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RESEARCH PAPER

Structure and Dry Binding Activity of Different Polymers, Including Kollidon® VA 64

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ABSTRACT

The dry binding activity of copolyvidone (Kollidon® VA 64), povidone (Kollidon® 30), microcrystalline cellulose (Avicel® PH-101), hydroxypropylmethylcellulose (HPMC) 2910 (Pharmacoat® 606), and maltodextrin (Maldex® 18) was investigated using a variety of formulations and methods. The effect of the dry binders in direct tableting and compaction was studied using a dicalcium phosphate formulation (water-insoluble ingredients) and a vitamin C formulation (water-soluble ingredients) applying three compression forces. The binder content was varied between 5% and 15% in both formulations, and the tablet properties were determined. All the tablets showed an improvement in mechanical properties (hardness, friability) with increasing dry binder concentration, with Kollidon VA 64 showing by far the greatest binding efficacy. A significant influence (prolongation) on drug release was observed only with HPMC 2910. The drying binding properties were analyzed for correlations with various powder and material properties. Especially, particle size, surface/surface structure, and plasticity were found to influence binding activity. The ideal dry binder should have small particles, high plasticity, and a large surface area.

Key Words: *Copolyvidone; Direct compression; Dry binder; Hydroxypropylmethylcellulose; Kollidon VA 64; Maltodextrin; Microcrystalline cellulose.*

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INTRODUCTION

The properties of dry binders, when used in low concentrations, consist of their ability to improve the tableting characteristics of the powder mixture markedly or greatly enhance granulation properties in compaction. In contrast to wet granulation, moistening and drying the powder masses is unnecessary when using dry binders. The main objectives are to increase hardness and reduce friability. The direct tableting/dry granulation process thus offers enormous savings of time and money.

This study was conducted to demonstrate the influence of different dry binders on direct tableting. The various structural classes were examined and compared.

In addition to povidone as the best-known binder and Kollidon VA 64®, a copolymer of vinylpyrrolidone and vinyl acetate (2), microcrystalline cellulose (MC) PH-101 (3,4), hydroxypropylmethylcellulose (HPMC) 2910 (5), and maltodextrin DE 18 were used. Three formulations—a pure binder formulation, a formulation with dicalcium phosphate as the insoluble ingredient, and a formulation containing ascorbic acid as the soluble ingredient—were examined, with the last formulation also containing further water-soluble excipients.

The influence of different types and quantities of dry binders on powder properties and compressibility was evaluated.

Dry binders require a certain plasticity to be effective in binding powder particles together during compression or compaction (6–13). The plasticity was determined by compressing the pure binder on an instrumented single-punch tablet press.

A general attempt was made to establish a correlation between the powder and material properties and the dry binder activity.

EXPERIMENTAL

Materials

The dry binders used for this study are listed in Table 1; the other materials are given in Table 2.

Methods

Powder Properties

The flow rate of the dry binders was determined using a Dr. Pfrengle type 3201 apparatus (Hans W. Schmidt, Mainz, Germany). The volume of 150 ml required for the dry binder determinations was sampled with the aid of a graduated cylinder. The results are reported as means of three measurements.

Bulk density measurements were carried out using a flat-ground measuring cylinder with a volume of 200 ml. The calculation was performed using the following formula:

$$\text{Bulk density} = (\text{Filled graduated cylinder} - \text{Empty graduated cylinder})/200 \quad \text{g/ml}$$

The tapped density of the dry binders was determined on a tapped volume determination apparatus (Engelsmann, Ludwigshafen, Germany), applying 1000 taps, and was calculated using the following equation:

$$\text{Tapped density} = (\text{Sample weight})/\text{Volume} \quad \text{g/ml}$$

The Hausner ratio could then be calculated from the results of the bulk and tapped density determinations:

$$\text{Hausner ratio} = (\text{Tapped density})/(\text{Bulk density})$$

Table 1

Dry Binder

Brand Name	Manufacturer	General Name	Batch
Kollidon VA 64	BASF AG, Ludwigshafen, Germany	Copolyvidone	29-2638
Kollidon 30	BASF AG, Ludwigshafen, Germany	Povidone	36-0891
Avicel PH-101	FMC Europe N.V., Brussels, Belgium	Microcrystalline cellulose PH-101	6326
Pharmacoat 606	Shin Etsu Chemical Co., Ltd., Tokyo, Japan	Hydroxypropylmethylcellulose 2919	503104
Maldex 18	Amylum N.V., Aalst, Belgium	Maltodextrin	9410392

