ELSEVIER

International Journal of Pharmaceutics 182 (1999) 71–77

international journal of pharmaceutics

Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions

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Received 8 October 1998; received in revised form 15 January 1999; accepted 8 February 1999

Abstract

Water is normally the liquid of choice in extrusion/spheronisation systems. Its behaviour during the process is crucial to its success. In most extrusion formulations water moves under the pressures involved. It is important to understand how to control and limit water movement, and to understand its consequences. Five drug models were mixed with microcrystalline cellulose and with three different ratios of water and extruded at two different speeds using a ram extruder. Whilst extruding, the extrudates were collected in small fractions and dried to constant weight. Different parameters were calculated to quantify the extent of water movement that occurred. The same formulations were also extruded and than spheronised to pellets, for which size and shape factor were measured. The correlation between water level and extrusion force at the same given time was calculated. It was found that at the faster speed and in the wettest formulation there was less water movement. A significant correlation was found between extrusion force and water going through the die. The extrusion/spheronisation technique was found to be tolerant to some extent of water movement during the extrusion process. Nevertheless, excessive water movement is not appropriate.

Keywords: Extrusion; Water movement

1. Introduction

Water is usually the liquid of choice in an extrusion/spheronisation formulation, and it is known to play a major role in the success of the process. The function of water is two-fold: (1) to increase the plasticity of the mixture; and (2) to act as a lubricant at the wall of the die during the process. In the majority of extrusion formulations water movement occurs. Nevertheless, understanding of the reason why water moves more extensively in one formulation and less in another is lacking. The existence of water movement during extrusion is essential for the process. This

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0378-5173/99/$ - see front matter
PII: S0378-5173(99)00061-7

allows water to soften the mass for easier extrusion and for water to migrate to the die walls to act as a lubricant. Benbow and Bridgwater (1993) reported that in the die liquid moves towards the die walls forming a thin liquid layer and that shearing occurs only on this layer of liquid. Nevertheless, an extensive water movement can be bad for some formulations, hence it can lead to shark-skinned extrudates (when water moves, leaving the extrudates too dry), or results in extrudates with different water content which turn into spheres that vary in size on the spheronizer plate. Therefore, it is very important to understand, evaluate and control, if possible, water movement during extrusion.

Many workers noted this phenomenon occurring 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. They applied pressure to a wet powder mass supported on a membrane using nitrogen gas and measured the amount of water leaving the sample chamber with time. This experiment was repeated under different pressures, increasing and decreasing pressures to evaluate the 'drying' and 'wetting' of the mass.

Burbidge et al. (1995) examined the water migration while consolidating wet ceramic pastes using a membrane filter instead of a die. Chen et al. (1997) looked at water migration in carbohydrate pastes by centrifuging the paste and looking at the amount of water the paste lost 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 mechanics and in the food industry (Rhee et al., 1981; Ronday, 1997).

Harrison (1982), Baert et al. (1992) and Knight (1993) examined the extent of water movement during the extrusion process using a ram extruder by evaluating the water content of the extrudates as a function of time. They collected fractions of extrudates and dried them to constant weight and found that in most cases the first extrudates are wetter than the last ones and that the extrudates are normally wetter than the plug remaining in the barrel. While this system is not generally used in the manufacturing process, the ram extruder does offer a potential method of evaluating the sensitivity of a formulation to water mobility.

2. Materials and methods

The five following materials of similar chemical structure were chosen as drug models: (1) methyl paraben (MePara), lot M20225; (2) propyl paraben (ProPara), lot P7822; (3) butyl paraben (BuPara), lot N433; (4) *p*-hydroxybenzoic acid (4-HBA), lot 401251; (5) propyl gallate (ProGal), lot 4491; all manufactured by Nipa Laboratories (Pontypridd, Mid Glamorgan, UK). The particle size of the model drugs was determined by image analysis (Seescan Solitaire 512; Seescan, Cambridge, UK). The value as a number average of Ferret diameter (an average of 32 values) was determined from 512 particles from each material. These materials were chosen because, while being chemically similar, they also have similar various physical properties, and processing them may assist in establishing relationships between water movement and chemical structure.

Binary mixes of microcrystalline cellulose (Avicel PH-101, lot 6521; FMC Corporation, Cork, Ireland) and each of the model drugs in a 5:7 ratio, respectively, were mixed using a planetary mixer (Hobart, London, UK) for 5 min. To each type of binary mix three different water contents were added to make wet masses of 36.84% (formulation H), 40.00% (formulation K) and 45.45% (formulation Q) water and mixed for an additional 10 min. The wet components were fed into a stainless steel barrel (2 cm internal diameter and approximately 20 cm in length) of an ACER2000 extruder (Polymer Laboratories, Belton Park, Loughborough, UK) fitted with a die 5 mm in length, 1 mm in diameter and die entry angle of 60°. The pressure is measured by a pressure transducer fitted at the bottom of the barrel next to the die.

