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A centrifuge technique for the evaluation of the extent of water movement in wet powder masses

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Abstract

A centrifuge method has been applied to the assessment of water retention in pharmaceutical powders. Five drug models and microcrystalline cellulose (MCC) were each mixed with different amounts of water and centrifuged at different speeds. The amount of water retained by the wet mass was evaluated by drying the powders to constant weight. Binary mixtures of each of the five model drugs, MCC and water were also processed in the same way. From the amount of water extracted the moisture retention capacity (*MRC*) was calculated. The MCC retained water more strongly than the different drug models over a wider range of initial water contents. The five drug models, although similar in their chemical structure, were divided into two groups, in terms of their *MRC* values. 4-HBA and propyl gallate recorded higher *MRC* values than methyl, propyl and butyl paraben. For the drug models mixed with MCC, the *MRC* values recorded were similar, though it was still possible to divide the drugs into the two subgroups. A correlation between the *MRC* value recorded for the different systems and the hydrogen bonding solubility component was found. The application of different centrifuge speeds indicated that within the same material there were different mechanisms of water retention. © 1999 Published by Elsevier Science B.V. All rights reserved.

Keywords: Water retention; Centrifuge; Hydrogen bonding

1. Introduction

Formulations used in the preparation of spherical pellets by the process of extrusion formulation contain water levels which are usually higher than those used in the preparation by wet granulation. In the majority of pharmaceutical extrusion formulations, the water can often move faster than the solid phase when subjected to the stress of extrusion. This can give rise to phase separation. The reason why water moves more extensively in one formulation and less in another other is still not known. Water movement can be crucial in some formulations. It can lead however to shark-skinned extrudates (when water moves leaving the extrudates too dry); or can result in extrudates with different water content, which will turn into spheres which vary in size during spheronization. On the spheronizer plate, excessive migration of water to the surface of the pellets can lead to their

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agglomeration. Therefore, it is very important to understand, evaluate and control, where possible, the water movement during the extrusion and spheronization processes.

Several workers have examined water separation during extrusion and have tried to evaluate the extent of water movement in different ways: Fielden et al. (1992), Knight (1993) and Boutell (1995) used a pressure membrane apparatus to measure the movement of liquid through powder beds. The system used by these workers employed compressed nitrogen gas to apply a known pressure to a paste supported on a membrane and measured the amount of water leaving and entering the sample chamber with time as the gas pressure was applied and then removed. This experiment was repeated under different pressures. Increasing and decreasing the pressure allows the evaluation of the 'drying' and 'wetting' of the paste. These studies showed that powder beds of different structures or of different mean particle size demonstrated different levels of water saturation and different extents of inhibition and expression of water. The method provides information on the structure of the bed, allowing estimation of pore size distribution.

Burbidge et al. (1995) examined water migration while consolidating wet ceramic pastes using a membrane filter. Harrison (1982), Baert et al. (1992) and Knight (1993) examined the extent of movement of water during the extrusion process using a ram extruder by evaluation of the water content of the extrudates as a function of emergence from the die. They collected fractions of extrudates and dried them to constant weight and found that in most cases the first extrudates were wetter than the last and that the extrudates were normally wetter than the plug remaining in the barrel. Formulations which spheronised had an even distribution of water whereas those which were subject to agglomeration tended to show significant differences in water levels.

Chen et al. (1997) looked at water migration in carbohydrate pastes by centrifuging the paste and looking at the amount of water lost by the paste during centrifugation and the amount of water the paste was able to retain. The use of centrifugal force to measure the amount of water separated from a sample had been used previously, both in soil science (Ronday, 1997) and in the food industry (Rhee et al., 1981). The advantage of this method over other methods of investigating water movement are: (1) its small scale—an important fact especially when examining expensive or toxic materials; (2) the relatively simplicity and ready availability of the equipment required.