Table 2

Ingredients

Brand Name	Manufacturer	Batch
Ascorbic acid powder	BASF AG, Ludwigshafen, Germany	24-1274
Ludipress	BASF AG, Ludwigshafen, Germany	51-0465
Di-Tab	Rhône-Poulenc, Frankfurt, Germany	7059
Kollidon CL	BASF AG, Ludwigshafen, Germany	76-0831
Aerosil 200	Degussa AG, Frankfurt, Germany	S 326030
Magnesium stearate	Bärlocher GmbH, Munich, Germany	MF 19-30482

Mean particle size was determined by laser diffraction on a Malvern Mastersizer X (Herrenberg, Germany). For this parameter, the mean of triplicate measurements on the same batch is reported.

The plasticity and *K* value of the above materials were determined by compressing material on an EK0 instrumented single-punch tablet press (Korsch, Berlin, Germany). The dry binders were simply mixed with 0.5% magnesium stearate and compressed into tablets with two flat faces, a diameter of 12 mm, and a nominal weight of 500 mg. The various compression data were determined using an evaluation program especially developed at BASF AG (Ludwigshafen, Germany).

Plasticity was calculated as follows:

$$\text{Plasticity} = [(\text{Plastic energy})/(\text{Total energy})] \times 100 \quad \%$$

Compression resistance (*K* value) was calculated as follows:

$$K \text{ value} = (\Delta \log p)/(\Delta \log \rho)$$

where p is the compression pressure, and ρ is the apparent density.

Formulations

The dry binders were tested in two tablet formulations, as shown in Table 3, with different binder contents. The total product was weighed, passed through an 0.8-mm sieve, and mixed for 10 min in a Turbula T2C mixer (WAB Maschinenfabrik, Basel, Switzerland).

Tableting

Tablets weighing 500 mg with a diameter of 12 mm (both sides flat with beveled edges) were produced using a Korsch PH 106 rotary tablet press with CRS (Compression Research System; Emil Korsch, Berlin, Germany). The compression forces used for tableting in the individual test series were varied among 10, 18, and 25 kN, while the speed was maintained constant at 30 rpm.

Table 3

Formulations

Ingredient	Formulation 1 (%)	Formulation 2 (%)
Ascorbic acid	—	40.0
Ludipress	—	51.3, 46.3, 41.3
Di-Tab	90, 85, 80	—
Dry binder	5.0, 10.0, 15.0	5.0, 10.0, 15.0
Kollidon CL	4.5	3.0
Aerosil 200	—	0.24
Magnesium stearate	0.5	0.5
Total	100.0	100.0

Tablet Properties

Hardness and uniformity of weight were determined using an HT-TMB-Cl-12F tablet testing system (Kraemer, Darmstadt, Germany). For each batch, 20 tablets were tested.

Friability was determined by placing 10 tablets of a batch in a TAR20 friabilator (Erweka, Heusenstamm, Germany) and operating the drum for 4 min at 25 rpm. Friability was determined using the following formula:

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight})/(\text{Initial weight})] \times 100 \quad \%$$

Disintegration time was determined with a DES-4AS disintegration tester (Kraemer, Darmstadt, Germany) by testing six tablets per batch in simulated gastric fluid.

Drug release was determined on sets of six tablets using a PTWS drug release testing apparatus (Pharma Test Apparatebau GmbH, Hainburg, Germany). Absorbances were measured on an 8452A spectrophotometer (Hewlett Packard GmbH, Böblingen, Germany).

RESULTS AND DISCUSSION

Structure and Properties of Dry Binders

The dry binders tested in some cases exhibited considerable differences in their powder properties. The parameters listed in Table 4 are of interest with reference to tabletability.

