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RESEARCH PAPER

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

D. Becker,[1] T. Rigassi,[1] and A. Bauer-Brandl[2]

[1]*Novartis, Inc., Building K-401.2.65, CH-4002 Basel, Switzerland*
[2]*Universität Freiburg, Pharmazeutische Technologie, Hermann-Herder-Str. 9, D-79104 Freiburg, Germany*

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

		Placebo	Paracetamol
	Material	Proportion [M/M]	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 1 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

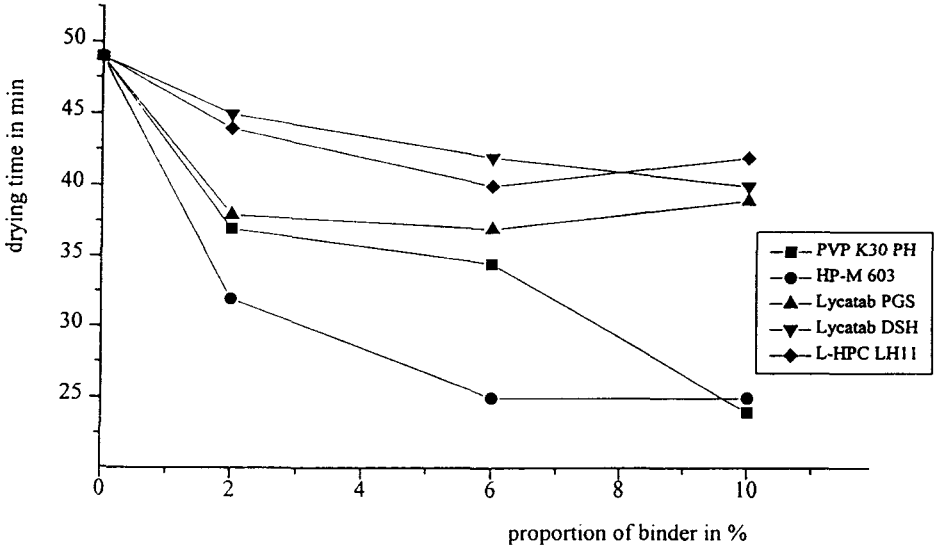


Figure 1. Drying time of placebo granulates.

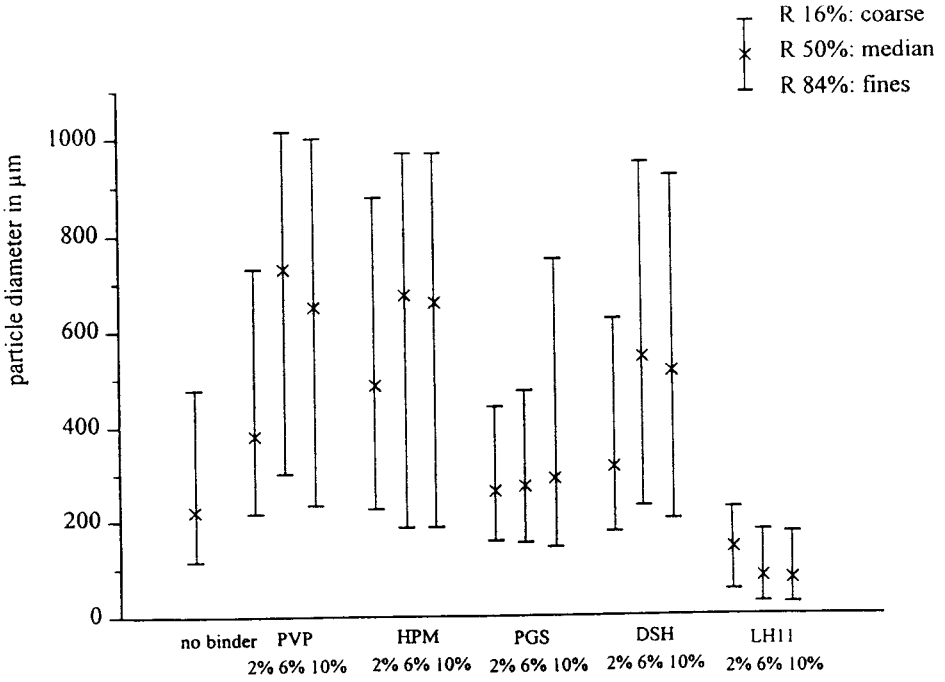


Figure 2. Particle size distributions of placebo granulates.

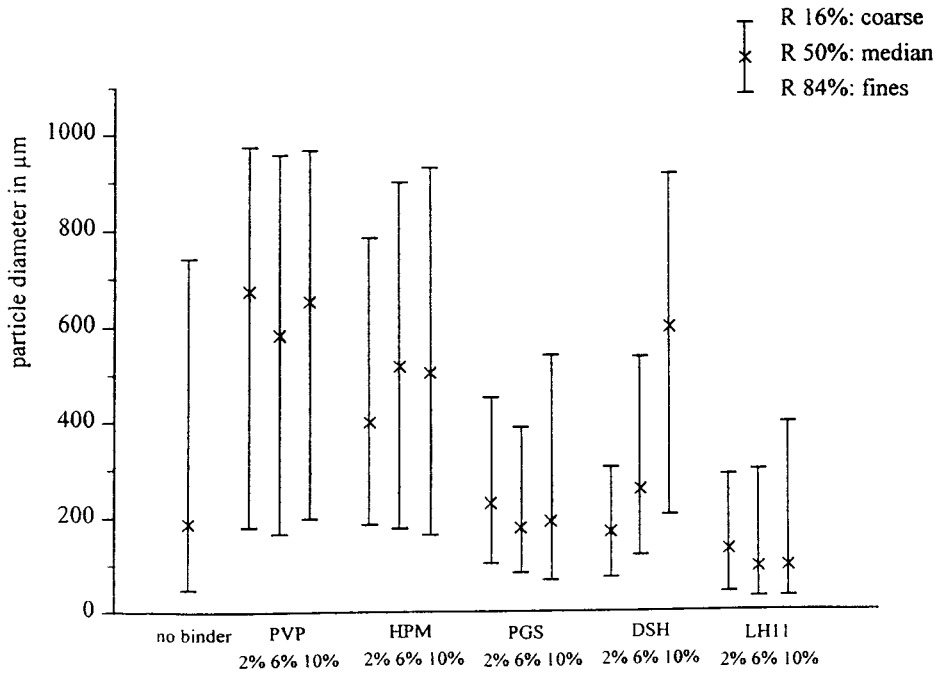


Figure 3. Particle size distributions of paracetamol granulates.

in the mean particle size (R 50%) of the placebo granulate can in fact be seen with the binders PVP K30 PH, Cellulose HP-M 603, and Lycatab DSH at concentrations of up to 6% (Figure 2). Particle size cannot be increased further when the concentration of these binders is raised (to 10%), which suggests that the binding mechanism changes above a certain critical concentration limit.

Use of L-HPC leads to a reduction in granulate particle size. This tendency continues as concentrations increase due to the small mean particle size (about 50 μm (11)) and poor binding properties of L-HPC.

The particles of paracetamol granulate are more irregular in size (Figure 3) and more oversized, but show characteristics similar to those noted for the placebo granulate.