2. Materials and methods

The following five materials of similar chemical structure were chosen as drug models (parentheses denote their number average particle size and their apparent particle density measured using an air compression pycnometer): (1) methyl paraben lot: M20225 (26.6 μm, 1.36 g/cm^3); (2) propyl paraben lot: P7822 (24.8 μm, 1.27 g/cm^3); (3) butyl paraben lot: N433 (44.1 μm, 1.23 g/cm^3); (4) *p*-hydroxy benzoic acid lot: 401251 (27.9 μm, 1.46 g/cm^3) and (5) propyl gallate lot: 4491 (31.7 μm, 1.35 g/cm^3), all manufactured by Nipa laboratories (Pontypridd, Mid Glamorgan, UK).

The excipient used in the formulations was microcrystalline cellulose (MCC) (Avicel PH101, FMC Corporation, Little Island, Cork, Ireland). The MCC average particle size is 50.0 μm and its apparent particle density is 1.54 g/cm^3.

The five different model drugs and microcrystalline cellulose were each mixed with four different water contents. Binary mixtures of microcrystalline cellulose and each of the five model drugs were also prepared in a 5:7 ratio, drug to MCC. This ratio was chosen because most formulations produced pellets when subjected to extrusion/spheronization. Three different water contents were added to each of the binary components.

Specially prepared 25-mm diameter plastic caps were perforated with 1-mm holes (Fig. 1). A filter membrane of 0.2 μm pore-size (Whatman Cyclopore membranes, 25 mm diameter) was placed at the bottom of the cap. A wet mass was produced by mixing the solid and liquid using a pestle and mortar for 5 min. Four caps were filled with 5 g of wet sample and placed inside a specially prepared carrier. The four carriers were

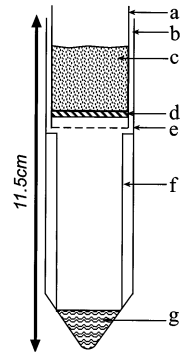

Fig. 1. Schematic diagram of the cap and carrier used: a, cap; b, carrier; c, wet powder; d, membrane filter; e, perforated bottom; f, spacers; g, water collection region.

placed inside a centrifuge (BR401, Denley, Sussex, UK) and centrifuged for 30 min at three different speeds with the corresponding centrifugal force values in brackets: 5500 ($3050 \times g$), 4125 ($1715 \times g$) and 2750 rev./min ($762 \times g$), all at room temperature. After centrifugation, the caps were weighed and oven dried at 50°C (using an oven with fan (Hotbox, Gallenkamp, London, UK) until they reached constant weight (typically for 3 days). Their dry weight was recorded. Using the following equation, the Moisture Retention Capacity (*MRC*) is calculated (Rhee et al., 1981):

$$MRC = \frac{W_{pre}}{W_{post}} \times 100$$

where W_{post} is the weight of moisture before centrifugation (% of dry mass) and W_{pre} is the weight of moisture after centrifugation (% of dry mass).

The centrifuge method gave reproducible *MRC* values with a typical coefficient of variation of not more than 10%.

3. Results

3.1. Single components

From an examination of the single components, different *MRC* values were recorded for the different materials (Fig. 2). The values for MCC were considerably higher than of the other materials. This shows that the MCC is capable of retaining much more water than the other materials, after the application of centrifugal force. From Fig. 2, it is noticeable that the drug models could be divided into two groups. 4-HBA and propyl gallate had greater *MRC* values than the three other drug models (methyl, propyl and butyl paraben), which had similar *MRC* values. These differences between the drug models were obvious at all three centrifuge speeds used. When looking at the rate of change of the *MRC* values with initial water content, MCC had the lowest value from the six materials examined, hence showed