Table 4

Powder Properties

	Mean Particle Size D[4,3] (μm)	Bulk Density (g/ml)	Hausner Ratio	Flowability	
				Angle of Repose (°)	Flow Time (s)
Kollidon 30	50	0.389	1.24	28	7.5
Kollidon VA 64	43	0.241	1.37	35	Block
MC PH-101	65	0.326	1.40	41	Block
HPMC 2910	82	0.367	1.37	42	Block
Maltodextrin DE 18	74	0.522	1.34	44	Block

The particle size determinations clearly show that Kollidon VA 64 is the finest product and should therefore be able to coat fillers and bind filler particles together. This can be illustrated by a theoretical example.

If the dry binder is used in the formulation in a concentration of 10% (m/m) and has a similar particle size and density to the other ingredients of the formulation, the number ratio of dry binder/filler particles is 1/9 (Fig. 1). This also means that only a small number of filler particles are bound together by dry binder particles, and weaknesses in particle cohesion remain.

Since the volume of a sphere is $V = (4/3)\pi r^3$, reducing the particle diameter will inevitably have major effects on efficacy. If the particle size is reduced to 1/3, the volume (and therefore the mass) of a particle is reduced to 1/27. It therefore follows that, when the dry binder content of the formulation is 10% and differences in density are negligible, there will be three dry binder particles for each filler particle. Furthermore, the size of the particles cannot be regarded as the sole parameter determining dry binder efficacy since otherwise Kollidon 30 and Maldex 18 would exhibit at least similar effectiveness. The flow properties of Kollidon VA 64 are better than those of MC PH-101 and HPMC 2910, and only Kollidon 30 has even better flow properties. This is not surprising, however, since the scanning electron micrograph (Fig. 2) clearly reveals the spherical structure of Kollidon 30.

A further consideration is that Kollidon VA 64 (Fig. 3) has a much greater proportion of damaged spheres, which reduces flowability but, because of their shell-like structure, they cover a greater surface area of the filler particles and thereby substantially contribute to the dry binder efficacy.

Sphericality is certainly not the ideal particle shape for this application since the contact surfaces are very small, but especially with very plastic materials, they enlarge under pressure. This means that hard, brittle materials of spherical shape are not suitable as dry binders. The adhesive effect, which to a certain extent is related to

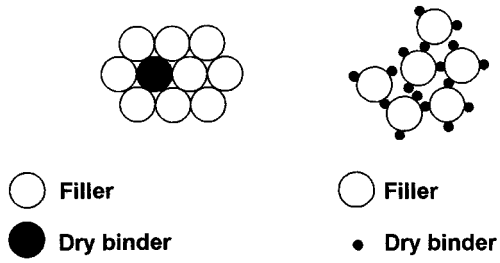

Figure 1. Ratio of dry binder particles to filler particles when reducing the diameter of the dry binder particles to one-third (dry binder concentration 10% m/m).

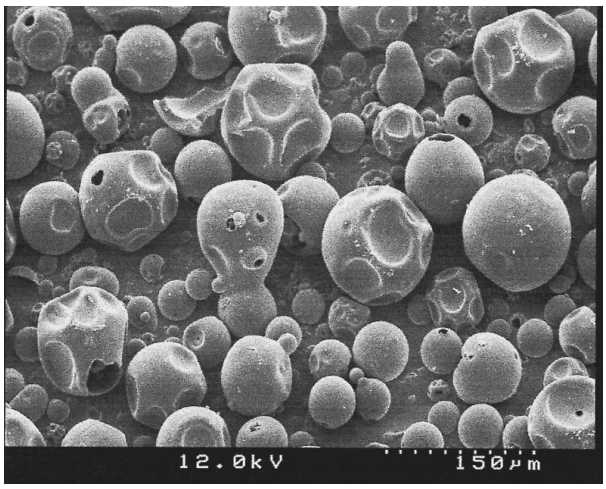

Figure 2. Scanning electron microscopy of Kollidon 30.

