Investigation of the powder flow behaviour of binary mixtures of microcrystalline celluloses and paracetamol

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ABSTRACT

The flow behaviour of binary mixtures of paracetamol and different grades of microcrystalline celluloses (Avicel® PH101, PH102 and PH200) was studied using a new testing method. The effect of physical characteristics of the powder including tribocharging and the addition of lubricant on the flow properties of the different mixtures was investigated. As expected, the flowability of the samples was affected both by the amount of paracetamol and the physical properties of microcrystalline celluloses (MCC) and the mixtures. The effect of lubricant varied depending on the MCC grade: magnesium stearate was able to improve the flowability of the mixtures containing PH102 and PH200 while it did not affect the flowability of PH101. Multivariate analysis showed that the flow of the binary excipient-drug mixtures through an orifice is affected by several phenomena, such as charging, surface moisture, carrier payload and particle size.

KEY WORDS: Flowability, powder flow measurement, binary mixture, microcrystalline cellulose, paracetamol, carrier payload, tribocharging, multivariate data analysis

INTRODUCTION

The flowability of a powder is an important property influencing several drug manufacturing steps. In the tablet manufacturing process, for instance, flowability plays a role in mixing and compaction. For example powder flow in hoppers is a crucial factor for direct compression excipients in drug manufacturing to achieve content and weight uniformity of the final dosage form. Flowability is affected by the physical properties of the powder, such as particle size and shape, the loading experienced by particles (gravity, interaction with air flow and container etc.), the current state of the powder (i.e. tap, free flowing etc.) and the processing environment (e.g. humidity). Particles larger than 250 μm usually flow freely while particles below 100 μm are generally cohesive and prone to flowability problems (1).

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When the particle size is smaller than 10 μm, powders are very cohesive and resist flow under gravity. Flow properties are also related to the internal friction angle of the powder (2). Moreover, the preconditioning of a powder affects the flow of especially poorly flowing powders and thus has to be specified very carefully to obtain repeatable results when performing powder flow measurements. There is also evidence that electrostatic charging has an effect on the cohesion and stability of binary mixtures (3–4).

Due to the large number of factors influencing the flow rate of a powder, only a few direct methods for measuring flowability of powders have been developed (5–7). In these recent hopper methods, the flow properties can be determined based on the strength of the bulk material arches. Another new method based on the powder flow to tablet die has been reported (8–10). Several flow characterization methods, such as Jenike's shear cell, powder rheometer, the angle of repose, Hausner ratio and Carr index calculated from bulk and tap densities, the avalanching tendency etc. have also been used for evaluating flowability (11–13). However, shear test are challenging to operate, and the simpler indirect tests are not always accurate and usually are only applicable to certain processes. It has been argued that the calculations according to the Jenike approach can give unexpected values for the hopper opening size, and that the Hausner ratio is unreliable (14–15). Different methods are needed for the characterization of different types of flow, such as static and dynamic flow (16). Thus, the flow characterization method should be chosen based on the process under investigation, since the different methods do not always rank the powders in the same order. Nevertheless, good correlation has been found between tap density and angle of repose (17).

Another reason for many direct methods failing to accurately measure the flow rate of poorly flowing materials is the arching tendency of cohesive powders. This applies for example to the Ph. Eur funnel flow method (18), in which stagnation causes a problem when cohesive powders are studied. Arching can occur if the powder forms a cohesive arch across the hopper opening having sufficient strength within the arch to be self-supporting (14). The average arch destruction time is the mass outflow time divided by the number of arches that have been destroyed in a run (7). As the number of arches does not depend on the cohesiveness of the sample, in this time period the arch destruction time depends linearly on the mass outflow time. A novel direct method for measuring powder flow from an orifice has recently been introduced (19). The method was successfully used for classifying the flow behaviour of a range of pharmaceutical excipients. In the present study the same technology was applied to studying binary mixtures of paracetamol and microcrystalline celluloses (MCC) to increase the understanding of the flow behaviour of the excipients, and how the powder flow of the binary mixtures is interlinked to their physical properties. One primary aim was to gain understanding of how the drug loading of a micronised API influences the flow of the different grades of MCC, and whether this can be determined rapidly. In this context, charging of the powders and the effect of lubricant (magnesium stearate) on the flow properties of the different mixtures were also investigated.

MATERIALS

Binary mixtures of paracetamol (Hawkins Inc, Minneapolis, USA) and microcrystalline celluloses (Avicel® PH101, PH102 or PH200, all from FMC BioPolymer, Little Island, Ireland) were prepared under controlled conditions (24±1°C, 50±2% RH).

METHODS

Mixing

The raw materials were conditioned for three days and passed through a 1.68 mm sieve to break aggregates prior to mixing. Altogether 48 samples containing Avicel® PH101, PH102 or

PH200 and 0 to 25% (w/w) paracetamol with 2.5% intervals excluding 22.5% were mixed in 100 ml glass containers using a laboratory-scale Turbula® mixer at 22 rpm (Willy A Bachofen AG, Basel, Switzerland). Triplicate samples were prepared of three samples of each MCC series, 2.5, 12.5 and 25% paracetamol. The mixing time was ten minutes, after which 0.5% (w/w) magnesium stearate (MS, Ph.Eur. grade) was added in the middle of the powder bed and mixed for two more minutes at 22 rpm.

