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# The preparation of pellets containing non-ionic surfactants by extrusion/spheronization

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ABSTRACT

The aim of the study was to investigate the possibility of incorporating non-ionic surfactants into pellets produced from microcrystalline cellulose by the process of extrusion/spheronization and the properties of the pellets. A hydrophilic surfactant, polysorbate 60 (PS 60), and two hydrophobic surfactants, sorbitan monostearate (S 60) and sorbitan monooleate (S 80), were included in the water used to form the pellets in concentrations ranging from 5 to 95%. The presence of the surfactants influenced the type of the extrusion profile and improved the ability to provide round pellets, and the addition of the surfactants changed the range of liquid levels required to prepare the pellets. At a low level, i.e., 5%, all the surfactants increased the range of water contents possible, compared to the use of water alone. At high surfactant levels, the level of liquid, which could be used, became restricted. The median size of the pellets was dependent on the type of surfactant and the concentration included in the formulation. The range of sizes produced was generally quite narrow and there were many systems with more than 90% of the pellets in the modal fraction. The highest concentration of the surfactant in water that can be used to form pellets ranged from 50% for S 60, to 80% for S 80 and 95% for PS 60. The maximum amount of the surfactant, which could be incorporated into the final pellet, however, was found to be approximately 22.5% for both the hydrophobic surfactants and 32.5% for the hydrophilic surfactant.



## 1. Introduction

The problems of formulating drugs which have low aqueous solubility is still of concern to the pharmaceutical industry, as emphasised in the preface to a recent issue of the journal 'Advanced Drug Delivery Reviews', which considered the problem of measuring and improving drug solubility (Dressman and Reppas, 2007). For drugs intended to be delivered by the oral route, the method of enhancing the solubility by the use of surfactants and self-emulsifying systems offers one approach. A problem, however, with the use of either of these systems as aids to dissolving water insoluble drugs is, that for oral use they require the presentation as soft gelatin or liquid-filled hard gelatin capsules to avoid their unpleasant taste. While this is possible (Rowley, 2004; Podczeck, 2004), dry unit dose preparations are often preferred. Newton et al. (2001) have shown that it is possible to prepare pellets by extrusion/spheronization, which contained appreciable quantities of self-emulsifying systems. In a later study by Newton et al. (2007) the individual components of these systems, i.e., the non-ionic surfactant polysorbate 80 (PS 80) and a mixture of mono- and di-glycerides were also shown to form pellets. A further advantage of this type of preparation was described in a recent publication (Serratoni et al., 2007). Here it was demonstrated that it was possible to provide a control of the *in vitro*-drug release profile from pellets, by the application of conventional film coating techniques to the pellets, which contained a model drug dissolved in a self-emulsifying system. Such an approach could be used with pellets containing surfactant/drug systems to provide further formulation options for the preparation of solid dosage forms, especially for drugs with low aqueous solubility.

Except for the study by Newton et al. (2007), there is limited information on the inclusion of appreciable quantities of surfactants in pellet formulations. Vervaet et al. (1994) reported that up to 21% (w/w) of the non-ionic surfactant polyoxyl 40 hydrogenated castor oil (Cremophor RH40) could be incorporated into pellets before the pellets became too soft to be handled. They found that the addition of the surfactant increased the *in vitro*-dissolution of the model drug – hydrochlorothiazide, which had been solubilised in the surfactant – from the pellets. At the other end of the scale, low concentrations (0.01 and 0.001%) of the non-ionic surfactant Pluronic PF 68 and the anionic surfactant sodium laurylsulphate (0.1%) influenced the movement of the liquid in the wet mass during

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the extrusion process but did not prevent the formation of satisfactory pellets made from microcrystalline cellulose (Avicel PH101) alone and when mixed with different ratios of barium sulphate (Boutell et al., 2002).

In their review "Microemulsions as carriers for drugs and nutraceuticals", Spernath and Aserin (2006) concluded that "the selection of the microemulsion components for the formulation is a key factor in the enhancement of the bioavailability of active molecules." Indeed Kang et al. (2004), as part of their study of the development of a self-emulsifying drug delivery system, had reported considerable differences in the solubility of the drug simvastatin in a range of surfactants. Thus, if pellet formulations containing drugs dissolved in surfactants are to be developed, it is important to know how other surfactants perform. To this end an additional hydrophilic surfactant (Tween 60) and two hydrophobic surfactants (Span 60 and Span 80) will be tested.

## 2. Materials and methods

### 2.1. Materials

The basic pellet forming material, microcrystalline cellulose US/NF grade was Avicel PH101 (MCC, FMC International, Little Island, Cork, Ireland). Polysorbate 60 (Tween 60) (PS 60), sorbitan monostearate (Span 60) (S 60) and sorbitan monooleate (Span 80) (S 80) were all of US/NF grade and were supplied by Honeywill & Stein, Sutton, Surrey, UK. Deionised water manufactured by reverse osmosis was used to prepare a range of concentrations (5–95%, w/w) of the surfactants. The PS 60, being hydrophilic (HLB 14.9) provided solutions. The S 60 (HLB 4.7) and S 80 (HLB 4.3), however, required the use of a high speed homogeniser (Silverson Machines, Ltd., Chesham, UK) to produce dispersions, which showed no visible phase separation within the time required for the preparation of the pellets.