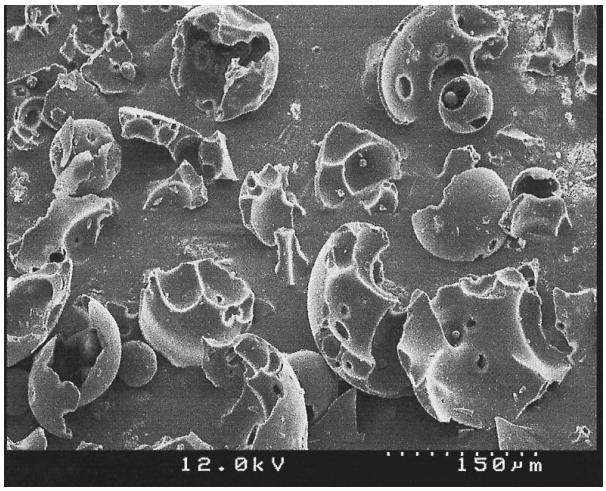

Figure 3. Scanning electron microscopy of Kollidon VA 64.

brittleness and plasticity, must also be considered. For example, very brittle materials do not have adhesive properties even under pressure and can only contribute to tablet cohesion by forming interlocking bonds, as the results obtained demonstrate.

The great efficacy of Kollidon VA 64 thus derives not only from its small particle size, but also from the polymerized vinyl acetate component, which makes Kollidon VA 64 softer and more plastic than Kollidon 30. This is also evident from the glass transition temperature, which is 168°C for Kollidon 30 and only 103°C for Kollidon VA 64.

Tablet Properties (Substance Tableting)

The materials mentioned were compressed into tablets in pure form, mixed only with 0.5% magnesium stearate, on an EK0 single-punch press. Kollidon VA 64 has a very high compression ratio, which can be attributed to the low bulk density and easy compressibility. The easy compressibility is evident from the *K* value. The *K* value is determined from the force-displacement curve (Fig. 4) and is also known as the compression resistance.

The *K* value therefore states, on a logarithmic scale, the change in compression pressure required to produce a reduction of volume or density.

With *K* values less than 4, Kollidon VA 64, Kollidon 30, and MC PH-101 are readily compressible materials, while values greater than 4 (exhibited, for example, by HPMC 2910) characterize materials more difficult to compress (Fig. 5).

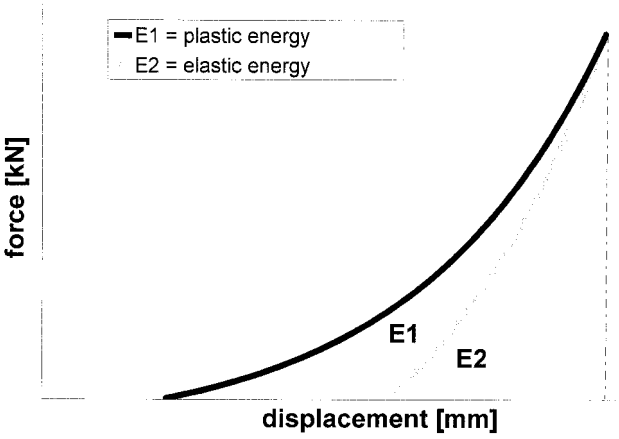

Figure 4. Force displacement curve.

The plasticity values of the products were also determined from the force-displacement curve (Fig. 4). The areas shown in Fig. 4 correspond to the elastic and plastic energy. Plasticity is expressed as the ratio of plastic energy $E1$ to total energy ($E1 + E2$) in percentage. Kollidon VA 64 has constant plasticity greater than 90% over the entire range of 10 kN to 25 kN compression force (Fig. 6).

At a compression force of 25 kN, the plasticity of the dry binders tested in this study decreased from Kollidon VA 64 with 96%, through 92% for MC PH-101, and 78% for Kollidon 30, to as low as 60% for HPMC 2910.

Particle comminution does not occur, or occurs only to a limited degree, during compression. Tableting of pure substances allows conclusions to be drawn regarding the suitability of the product as a dry binder. It is not possible, however, to use an individual parameter for this pur-

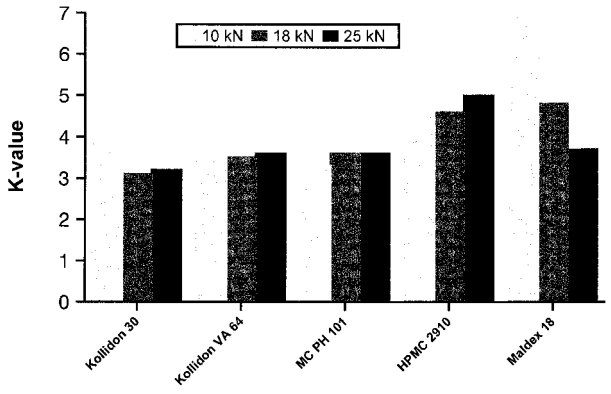

Figure 5. Resistance to compaction.