Granule Strength

Strong granulates are advantageous for subsequent steps in the production process, such as final mixing and transport because powdery, friable granulate has a detrimental effect on flow properties and can cause demixing. For both types of granulate, and for all binder concentrations tested, the highest granule strengths were achieved using the tried and trusted binders PVP K30 PH and Cellulose HP-M 603 (Figure 4).

The binders Lycatab PGS and Lycatab DSH showed different effects in the placebo and paracetamol formulations. The granule strength of the paracetamol granulate remained constant for all 3 concentrations of Lycatab PGS but rose in the placebo granulate as concentrations of Lycatab PGS increased. However, even at a binder concentration of 10%, granule strength was lower than in granulate prepared without a binder. The maximum granule strength for paracetamol granulate is achieved with Lycatab DSH at a concentration of 10%. Granule strength is very dependent on the binder used. However, the granule strength of the placebo granulate is largely unaffected by the concentration of Lycatab DSH.

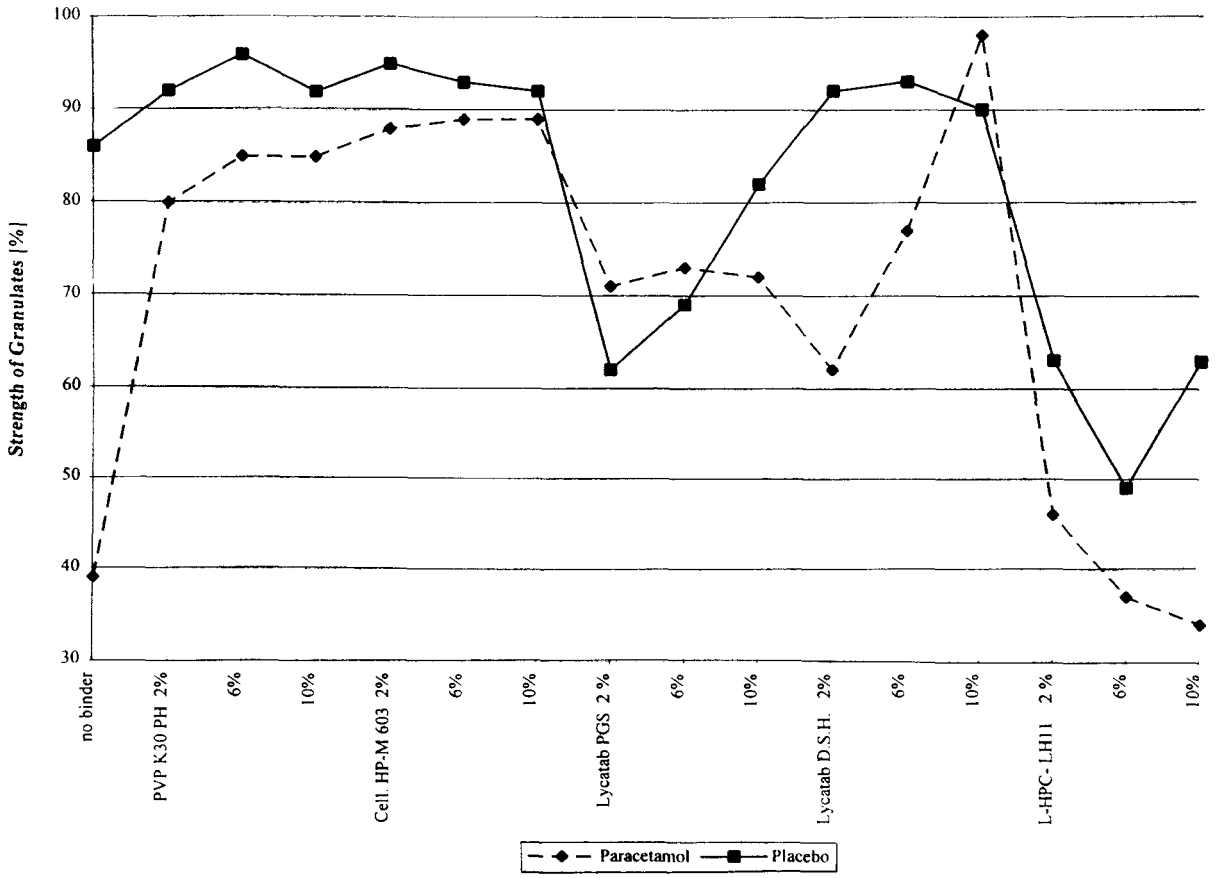


Figure 4. Strengths of placebo- and paracetamol granulates.

Granulate prepared using L-HPC shows low granule strength, in many cases even lower than that achieved when no binder is used.

Flow Properties

The flow capacity (expressed as flow angle quotients) observed in the analysis of granulate flow are shown in Figure 5. The placebo granulates proved to have very good flow characteristics with most binders. However, use of increasing concentrations of L-HPC leads to an increasing inhibition of flow, presumably due to a rise in the quantity of fine particles (Figure 2).

The relationship between flow characteristics and binder is even clearer with the paracetamol granulates. The flow characteristics of the granulate are poor without binder, but improve when even small amounts (2%) of PVP K30 PH or Cellulose HP-M 603 are added. The flow characteristics are not affected by further increases in the concentrations of these binders. Similarly good flow characteristics are achieved with Lycatab DSH at concentrations above 6%. The optimum binder concentration for Lycatab PGS is 2%, with all further additions leading to a rise in the amount of fine particles (Figure 3) and thus to reduced flow capacity. Paracetamol granulates prepared using L-HPC all flow poorly, particularly when the concentration of binder is high (compare also particle sizes in Figures 2 and 3).

Bulk and Tapped Densities

Figure 6 shows the bulk and tapped densities for the placebo granulates after 1250 taps. Figure 7 shows the corresponding results for the paracetamol granulates. Bulk and tapped densities of both sorts of granulates tend to fall as binder concentrations rise (Figures 6 and 7). This is explained by the fact that, generally speaking, larger agglomerates form. What is unusual in the