### 2.2. Methods

#### 2.2.1. Preparation of the pellets

To prepare the wet mass for extrusion, 50 g of MCC was placed in the bowl of a planetary mixer (Kenwood Chef, Kenwood, Croydon, UK). The required quantity of the appropriate liquid was added slowly to the powder and the system mixed for 10 min, scraping the sides of the bowl and the blade at regular intervals. The quantity of liquid used started with an equal weight (50 g) of liquid added to the MCC. The wet mass was processed to produce pellets. If the system produced pellets, the amount of fluid was increased or decreased by 2 g quantities until the system no longer produced satisfactory pellets. The liquid content is expressed as a percentage of the dry mass. The wet mass obtained was packed by hand into a 2.54-cm diameter barrel of a ram extruder fitted with a die, which had a diameter of 1 mm and a length of 6 mm. The plunger was inserted into the barrel and then attached to the crosshead of a physical testing instrument (Lloyds MX50, Lloyds Instruments, Ltd., Southampton, UK). The wet mass was extruded at a ram speed of 200 mm/min, the displacement/extrusion pressure curve being fed to a computer and then recorded with an XY recorder (Recorderlab, Gould, Surrey, UK) from which the extrusion forces could be quantified. The extrudate was spheronised for 10 min at 1800 rpm on a 12-cm diameter crosshatched plate of a spheronizer (Caleva Model 120, Caleva Processes, Sturminster Newton, Dorset, UK). The pellets were dried in a hot-air oven (Pickerston Instruments, Ltd., Romford, UK) at 20 °C for 24 h to achieve a constant weight.

#### 2.2.2. Characterisation of the pellets

The size distribution of each batch of the pellets was determined by subjecting the pellets to sieving on a sieve shaker (Endecotts, London, UK), fitted with a set of British Standard sieves in a $\sqrt{2}$ progression of size. From the weight distribution, a cumulative weight undersize graph was constructed from which the median and the interquartile range were obtained. The % of the pellets in the modal fraction was also recorded. The two-dimensional shape factor $e_R$ (Podczeck and Newton, 1994) with the conditions set out by Podczeck et al. (1999) was determined on 100 pellets taken from the modal size fraction as described in these papers.

## 3. Results and discussion

### 3.1. Extrusion properties

Benbow and Bridgwater (1993) have described several basic types of extrusion profile obtained when a wet powder mass is extruded and Harrison et al. (1985) observed this type of behaviour for pharmaceutical formulations. A profile, which provides a constant level of the extrusion force, taken as the steady-state force, and which has been used to derive rheological properties of the wet mass used in pharmaceutical formulations (e.g., Harrison et al., 1987; Raines et al., 1990; Chohan and Newton, 1996; MacRitchie et al., 2002; Newton et al., 2005). Such a profile usually gives good pellets, i.e., pellets, which have a median size between 0.5 and 2.4 mm, a restricted size range (an interquartile range, IQR of not more than 25% of the median) and a shape factor $e_R$ (Podczeck and Newton, 1994) of greater than 0.5. Under conditions of fluid migration, this pattern changes to provide a forced flow profile, which is also described by Benbow and Bridgwater (1993) and Harrison et al. (1985). Here the extrusion force increases with piston displacement. This type of curve does not usually form pellets, as the liquid mobility, which occurs with this type of profile, can also occur in the spheronization stage of the process. This can lead to agglomeration of the pellets. Chatchawalsaisin et al. (2005), however, have shown that for some formulations it is still possible to produce satisfactory pellets even when the extrusion process involves forced flow. To be consistent, however, in the present study only the extrudate that was collected during the steady-state flow, prior to the onset of forced flow, was used to make pellets and the recorded extrusion force is the steady-state force.

Variations of these two types of flow can also be observed. The first is where the pressure/displacement profile shows significant irregular fluctuations in pressure. This can occur for both steady state and forced flow systems. It has been attributed to inadequate mixing of ceramic pastes, which could be overcome by repeated extrusion of the wet mass (Bohm and Blackburn, 1994a) or the breakdown of agglomerates within the system (Bohm and Blackburn, 1994b). Chen et al. (1997) reported that there was a correlation between the standard deviation of the signal and the properties of ceramic pastes, while Russell et al. (2003) demonstrated that it was important to consider the quality of the pressure detection system, especially if the extrusion process was rapid. For the systems studied here, repeated extrusion did not change the profile, therefore mixing was not an issue, but there may be breaking of agglomerates. The extrusion rate of 200 mm/min was not too fast and smooth curves could be obtained for some systems. Hence the pressure measurement was not the source of the variation and variations are therefore a property of the formulation. Chen et al. (2000) have demonstrated that the formulation issues of particle size, binder type and the presence of plasticizer can influence both the occurrence of forced flow and pressure fluctuations for pastes containing stainless-steel particles. In the present study,

where there were variations in the extrusion force, the steady-state force in the current study was estimated from an average of the fluctuations by eye.