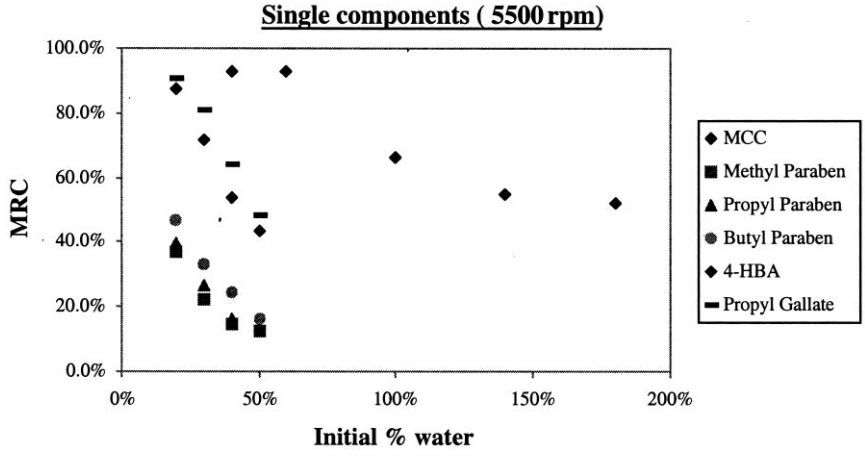

Fig. 2. Results of the *MRC* values for the different single components after centrifuging at 5500 rev./min

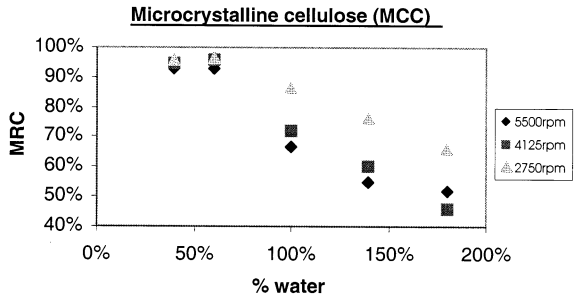

Fig. 3. *MRC* values recorded at different speeds of centrifugation for MCC.

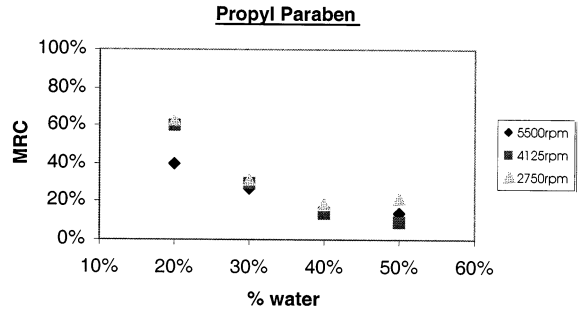

Fig. 5. *MRC* values recorded at different speeds of centrifugation for propyl gallate.

the lowest sensitivity of *MRC* to the initial water content in the formulation.

The influence of centrifuge speed on the *MRC* value is illustrated for the different materials in Figs. 3–8. When working with pastes, it is clear that an increase in the centrifugation speed decreases the *MRC* value. This indicates that because more pressure is applied to the wet mass, more water is extracted from the mass, suggesting that the permeability of the wet mass is a weak function of stress.

The influence of the centrifuge speed on the *MRC* values for MCC, 4-HBA and propyl gallate (Figs. 3–5) with the formulations with low water content, is minimal for *MRC* values, which are above 90%. With an increase in water content in all the formulations (Figs. 3–8), the increase in centrifuge speed decreases the *MRC* value. The suggested relationship between the *MRC* values and the initial water content for various centrifuge speeds is illustrated in Fig. 9. At low water content in the wet mass, the retention value is high and is not dependent on the speed because all the water is sufficiently bound to the solid and the three speeds used cannot remove any water. From a certain water content (point **a** in Fig. 9) the centrifugal force is able to release some water from the wet mass, the amount being dependent on the force applied. The amount of water at this point is the amount of water which can be tightly bound, by that particular mixture so that any additional water present will be less tightly bound. The faster the centrifuge spins, more water is extracted from the wet mass. At a certain water level, which differs for each material, a point where the majority of added water is not bound to the solids and is readily available for extraction is reached. At this point, a certain amount of water is loose enough to be extracted by any centrifuge speed used (point **b** on Fig. 9). Point **a** for MCC is between 40 and 60% of water and for 4-HBA and propyl gallate is at around 20%. For

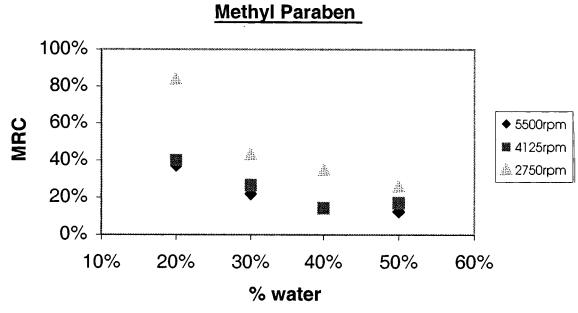

Fig. 4. *MRC* values recorded at different speeds of centrifugation for 4-HBA.