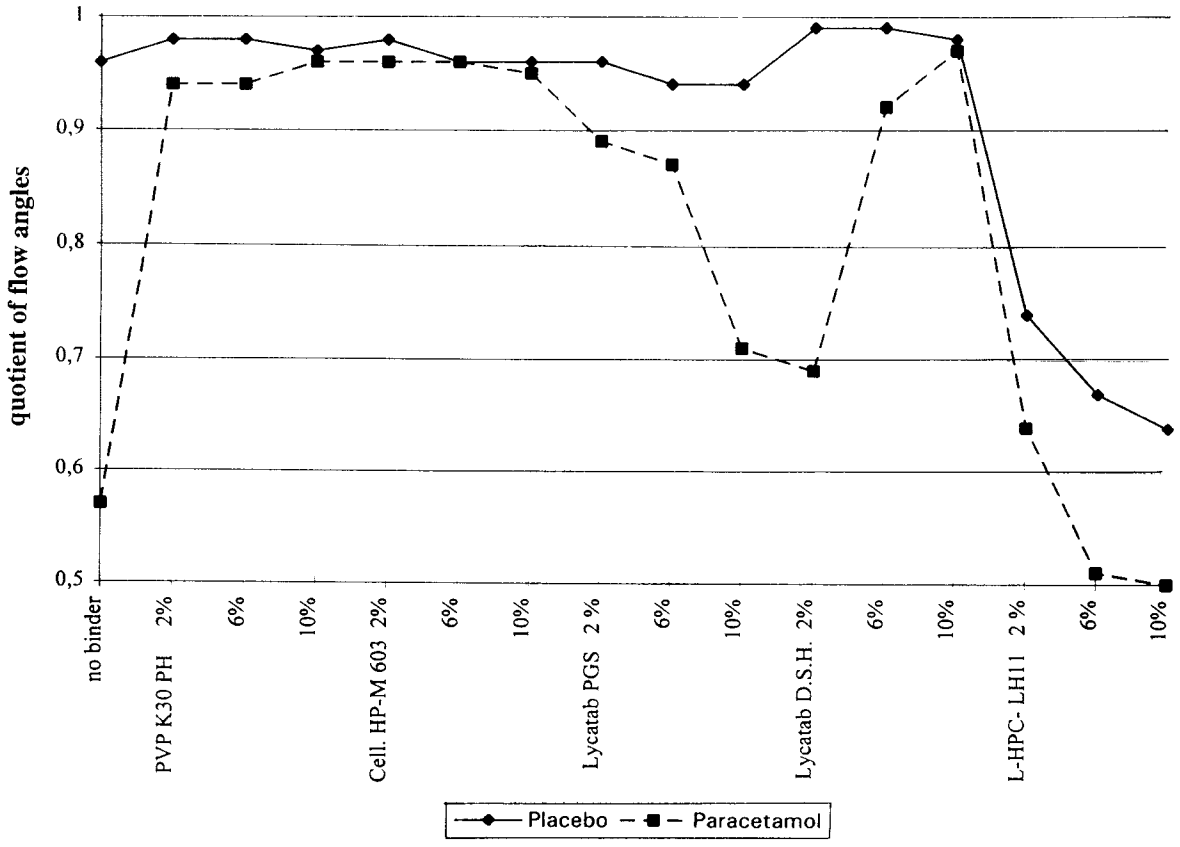


Figure 5. Flow properties of granulates (placebo and paracetamol).

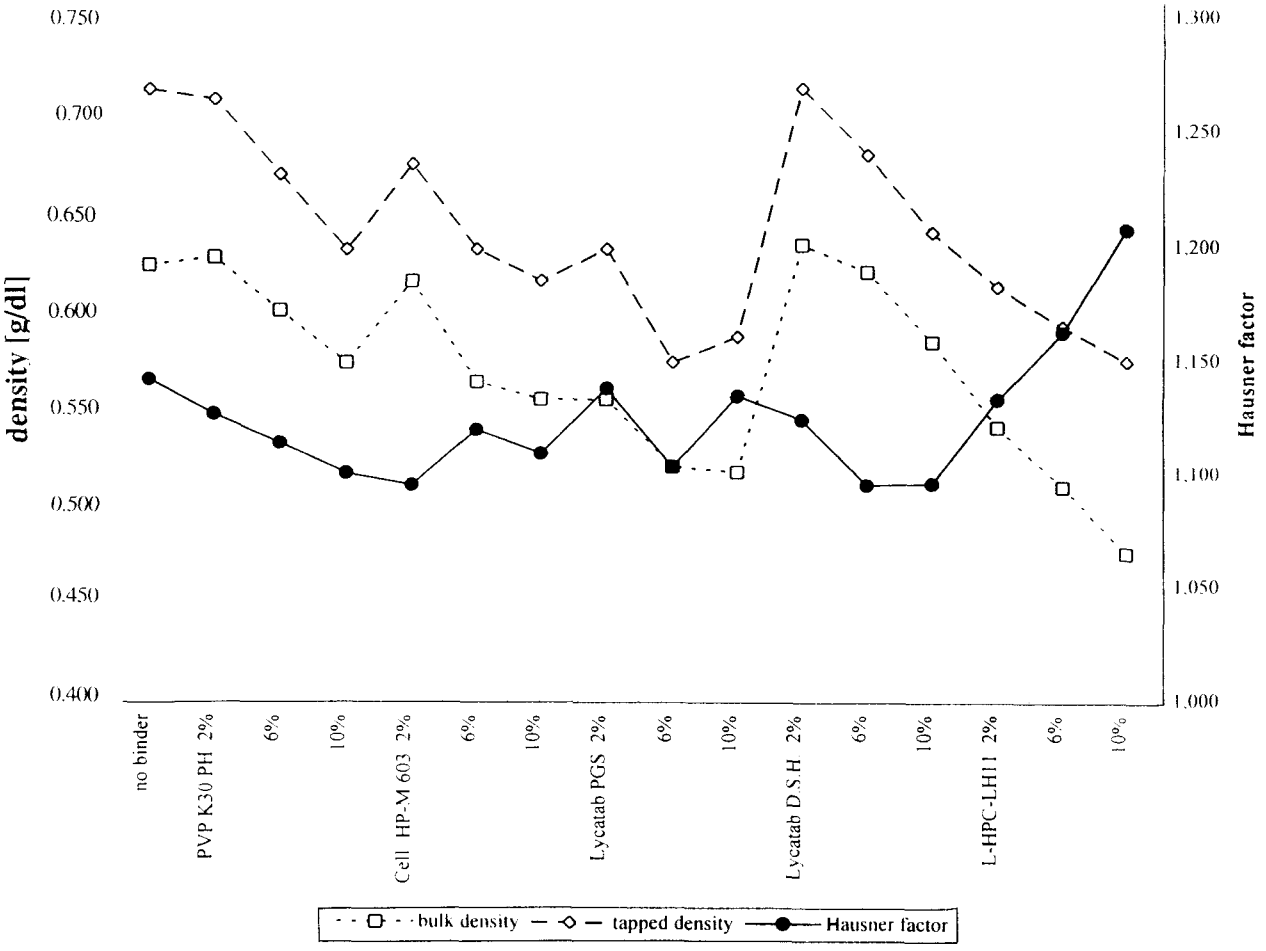


Figure 6. Bulk/tapped densities and Hausner factor of placebo granulates.

case of the L-HPC-paracetamol granulates is that all of them, despite increasing looseness as binder concentrations increase, show about the same final tapped density. This is probably related to their low granule strength (Figure 4).

The Hausner factor (the quotient of bulk density and tapped density) expresses the relative mechanical compression of the granulate (which can occur during transport or as a result of vibrations in the tablet press). It thus allows us to make inferences regarding the uniformity of particle size, shape, and crushing strength. With the help of the Hausner factor, attempts can be made at predicting both the extent of compression, and the flow problems which may occur during tabletting. With the exception of granulates containing high concentrations of L-HPC, the granulates tested had a Hausner factor lower than 1.2, and were thus within a range in which no problems were to be expected.

Tablet Properties

Crushing Strength

Figures 8 and 9 show profiles for compaction force and tablet crushing strength in relation to the binder used.