A further deviation from the standard curves is the existence of an initial peak in the pressure before the steady state or the forced flow curves. This can be observed in the paste systems reported by Bohm and Blackburn (1994a) and Chen et al. (2000); it can be seen in the cold extrusion of chocolate (Beckett et al., 1994) and for pharmaceutical formulations as reported by Fitzpatrick et al. (2006). It appears to be associated with the yield properties of the paste as it is forced from the large diameter of the barrel into the small diameter die. It can be followed either by a smooth profile or an irregular profile. It can also be associated with the presence or absence of forced flow. Thus the extrusion profiles can be classified into the following types:

(1) Smooth steady-state flow (Harrison et al., 1985).
(2) Irregular steady-state flow (Bohm and Blackburn, 1994a).
(3) An initial peak followed by steady-state flow (Bohm and Blackburn, 1994a).
(4) An initial peak followed by irregular flow (Fitzpatrick et al., 2006).
(5) Forced flow with either smooth or irregular profile with or without an initial peak (Harrison et al., 1985).

The type of curve, which was obtained with the three surfactant solutions at the different concentrations in water as a function of the liquid contents using this classification is presented in Table 1. The formulation consisting of only water and MCC shows forced flow at the lower water level with either smooth or irregular steady-state flow once the water level is between 45 and 50% (Table 1). The addition of 5% of all the surfactants changes this pattern. The addition of PS 60 results in steady flow, which is smooth over a much wider range of liquid levels, but becoming irregular above 47% and below 40%. There is no forced flow in the range of liquid contents tested, indicating that liquid migration does not occur. The addition of S 60 only provides smooth flow at liquid levels between 40 and 46% and between 57 and 58%, while between 49 and 57% the flow is irregular. The low levels of liquid provide a system with an initial peak. For S 80, there is smooth flow between 40 and 46%, the remainder being irregular and at times with an initial peak. The presence of this level of surfactants generally removes the tendency to forced flow. The addition of 20% surfactant continues this trend with only the lowest level, i.e., below 38% showing forced flow for PS 60. Otherwise, the PS 60 systems provide predominantly smooth flow. The S 80 systems tend to be irregular while the S 60 systems often have an initial peak followed by an irregular curve. When the surfactant level is increased to 35%, S 60 produces profiles, which have an initial peak followed by an irregular profile. PS 60 provides systems, which are smooth after the initial peak when the liquid level ranges from 45 to 50%, and there is just one level (43.2%) with a smooth curve and one with forced flow (when the liquid content is the lowest). S 80 provides systems which do not have an initial peak and are predominately irregular. Increasing the surfactant level to 50% illustrates that again S 80 systems do not have an initial peak whereas S 60 systems do. The initial peaks for the S 60 systems are followed by an irregular curve whereas the peaks obtained with the PS 60 systems are mostly followed by smooth profiles. Once the surfactant content has reached the 65% level the S 60 systems will not extrude under the conditions of the test, whatever the liquid level. This is a similar situation to the inclusion of the mixed mono- and di-glycerides levels that ceased to form pellets at a 68% level, reported by Newton et al. (2007). The 65% S 80 systems provide extrusion profiles, which do not have an initial peak and are irregular at contents between 35.9 and 39%. The 65% PS 60 systems have an initial peak and are irregular from 44.4 to 46.8%, whereas they are smooth from 47.9 to 50%. The two liquid contents which form pellets with 80% PS 60 and S 80 are all irregular in profile with an initial peak. Only the PS 60 systems will form pellets at the 95% liquid level and the two liquid contents where this is possible, produce an initial peak.

**Table 1**
The type of extrusion profile for different concentrations of surfactants at different liquid levels

| Liquid% | Surfactant% | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 5 | | | 20 | | | 35 | | | 50 | | | 65 | | 80 | | 95 |
| | | PS 60[a] | S 60[a] | S 80[a] | PS 60[a] | S 60[a] | S 80[a] | PS 60[a] | S 60[a] | S 80[a] | PS 60[a] | S 60[a] | S 80[a] | PS 60[a] | S 80[a] | PS 60[a] | S 80[a] | PS 60[a] |
| 34.2 | | | | 5 | | | | | | | | | | | | | | |
| 35.9 | | | 5 | 2 | | | | | | | | | | | 2 | | | |
| 37.5 | | 2 | 4 | 4 | 5 | | 4 | | | 2 | | | | | 2 | | | |
| 39.0 | | 2 | 4 | 4 | 2 | | 4 | | | 2 | | | 2 | | 2 | | | |
| 40.5 | 5 | 1 | 3 | 1 | 1 | 4 | 4 | 5 | | 1 | | | 2 | | | | 4 | |
| 41.9 | 5 | 1 | 1 | 1 | 1 | 4 | 1 | 2 | | 1 | | | 2 | | | 4 | 4 | 3 |
| 43.2 | 5 | 1 | 1 | 1 | 1 | 4 | 1 | 1 | 4 | 1 | | | 2 | | | 4 | | 4 |
| 44.4 | 5 | 1 | 1 | 1 | 1 | 4 | 1 | 2 | 4 | 1 | 4 | | 2 | 4 | | | | |
| 45.7 | 2 | 1 | 1 | 1 | 1 | 4 | 1 | 3 | 4 | 2 | 3 | | 1 | 4 | | | | |
| 46.8 | 1 | 1 | 3 | 4 | 1 | 4 | 4 | 3 | 4 | 2 | 3 | | 1 | 4 | | | | |
| 47.9 | 2 | 2 | 1 | 2 | 1 | 4 | 2 | 3 | 4 | 2 | 3 | | 2 | 3 | | | | |
| 49.0 | 1 | 2 | 2 | 2 | | 3 | 2 | 3 | 4 | 2 | 3 | 4 | 1 | 3 | | | | |
| 50.0 | 2 | 2 | 2 | 2 | | 3 | 2 | 3 | 4 | 2 | 3 | 4 | 2 | 3 | | | | |
| 50.9 | | 2 | 2 | 2 | | | 2 | | | 2 | 4 | 4 | | | | | | |
| 51.9 | | | 2 | 2 | | | 2 | | | 2 | | 4 | | | | | | |
| 52.8 | | | 2 | | | | 2 | | | 2 | | 4 | | | | | | |
| 53.7 | | | 2 | | | | | | | 2 | | | | | | | | |
| 54.6 | | | 2 | | | | | | | | | | | | | | | |
| 55.4 | | | 2 | | | | | | | | | | | | | | | |
| 56.1 | | | 2 | | | | | | | | | | | | | | | |
| 56.8 | | | 2 | | | | | | | | | | | | | | | |
| 57.6 | | | 1 | | | | | | | | | | | | | | | |
| 58.3 | | | 1 | | | | | | | | | | | | | | | |