Each formulation was extruded once at 20 mm/min and once at 200 mm/min. By changing preweighed, numbered beakers below the die, extrudate fractions were collected. At the slow

piston speed (20 mm/min) the beakers were changed every 20 s. At the fast piston speed (200 mm/min) the beakers were placed on a specially made wooden tray and were changed every 3 s. Because some of the extrusion procedures were stopped before completion when reaching the 20-kN load safety limit, the number of fractions collected varied between the different formulations. The beakers were than weighed and placed into an oven with fan (Hotbox; Gallenkamp, London, UK) to dry to constant weight at 50°C (typically for 3 days). After drying the beakers were weighed again. To check that the drug models are stable during drying, dry samples of known weight were put in the oven at 50°C for 3 days, after which they were weighed again. No significant weight change was found. Hence, it is assumed that all weight loss is due to evaporation of water.

A computer program was used to analyse the force versus time data files produced by the extruder's computer system, which divided the extrusion profile into fractions, corresponding to the fractions collected, and calculated the area under the curve (AUC) for each curve section. Using Pearson coefficient correlation analysis the correlation between the water content in the extrudates and the pressures recorded whilst extruding the fraction (represented by the AUC value) was examined and its significant was calculated.

To quantify the extent of water movement measured by this method the following parameters were calculated:

1. Cov: coefficient of variation. This parameter describes the fluctuations in water content in the different fractions.
2. Av − Init: the initial water content (%) subtracted from the average water contents in the different fractions. This parameter measures the 'water lost' during the process through the die.
3. Av4 − Av4: the difference between the water average of the first four fractions and the average of the last four fractions. This parameter represents the extent of the water gradient created because of water movement along the barrel.
4. Av4 − Init: the initial water content (%) subtracted from the average water content of the four first extrusion fractions. This parameter describes the extent of the initial water movement, i.e. the extent of water moved down the barrel while compression occurred and during the first 24–40 mm of piston displacement.

When extrudates of all the above materials were processed by spheronisation using a standard procedure, in the case of 200 mm/min, good and round spheres, as assessed by the method of Podczeck and Newton (1994), were produced from all materials except *p*-hydroxybenzoic acid. In the case of 20 mm/min, all materials did not spheronise.

3. Results

From each material, all three formulations at the two different speeds were processed, with the exception of 4-HBA. The 4-HBA was unextrudable at the slower speed (20 mm/min). When trying to extrude this material at this extrusion speed, the extrusion force exceeded the 20-kN limit before reaching the steady-state force. This could be because of excessive water movement occurring prior to extrusion, as water drops were seen to emerge from of the die during the compression stage.

In all formulations and speeds, a decrease of water content in the extrudate fractions with time was observed. Hence, the first extrudate fractions are usually wetter and the last extrudate fractions are normally drier than the original water content in the formulation. This observation was previously reported by Harrison (1982), Baert et al. (1992) and Knight (1993) for a range of systems.

When comparing the different water distribution levels in each of the materials, a different water distribution behaviour between the two extrusion speeds can be noted. It is clear that the extrudates from the faster speed are much more uniform in their water contents. Inspection of the extrudates produced by the slower extrusion speed showed a gradient of water contents, whereas in the case of the faster speed this gradient was either smaller in magnitude or did not exist at all. The typical differences in water distribution be-