Even *placebo* granulate without binder could be processed into tablets with a good relationship between compaction force and crushing strength (Figure 8). Above a compaction force of 7.5 kN, an adequate crushing strength of 50 N is achieved for tablets with the selected diameters. The addition of binders did not necessarily lead to an increase in crushing strength. For

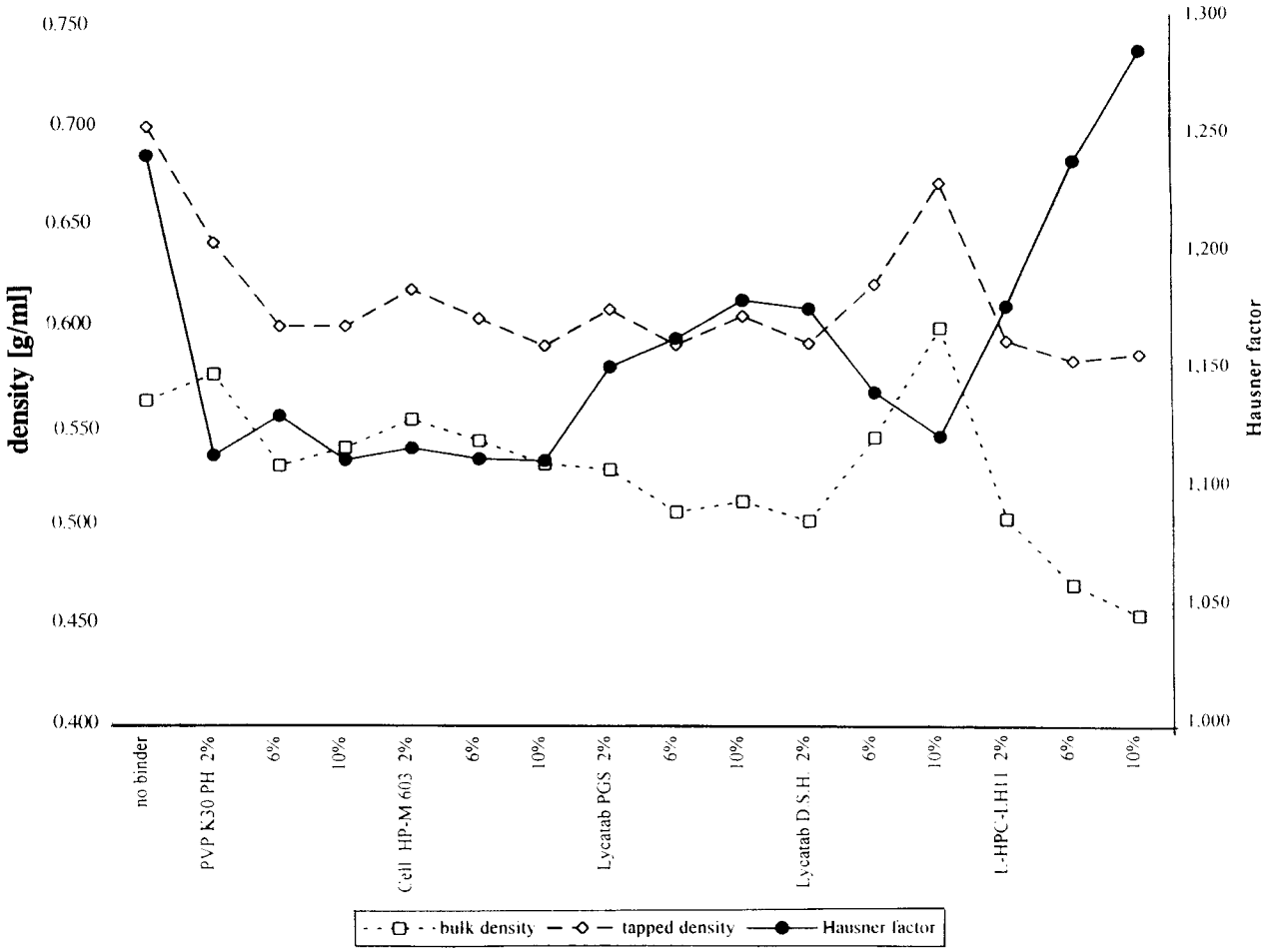


Figure 7. Bulk/tapped densities and Hausner factor of paracetamol granulates.

example, use of low concentrations of the binders PVP K30 PH, Cellulose HP-M 603, and Lycatab DSH (2% and, in the case of PVP K30 PH, 6% as well) led to a reduction in crushing strength. Use of Lycatab PGS at a concentration of 2% and Lycatab DSH at a concentration of 6% yielded crushing strength comparable to that of a granulate lacking a binder (cf. similar results in (12)). Only L-HPC at a low concentration improved crushing strength (by about 30%) as compared with the binder-free placebo formulation. PVP K30 PH does not bring about a similar rise in crushing strength until the concentration is 10%.

Cellulose HP-M 603 (6% and 10%), Lycatab DSH (10%), and Lycatab PGS (6%) can be characterised as differing very little from each other. These binders increase crushing strength by an average of 45%. The largest rise in crushing strength, approximately 75%, is achieved with a 10% concentration of the binder Lycatab PGS, which is also the concentration recommended by the manufacturer for raising crushing strength (13).

The *paracetamol tablets* without binder (Figure 9) show poor crushing strength and also are prone to capping, regardless of the compaction force applied. They are improved by the addition of binders (except for 2% L-HPC). As expected, differences relating to the type and concentration of binder are greater in this problematic formulation than in placebo. Cellulose HP-M 603 and PVP K30 PH are best here. Adequate crushing

