearly all cases the friability of the granules is lower when using a high shear granulator. This could indicate that, due to an increased massing effect, a higher fraction of mannitol is dissolved in comparison with the planetary mixer technique and an additional binding effect can be

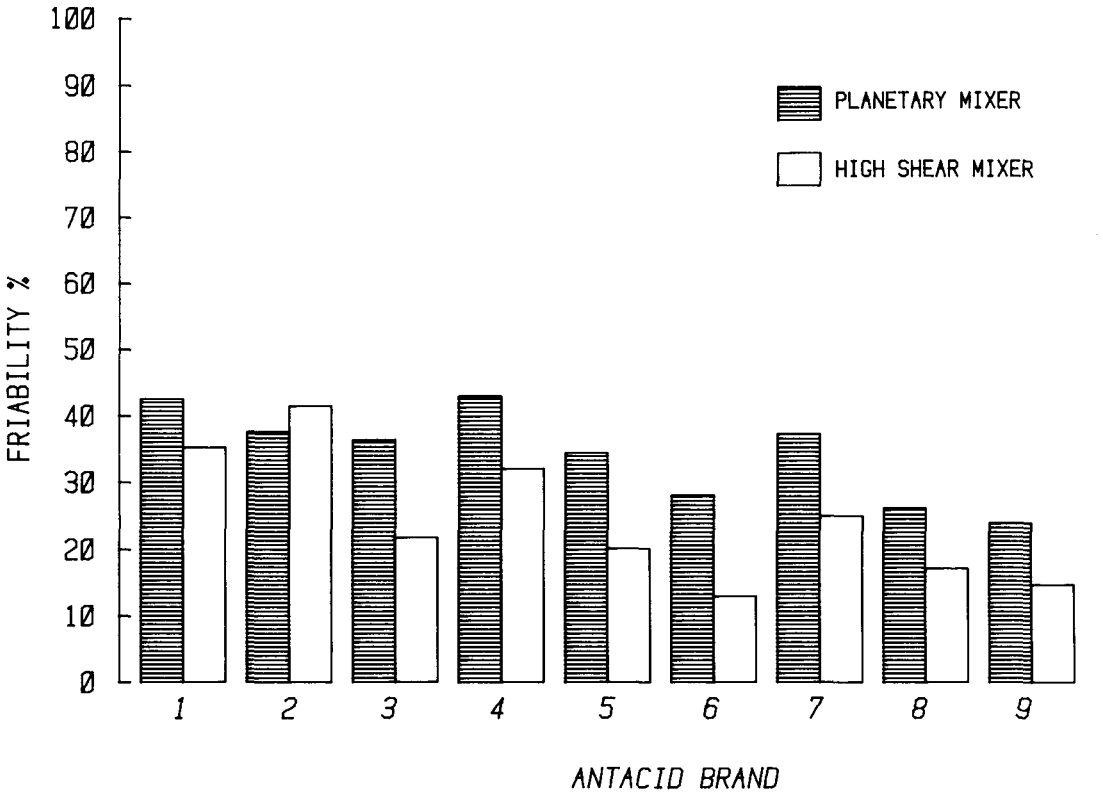

FIG. 1

Friability of oven dried granules, granulated with an aqueous polyvinylpyrrolidone solution using a planetary mixer or high shear granulator. The composition of the formulas is indicated in Table 1.

expected. Simultaneously a better distribution of the P.V.P. may be suggested.

The influence of the drying technique on the granule friability is shown in Fig. 2. One expects the granule friability to be lower for oven dried granules compared to fluidized bed dried granules,

