Drug Development and Industrial Pharmacy, 23(8), 791–808 (1997)

RESEARCH PAPER

Effectiveness of Binders in Wet Granulation: A Comparison Using Model Formulations of Different Tabletability

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ABSTRACT

Based on an analysis of model granulates and tablets, a comparison was made of the effectiveness of the binders PVP K30 PH, Cellulose HP-M 603, Lycatab DSH, Lycatab PGS, and L-HPC (type LH 11). A high shear mixer was used to prepare two model granulates (placebo and paracetamol) under processing conditions which were, as far as possible, comparable. The binders were added as proportions of 2%, 6%, and 10%. Water was used as the granulating liquid. The properties of the placebo granulates (particle size distribution, bulk and tapped density, granule strength, flow properties), and those of the tablets (crushing strength, friability) prepared from these granulates under different compaction forces, were generally good. However, with PVP, Cellulose HP-M603, and Lycatab, the disintegration time of the tablets did not meet pharmacopoeial requirements even though a "disintegrant" was used in the "outer phase." The paracetamol formulations were prime examples of high-dose drug substances with particularly poor granulating and tabletting properties, well suited to reveal differences between the binders. The paracetamol granulates were of higher friability and less flowability than the placebo granulates. The tablets tended to cap, friability was (with few exceptions) high, and disintegration times were long. In the preparation of model tablets containing paracetamol, PVP K30 PH (6%), and Cellulose HP-M 603 (6%) turn out to be the binders of choice with respect to crushing strength, but the disintegration times are too long. Lycatab PGS, Lycatab DSH, and L-HPC-LH 11 could not be used to produce paracetamol tablets that met the requirements.

An assessment method involving calculation of averages for all granulates is used to evaluate the effectiveness of the binders.
Key Words: *Wet granulation; High shear mixer; Binder; Tablet; Hydroxypropylmethylcellulose; Polyvinylpyrrolidone; Lycatab; L-HPC.*

INTRODUCTION

The properties of wet granulates, and of the tablets into which they are processed, are decisively influenced by binders. Not only are the type and amount of binder important, but also the processing procedure, e.g. the initial and then thorough wetting of the tablet mass (1). A standard method for wet granulation in a high shear mixer involves the dry addition of binder, followed by mixing, and then the addition of water. In this method a good correlation was found between granulate particle size and binder concentration (2), and in addition, this method does not require the preparation of a binder solvent.

The aim of the present study is to compare the effectiveness of different binders when used for wet granulation in a high shear mixer.

Commercial formulations of the binders polyvinylpyrrolidone (PVP K30 PH) and hydroxypropylmethylcellulose (Cellulose HP-M 603) are widely used (3) and serve here as a reference. Lycatab PGS™ (a pregelatinised maize starch), Lycatab DSH™ (a maltodextrin), and L-HPC, type LH 11™ (a low-substituted hydroxypropylcellulose) are used less frequently or are new.

Two models, a placebo formulation and a drug formulation, were assessed. The latter was given a very high content of paracetamol so that its tableting properties would be particularly unfavorable. The influence of different types and amounts of binders both on granulate properties (particle size distribution, bulk, and tapped density, granule strength, flow properties) and on tablet quality (crushing strength, friability, disintegration time) was investigated.

The degree to which wetting affects the particle size of the agglomerates depends to a large extent on the adhesion properties between binder and powder (4,5). Powder wettability is particularly important for binder distribution in the granules (6) and for the mechanical properties of the tablets (7). For this reason, it was not possible in the present study to go to the literature for data on the reference substances. However, since particle enlargement is for the most part unrelated to the the particular machines used (4,8), these observations can be applied to other manufacturing situations.

MATERIALS AND METHODS

Preparation of the Granulates

The raw materials used in the preparation of the granulates are listed in Table 1. Of the 1800 g in each granulate, 89.3% of the final mixture was the "inner" phase and 10.7% was the "outer" phase. Table 2 summarizes the compositions of the formulations.

The manufacturing steps for the granulates are listed in Table 3.

Properties of the Granulates

Particle size distribution of the granulates was determined twice in each case, on 50 g portions of granulate, using a laboratory VE 1000/s sieving machine (Kurt Retsch GmbH & Co. KG, 42781 Haan, Germany) set to run for 10 minutes at an amplitude of 1.5 mm. The stack consisted of analytical-grade screens conforming to DIN/ISO 3310/1, with mesh sizes of 1000, 710, 630, 500, 315, 250, 200, and 100 μm.

The *bulk and tapped density* of the granulates were assessed in accordance with the Germany pharmacopoeia (DAB 1966) using a JEL tamped volume measuring apparatus (STAV 2003, J. Engelsmann AG, 6700 Ludwigshafen, Germany). V_{250} is the result reported.