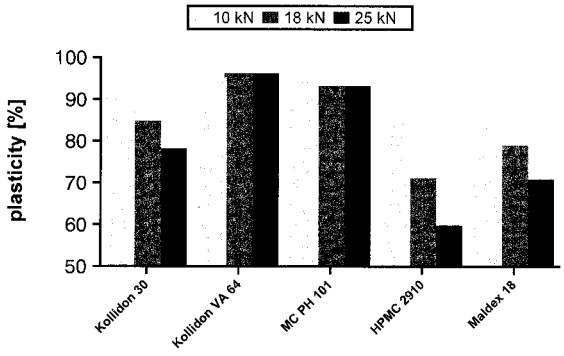

Figure 6. Plasticity of dry binders.

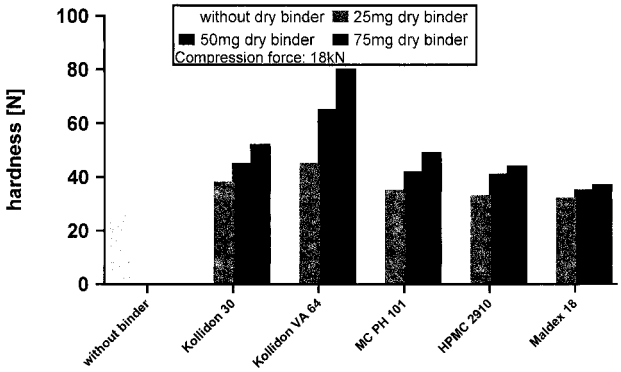

Figure 8. Hardness of dicalcium phosphate tablets with increasing amounts of dry binders.

pose, but rather it is necessary to analyze the interrelation between different parameters.

Tablet Properties

Formulation 1: Dicalcium Phosphate Tablet

Figure 7 shows the compression force–hardness profile of the various dry binders. Figure 8 plots the hardness of the tablets as a function of the dry binder quantity used. It is evident that dicalcium phosphate has poor tableting properties, so it is not surprising that only relatively low hardness values were achieved without dry binder. The addition of dry binder produced an increase in hardness compared to the blank.

Only a slight increase in hardness, however, is seen from HPMC 2910 through MC PH-101 to Kollidon 30. One particularly positive exception is Kollidon VA 64, which stands out clearly from the other dry binders (Fig. 7). For example, the hardness of a tablet produced with a compression force of 18 kN and a binder content of 50 mg per 500-mg tablet exceeds that of the corresponding blank by 120%. If the binder content of 25 mg is increased to 50 mg and then to 75 mg per 500-mg tablet, and if the same compression forces are applied in each case, Kollidon VA 64 produces the steepest increase in hardness.

The comparison of disintegration times in Fig. 9 immediately reveals that HPMC 2910 introduced a major disadvantage in this respect. Whereas MC PH-101 has no influence on disintegration time, polyvinylpyrrolidones influence disintegration time only slightly (prolongation by <1 min) and thus present no problem.

Formulation 2: Vitamin C Tablet

Vitamin C powder was chosen as the active ingredient in the second formulation. Ascorbic acid is a substance very difficult to compress and, in mixtures with excipients, also reduces compressibility more than proportion-

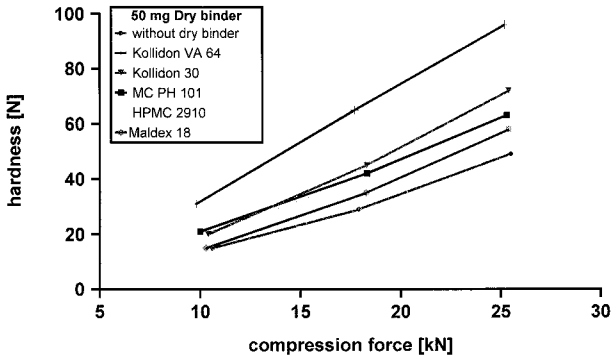

Figure 7. Compression force–hardness profile of dicalcium phosphate tablets.