Flowability measurements

The flowability of the samples was studied using FlowPro instrument (SAY Group, Helsinki, Finland) in controlled conditions (24±1°C, 50±2% RH). The samples were sieved through a 1 mm sieve before the experiments. The funnel of the instrument was cleaned with dried pressurised air prior to each measurement. When samples containing magnesium stearate were measured, the funnel was washed after experiments in order to prevent MS from coating the funnel. All the samples were measured five times (n=5).

The FlowPro instrument is composed of a frame, funnel with orifice and analytical scale connected to a computer (Figure 1). The volume of the funnel is 5.4 cm^3 and the orifice diameter 3 millimetres. The funnel moves vertically and the upward motion breaks the powder arch enabling the powder to flow freely through the orifice until arching occurs again. This cycle is repeated until the powder flow is complete. Thus, the device measures the arching tendency and arch strength of powders. Based on the experimental data, the flow rate of the powder and the shape of the mass function can be determined. A thorough description of the device can be found in reference 19.

Bulk and tapped density

Bulk and tapped densities of the raw materials were determined in controlled conditions with a tapping device (Erweka Apparatebau GmbH, Germany) using the Ph.Eur. method (18). The experiments were repeated three times. The results were used to calculate the Carr index (CI) for the materials according to the following equation:

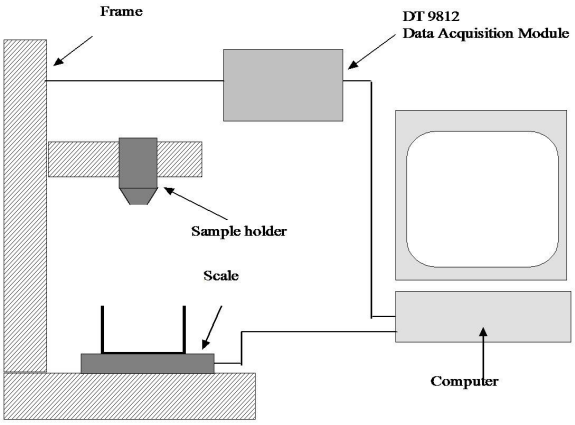


Figure 1 A diagram of the flow measuring instrument and the experimental set-up.

$$CI = ((TD - BD) / TD) * 100\% \quad \text{Eq 1}$$

where TD is the tap density and BD the bulk density of the material.

Scanning electron microscopy (SEM)

Three images of raw materials were taken with a Zeiss DSM 962 scanning electron microscope (Carl Zeiss, Oberkochen, Germany). The samples were fixed onto two-sided carbon tape and sputtered with platinum for 25 seconds with an Agar sputter device (Agar Scientific Ltd., Stansted, UK). The SEM-images were taken with 100x, 500x and 5000x magnification. Images of the mixtures containing MCC, 5 or 20% paracetamol and MS were also taken in order to investigate how MS is distributed on the surface of the MCC particles.

Water activity (a_w)

The water activity of the raw materials and samples was measured once with AquaLab 3

(Decagon Devices, Pullman, USA). The precision of the instrument is ±0.003. Raw materials were measured prior to and after conditioning and the samples after conditioning.

Particle size and carrier payload (CP)

The particle size of the raw materials was defined prior to conditioning using Helos laser diffractometer with a Rodos disperser unit and vibrational feeder (Sympatec Gmbh, Clausthal, Germany). Based on the particle sizes of the raw materials, carrier payloads (CP) for the samples were calculated according to Equation 2. CP is the ratio between the total projection surface area of the drug particles and the total outer particle surface area of the carrier particles. A payload below one indicates that the carrier has free surface, while if the CP is more than one, the surface of the carrier is completely covered with the drug particles (20).

$$CP = \frac{m_{paracetamol} d_{mean,\ mcc} \varrho_{mcc}}{4 m_{mcc} d_{mean,\ paracetamol} \varrho_{paracetamol}} \qquad \text{Eq 2}$$

Where m is the mass of the sample, d_{mean} is the mean particle size of a compound and ϱ is the density of a compound. The equation is derived for spherical particles but in the calculations it was assumed that the particles have a rectangular prism shape. It was also assumed that the longest side of the prism equals the diameter of the particle (d) and the lengths of the two shorter sides are 0.5d. The formula for spherical particles was used because in an equation derived for rectangular particles, the projection surface area would depend on the position of the rectangular prism. Thus, the equation for spherical particles gives a more accurate CP approximation.

Specific surface area

The specific surface area measurements were performed using TriStar 3000 gas adsorption analyser (Micromeritics, Norcross, USA). The five-point BET theory (21) was applied to calculate the specific surface areas of the samples. Argon was used as an adsorbant. The samples were dried in vacuum at 40°C for 16 hours prior to the measurements. The results are average values of two independent measurements.