Extrusion profile types: 1 = smooth steady profile; 2 = steady flow but irregular profile; 3 = initial peak followed by smooth profile; 4 = initial peak followed by irregular profile; 5 = forced flow. Where no value is given, it was not possible to extrude or make satisfactory pellets.

[a] Surfactant.

There are clearly different profiles for the different surfactants at different concentrations and different liquid levels. There are also very different ranges of liquid levels that can be used. The minimum and maximum levels of liquids that will form reasonable pellets are presented in Fig. 1. The two hydrophobic surfactants S 60 and S 80, with HLB values of 4.7 and 4.3, respectively, show that at a 5% level it is possible to have a system which can make pellets with liquid levels that are far greater and lower than the system containing water. This is particularly true for the systems with higher liquid levels where the two types of surfactant are able to function up to the same level of liquid. The 5% level of the hydrophilic surfactant PS 60 shows less difference when compared to the water system, with a slight lowering of the lower limit. When the surfactant level reaches 20%, the two hydrophobic surfactants again have the same upper level, which is now very similar to that for the water system, while the lower level shows a slight increase from the 5% concentration. The PS 60 shows a slight reduction in the range over which it is possible to make pellets compared to the 5% level. At the 35% level of surfactant, all three surfactants show the same upper level of liquid, which is approximately that obtained for the system con-

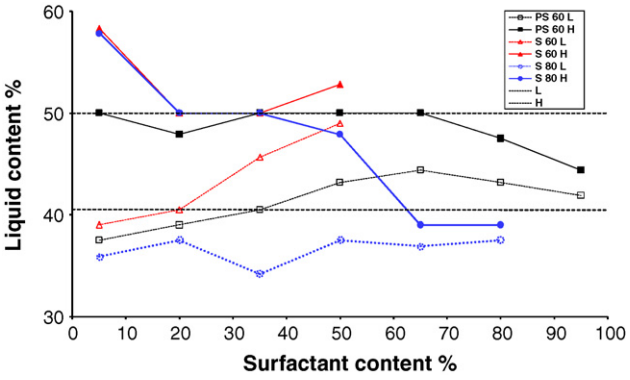


**Fig. 1.** The minimum and maximum levels (%) of solutions of the surfactant PS 60, S 60 and S 80, which can form satisfactory pellets. The two dashed lines parallel to the abscissa at 40 and 50% represent the range in which pellets can be made using only water.