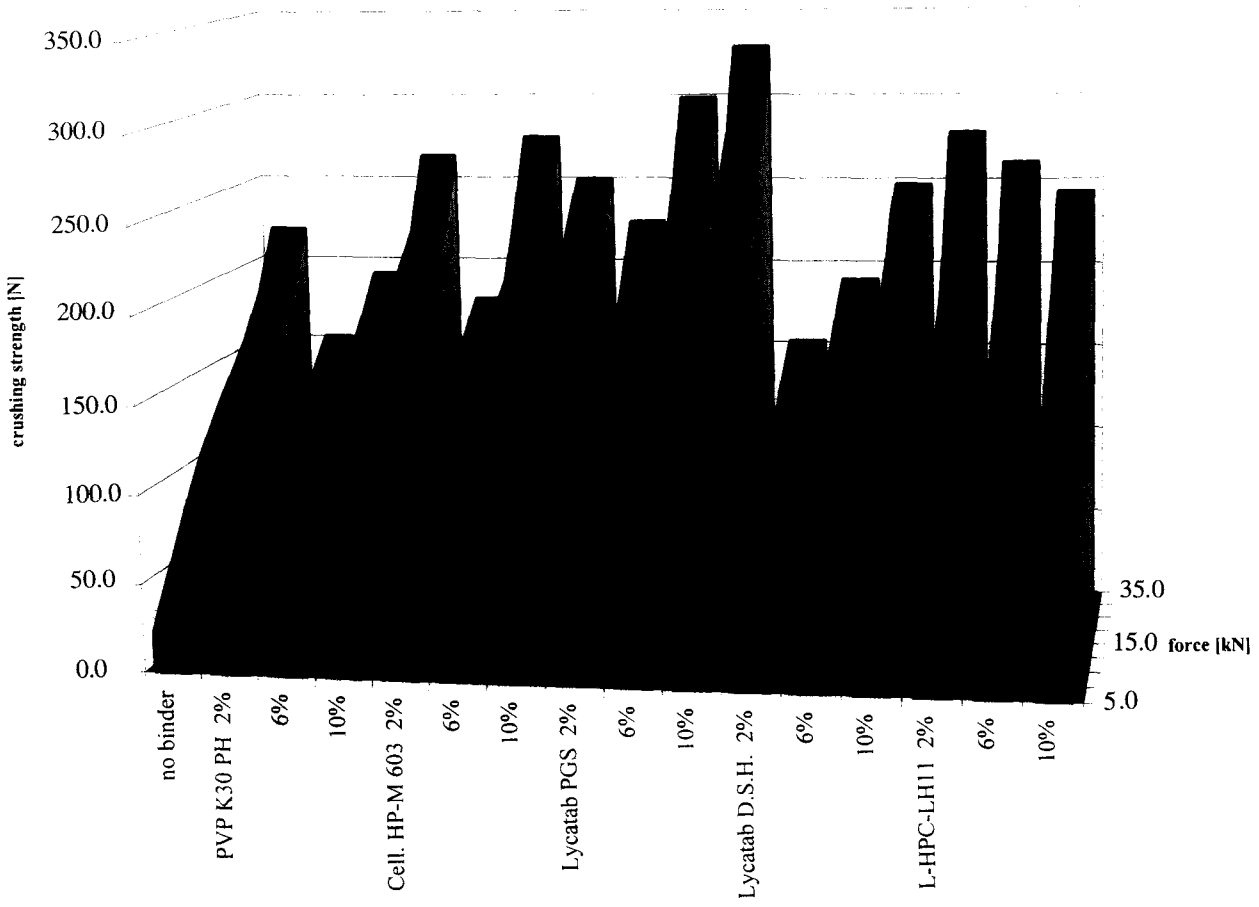


Figure 8. Compression force vs. crushing strength profile of placebo tablets.

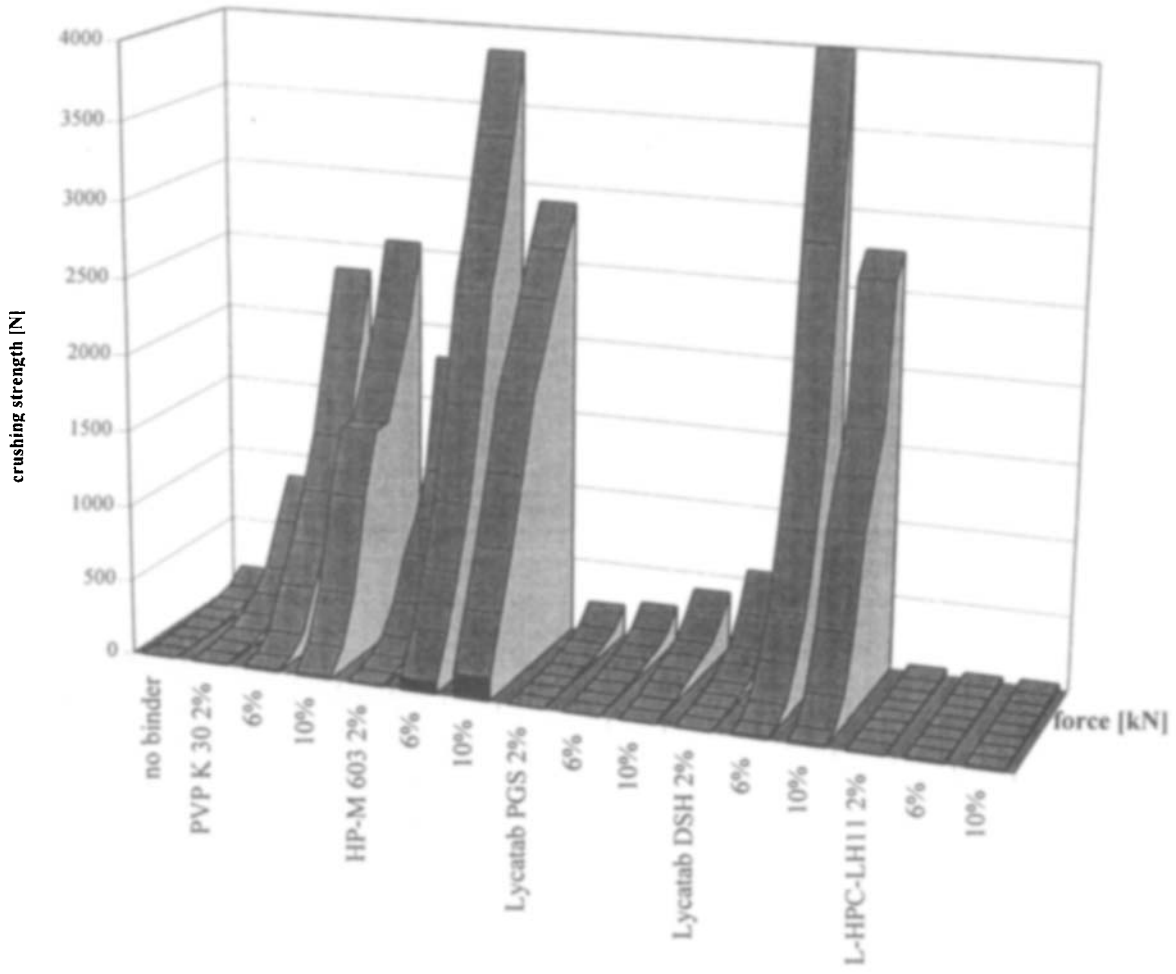
strength is achieved with these binders even at a concentration as low as 6%, and when tablets are produced using a low compaction force.

The binders Lycatab PGS and Lycatab DSH have nearly equal binding capacity in concentrations up to 6%. At higher concentrations, Lycatab PGS shows better binding capacity. The minimum concentrations of either of these binders should not be less than 10% in the paracetamol formulation discussed here. This recommendation is based on the large amount of drug substance and poor tableting properties (capping) of the paracetamol tablets. With other model formulations based on mixtures of lactose and starch, which have fewer problematic properties, there is reason to believe that an increase in binder content above the maximum of 6% investigated here could make possible further improvement in crushing strength (14). A binder concentration of 5% has been described as adequate for tablets containing a filler of anhydrous lactose and a 10% formulation of drug substance (hydrochlorothiazide) (15).

Improvement in tablet crushing strength was comparable for L-HPC, at concentrations of 6% and 10%, Lycatab PGS (6%), and Lycatab DSH (6%).

Friability

Another important mechanical property of tablets is friability (see Figures 10 and 11). When regarding the figures, keep in mind that the scale for compaction force



begins at the rear of the graph and moves forward. To enhance the intelligibility of the chart, no bars were drawn in for friability in excess of 2% (a degree of friability which would no longer be acceptable in practice).

For all placebo formulations, friability was low when compaction force was 7.5 kN or higher, but the friability of the paracetamol tablets was often high. Sufficiently abrasion-resistant tablets (usually understood to mean tablets with a friability of no more than 1%) could only be prepared using PVP and HP-M 603.

Disintegration Times

The disintegration time of the tablets is of critical importance of their efficacy. Although an effective "disintegrant" is added to the outer phase before tableting, there are considerable differences in disintegration times. Figure 12 compares the disintegration times of placebo tablets produced under different compaction forces, while Figure 13 provides similar information on paracetamol tablets. It can be seen that it is in fact the tried and trusted binders (PVP and HP-M 603) which delay disintegration. Lycatab DSH has the same effect.