Electrostatic charging

Neutralized samples were charged by sliding powder through a grounded stainless steel pipe into a Faraday cup. Length of the pipe was 500 mm and the inner diameter 25 mm. Prior to the measurements, the pipe was carefully cleaned and placed at the angle of 55° with respect to ground. The method has been explained in detail previously (22). In addition to binary mixtures containing MCC and paracetamol, raw materials were also charged.

Statistical analysis

The flowabilities of different grades of MCC and the flow rates of the unlubricated and lubricated samples were compared using a paired two-sample t-test.

Multivariate analysis

Principal component analysis (PCA) was performed to visualize the physical characterisation data in order to find the interdependencies in the data set using Simca-P software v 10.1. (Umetrics AB, Umeå, Sweden). Univariate scaling of the data was performed. The same software was used to create a partial least squares (PLS) model using cross-validation to evaluate how well the physical factors measured predicted the measured powder flow behaviour and which factors play the most important role in this context. The predictive abilities of the models were described using R^2 (goodness of fit) and Q^2 (goodness of prediction) values on a scale from 0 to 1.

RESULTS AND DISCUSSION

Effect of paracetamol and MCC grade

As expected, a decreasing trend was found in the flow rate of the MCC-paracetamol blends

with increasing paracetamol concentration (Figures 2 and 3). The flowability of the samples was affected not only by the proportion of paracetamol but also by the MCC grade. The greatest decrease in the flow rate of the Avicel® PH200 samples occurred between 0 and 5% paracetamol. However, the flowability of the samples containing the other two MCC grades was influenced less by the increase in paracetamol amount over the whole concentration range.

The flow rate of the binary mixtures containing Avicel® PH101 was poorer than those containing PH102 (P=0.001) or PH200 (P=0.001) (Figure 3d). Nevertheless, no significant difference between the flowabilities of the binary mixtures containing PH102 and PH200 samples was found even though PH200 has been reported to have better flowability than PH102 (23–24).