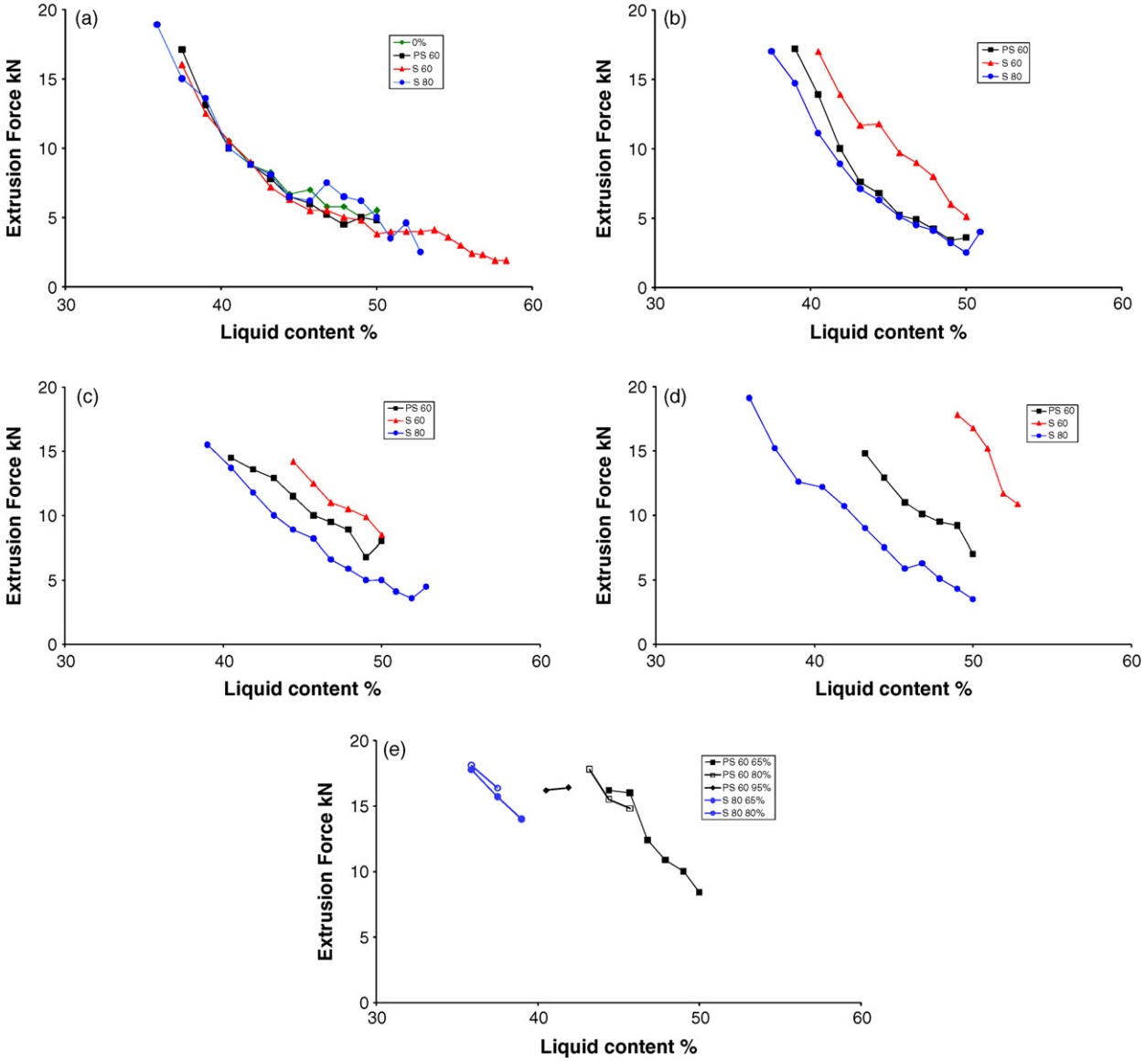


**Fig. 2.** The extrusion force as a function of liquid content (%) for (a) 0 and 5%, (b) 20%, (c) 35%, (d) 50% and (e) 65, 80 and 95% solutions of the surfactants PS 60, S 60 and S 80.

taining only water. The lower levels are, however, very different. That for the S 60 has increased to provide a restricted level compared to water, whereas the S 80 shows a further decrease in the level of liquid at which the system will function. At 50%, there is a slight increase in the upper level for S 60, but the range of levels is less than for previous S 60 contents. The PS 60 maintains approximately the same value for the upper level, but the lower level is higher at the 50% surfactant content. The lower S 80 level increases slightly and with the upper level declining, there is a reduction in the total range. At the 65% surfactant content the S 60 system will no longer extrude. There is also a considerable reduction in the range of liquid levels over which the S 80 systems will function and both the upper and lower levels are below the lower level for water to form pellets. The range is approximately the same for both the 65 and the 80% content of S 80. The systems containing the hydrophilic surfactant PS 60 show a similar narrowing of the range as the content of surfactant in the system increases, but this differs from the two hydrophobic surfactants in that it is still possible to make pellets when the liquid contains 95% of surfactant. This is approximately the same level reported for the self-emulsifying system containing 92% polysorbate 80 and a mixture of mono- and di-glycerides (Newton et al., 2001) and similar to the 92% content for the polysorbate 80 itself (Newton et al., 2007).

Having shown that differences exist in the extrusion profiles, it would be interesting to consider whether these differences are observable in terms of the force required to extrude the wet mass. These forces are shown as a function of the liquid content of the wet mass in Fig. 2. The values for the 5% level of surfactant are compared with the system, which contains only water in Fig. 2a. The values are quite similar and as has been observed many times before, increase as the liquid content decreases (Chatchawalsaisin et al., 2005; MacRitchie et al., 2002). At the 20% level, the systems start to separate, the values for the S 60 being higher at all liquid contents, Fig. 2b. This trend to separate continues for the 35% surfactant content, Fig. 2c and the 50% content, Fig. 2d, where it is clear that the two hydrophobic surfactants have very different values as well as having different types of profile (see Table 1). The values for the high levels of PS 60 and S 80 are presented in Fig. 2e. As the systems do not function at the same liquid levels it is difficult to compare the two systems. Each system, however, appears to have reached values of extrusion force which are related to the type of surfactant and the liquid content.

