Compression Shear Strength and Tableting Behavior of Microcrystalline Cellulose Agglomerates Modulated by a Solution Binder (Polyethylene Glycol)

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Purpose. To investigate the possibility of modulating the compression shear strength of agglomerates by the incorporation of a solution binder and to study the subsequent effect on the deformation behavior and tablet forming ability of the agglomerates.

Method. Various concentrations (0.5 to 10%) of polyethylene glycol were incorporated as a solution binder into microcrystalline cellulose agglomerates of different porosity (10 and 20%) and the shear strength of the agglomerates, as evaluated by the 1/b value of the Kawakita equation, and the permeability to air and tensile strength of tablets formed from them were determined.

Results. Increased agglomerate porosity and concentration of polyethylene glycol reduced the 1/b values, which led to the formation of tablets with a lower permeability. A decreased tablet permeability corresponded to an increased tablet tensile strength except that the highest binder content was associated with a drop in the tablet tensile strength.

Conclusions. The solution binder reduced the agglomerate shear strength, which was expressed as an increased degree of agglomerate deformation during compression. The latter seemed to be controlled by both agglomerate porosity and shear strength. The main role of the solution binder in improving the agglomerate compactability was to increase the degree of deformation of agglomerates during compression.

KEY WORDS: compression shear strength; agglomerate porosity; agglomerate deformation; tablet pore structure; tablet tensile strength; solution binder.

INTRODUCTION

In the manufacturing of tablets, fine drug particles are often preprocessed before tableting by forming agglomerates of the drug particles. The strength of the agglomerates is of obvious importance in their further handling and can be affected by, e.g., the incorporation of a solution binder into the agglomerates. The strength of single agglomerates, as assessed by diametral compression, seems normally to increase with an increased binder concentration (1–4), although there are some examples indicating that agglomerate strength was independent of the binder concentration (5,6). However, the relevance of the mechanical strength of single agglomerates to their tablet forming ability has not been resolved. A correlation between these two variables has been found for some binder-substrate combinations (2,7,8), but not for others (1,2,4,5,7,9). The conflicting results may be explained, at least partly, by the finding (10) that the mechanical strength of single agglomerates loaded diametrically, without lateral constraint, may not correlate with measures of the agglomerate strength derived from in-die compression data treated with the Kawakita equation (11,12). For three series of agglomerates (10), a correlation between this compression shear strength of the agglomerates and the pore structure and tensile strength of the tablets formed from them was obtained, and it was suggested that the compression shear strength may reflect the propensity of the agglomerates to shear and deform rather than to fracture while subjected to stresses in die.

Deformation of agglomerates was earlier suggested (13,14) to be caused by a flow of primary particles within the agglomerates, i.e., a shearing mechanism. Hence, factors that will interfere with the friction between primary particles within the agglomerate can potentially affect the agglomerate deformation behavior, e.g., the addition of a material that flows easily and thus can act as an internal lubricant within the agglomerates and facilitate particle repositioning. This latter assumption is supported by the finding (14) that the deformation behavior of agglomerates can change due to the addition of a material with a low yield strength (polyethylene glycol).

Binders used in pharmaceutical agglomerates can, relative to drugs and fillers, generally be described as materials of low yield strength. Binders are normally added in solution and are present in the agglomerates in low proportions, i.e,. below 10%. As previously discussed, the presence of a solution binder in agglomerates may affect their compression shear strength and thus also their deformation behavior during tableting. The purpose of this study was to investigate the possibility of modulating the compression shear strength of agglomerates by the incorporation of a solution binder and to study the subsequent effect on the deformation behavior and tablet forming ability of the agglomerates. A series of agglomerates consisting predominantly of microcrystalline cellulose and with various concentrations of polyethylene glycol (0 to 10%) were prepared.

EXPERIMENTAL

Materials

Microcrystalline cellulose (hereafter denoted MCC, Avicel PH101, FMC, Philadelphia, PA) from two different batches. One batch (apparent particle density: 1.562 g/cm^3) was used in the preparation of agglomerates referred to as L and H (see below and Table I) and the other (apparent particle density: 1.582 g/cm^3) used in the preparation of agglomerates referred to as N. Polyethylene glycol (PEG) 6000 (apparent particle density: 1.225 g/cm^3, Merck-Schuchardt, Germany). Ethanol (95% w/w, Solveco Chemicals AB, Sweden).