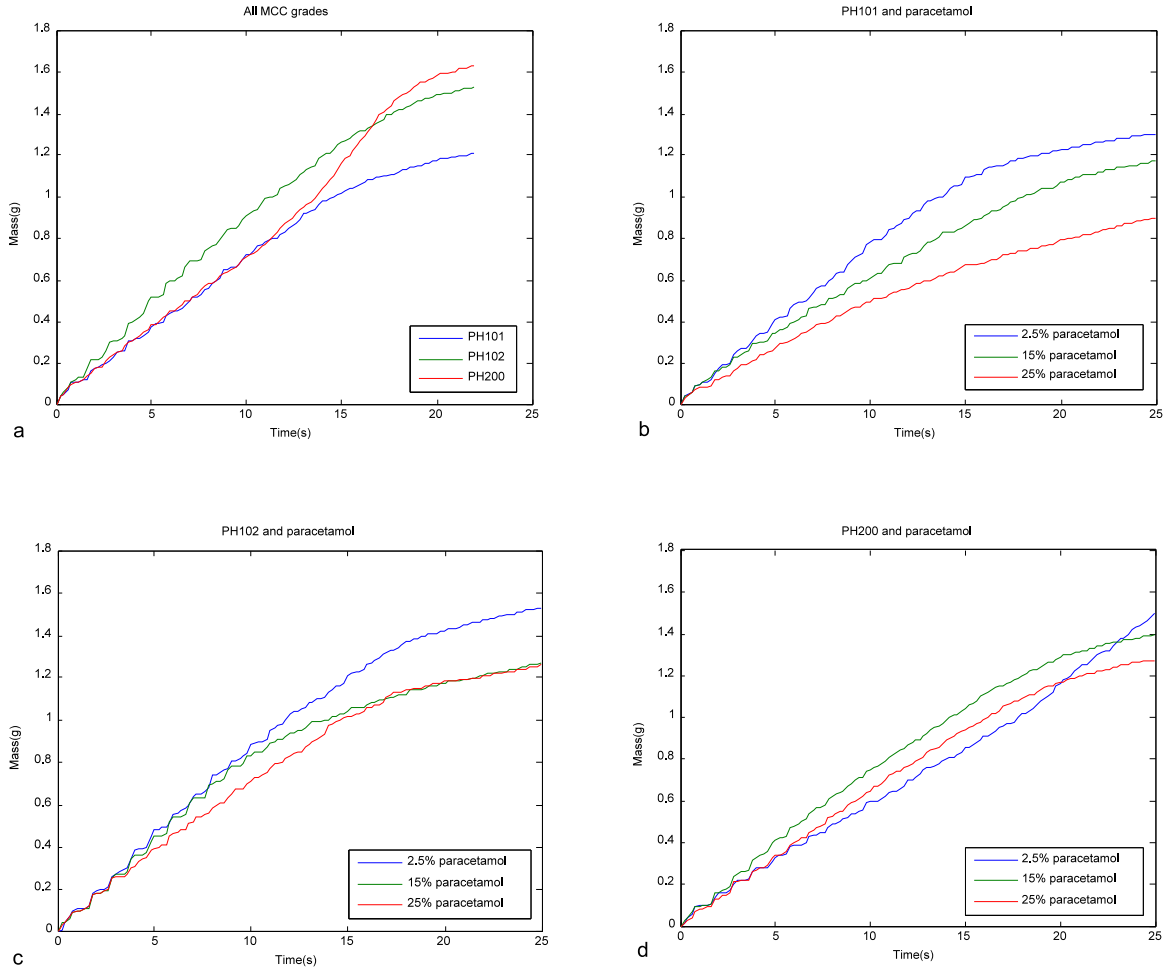
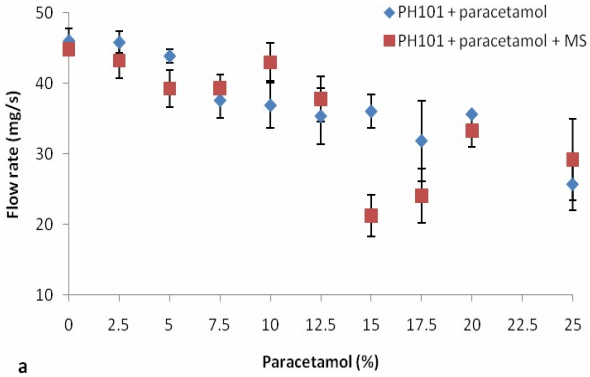
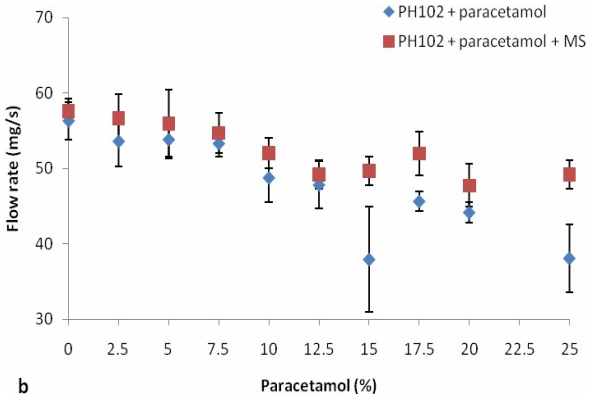
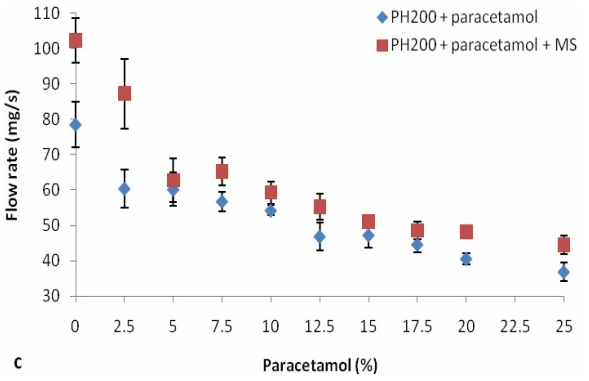
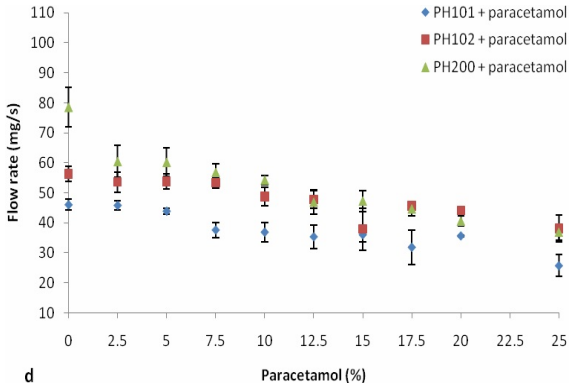


Figure 2a-d The effect of MCC grade (a) and different concentrations of paracetamol (b-d) on the flow rate of binary mixtures of paracetamol and MCC. The plots show the average of five measurements (relative standard deviation of most samples is below 6% and of all samples below 13%).









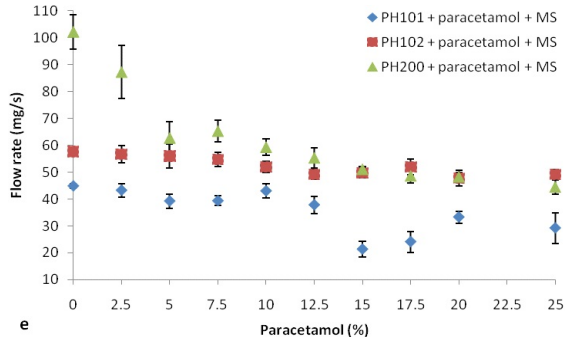


Figure 3a-c The effect of paracetamol concentration and magnesium stearate (MS) on the flow rate of binary mixtures of paracetamol and Avicel® PH101 (a), PH102 (b) and PH200 (c).

Figure 3d-e Comparison of the effect of MCC grade on the flowability of blends of MCC and paracetamol (d) and MCC, paracetamol and magnesium stearate (MS) (e) at different paracetamol concentrations.