The *granule strength* was determined by testing friability using the "Roche" oscillating friability testing machine. The testing drum, equipped with two steel rollers, alternately rolls 50 times to the left and right, rotating 170° each time. 10 g of granulate from the 250–800 μm sieve fraction was used for the test of granule strength. After the drum movement stopped, the granulate was sieved for 2 min through a 250 μm sieve, with an air throughput of (48–58) m^3/hr, using the Alpine 200 LS air-jet sieving machine (Alpine AG, 8900 Augsburg, Germany), and the residue remaining on the sieve was weighed. The granule strength was calculated using the following formula:

Table 1

Materials

Name	Manufacturer	Batch
Lycatab PGS	Roquette Fréres, F-Lille	E8213
Lycatab DSH	Roquette Fréres, F-Lille	E5810
L-HPC Typ: LH-11	ShinEtsu Chemicals, J-Tokio	501019
Cellulose HP-M 603	DOW Chemical USA, Midland, MI, USA	JJ15012N23
PVP K 30 PH	I.S.P., Guildford, U.K.	TX51028
Lactose, ground	De Melkindustrie Holland, NL-Veghel	024448
Avicel PH 102	FMC, Philadelphia, PA, USA	Y541
PVP XL	I.S.P., Guildford, U.K.	S50529
Aerosil 200	CABOT Corp., Tuscola, IL, USA	
Magnesium stearate	FACI Italien ??	MGS-30159
Paracetamol	Hou Zhou Syn. Pharm. Fact.	9512082(M) 9512105

$$\text{granule strength} = \frac{\text{final weight of sieve residue} * 100}{\text{weight of sample}}$$

The *flow properties* of the granulates were assessed using a Flowtester FT 300 from Sotax (Sotax AG, 4123 Allschwil, Switzerland). A single sample of 350 g of granulate was used for each of the 6 measurements (with differing funnel vibrations). The flow angle quotient is reported in each case as the result. According to Sotax (9), values in excess of 0.8 indicate that flow is good, while those below 0.6 indicate that it is poor.

Pressing Into Tablets

An EKO laboratory model eccentric tablet press (Emil Korsch, Berlin, Germany) was used to press 400 mg tablets, 10 mm in diameter and with bevelled edges, at a rate of 52 tablets per min.

The compaction forces and tolerances used in the preparation of batches of 100 tablets were: (5.0 ± 0.25) kN, (7.5 ± 0.35) kN, (10.0 ± 0.50) kN, (12.5 ± 0.60) kN, (15.0 ± 0.75) kN, (17.5 ± 0.90) kN, (20.0 ± 1.20) kN, (25.0 ± 1.80) kN, and (35.0 ± 2.00) kN.

Tablet Properties

Tablet friability was determined by placing 20 tablets each time into a "Roche" friability testing machine and then setting the machine for 500 revolutions. The friability of the tablets was calculated using the following formula:

Table 2

Composition of Finished Blends

	Material	Placebo Proportion [M/M]	Paracetamol Proportion [M/M]
Inner phase	1 paracetamol	0%	75%
	2 lactose/Avicel 2.45 : 1	ad 100%	ad 100%
	4 binder	0%, 2.0%, 6.0%, 10%	0%, 2.0%, 6.0%, 10%
Outer phase	6 Avicel	5.0%	5.0%
	7 PVP XL	5.0%	5.0%
	8 Aerosil 200	0.2%	0.2%
	9 magnesium stearate	0.5%	0.5%

Table 3

Preparation of the "Inner" Phase

Processing Step	Machines	Process Parameter
1. dry mixing	high shear mixer Diosna P10[a]	2 min impeller: 167 U min^{-1} chopper: 3000 U min^{-1}
2. wetting and kneading	high shear mixer Diosna P10[a]	30 sec; then scaping, addition of water, kneading impeller: 167 U min^{-1} chopper: 3000 U min^{-1}
3. deagglomeration	3 mm manual screen	
4. drying	fluidized bed dryer Strea 1[b]	60°C 25–50 min as required
5. moisture content	Mettler infrared dryer LP 16[c]	10 g samples, 30 min, 105°C
6. dry sieving	classifying screening machine Frewitt MGL[d]	oszillating mode, screen: 1.25 mm mesh size; diameter of wire 0.8 mm
7. finished blend	Turbula blender T10B[e]	42 U min^{-1} in 3 l lidded drum; outer phase added via 0.8 mm manual screen, blending for 10 min.; then magnesium stearate via 0.8 mm manual screen, blending for 5 min

[a]Dierks & Söhne, D-Osnabrück.
[b]Aeromatik AG, CH-Bubendorf.
[c]Mettler Instrumente AG, CH-8606 Nänikon-Uster.
[d]Frewitt AG, CH-Fribourg.
[e]W. A. Bachofen Maschinenfabrik, CH Basel.

$$\text{friability} = \frac{\text{weight of sample - final weight}}{\text{weight of sample}} \times 100$$

The *crushing strength* of 10 tablets from each lot was determined using a Schleuniger 6 D tablet tester (Dr. Schleuniger & Co., 4501, Solothurn, Switzerland).