Binder Effectiveness

Binder effectiveness refers to the degree to which the lowest possible concentration of a binder can contribute to the optimization of *all* granulate and tablet properties. For granulates, these properties include in particular flow characteristics, crushing strength, and mean particle size. The tablet property most strongly affected is crushing strength.

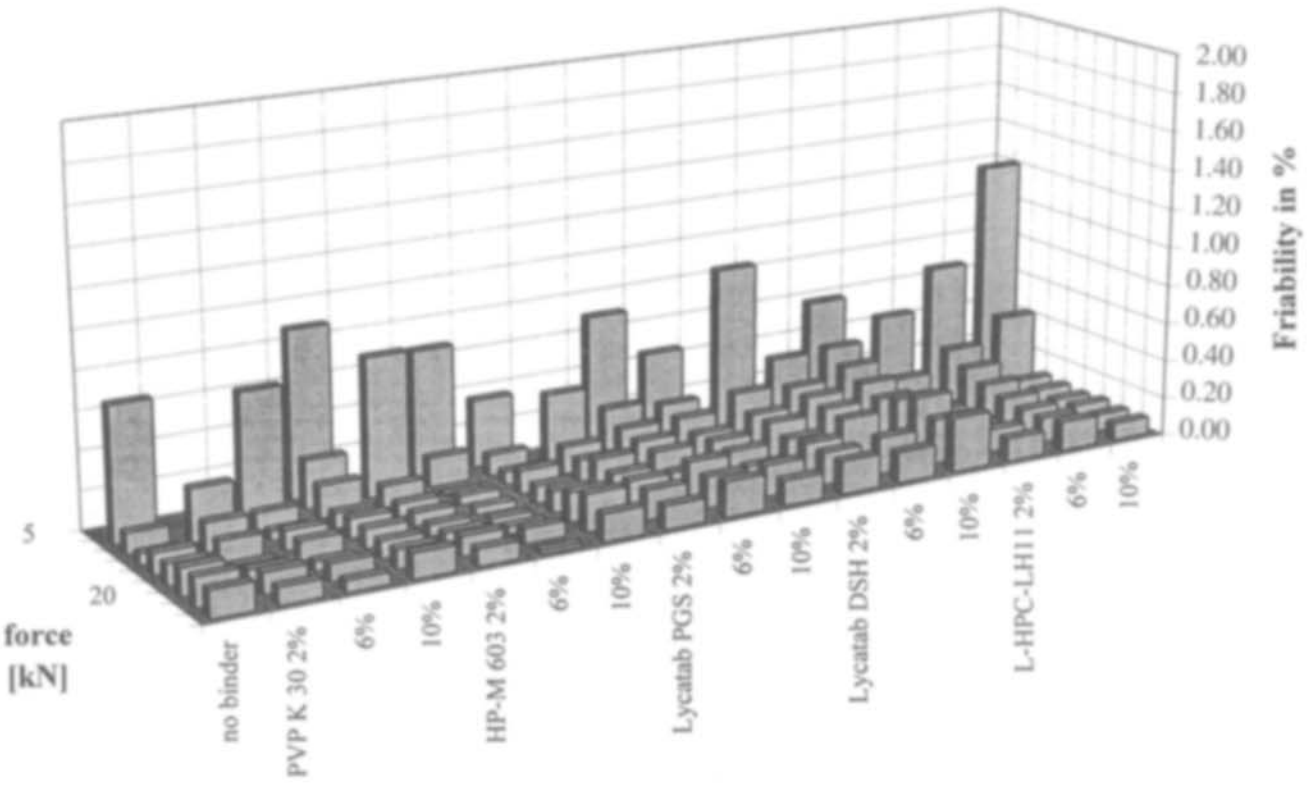
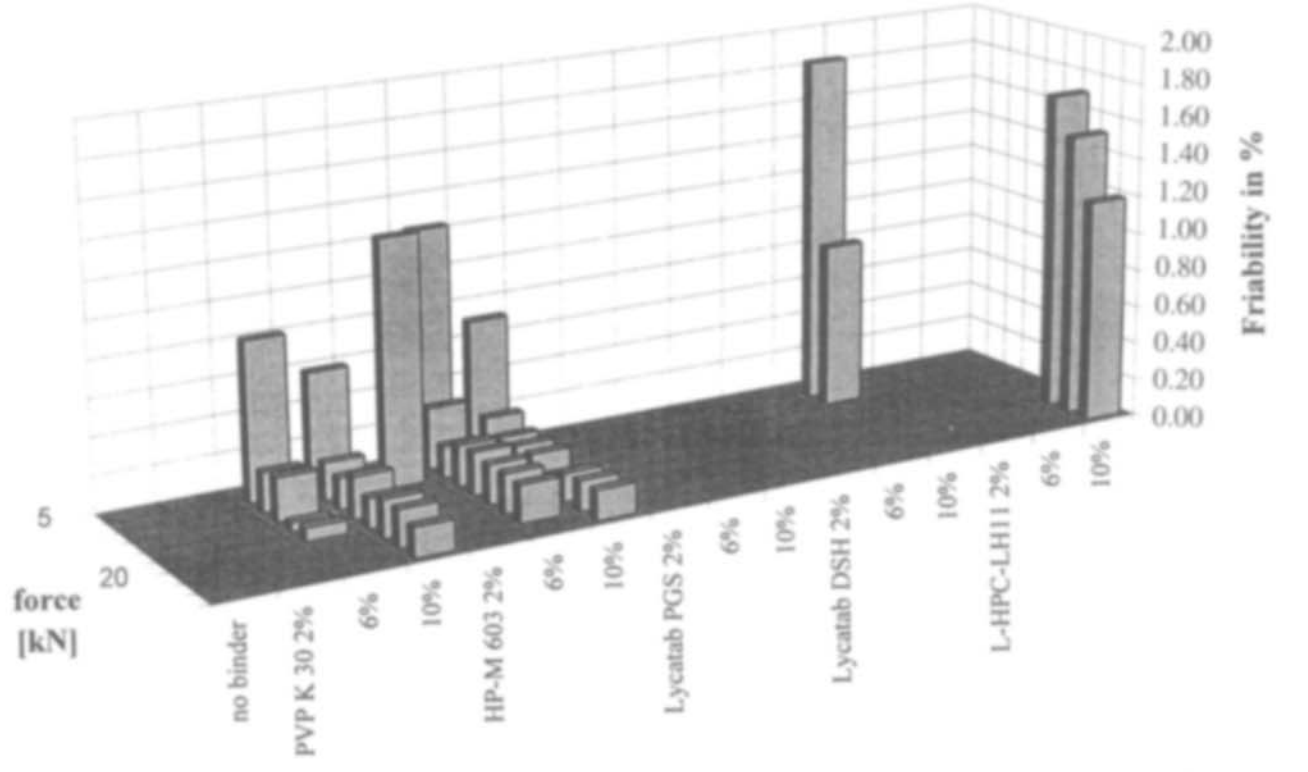


Figure 10. Friability of placebo tablets.