The mass function of PH200 has two linear parts and the first slope is smaller than the second one (Figures 2a and 2d). This behaviour misleadingly suggests that the flowability of PH200 would be similar to PH101 and the sample containing 2.5% paracetamol would have a lower flow rate than the samples with 15% or 25% drug. However, the two-slope behaviour disappears when the paracetamol concentration is higher than 5%. The two-slope flow behaviour of PH200 is likely to be due to powder packing in the beginning of the measurement, which leads to insufficient fluidisation and thus a decreased flow rate. The second slope results from increased sample fluidisation and thus better flowability after the powder remaining in the hopper falls below a critical mass. The packing phenomenon partly explains why the flow rate of PH200 was not statistically significantly higher than the flow rate of PH102.

The flowabilities obtained with FlowPro correlate well with the Carr index of the raw materials (Table 1). Paracetamol decreases the flow rate of the binary mixtures due to its plate-like morphology and small particle size and consequently high cohesiveness (Figure 4d). Moreover, triboelectrification of paracetamol easily occurs during handling and mixing. Charging influences both the mixing homogeneity and flow behaviour and could increase segregation in the samples. It was also observed that paracetamol tended to aggregate during weighing despite the fact that it was sieved immediately prior to sample preparation. Furthermore, the paracetamol particles were bigger than the d50-value suggests as there was a large number of large particles at the higher end of the particle size distribution (Figure 5).

The deterioration in the flow rate after adding paracetamol may also be explained by the effect of moisture on the flowability of the powders. The critical humidity at which powder flow becomes poor depends on particle size (25). This critical humidity is higher for larger particles. Thus, at relatively high humidity, van der Waals forces between small particles are higher than between large particles, which leads to poorer flowability of powders consisting of small particles. Hence, as paracetamol particles are smaller than MCC particles, samples containing a larger concentration of paracetamol exhibit poorer flow behaviour at 50% relative humidity than those containing a smaller amount of the drug. Furthermore, moisture lubricates the MCC particles in a similar manner to MS (26–27).

Table 1 The physical properties of the raw materials. Water activity (a_w), bulk and tap density (d_{bulk}, d_{tap}) and Carr index (CI) are measured using conditioned materials and the specific surface area (BET) using dried materials.

Material	Particle size (µm)			BET (m^2/g)	a_w	d_{bulk} (g/cm^3)	d_{tap} (g/cm^3)	CI (%)
	d10	d50	d90					
Paracetamol	5.57 ± 0.02	27.57 ± 0.23	96.88 ± 1.88	0.29	0.108	0.195 ± 0.008	0.259 ± 0.006	25
PH101	14.09 ± 0.19	60.46 ± 0.16	149.57 ± 0.68	1.06	0.398	0.270 ± 0.004	0.333 ± 0.001	19
PH102	15.88 ± 0.19	91.97 ± 1.25	254.85 ± 2.6	0.97	0.451	0.329 ± 0.004	0.393 ± 0.001	16
PH200	38.19 ± 1.51	160.25± 5.99	297.04 ± 3.67	1.07	0.471	0.331 ± 0.003	0.388 ± 0.003	15