For the first two series of agglomerates, the letters L and H refers to agglomerates of low and high porosity, respectively. The N series, prepared from the second batch of MCC, consisted of agglomerates of the lower porosity. The figures in the denominations of the agglomerates indicate the proportion of binder in the agglomerates (between 0 and 10% w/w, see Table I).

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Table I. Conditions Used During Preparation of Agglomerates

Agglomerate denomination	Concentration of PEG in dry agglomerates (%)	Amount of MCC (g)	Amount of PEG (g)	Total amount of agglomeration liquid (g)	Relative amount of water/ethanol (% w/w)
N0	0	500	0	550	100/0
N05	0.5	497.5	2.5	547	100/0
N1	1	495	5	544	100/0
N2	2	490	10	539	100/0
L0	0	500	0	550	100/0
L5	5	475	25	520	100/0
L10	10	450	50	490	100/0
H0	0	500	0	550	50/50
H5	5	475	25	520	50/50
H10	10	450	50	440	50/50

Method

Preparation of Agglomerates

Agglomerates consisting of MCC and different amounts of PEG (between 0 and 10% w/w) as a solution binder were prepared by extrusion-spheronization. To prepare agglomerates with varying intragranular porosity, the composition of the agglomeration liquid was varied (Table I).

The MCC powder was dry-mixed for 1 min at 500 rpm in a high shear mixer (QMM micromixer, Donsmark Process Technology, Denmark). The PEG was dissolved in the agglomeration liquid, which was then poured into the mixer bowl over 2.5 min during agitation. The wet mass was then mixed for 2 min, extruded through a radial screen (model E140, Nica system, Sweden) with 1 mm circular openings, and then immediately spheronized at 964 rpm on a 45.0 cm diameter plate (model S450, Nica system, Sweden) for 3 mins. The agglomerates were dried overnight in a tray drier at 40°C, after which the 0.71–1.00 mm fraction was collected by dry sieving. The agglomerates were then stored in a desiccator at 40% relative humidity for at least 7 days before any experiments were performed.

Characterization of Agglomerates

The bulk density of the agglomerates was determined (n = 3) from the weight and volume of the agglomerate bed before and after 200 taps in a tap volumeter (J. Engelsmann, Ludwigshafen, Germany). A 25 ml cylinder with an inner diameter of 15 mm was used in the tap volumeter.

The porosity of the agglomerates was calculated from the apparent and effective particle densities (n = 3). The apparent particle density was measured using a helium pycnometer (AccyPyc 1330, Micromeritics, Norcross, GA). The apparent particle density of the MCC + PEG agglomerates was calculated from the density values of the two components (15). The effective particle density was determined by mercury pycnometry at a pressure of 90.3 kPa (equivalent to 677 mm Hg) using a mercury porosimeter (Autopore III, Micromeritics). A mercury intrusion pressure of 677 mm Hg was chosen based on earlier experiences (13) that pycnometry data obtained at a similar pressure corresponded reasonably with porosity data obtained by mercury intrusion. Hence, the calculated granule porosity will give a reasonable indication of the porosity of the agglomerates.

The external surface area of the agglomerates was determined by steady-state air permeametry using the method of Eriksson *et al.* (16), but modified by the use of a digital differential manometer (P200 S, Digitron Instrumentation Ltd, UK) instead of a u-tube manometer.

The compressibility of the agglomerates during tableting was studied using a compaction simulator (PCS-1, Puuman OY, Finland) and the compression procedure described earlier (14). The collected punch pressure–displacement values were corrected for displacement measurement errors caused by punch deformation during compression and then used to construct Kawakita profiles (11) (n = 3) to calculate the agglomerate shear strength during confined uniaxial compression (1/b) of the agglomerates (10,12). The Kawakita equation describes the relationship between the degree of compression of a bed of agglomerates (C) held within the die and the applied pressure (P) during compression in the following way:

$$(P/C) = (1/ab) + (P/a)$$

The inverted value of the compression parameter b in the equation has been suggested (10,12) to give an indication of the failure strength of agglomerates during compression.

Characterization of Tablets

Tablets for tensile strength testing were prepared in an instrumented single punch press (Korsch EK 0, Germany) at applied pressures of 50, 75, 100, and 150 MPa (13). Tablets were then loaded diametrically (Holland C50, Great Britain) at a loading rate of 5 mm/min until they fractured (n = 10). The tensile strength was derived from the force needed to fracture the tablets (17).