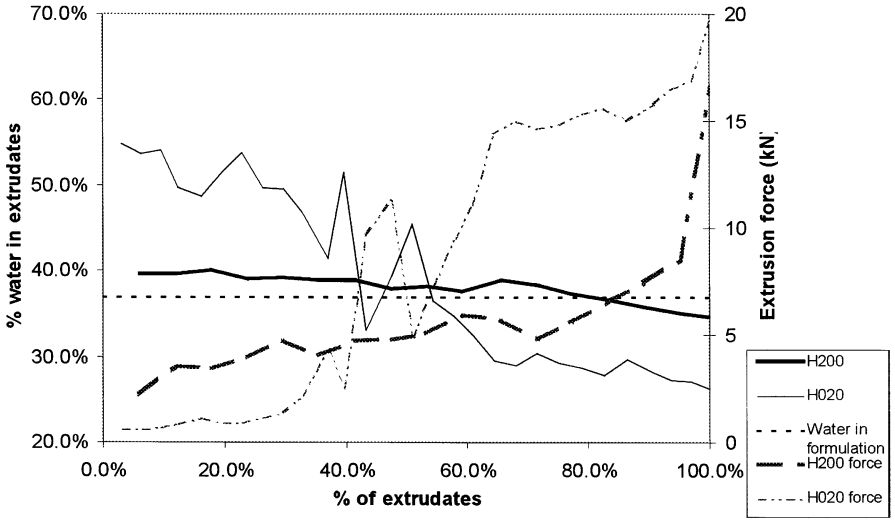

Fig. 1. Percentage water in propyl paraben extrudate fractions collected as a function of the % of extrudate collected, demonstrating the typical water distribution differences between the two extrusion speeds and the corresponding extrusion forces recorded. H200, water found in extrudates from formulation H (36.84% water) extruded at 200 mm/min; H020, as before, but extruded at 20 mm/min, water in formulation is the initial water content added to the formulation; H200 force, the extrusion force recorded when extruding formulation H at 200 mm/min; H020 force, as before, but extruded at 20 mm/min.

tween the two speeds throughout the barrel are demonstrated in Fig. 1. When examining the extrusion force profiles, it is possible to see that at the fast speed both water distribution and force fluctuation are minimised when compared to the slower speed. When looking at the different parameters calculated to quantify the extent of water movement (Table 1), larger values normally are listed for the slower speed than for the faster, implying also that greater water movement occurs. This phenomenon can be explained by the fact that, when extruding at a slower extrusion speed, more time is available for the water to find a path of least resistance through the voids between the particles. This difference in the extent of the water gradient between the two extrusion speeds is minimised in the wettest formulation (formulation Q), where the moisture contents from the two extrusion speeds follow very similar patterns.

That the increase in water content in the formulation leads to a decrease in the extent of water variation throughout the barrel can be easily detected by examining the values in the Table 1. A decrease in those values is seen with increasing water levels in the formulations in both extrusion speeds.

The results of the Pearson coefficient correlation between the extrusion force and the water going through the die (represented by the water found in a specific extrudate fraction) showed, in most cases, a highly significant negative correlation (Table 2). This means, as expected, that when the wet mass going through the die is wetter there is less force needed to push it through the die, because the wet mass inside the die is softer and there is more water to lubricate the flow through the die.

From the results it is clear that, in the wettest formulation (Q) when extruded at the fastest speed (200 mm/min), all three parabens (methyl, propyl and butyl) did not show significant correlation between water content and extrusion force, neither did the wettest formulation of methyl paraben when extruded in the slowest speed. This can be due to the lack of water gradient developing throughout the barrel, resulting in a very soft mass for which the extrusion force needed is not related to the relatively constant water content. At the slower speed, some water movement is ini-

Table 1
Results of different water movement parameters calculated for the different formulations[a]

Water movement variable[b]	Model drug[c]	Extrusion speed 200 mm/min			Extrusion speed 20 mm/min		
		Water content			Water content		
		36.84%	40.00%	45.45%	36.84%	40.00%	45.45%
Cov	4-HBA	9.0	8.1	2.6			
	MePara	5.4	5.1	1.1	6.1	13.2	3.4
	ProPara	4.3	2.6	1.5	26.8	16.8	5.4
	BuPara	9.0	2.4	5.3	36.2	21.5	5.9
	ProGal	7.2	5.5	1.5	16.1	15.9	6.3
Av−Init	4-HBA	8.2	3.2	1.3			
	MePara	0.4	0.0	0.2	7.9	0.3	0.2
	ProPara	2.1	0.8	0.3	2.5	0.7	0.3
	BuPara	4.4	0.7	−1.1	1.1	0.3	−0.1
	ProGal	2.7	1.5	0.6	13.6	10.6	2.4
Av4−Av4	4-HBA	8.0	7.5	2.4			
	MePara	4.4	4.6	0.0	0.6	9.9	−0.6
	ProPara	4.1	1.7	−0.4	25.9	13.1	5.1
	BuPara	8.3	2.3	0.4	29.7	17.6	4.0
	ProGal	7.4	5.9	1.1	20.2	22.2	6.1
Av4−Init	4-HBA	11.2	6.5	2.4			
	MePara	1.2	1.3	0.1	8.0	4.3	−0.7
	ProPara	2.8	1.1	−0.1	16.2	6.7	2.1
	BuPara	5.7	1.9	−0.6	19.6	9.9	0.2
	ProGal	5.1	3.9	1.1	22.8	19.5	4.0

[a] All values are expressed as percentage.
[b] See text for explanation.
[c] See text for full names.

tiated, which results in a change in the extrusion force.