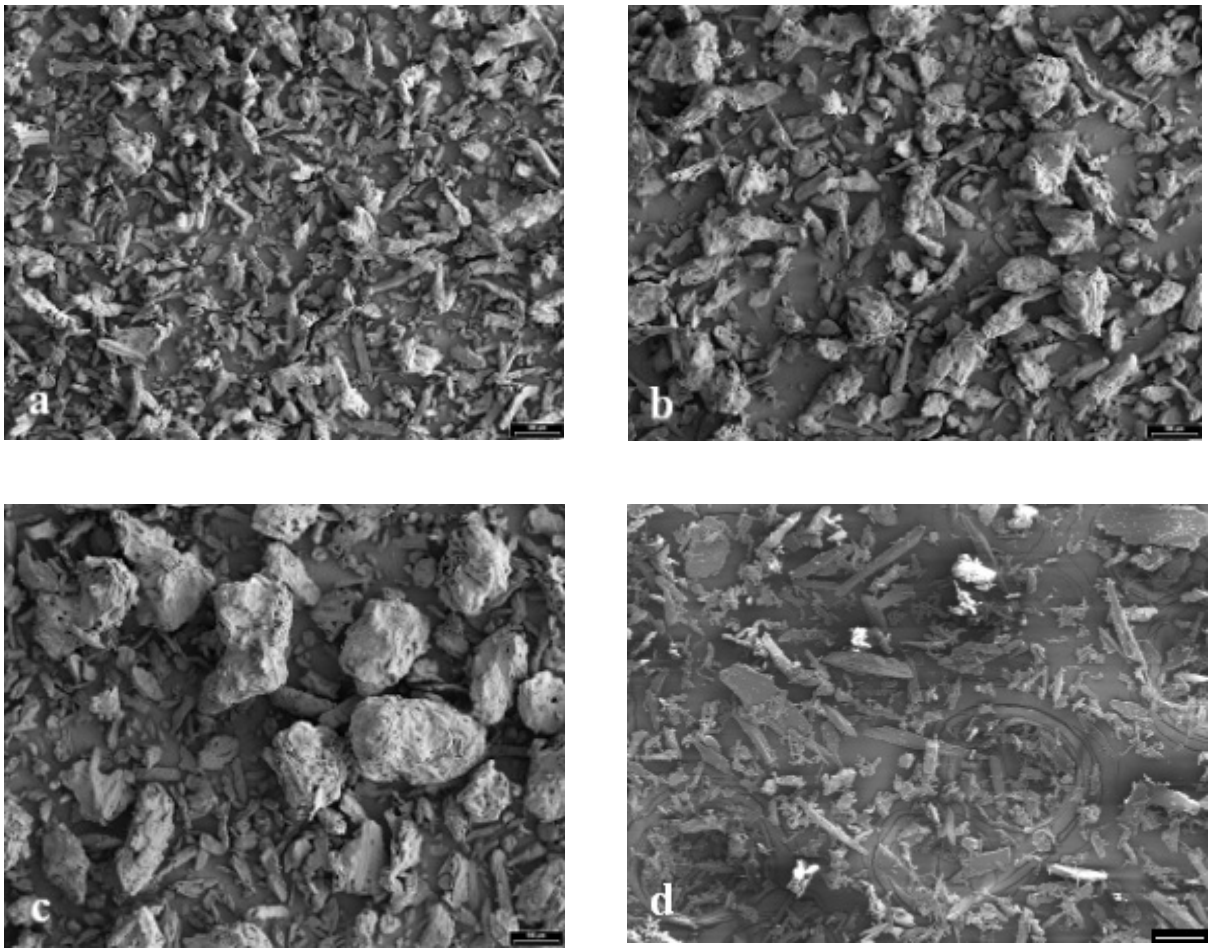


Figure 4a-d SEM images of Avicel® PH101 (a), PH102 (b), PH200 (c) and paracetamol (d) with 100x magnification (bar length 100µm).

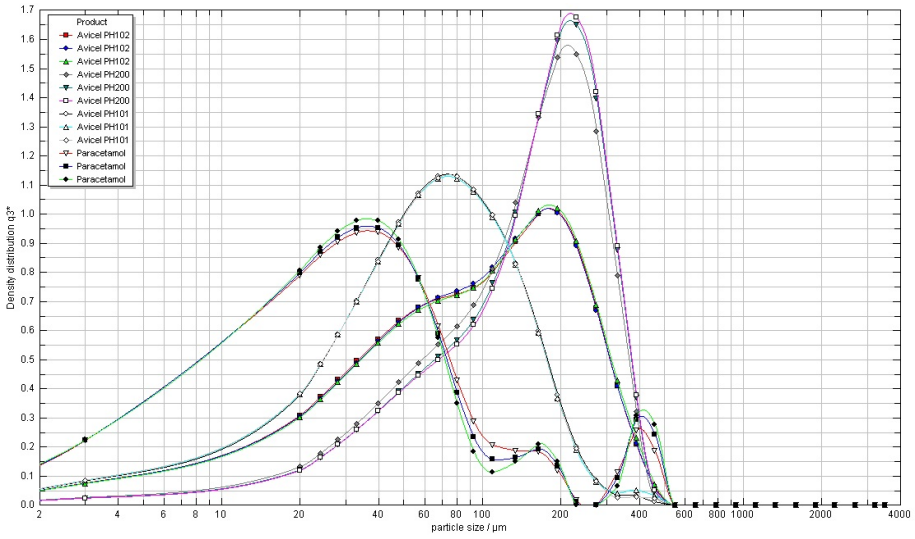


Figure 5 The particle size distribution of paracetamol, Avicel PH101, PH102 and PH200.

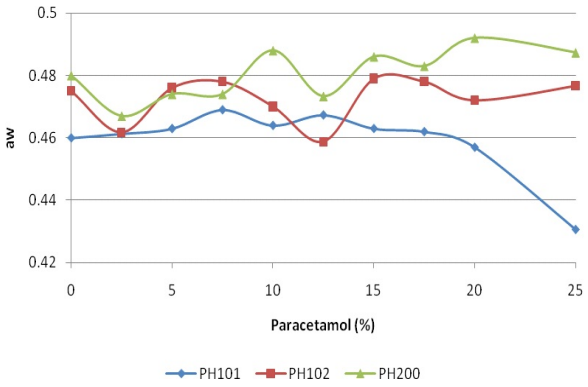


Figure 6 Water activity (a_w) of the samples containing MCC, paracetamol and magnesium stearate as a function of paracetamol concentration.

Table 2 Calculated carrier payloads of binary mixtures containing Avicel® PH101, PH102 or PH200 as carrier and paracetamol as drug

Paracetamol concentration (%)	Carrier payload		
	PH101	PH102	PH200
0.0	0.00	0.00	0.00
2.5	0.02	0.03	0.05
5.0	0.04	0.05	0.09
7.5	0.05	0.08	0.14
10.0	0.07	0.11	0.20
12.5	0.10	0.15	0.25
15.0	0.12	0.18	0.31
17.5	0.14	0.22	0.38
20.0	0.17	0.25	0.44
25.0	0.22	0.34	0.59

The water activity of the samples containing MCC, paracetamol and magnesium stearate is shown in Figure 6. It is unclear why the water activity decreases for the PH101 sample when the amount of paracetamol is at its highest. One possibility is the fact that magnesium stearate does not cover paracetamol particles as efficiently due to more free sites to bind in the PH101 particles as compared to the PH102 and PH200 samples. This fact could expose more of the paracetamol surfaces which have a lower water activity per se.