Tablets used for tests of permeability to air were prepared at 50, 75, and 100 MPa applied pressure, and the permeability to air of the tablets were measured by constant volume permeametry (n = 3), as described earlier (18). The permeability coefficient was finally calculated for each tablet (19).

RESULTS

The agglomerates were spherical and had smooth external surfaces. The preparation procedure gave intragranular porosities of about 10% for agglomerates of denominations L and N, and 20% for the H-denominations (Table II).

The compression shear strength of agglomerates, as assessed by the Kawakita 1/b parameter, decreased with in-

Table II. Some Physical Characteristics of Agglomerates

Agglomerate denomination	Porosity (%) (n = 3)	External surface area (cm^{-1}) (n = 3)	Poured density (g/cm^3) (n = 3)	Tapped density (g/cm^3) (n = 3)	Integranular voidage[a] (%)	Compression shear strength (MPa) (n = 3)
N0	8.1 (2.4)[b]	82.4 (0.2)	0.826 (3.4)	0.860 (0.8)	42.4	46 (0.2)
N05	9.6 (5.1)	82.2 (1.2)	0.790 (0.6)	0.840 (1.0)	44.0	27 (0.9)
N1	10 (3.1)	81.1 (1.2)	0.802 (3.6)	0.843 (1.1)	42.6	17 (2.3)
N2	11 (1.0)	79.6 (0.6)	0.814 (2.6)	0.850 (0.2)	41.1	27 (2.5)
L0	6.7 (2.4)	88.0 (1.0)	0.837 (0.2)	0.870 (0.2)	42.5	18 (0.5)
L5	9.0 (1.5)	82.8 (0.6)	0.801 (1.5)	0.830 (0.4)	42.9	13 (2.1)
L10	12 (1.5)	80.4 (1.5)	0.799 (0.5)	0.819 (0.2)	40.1	52 (1.9)
H0	21 (2.1)	84.1 (1.0)	0.709 (1.1)	0.730 (1.0)	42.3	50 (2.5)
H5	20 (1.6)	82.8 (0.6)	0.689 (1.0)	0.716 (0.6)	44.1	44 (1.5)
H10	23 (1.0)	80.6 (0.9)	0.676 (0.4)	0.702 (0.9)	42.4	40 (2.2)

[a] Calculated from poured bulk density and agglomerate density.
[b] Relative standard deviations (%) in parentheses.

creases in either the porosity or in the intragranular binder content of the agglomerates (Table II). One can also notice that the agglomerate shear strength differed between the agglomerates of denominations N0 and L0, although they were prepared using the same procedure and the same formulation, except for the batch of MCC. There might thus be batch-related differences in the properties of the MCC primary particles, such as their crystallinity, hygroscopicity, and porosity, which can explain the derived difference in compression shear strength. It was not however within the scope of this study to investigate and explain a potential batch effect of the substrate particles for the agglomerate shear strength.

The air permeability of the tablets decreased with increasing applied pressure and with increasing porosity and intragranular binder content of the agglomerates (Table III). Thus, both the porosity and the binder content are granular properties that affected the intergranular pore structure in the tablets (13,14).

The tensile strength of the tablets increased with agglomerate porosity and applied pressure and was also affected by the binder content (Table III). Specifically, 5% of binder appeared to increase the mechanical strength of the tablets, but further increasing the binder content did not further increase their tensile strength.

Based on earlier experiences (13,14), it is expected that the type of agglomerates used in this study will not fracture significantly during powder compression, i.e., deformation and densification of the agglomerates are the dominating mechanisms involved in the compression process. Visual examination of tablets, intact and fractured tablets, supported that the agglomerates used in this study showed limited fragmentation or fracturing during compression.