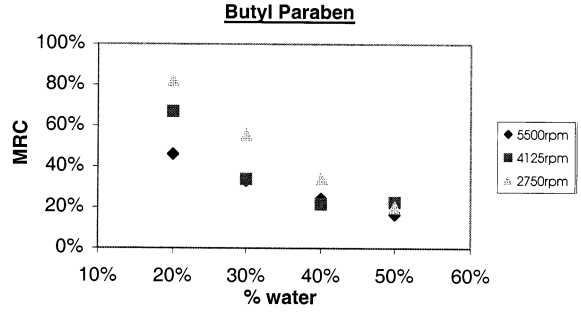

Fig. 6. *MRC* values recorded at different speeds of centrifugation for methyl paraben.

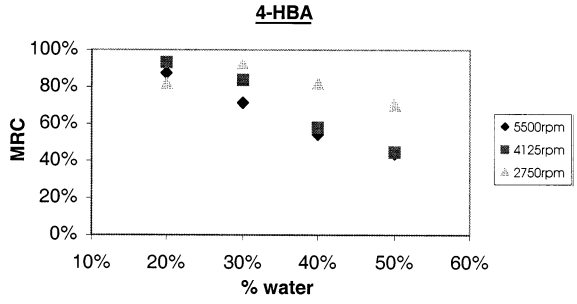

Fig. 7. *MRC* values recorded at different speeds of centrifugation for propyl paraben.

the three parabens, however, point **a** appears to occur at a water content lower than 20%, the lowest water content used in this work. With these three materials, point **b** is observed and is around 50% of water. Point **b** is not reached with MCC, 4-HBA and propyl gallate because it appears to exceed the maximum water content used in this work. Higher water contents were not used because adding more water to the powders changes the consistency of the mixtures, so that they can no longer be defined as wet masses and looks more like a milky liquid. Under these conditions, the liquid flows under the filter membrane and through the perforated bottom and hence did not give reliable results.

3.2. Binary components

When MCC was added to the model drugs, although at a lower proportion than the model drug, the components demonstrated similar behaviour, in term of *MRC* values (Fig. 10). 4-HBA and propyl gallate mixtures still had the largest *MRC* values, though the differences in *MRC* values between them and the other three model drugs were much smaller in magnitude when compared to the differences reported for the single components (Figs. 3–8). The addition of MCC to the components also resulted in the formation of a uniform rate of change of *MRC* with initial water content. Similar observations were seen in results of all three-centrifuge speeds.

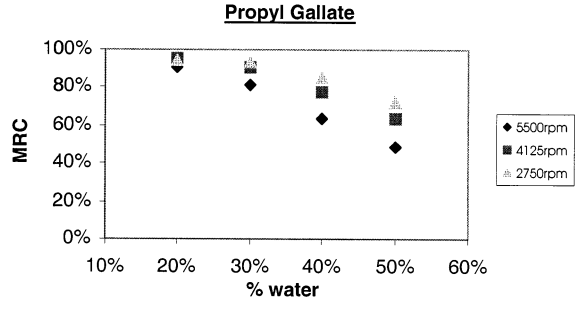

Fig. 8. *MRC* values recorded at different speeds of centrifugation for butyl paraben.

When examining the influence of centrifuge speed on the *MRC* values recorded for each of the binary formulation throughout all the water ranges, a decrease in *MRC* value was found with increase of the centrifuge speed.