Particles smaller than 100 μm are usually cohesive and are prone to flowability problems (1). The particle sizes (as measured by d50) of PH102 and PH200 are close to or greater than this while the particle size of PH101 is below 100 μm (Table 1, Figure 4a), which is the main factor explaining its poorer flow rate (Figure 3d-e). Due to its relatively small particle size, PH101 also charges more easily than PH102 or PH200. Moreover, also CP correlates with the flow rate of different MCC grades (Table 2). This is logical as the reason for both the poorest flowability and the smallest CP of PH101 samples is the smaller particle size of PH101 compared to PH102 or PH200.

Effect of lubricant

The effect of lubricant depended on the MCC grade. The flow rate of the binary mixtures containing the PH102 and PH200 grades increased after the addition of MS (P=0.003 for both grades, Figure 3). Magnesium stearate affected both MCCs similarly and a significant difference between the flow rates of lubricated PH102 and PH200 was not observed. The lubrication of the PH102 samples was clearly detectable when the amount of paracetamol exceeded 15%. Similar results indicating the effect of lubricant becoming more pronounced with increasing cohesion have been reported earlier (28). By contrast, MS was not able to improve the flowability of the even more cohesive PH101 samples (Figure 3). This surprising result could be explained by the small particle size of PH101 leading to relatively less MS particles covering the surface of PH101 compared to PH102 or PH200.

It was not possible to determine the distribution of MS on the carrier particles based on the SEM images. The location of MS may be determined by element-TEM (Transmission Electron Microscopy) or energy dispersive x-ray analysis (EDAX) but was not possible in this study. Also, the electrostatic charging of the samples containing MS could be studied to obtain more information on the electrostatic phenomena affecting the flow

behaviour of the samples and the influence of MS on tribocharging.

The repeatability of the flow rate measurements of lubricated samples started to decrease after a few measurements with the relative standard deviations ranging from 21% to 40%. This is likely to arise from the lubricant coating the surface of the funnel of FlowPro. Magnesium stearate adheres to steel surfaces more strongly than to itself or MCC particles (29). The problem could be eliminated by washing the funnel after the measurements. The instrument was able to rank the flowabilities containing the same raw materials with a varying cohesiveness, such as the PH101 and paracetamol series, accurately and reliably. Moreover, it is likely that the two-sloped flow behaviour of PH200 can be eliminated by modifying the funnel. The method is also simple and very fast compared to many indirect methods. Nevertheless, the disadvantages of the method include coating of the funnel when samples containing lubricant are measured, which causes variability in the results. Furthermore, FlowPro may not be the best method for distinguishing between the flowability differences of samples with very similar cohesion, such samples with a 2.5% change in paracetamol concentration. Thus, shear cell experiments might provide a deeper insight on the flow behaviour of formulations with small differences in cohesion as the internal friction of the samples could be determined.

Effect of charging

The PH101 samples produced the highest negative charge followed by the PH102 and PH200 samples (Figure 7). When the paracetamol concentration of PH200 samples exceeded 20%, the charge turned positive. The net charge of PH200 was negligible between concentrations from 10% to 17.5%. All pure materials charged negatively in contact with stainless steel, including paracetamol. Thus, observed positive charging of PH200 with high paracetamol concentration was due to adhesion of paracetamol on the pipe surface. Simultaneously, the coarse MCC PH200 particles did not adhere. Since MCC charges positively in contact with paracetamol, the net charge of powder mixture is drawn to positive direction as the adhesion of paracetamol takes place. Both components will obtain a negative charge in contact with a steel surface, but in particle-particle contacts MCC will be positively charged due to MCC being closer to zero in the triboelectric series of the materials. Opposite charges on particles would increase the cohesion while like charges would reduce it. In this study, the overall charge distribution was moderate and the effect of charging on the flow properties of the mixtures remains yet unclear.

Multivariate analysis

To shed some light on the overall effects of the physical properties of the materials and unlubricated binary mixtures on powder flow, principal component analysis was performed to visualize the interdependencies in the data. The PCA indicated that principal component (PC1) explains approximately 60 % of the variability of data and PC2 about 24 %. The visualisation is made for the two PCs and is shown as a correlation bi-plot with the scores (samples) and the loadings (measurements) and how they are interrelated (Figure 8).

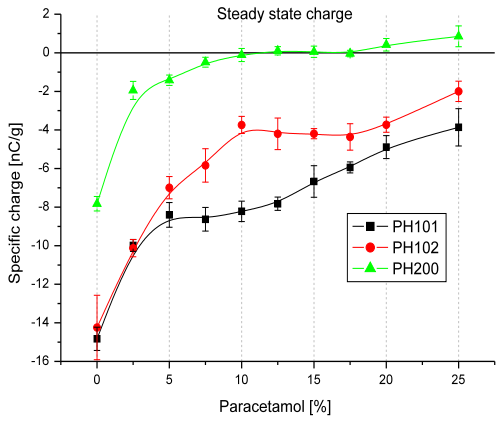


Figure 7 Specific charge of different binary mixtures of MCC and paracetamol as a function of paracetamol concentration.