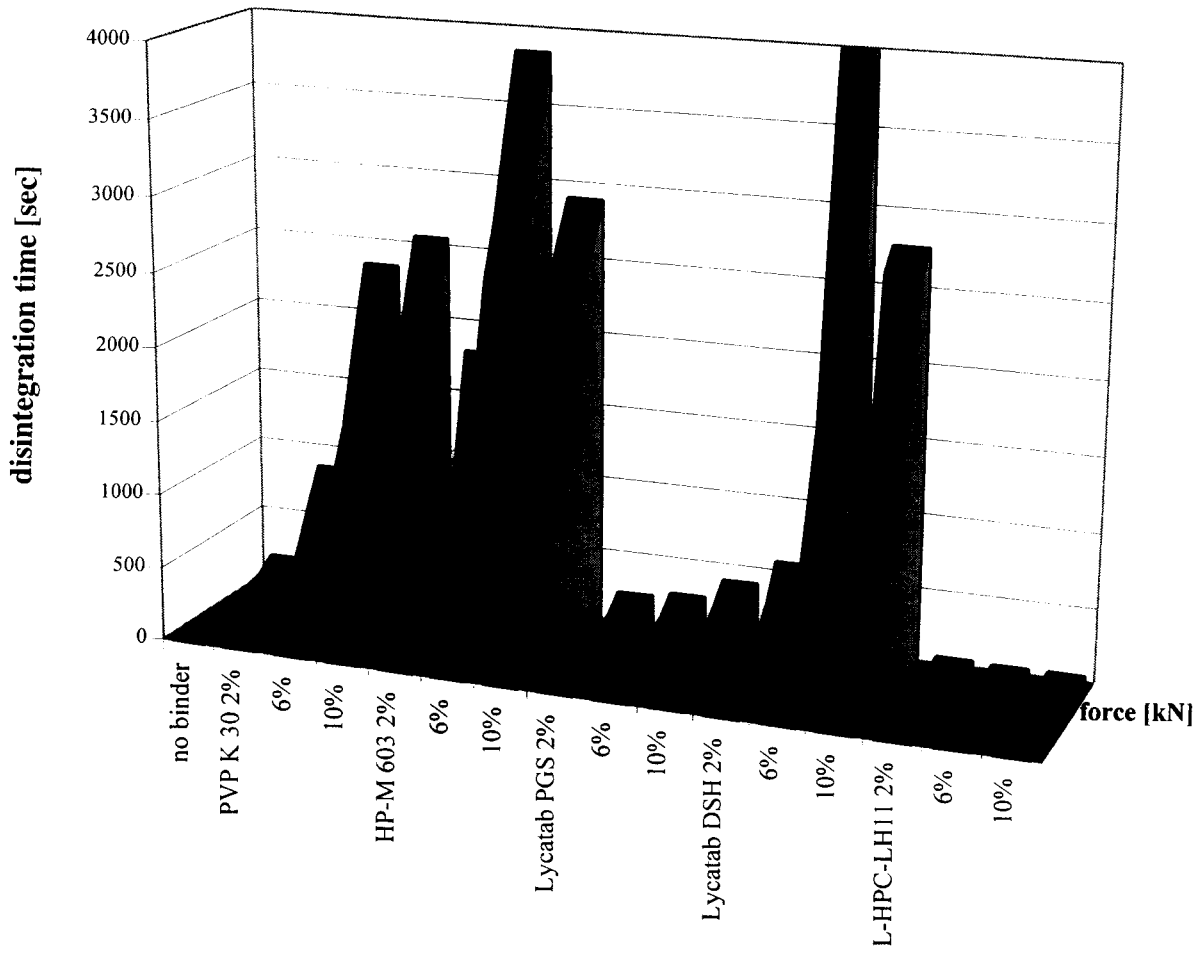


Figure 12. Disintegration time of placebo tablets.

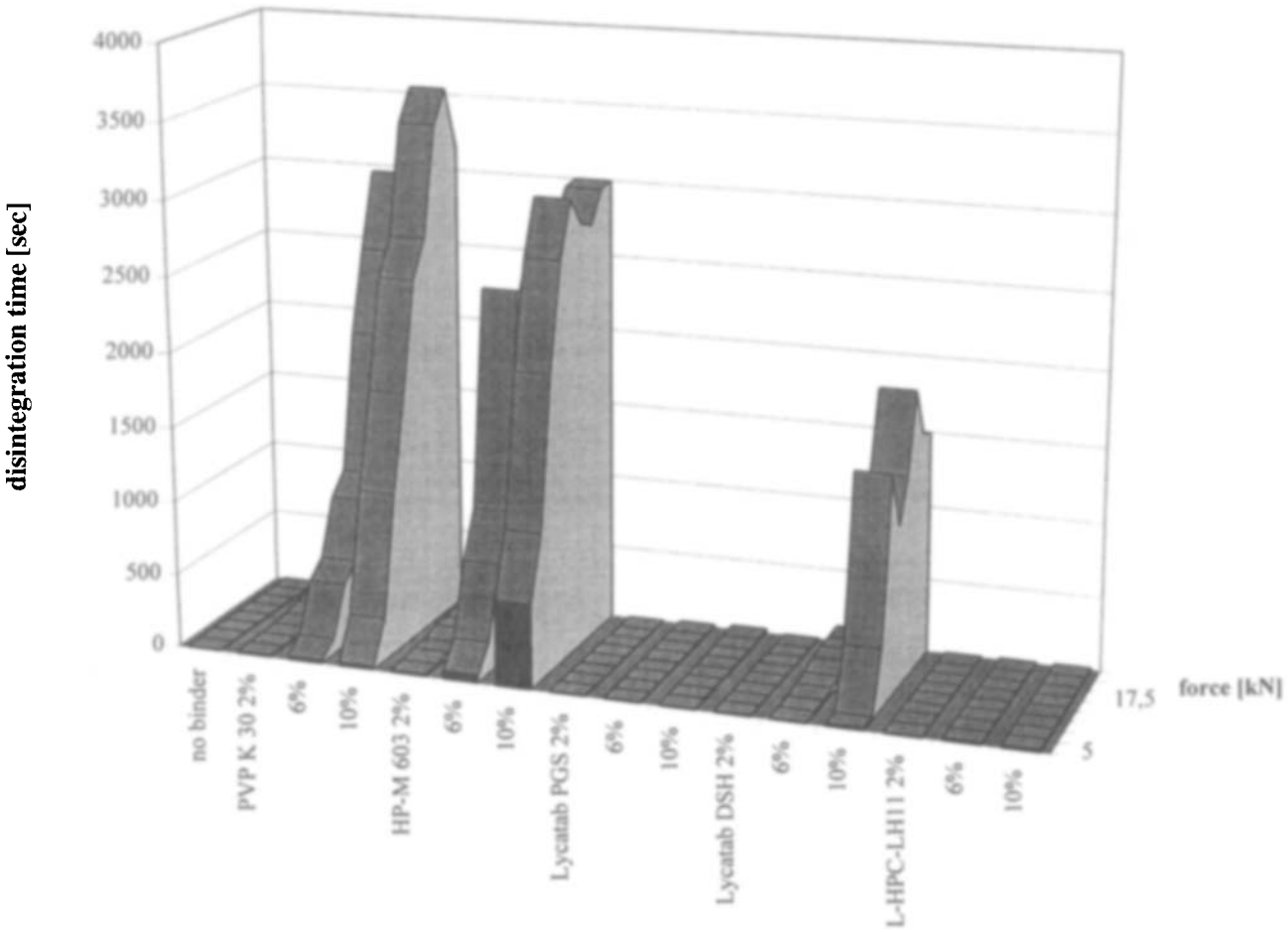


Figure 13. Disintegration time of paracetamol tablets.