The *disintegration time* for 6 tablets in each case was tested in accordance with DAB 1996 using the DT 3 testing apparatus (Sotax AG, 4123 Allschwil, Switzerland).

RESULTS AND DISCUSSION

Preparation of the Granulates

The time required for kneading and drying the placebo granulates is summarized in Table 4. The paracetamol granulates required markedly less granulating fluid than did the placebo granulate. The kneading and drying times are not directly comparable.

A higher content of binder would be expected to accelerate formation of the granulate, thereby necessitating shorter kneading times, and this is precisely when happens during granulation in the high shear mixer with most of the binders tested (Table 4), the only exception being L-HPC. L-HPC presumably differs in this regard due to the high swelling capacity (10) which causes it to absorb a large amount of water, thereby delaying the wetting of the particle surfaces of other substances. In addition, the particles of binder increase in volume as swelling progresses, physically separating the particles to be bound.

The drying time in the fluid-bed dryer also depends on the amount of binder used (Figure 1). In the case of PVP, HP-M, and Lycatab DSH, the higher the binder concentration, the shorter the drying time. On the other hand, the drying time remains constant or even increases slightly when the amount of Lycatab PGS or L-HPC is increased. In both of these cases, this is also due to the large water-absorbing capacity of the binders, which precludes a rapid drying time. As a kinetic factor, drying time is nevertheless also highly dependent on particle size distribution and other particle properties (porosity, particle shape, and surface properties).

Properties of the Granulates

Particle Size Distribution

Figure 2 (below) shows the particle size distribution of the placebo granulates. The values reported for total

Table 4

Kneading and Drying Times of Granulates

Binder	Proportion of Binder	Placebo Kneading Time (s)	Placebo Drying Time (min)	Placebo Water Content (%)	Paracetamol Amount of Water (%)	Paracetamol Kneading Time (s)	Paracetamol Water Content (%)	Paracetamol Drying Time (min)
Without binder	—	240	49.0	2.5	29.5	30	0.3	32
PVP K30 PH	2%	240	37.0	2.5	26.7	30	0.5	30
	6%	90	34.5	2.5	24.4	20	0.9	30
	10%	30	24.0	3.1	11.1	210	1.6	17
Cellulose HP-M 603	2%	180	32.0	2.0	18.1	360	0.4	28
	6%	90	25.0	1.8	16.7	150	0.6	23
	10%	60	25.0	2.6	16.7	90	0.5	23
Lycatab PGS	2%	240	38.0	2.1	18.1	150	0.5	29
	6%	120	37.0	2.5	18.1	150	0.8	29
	10%	90	39.0	3.2	18.1	150	1.4	37
Lycatab DSH	2%	240	45.0	2.4	13.9	120	0.5	24
	6%	90	42.0	2.5	13.9	120	0.8	23
	10%	30	40.0	2.8	13.9	120	0.8	25
L-HPC Type: LH11	2%	170	44.0	2.1	16.7	90	0.4	27
	6%	150	40.0	2.9	16.7	90	0.7	33
	10%	180	42.0	3.2	16.7	90	0.9	33

residues are 16% (oversize particles), the median (R 50%), and the percentage of fine particles (R 84%). The values shown are the mean in each case for sieve analyses carried out in duplicate. They can be compared, in Figure 3, with the corresponding figures for sieve analysis of the paracetamol granulates.

A rise in binder concentration would lead one to expect an increase in particle size, and a large upturn

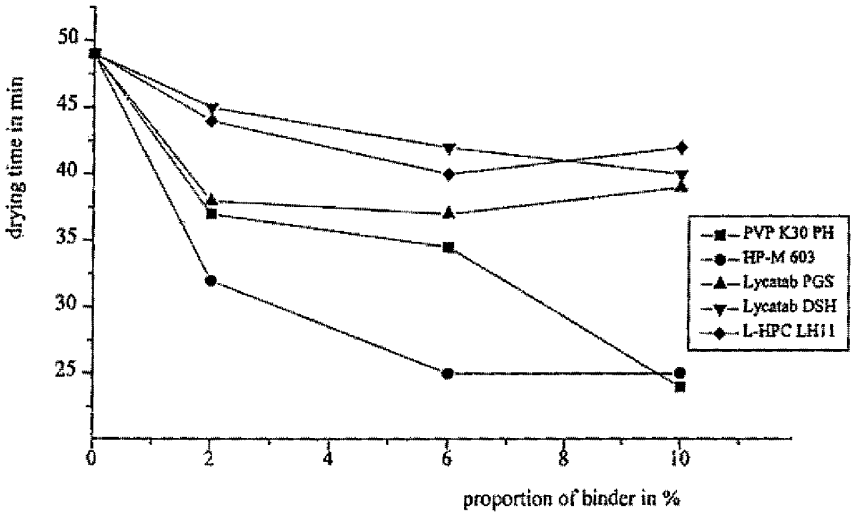

Figure 1. Drying time of placebo granulates.

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