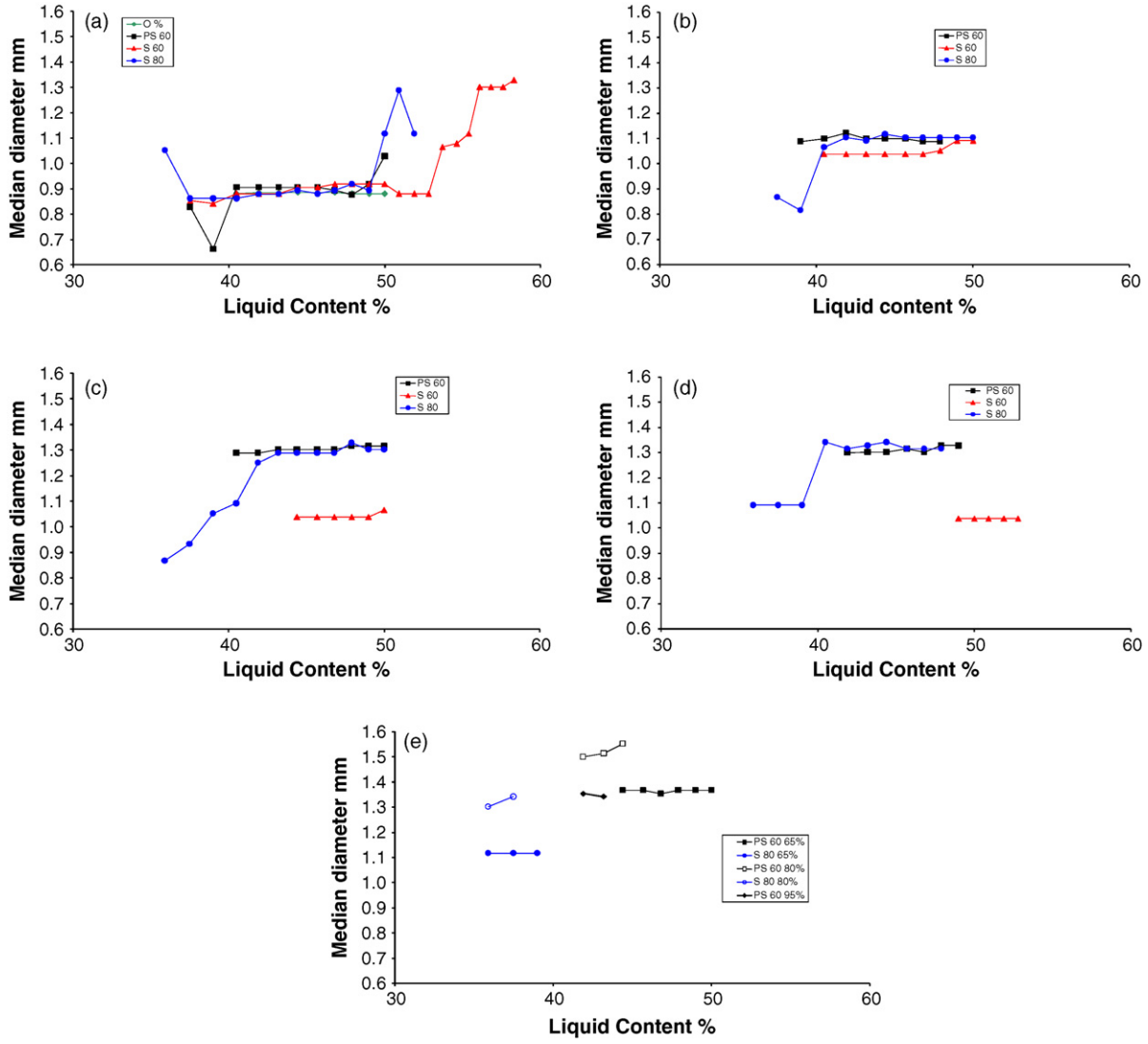


**Fig. 3.** The median pellet diameter as a function of the liquid content (%) for (a) 0 and 5%, (b) 20%, (c) 35%, (d) 50% and (e) 65, 80 and 95% solutions of the surfactants PS 60, S 60 and S 80.

### 3.2. Pellet characterisation

#### 3.2.1. Pellet shape

The pellets produced with water had values for the shape factor $e_R$ in the range 0.5–0.6 and there was no consistent pattern related to the liquid content or the surfactant type and concentration. Once a surfactant was added, the values of $e_R$ always exceeded 0.6 indicating an improvement in the quality of the pellets and that they were of satisfactory shape. The lack of influence of formulation input factors on the quality of pellets in terms of their shape in the case of the formulations containing self-emulsifying systems has been previously reported by Newton et al. (2001) and for formulations containing PS 80 by Newton et al. (2007). These observations are not unexpected.

#### 3.2.2. Pellet size

The values of the median diameter of the pellet size as a function of liquid content for the different preparations are set out in Fig. 3. At a 5% level of surfactant, the median diameters of the pellets are very similar in the range of 40–50% liquid content and are equivalent to those prepared with water as the liquid, see Fig. 3a. There are deviations at the upper levels of liquid for each of the three surfactants, especially S 60, where there is evidence of pellet agglomeration. With the addition of 20% surfactant, there is an increase in the value of the median diameter, but again consistent values are observed at the different liquid levels (Fig. 3b). Of the three surfactants, there is evidence that the pellets produced with S 60 are slightly smaller in their median diameter. Increasing the surfactant level to 35% now shows this difference for S 60 systems very clearly (Fig. 3c), suggesting the possibility of a different mechanism of spheronization, especially as the values are similar to those of the 20% content of S 60. The values for PS 60 and S 80 containing pellets produced with 35% surfactant are very similar, except for the lower levels of liquid binder where the PS 60 system will not form pellets. This difference between the two sets of surfactants is maintained for the 50% level of surfactant. Again the S 60 system produces pellets which are smaller than obtained with the other two surfactants, and they are similar in median diameter to those produced with 35 and 20% surfactant. Differences between the PS 60 and S 80 occur at the levels above 50%, which prevent exact comparisons, because different levels of liquid for the two surfactants are involved (Fig. 3e). For the two surfactant systems still forming pellets, the pellet diameter increases as the surfactant content increases from 65 to 80%. Increasing the content of PS 60 to