4. Discussion

In all formulations and at both the two extrusion speeds, water movement occurred. This resulted in the first extrudates emerging from the die being wetter than the initial moisture content. With time, the water content in the extrudates declines until the last extrudates are normally drier than the original water content. This happens in most pharmaceutical formulations because water finds the path of least resistance, moving down the barrel faster than the solids (Harrison, 1982; Baert et al., 1992; Knight 1993). The water distribution throughout the barrel at the faster speed is much more uniform than at the slower speed, a trend previously reported by Knight (1993). This happens because, when extruding faster, the water has less time to move efficiently down the barrel. The decrease in water movement leads to a more uniform extrusion profile. When the water content within the formulation was increased, it was seen that the gradient of water developing throughout the barrel decreased up to a point where the differences in water movement when extruding at different speeds were no longer detectable. Jerwanska et al. (1995) reported that an increase in water content facilitates the extrusion process by reducing particle–particle interactions. Hence, the wetter paste becomes softer and less force is needed for extrusion. This decrease in extrusion force reduces the pressure which induces water separation.

A negative correlation between the water content in the extrudates and the force needed to

Table 2
Pearson coefficient correlation results between water in an extrudates fraction and the force needed to extrude it[a]

	H200	K200	Q200	H020	K020	Q020
MePara	−0.72[b]	−0.85[b]	−0.03[d]	−0.40[d]	−0.90[b]	−0.16[d]
ProPara	−0.84[b]	−0.85[b]	−0.02[d]	−0.97[b]	−0.91[b]	−0.72[b]
BuPara	−0.80[b]	−0.66[b]	0.02[d]	−0.93[b]	−0.97[b]	−0.8[b]
4-HBA	−0.92[b]	−0.77[b]	−0.82[b]			
ProGal	−0.98[b]	−0.90[b]	−0. 48[c]	−0.80[b]	−0.84[b]	−0.62[b]

[a] The column heads consist of the formulation designation followed by three digits for the extrusion speed used.
[b] Significant at the 0.01 level.
[c] Significant at the 0.05 level.
[d] Not significant.

extrude them was found. The correlation values calculated by Spearman's coefficient correlation analysis were found to be significant, except for the three parabens when extruding the wettest formulation at the faster speed. This is because no water movement occurs, and hence the water content in the extrudates does not influence the extrusion force recorded.

The finding of a direct correlation between water movement and the extrusion force emphasises another important reason for controlling water movement, which is to ensure a steady extrusion force. This also emphasises the need to have a uniform distribution of water in the wet mass prior to extrusion; otherwise, an uneven water distribution will cause a non-steady extrusion profile which will encourage more water separation and further loss in quality of the extrudate.

When extrudates produced with a range of water contents at 200 mm/min were spheronised using standard conditions, spheres were produced which had a narrow size range and were round, except for those containing *p*-hydroxybenzoic acid. This material had the greatest water movement. None of the extrudates produced at 20 mm/min piston speed produced satisfactory pellets. In the case of the slow extrusion speed, water separation was considerable. Hence it appears that, while the process will tolerate a degree of water mobility, formulations which allow too much water movement can lead to problems. These experiments were conducted in dies with length-to-radius ratio of 10 and constant ram speed. The extent of water movement would be maximised and would be potentially greater than in screen extrudates, often used in extrusion/spheronisation, where the die length-to-radius ratio seldom exceeds 2, and where the application of force is intermittent. Thus, water movement could be reduced and extrusion formulations which spheronise after a degree of water movement in the current system should readily extrude and spheronise when processed using a screen extruder. This assumes, however, that water movement is the only factor involved. Unfortunately, this is not the case and extrudates from a screen extruder will not have the same consistency as those produced by a long die. Nevertheless, water movement experiments carried out on formulations could provide valuable information about their properties whatever the method of extrusion and provide a basic screening procedure for formulation. Those with excessive water movement will probably not function well.

Monitoring of the formulation could lead to the possibility of definition of what level of water movement is excessive.

5. Conclusion

The technique of assessing water movement in mixtures of drug and excipients by measuring variation of the water content in extrudates allows the screening of formulations for their suitability for use in the process of extrusion/spheronisation. Therefore, the extrusion/spheronisation technique

was found to be tolerant to some extent of water movement during the extrusion process. Excess water movement is not appropriate.

Acknowledgements

G.T. would like to thank the Overseas Research Students (ORS) scholarship scheme and the Leo Baeck scholarship for their support.

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