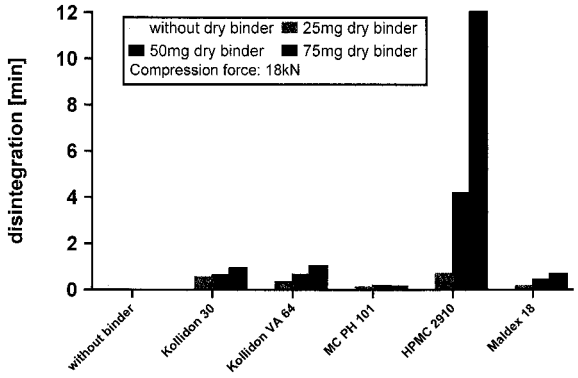

Figure 9. Disintegration of dicalcium phosphate tablets.

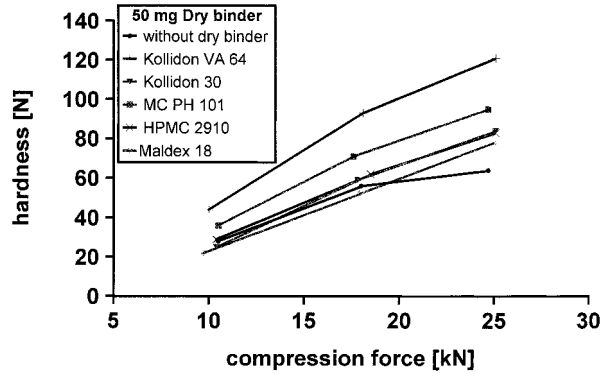

Figure 10. Compression force–hardness profile of vitamin C tablets.

ally. This formulation with 40% ascorbic acid was chosen to facilitate determination of the dry binding properties.

The compression force–hardness curve (Fig. 10) shows approximately the same behavior as for formulation 1. For example, as with formulation 1, only low hardness is achieved without dry binders. Mixtures with HPMC 2910, Kollidon 30, and MC PH-101 as a binder are only slightly above the blank value. Again, Kollidon VA 64 is clearly superior to these materials.

Compression with only 25 mg dry binder per 500-mg tablet yielded very poor friability values (Fig. 11).

Without dry binder, a friability of 3.24% was measured. This value was reduced to 1.06% by the addition of Kollidon 30, to 0.81% with HPMC 2910, and to 0.61% with MC PH-101. Friability could be restricted to less than 0.5% by the addition of Kollidon VA 64. No significant effect was detected on the release properties of vitamin C.

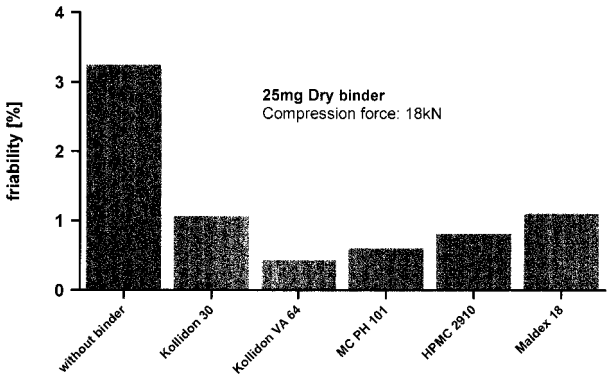

Figure 11. Friability of vitamin C tablets.

CONCLUSION

The dry binding properties of a substance depend on a variety of physical characteristics. The most important parameters have been found to be particle size and particle size distribution. Other factors with major effects on the tablets are surface area and structure, adhesive properties, and especially plasticity. The substance compression experiments yielded valuable impressions of the utility and effectiveness of dry binders. All the trials showed that, regardless of the formulation, Kollidon VA 64 has unique dry binding properties that far exceed those of Kollidon 30, MC PH-101, HPMC 2910, and many others. The use of Kollidon VA 64 as dry binder allows the manufacture of tablets with outstanding mechanical properties.

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