Table 5

Effect of Binder on Some Properties of Granulates and Tablets: Binder Effectiveness

Binder	Proportion of Binder	Particle Size (R 50%)	Flow-ability	Granulate Strength	Tablet Crushing Strength
PVP K30 PH	2%	166%	33%	56%	18%
	6%	221%	33%	65%	65%
	10%	221%	35%	62%	121%
Cellulose HP-M 603	2%	117%	35%	68%	33%
	6%	191%	34%	68%	120%
	10%	183%	33%	68%	163%
Lycatab PGS	2%	20%	28%	27%	11%
	6%	9%	25%	34%	46%
	10%	16%	11%	40%	83%
Lycatab DSH	2%	16%	12%	33%	-6%
	6%	90%	32%	53%	26%
	10%	174%	36%	78%	54%
L-HPC Typ: LH11	2%	-34%	-5%	-4%	11%
	6%	-57%	-20%	-24%	35%
	10%	-58%	-23%	-20%	37%

The present assessment has been restricted to these features in order to allow conclusions about binder effectiveness in different formulations to be drawn more easily.

For the graphs, the results obtained with binder-free placebo and drug preparations were taken as reference values and set at zero. The percentage deviations of the properties of the other granulates and tablets were always calculated in relation to these reference values. The arithmetic mean of the values obtained was then calculated for both the placebo and paracetamol granulates (Table 5) and plotted (Figure 14).

PVP K30 PH and Cellulose HP-M 603 show the greatest binder effectiveness. A 10% concentration of Lycatab DSH can be used as an alternative.

The main effect of Lycatab PGS is the improvement of tablet crushing strength. Although L-HPC worsens granulate properties, it nevertheless improves tablet crushing strength to some extent.

CONCLUSIONS

Use of the standard binders PVP and Cellulose HP-M 603 makes possible the manufacture of tablets with the best mechanical properties but the worst disintegration times. Hydroxypropylmethylcellulose in particular is used in granulate formulations to achieve delayed release (16). Lycatab PGS has fewer soluble components than other pre-gelatinized maize starches currently on the market (17) and is therefore expected to have a relatively good disintegrating effect (18). This has been confirmed in the present study.

Lycatab DSH is spray-dried maltodextrin and dissolves completely in water. According to the manufacturer, it is not supposed to interfere with disintegration and dissolution at recommended concentrations of 2–10%, and it is supposed to promote good flow in granulates and hardness in tablets. This claim was not necessarily confirmed, particularly because the disintegration time of the placebo tablets was markedly increased. And the advantage of a lactose-starch formulation over PVP in improving the relationship between crushing strength and disintegration, noted by Delacourte et al. (19), could not be verified here over the entire range of binder concentration and compaction force, either for placebo or for paracetamol. At a 10% concentration, however, Lycatab DSH can be substituted for PVP or HP-M 603.

When L-HPC is used as a dry binder, its small particle size makes it particularly suitable for the manufacture of hard tablets. Thanks to its high swelling capacity (greater that of PVP XL, which is used as a

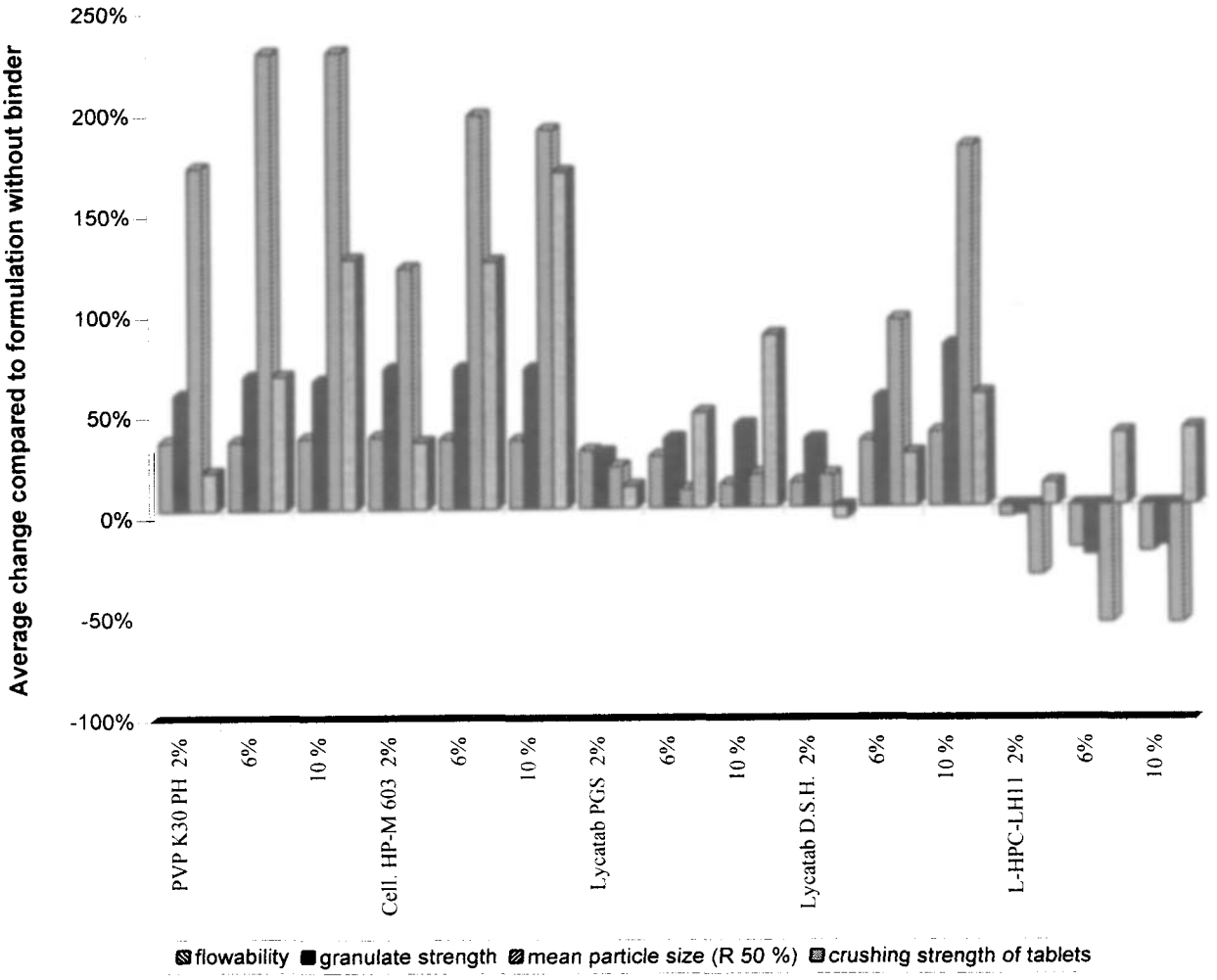


Figure 14. Binder efficiency.

disintegrant (20)), it reduces the disintegration time of tablets even after wet granulation. However, it shows little binding efficacy in granulates.

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