To establish possible connections between the *MRC* values calculated and the actual water movement occurring during extrusion, results from a previous experiment were compared where the same five drug models were analysed for the water movement which occurs during extrusion by drying fractions of extrudates to constant weight (Tomer and Newton, 1999). In these experiments, both propyl gallate and 4-HBA formulations recorded a higher extent of water movement down the barrel, calculated from the difference between the initial water content in the formulation and the amount of water found in the first portions of extrudates coming out of the die (depending on the initial water content, the value calculated for propyl gallate and 4-HBA was six and four times greater, respectively, compared to the same value for the other drug models). Furthermore, those two drug models recorded the highest steady-state forces during extrusion at a set ram speed, compared to the other three drug models. One might anticipate that higher water retention, as measured by the centrifuge system, leads to a decrease in water movement during extrusion. In fact, the opposite effect is found. One would assume that if a material has the ability to hold its water tightly, then less water movement under the forces of extrusion would occur. Hence, this finding indicates that by retaining more water, the material can carry more water through the die inside the extrudate, without water migration. This explanation is strengthened when taking into consideration the higher extru-

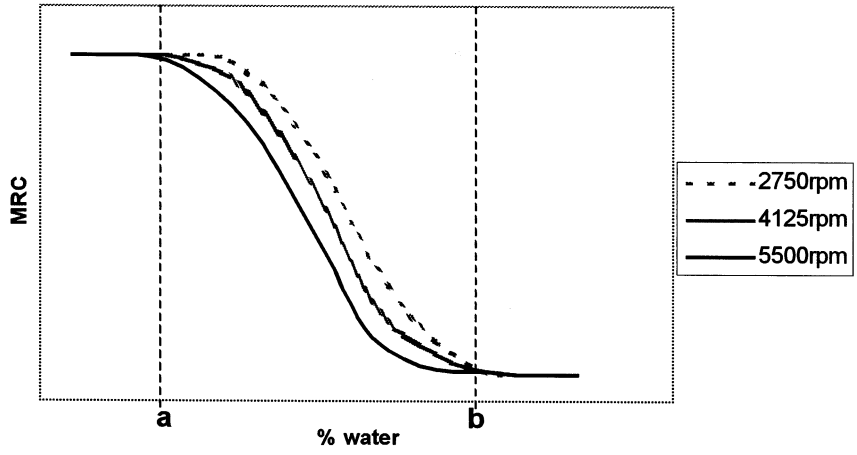

Fig. 9. Suggested schematic relationship between the *MRC* values and the initial water content at different centrifuge speeds.

sion forces recorded. The explanation for this relation is similar to the previous suggestions, when a material has the ability to retain water strongly, it prevents water from leaving the material and migrating to the die wall. Therefore, there is no lubricating layer of water at the wall of the die which increases the extrusion force.

When comparing the water retention values measured by the centrifuge system and the ability of the different materials to form hydrogen bonds (Table 1), a force which takes part in water retention, the same ranking between the different subgroups is noted. Hence, the δ_H values of both propyl gallate and 4-HBA were higher than the three other drug models.

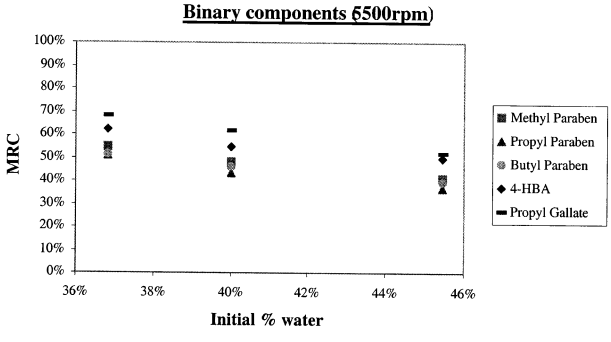

Fig. 10. *MRC* values recorded for the binary components centrifuged at 5500 rev./min (model drug/MCC, 7:5 w/w).

4. Discussion

High *MRC* values were recorded for MCC, in comparison to the other materials tested. In addition, MCC showed the smallest variation in *MRC* values with change of amount of initial water. When mixing MCC with drug models, which separately showed different water retention values, the differences in the *MRC* values of the binary components were reduced extensively, although the MCC is the lower proportion material in the formulation, in terms of weight fraction. This implies that although MCC is not the major ingredient in the formulation, its influence on controlling the water movement is larger than of the other ingredient. The above observations could be the reason that MCC is such a valuable and essential material in the extrusion/spheronisation process, and is in accordance to the MCC 'sponge model' theory (Fielden et al., 1988).