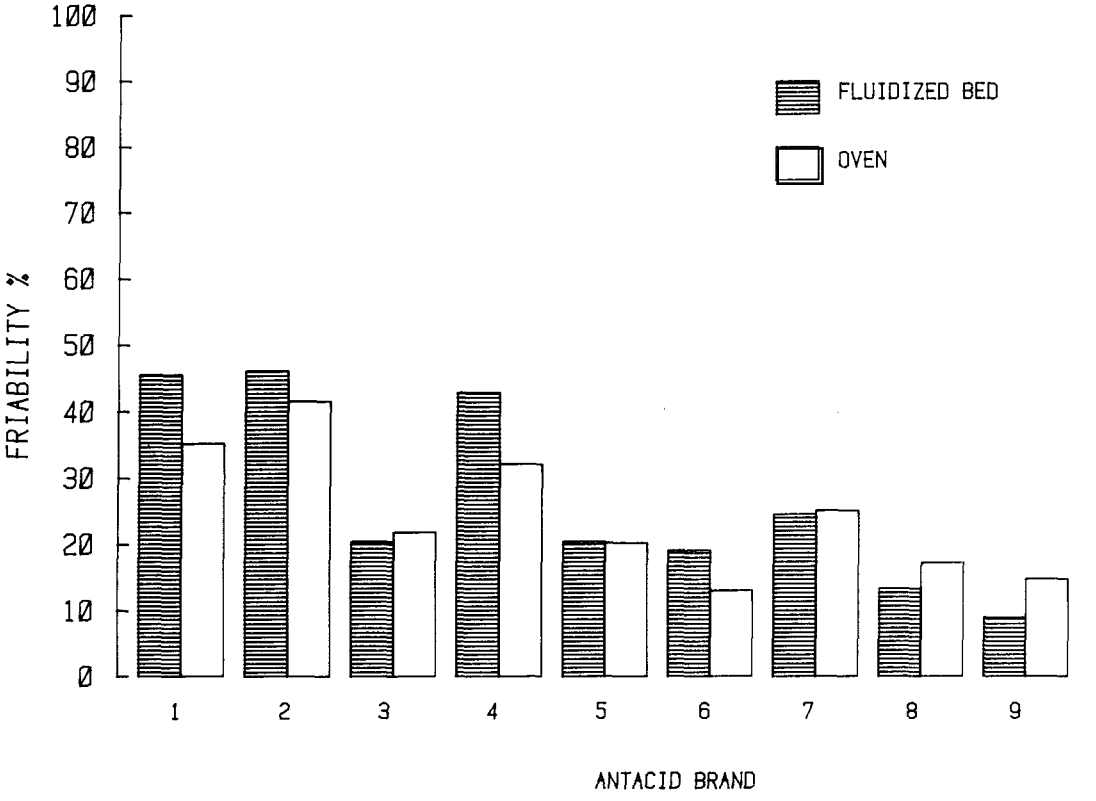

FIG. 2

Friability of oven or fluidized bed dried granules, granulated with an aqueous polyvinylpyrrolidone solution using a high shear granulator. The composition of the formulas is indicated in Table 1.

because more fines are produced during the fluidization step, but in the case of high concentrations of high molecular weight P.V.P., the friability of the oven dried granules became even higher than the friability of the fluidized bed dried granules.

Volume reduction after tapping is low (below 2,5 % in all cases). No important differences in

TABLE 5

Composition and Evaluation of the Antacid Tablets

P.V.P. type	K 30						K 90					
Binder concentration (w/w).	5	5	10	10	10	10	2.5	2.5	5	5	5	5
Granulation/drying technique	H/O	H/F	H/O	H/F	F1/O	F1/F	H/O	H/F	H/O	H/F	F1/O	F1/F
Hardness ($Kg.cm^{-2}$) n=6 $SD_{max} = \pm 2.05$	15.5	12.5	11.0	12.6	13.5	13.4	> 16.0	13.6	14.0	13.2	13.9	8.95
Friability (%) n=3 $SD_{max} = \pm 0.01$	0.22	0.31	0.04	0.00	0.02	0.00	0.01	0.08	0.08	0.04	0.00	0.00
Antacid capacity ($meq.g^{-1}$) n=3 $DS_{max} = \pm 0.6$	20.0	16.0	13.3	14.2	13.6	13.0	13.7	14.1	14.8	13.7	14.9	14.3

volume reduction are observed between high shear and planetary mixer granulated blends neither between fluidized bed and oven dried granules. These findings support the relative low differences observed in

Tablet evaluation

Only the high quality granules were compressed and tested on their hardness, friability and antacid capacity (Table 5). The friability of the tablets is low (< 0,5 %) in all cases. The antacid capacity is comparable, except for the high shear granulated-oven dried or fluidised bed dried granules, prepared

with a 5 % aqueous K 30 binder solution where an exceptional high antacid capacity was observed.

CONCLUSION

The use of water as binder solution and the addition of a specific binder is essential to granulate antacids.

The granule properties are strongly dependent on the type and concentration of P.V.P. used during the granulation process. The use of low molecular weight P.V.P. or a low concentration of binder reveals a high friability. The increase of molecular weight and concentration of binder reduces the antacid capacity.

Granule properties are improved by the use of a high shear granulator and oven drying.

The compressed granules show excellent friability and hardness. Tablets containing 5 % K 30 revealed excellent antacid capacities.

ACKNOWLEDGEMENT

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REFERENCE

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