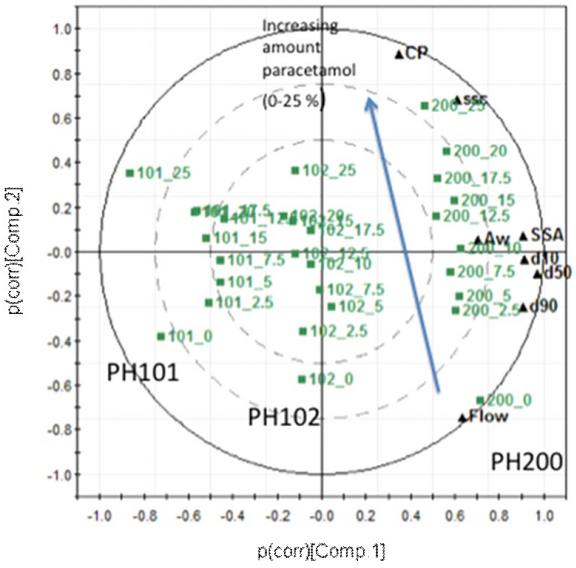


Figure 8. A correlation bi-plot showing how the different MCC mixtures (boxes) are related to the measured physical properties (triangles). The increasing amount of paracetamol is indicated with an arrow. (CP=carrier payload, SSC= steady state charge, a_w= water activity, SSA = Spesific Surface Area). (PC1:60%, PC2: 24%).

The location of a property (e.g. CP) indicates a high value of a property and the closer it is to a sample, generally the higher the correlation to that property. The main information showing the interdependencies of the data are in the first two PCs. In the direction of PC1, the largest variation comes from particle size data (d10, d50 and d90), specific surface area (SSA) and water activity (a_w) values. PC2 shows that the CP and steady state charging (SSC) of samples correlate to powder flow of the binary mixtures. In general it seems as stated above, the powder flow within a sample set (e.g. PH101 and paracetamol) becomes poorer with increasing CP whereas, when MCC grades are compared, higher CP values are linked to better flowability. Moreover, all powders are driven towards a positive charge with increasing drug loading resulting in poorer flow properties.

As indicated before, a partial least squares (PLS) model was created to evaluate how well the physical factors measured predict the powder flow behaviour and which factors play the most important role in this context. The model was created using carrier payload, particle size data (d10, d50 and d90 values), water activity, steady state charge and BET surface area values as observations (X) and powder flow (mg/s) values as responses (Y) from the 30 MCC mixture samples studied. The predictive ability of the model is good with R^2 value of 90% and Q^2 87%. Generally, $Q^2>0.5$ indicates a good predictive model and $Q^2>0.9$ is considered as an excellent model if the difference between R^2 and Q^2 is in the less than 0.2–0.3. It has been shown previously that different flow properties can be predicted in a similar way using particle size information for granular material (30). This study shows that the carrier payload and particle size related information are the most important factor influencing prediction of flowability for the binary powder mixtures (Figure 9). Nevertheless, all other physical properties measured make a contribution to the flow behaviour as well with smallest and inconclusive influence of water activity.

In order to establish the relationship between the properties studied with true behavior of these binary mixtures upon tabletting, further studies are needed. In general the powder flow measurements performed rapidly provide information on the behavior and similarity or dissimilarity of materials.

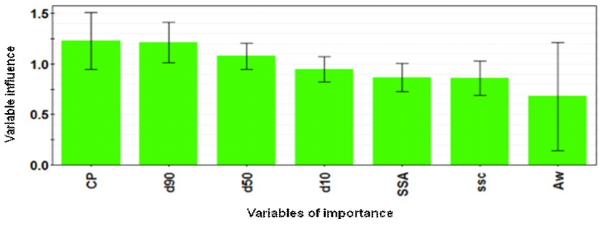


Figure 9 Variables of importance (VIP) plot of the PLS model for prediction of powder flow. Terms with large VIP, larger than 1, are the most relevant for explaining Y (flow).

If the relationships between these flow measurements and e.g. mass variation during tabletting or capsule filling can be established, the methods could provide a fast small scale screening tool for choosing direct compression excipients and optimal drug loading levels to be used in formulations.

CONCLUSIONS

The flowability of the binary mixtures of microcrystalline cellulose and paracetamol decreased when the amount of paracetamol increased. However, as expected, the flow rate depended also on the MCC grade: the samples containing Avicel® PH200 and PH102 had the best flowability while the mixtures of PH101 and paracetamol were the poorest flowing. Magnesium stearate was able to increase the flowability of PH102 and PH200 samples but not the ones containing PH101. The phenomena affecting powder flow of the binary mixtures are complex and thus several aspects such as tribocharging, carrier payload and surface moisture need to be taken into account when assessing powder flow behaviour and choosing suitable excipients for formulations.

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