DISCUSSION

The incorporation of PEG 6000 as a solution binder into MCC agglomerates reduced their compression shear strength, as quantified by the Kawakita 1/b parameter (Table II), which is interpreted as a decreased resistance to deformation of the agglomerates during confined compression. This ability of a substance with a low yield strength to modulate the resistance to deformation of agglomerates formed from a binary mixture during confined compression is consistent with earlier experiences (14) on the deformation behavior of MCC agglomerates into which PEG 6000 was incorporated in particulate form (in the proportion 1/1 of MCC/PEG). Also, the porosity of the agglomerates affected their compression shear strength, which also is consistent with earlier findings (10). Thus, the propensity of agglomerates to deform, due to the repositioning of substrate particles in the agglomerate, can thus potentially be facilitated by incorporating a solution binder with a low yield strength and by increasing the agglom-

Table III. Tensile Strength and Air Permeability of Tablets Formed at a Series of Compaction Pressures of the Different Types of Agglomerates

Agglomerate denomination	Tablet tensile strength at 50 MPa (MN/m^2)	Tablet tensile strength at 75 MPa (MN/m^2)	Tablet tensile strength at 100 MPa (MN/m^2)	Tablet tensile strength at 150 MPa (MN/m^2)	Tablet permeability at 50 MPa ($m^4/Ns \times 10^{-8}$)	Tablet permeability at 75 MPa ($m^4/Ns \times 10^{-8}$)	Tablet permeability at 100 MPa ($m^4/Ns \times 10^{-8}$)
N0	—	0.018 (26)	0.031 (22)	0.072 (12)	231 (1.8)	133 (4.2)	66.0 (13)
N05	0.014 (23)[a]	0.029 (16)	0.065 (11)	0.15 (16)	184 (1.5)	90.8 (9.2)	39.5 (14)
N1	0.023 (19)	0.052 (16)	0.10 (13)	0.22 (6.8)	174 (0.6)	79.7 (4.3)	34.4 (4.6)
N2	0.024 (16)	0.051 (6.1)	0.099 (12)	0.21 (12)	142 (2.4)	59.7 (8.9)	24.1 (5.4)
L0	—	0.029 (11)	0.050 (24)	0.11 (12)	170 (1.1)	74.9 (0.1)	35.0 (2.8)
L5	0.088 (11)	0.26 (10)	0.33 (18)	0.69 (7.7)	67.2 (2.2)	16.6 (1.5)	4.96 (13)
L10	0.016 (11)	0.096 (14)	0.14 (20)	0.42 (9.0)	21.4 (9.9)	4.66 (2.9)	1.37 (9.5)
H0	0.12 (12)	0.42 (5.5)	0.54 (9.1)	1.4 (4.9)	42.8 (7.8)	10.2 (15)	2.59 (12)
H5	0.26 (9.2)	0.81 (6.9)	0.99 (11)	1.9 (4.5)	11.3 (22)	1.70 (38)	0.472 (39)
H10	0.34 (7.6)	1.0 (9.5)	1.0 (8.8)	1.6 (6.2)	2.33 (16)	0.366 (15)	0.108 (16)

[a] Relative standard deviations in parentheses.

erate porosity. Even the presence of relatively low amounts of a solution binder, i.e., in this case 0.5% PEG (Table II), seemed to affect the agglomerate compression shear strength (although the effect at this binder concentration was not statistically significant).

A reduced compression shear strength of the agglomerates, due to increased binder concentration and porosity of the agglomerates, corresponded in general terms to a reduced permeability to air of the formed tablets (Table III and Fig. 1). Because the intergranular voidage was similar before tableting for beds of all types of agglomerates (Table II), and because the agglomerates did not fragment significantly during compression, the permeability coefficient for tablets formed at a certain pressure may be used as an indicator of the degree of deformation the agglomerates underwent during compression (13). Thus, the reduced agglomerate compression shear strength was expressed as an increased degree of deformation that the agglomerates underwent during compression (10). One can notice that the evolution of tablet structure was affected by relatively small amounts of the solution binder (Table III).

The relationship between agglomerate compression shear strength and tablet permeability (Fig. 1) was different for agglomerates with higher original porosity (the H-denomination) than for those with lower original porosity (L-denominations). Thus, agglomerates of a specific shear strength, as measured by the 1/b value from the Kawakita equation, with higher porosity formed tablets with a more closed intergranular pore structure than agglomerates with lower porosity and the same shear strength. A possible explanation of this finding is that the expressed deformation of agglomerates during compression was regulated by the combined effect of the compression shear strength and the porosity of the agglomerates. A low intragranular porosity represents a restriction toward deformation, and the expressed degree of deformation may be limited even if the shear strength of the agglomerates is relatively low. An increased agglomerate porosity may thus increase the potential for deformation by increasing the space into which primary particles can reposition. This porosity-related effect on the degree of agglomerate deformation will probably affect the degree to which the agglomerates are flattened during compression (13,14,20).