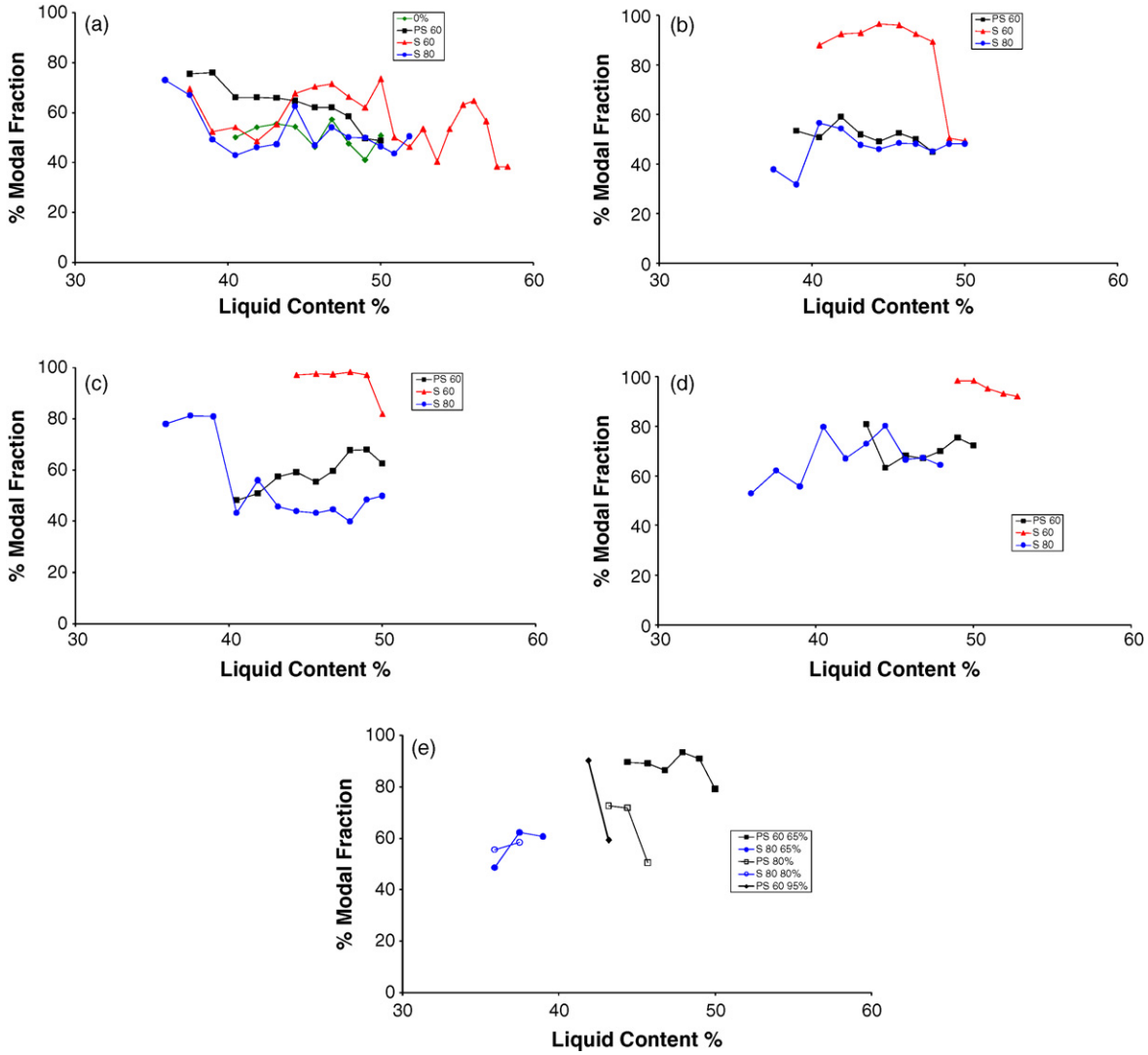


**Fig. 4.** The % of pellets in the modal size fraction as a function of the liquid content (%) for (a) 0 and 5%, (b) 20%, (c) 35%, (d) 50% and (e) 65, 80 and 95% solutions of the surfactants PS 60, S 60 and S 80.

95%, however, results in a median diameter, which is approximately the same as for the system containing 65% surfactant, which again could indicate a different mechanism of pellet formation.

### 3.2.3. Pellet size distribution

The ability to be able to produce pellets with a narrow range of size has been a claim for the method since the early publications (Reynolds, 1970; Conine and Hadley, 1970). Two methods of assessing the distribution of size were used, i.e., the interquartile range (IQR) and the % of pellets in the modal fraction. There is some fluctuation of the value of the IQR especially at the lower and higher levels of liquid content. The results show no constant trends in the values with changes in the level and type of surfactant and hence will not be given in detail. The value of the IQR is at most about 20% of the median value and the more usual value being about 10%, indicating a narrow size distribution. As the surfactant level increases, the value for the IQR becomes more consistent for each liquid level and surfactant concentration, and even for those systems where there is an increase in the median diameter, the values are nearer the 10% than the 20% of the median diameter, again indicating the uniformity of the size of the pellets. The values of the IQR are considerably lower than those reported for the inclusion of other surfactants in the form of 0.1% of sodium laurylsulphate and 0.0001 or 0.01% Pluronic PF68 (Boutell et al., 2002).