The centrifugation technique was sensitive enough to measure different values between materials of similar chemical structure and properties. 4-HBA and propyl gallate had larger values in comparison to the other three drug models, both on their own, mixed with water and in a combination with MCC.

From examination of the *MRC* values of the different speeds throughout the whole water range, it is possible to measure the amount of two phases of bound water (Fig. 9), the first of which

Table 1
Physiochemical properties of the drug models[a]

Material	M_G (g mol^{-1})	V_M (cm^3 mol^{-1})	δ_D (MPa$^{1/2}$)	δ_P (MPa$^{1/2}$)	δ_H (MPa$^{1/2}$)	δ (MPa$^{1/2}$)	Water solubility[d]
4-Hydroxy benzoic acid[b]	138.12	95.26	17.18	12.67	17.48	27.60	1 in 125
Methyl paraben[b]	152.12	108.66	17.40	11.11	16.37	26.35	1 in 400
Propyl paraben[b]	180.20	140.78	17.30	8.58	14.38	24.07	1 in 2000
Butyl paraben[b]	194.23	155.38	17.42	7.77	13.69	23.48	1 in 6500
Propyl gallate[c]	212.20	155.57	13.54	10.93	21.02	27.29	1 in 286

[a] M_G, molecular weight; V_M, molar volume; δ_D, dispersion solubility component; δ_P, polar dispersion solubility component; δ_H, hydrogen bonding solubility component; δ, total solubility parameter and solubility in water.
[b] Data taken from Newton et al. (1993).
[c] Values of solubility parameters were calculated from the approach by Hansen (1967).
[d] Data taken from Wade and Weller (1994).

is tightly bound and the second loosely bound, though, in the materials used in this work, the whole range of water content could not be used, which then only gives information on one of the water phases.

When examining previous results from the extrudate fractions experiments (Tomer and Newton, 1999), a relationship was found between the extent of water movement during extrusion and moisture retention capacity. From this relationship it emerges that when a material has a stronger retention capacity, more water moves during the extrusion process. This observation can be explained by the fact that when a material retains its water more strongly then it will hold more water within its structure, which results in wetter extrudates. The steady state extrusion forces that were recorded for those materials (Tomer and Newton, 1999) showed that higher extrusion force resulted in higher water movement. Hence, stronger water retention resulted in higher extrusion forces. Benbow and Bridgwater (1993) reported that in extrusion, liquid moves towards the die walls to form a thin liquid layer there, so that shearing occurs only on a layer of liquid. This assumption can explain the relationship between extrusion force and *MRC* values, because when the material retains water more strongly, less water can migrate to the die walls, hence, less lubrication exists.

The hydrogen bonding solubility component values (δ_H) fitted to a linear relationship with the *MRC* values for the binary components for all three centrifuge speeds (5500, 4125 and 2750 rev./min), where *R* (correlation coefficient) has values of 0.95, 0.93 and 0.84 respectively and are all significant at the 1% level. No comparable correlations were found between the *MRC* values and the solubility in water, or to any other solubility components, such as: the dispersion component (δ_D), the polar component (δ_p) and the total solubility parameter (δ). This suggests that hydrogen bonding plays the most significant role in retention of water in these systems.

5. Conclusions

A method of centrifugation for the measurement of water retention capacity which has been used for the investigation of water migration in different kinds of systems, such as soil and α-alumina, has been applied here to pharmaceutical systems used to produce pellets by extrusion/spheronization. Such systems have often been shown to allow water migration during processing.

The centrifugation method produced different moisture retention values (*MRC*) for the different materials tested. For the model drugs, the value was related to the hydrogen bonding component of solubility.

Microcrystalline cellulose had an extremely high moisture retention capacity over a range of

initial water levels. When mixed with model drugs, the *MRC* values of the paste were dominated by the presence of MCC, but could still be separated into two groups: 4-HBA and propyl gallate, and methyl, propyl and butyl paraben.

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