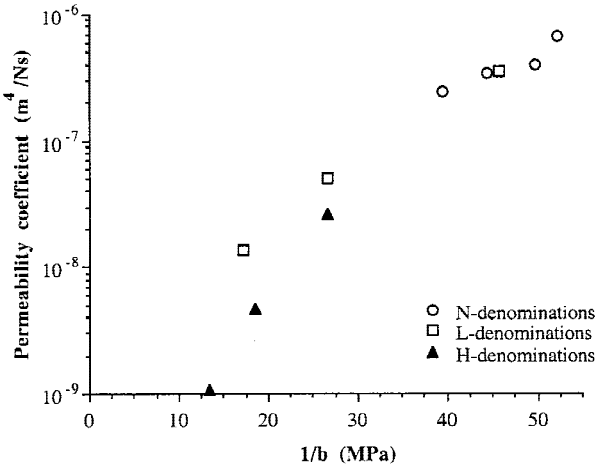

Fig. 1. Shear strength of agglomerates during powder compression (as measured by the 1/b parameter from the Kawakita equation) as a function of the permeability coefficient of tablets formed at 100 MPa compaction pressure. Symbols are defined in the graph.

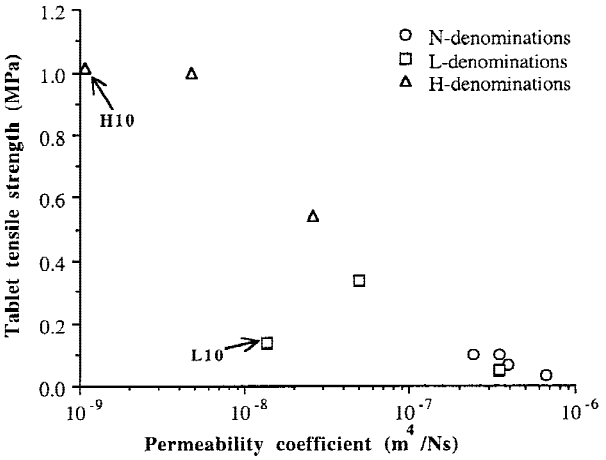

Fig. 2. The permeability coefficient as a function of the tensile strength for tablets formed at 100 MPa compaction pressure. Symbols are defined in the graph.

Since an increased PEG content of the agglomerates correlated with the formation of a more closed intergranular tablet pore structure (Fig. 1), it can be expected, based on earlier experiences (10,13,14,21), that an increased PEG content generally should also increase the tensile strength of the tablets. Up to a concentration of 5% PEG (Table III), the incorporation of the solution binder in the agglomerates improved the agglomerate compactability, but at a concentration of 10% PEG, the tensile strength of the tablets was not improved further, or was even reduced. Thus, the incorporation of PEG in the agglomerates may be associated with a reduction in the ability of the agglomerates to cohere, i.e., the strength of the adhesive interaction between the agglomerates is lower when the agglomerates contain PEG compared with the MCC only agglomerates. Accordingly, because the solution binder in most cases increased the agglomerate compactability although it decreased the effective adhesion strength of the bonds formed between the agglomerates, the solution binder used probably functioned as a binder mainly by modulating the deformation properties of the agglomerates. This is illustrated in Fig. 2, which shows that the two agglomerates containing 10% binder deviated from the relationship between intergranular pore structure and tablet tensile strength that seemed to apply to all other agglomerates used in this study.

To summarize, from the results reported in this article we conclude that the incorporation of a solution binder into agglomerates can reduce the agglomerate compression shear strength. This reduction in compression shear strength can occur at relatively low levels of binder content and will be expressed as an increase in the degree of deformation that the agglomerates undergo during compression. We conclude also that the degree of deformation that agglomerates undergo during compression may be regulated simultaneously by two physical characteristics of the agglomerates: the resistance to shearing during confined compression and the intragranular pore space (the porosity) available for repositioning of the primary particles. Finally, for the agglomerates used in this study, the main role of the binder in improving their tablet

forming ability seemed to be to increase their degree of deformation during compression rather than affecting the adhesion strength of the bonds formed between the agglomerates.

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