The proportion of the pellets in the modal fraction for the three surfactants at different levels and different liquid contents is presented in Fig. 4. Compared with the system prepared with water, those formulations containing 5% of surfactants often have a higher proportion of pellets in the modal fraction (Fig. 4a). The proportion is never less than 40% of pellets and can be as high as 75%. When 20% of surfactant is present (Fig. 4b), the proportions stay about the same for PS 60 and S 80 but those for S 60 increase to provide over 90% of pellets in the modal fraction. This level of achievement was limited in previous reports, e.g., 6 out of 18 formulations by Sousa et al. (2002), 1 of 13 formulations by Newton et al. (2001) and 4 out of 60 formulations by Chatchawalsaisin et al. (2005). This high level of performance of size uniformity found in the present study is maintained for the 35 and 50% surfactant formulations of S 60 (Fig. 4c and d). This high level of performance is also attained with the formulations containing 65% of PS 60 and one of the formulations containing 95% of PS 60 (Fig. 4e). The S 80 formulations have their highest values when there is 50% of the surfactant present (Fig. 4d). In general, the formulations compare favourably with formulations prepared with water as the binder liquid.

This ability to provide pellets with a narrow size distribution has implications for conventional pellet formulations other than those where the surfactant is included for issues of bioavailability. This could be exploited where formulations fails to provide adequate round pellets.

### 3.3. Surfactant content and formulation

In terms of formulation it is important to know how much surfactant can be incorporated into the final drug pellets. Vervaet et al. (1994) considered that it was not possible to incorporate more than 21% of Cremophor RH40 before the pellets became too soft to be handled. Tuleu et al. (2004) used a pellet formulation containing 31% of a self-emulsifying system in an *in vivo*-study in dogs. The content appears to depend, as one might expect, on the individual surfactant, in view of the range of physical and chemical properties of surfactants. The amount of surfactant that can be incorporated into the final pellet will depend on the concentration of the surfactant in solution used to prepare the pellets and the amount of the liquid that is required to be able to produce the pellets. Fig. 5 illustrates how much surfactant will remain in the pellets when

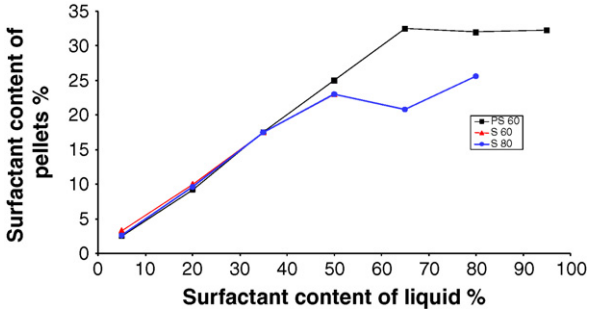


**Fig. 5.** The surfactant content of the pellets as a function of the surfactant content of the liquid used to form the pellets for the surfactants PS 60, S 60 and S 80. The quantity of liquid used to form the pellets is the maximum quantity, which will form satisfactory pellets, for the given concentration of surfactant.

formed with the maximum amount of liquid at each of the concentrations of surfactant. The two hydrophobic surfactants S 60 and S 80 provide approximately the same values up to a solution containing 50% of the surfactant when the resulting pellets contain about 23% of the surfactant. Pellets cannot be prepared with solutions containing more than 50% solution of S 60, so this represents the maximum content possible with this surfactant. For the S 80, pellets can be produced with solutions containing more surfactant but as the amount of liquid possible with such solutions is considerably reduced, there is little increase in the final amount of the surfactant in the pellets. A similar situation arises with the hydrophilic surfactant PS 60, but here the concentration of solution, which provides the highest level of surfactant in the final pellet (32.5%), is the 65% solution.

## 4. Conclusions

The addition of the non-ionic surfactants, both hydrophobic (HLB 4.3 and 4.7) and hydrophilic (HLB 14.9), has a considerable effect on the ability to produce pellets and the properties of the pellets made from MCC by the process of extrusion/spheronization. The presence of the surfactants changes the extrusion behaviour of the wet mass in terms of the extrusion profile and extrusion force. At a low level, 5%, all the surfactants increase the range of water contents over which pellets can be produced compared to the use of water alone. This could have implications for reducing the water content of formulations in the case of drugs, which are sensitive to water. In all cases, the presence of all the surfactants improved the ability to provide round pellets. The median size of the pellets was dependent on the type of surfactant and the level included in the formulation. For formulations containing PS 60 and S 80 the higher the surfactant content of the solution, the greater the values of median pellet diameter. For pellets containing S 60, however, the median value was similar for solution contents between 20 and 50%. The range of sizes was generally quite narrow and there were several systems with more than 90% of the pellets in the modal fraction. The maximum concentration of the surfactant in water that can be used to form pellets ranged from 50% for S 60, 80% for S 80 to 95% for PS 60. The amount of surfactant, which could be incorporated into the final pellets, however, was found to be the same, approximately 22.5%, for the hydrophobic surfactants and 32.5% for the hydrophilic surfactant. Thus it is clearly possible to form pellets to contain different non-ionic surfactants, which could assist the formulator in the choice of surfactant to provide the best solubilisation performance. There may also be the need to consider inclusion of a surfactant to aid the permeability of the drug through the wall of the gastro-intestinal tract.

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