Factorial designed experiment to study the effects of excipients on the mechanical properties of pellets

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Abstract

The aim of this work was to determine the effects of formulation factors on the mechanical properties of pellets produced by the process of extrusion and spheronisation. A range of properties from a simple fracture load to detailed load/displacement curves were used to study the effects of the levels of lactose monohydrate and glyceryl monostearate on the mechanical properties of pellets in terms of their surface tensile strength, pellet deformability and linear strain. A series of independent 2^2-factorial designs were employed to establish the relationships between composition of the formulations and pellet properties, whereby the concept of an excess variable was explored. It was found that the spheronisation aid used, microcrystalline cellulose, is the domineering factor in most mechanical properties studied, except for the surface tensile strength, which decreased significantly with an increase in glyceryl monostearate concentration. The change in binder liquid from water to a water/ethanol mixture further changed the behaviour of the systems significantly. The assumption of an excess variable being less critical for the statistical outcome of a factorial experiment has not been found feasible for the systems studied.

Introduction

The usual oral dosage form for the presentation of pellets to a patient is as hard gelatin capsules. Provided that the pellets do not depart from the spherical form (Chopra et al (2002) suggested a value for the aspect ratio of less than 1.2), uniform filling can be readily achieved. The mechanical properties of the pellets, provided that they are not too soft, present no particular problems and there is little work published to indicate that this is a problem. When, however, there is a need to increase the production rate or reduce the volume of the dosage by converting the pellets into tablets, then the mechanical properties of the pellets become an important issue. There is the concern of whether the pellets will in fact compress to form tablets. It is also important to know whether the pellets have a higher mechanical strength than the soft granules or pellets used to cushion the coated active pellets. The approach of using mixtures of pellets used to prevent the fracture of the coating applied to control the release of drug from the pellets has been described by several authors (Ragnarsson & Johansson 1988; Sandberg et al 1988; Bechard & Leroux 1992; Aulton et al 1994; Torrado & Augsburger 1994). Stanley et al (1981) provide theoretical evidence as to whether the coat or the core of a coated tablet fractured first, depending on the relative value of the Young's modulus of the coat and the core. These findings should be equally applicable to coated pellets and therefore it becomes an important formulation consideration to be able to control the mechanical properties of the pellets. It could be required either to increase or decrease the strength and Young's modulus of the pellets to meet the required situation.

The mechanical properties of pellets are a complex function of the components of the pellets and the method of preparation. The surface tensile strength can be determined by diametral compression under careful conditions and application of the equation presented by Shipway & Hutchings (1993). From the same test procedure, Dyer et al (1994) described how the deformability, including a value of the Young's modulus of the pellets, could be assessed. The actual numerical value of the Young's modulus determined by this approach was found to differ from that determined by the more reliable dynamic mechanical analysis (DMA) but the

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relative order of the values for a range of pellets was found to be the same (Bashaiwoldu et al 2004a, b).

Changing the mechanical properties of the pellets produced by the process of extrusion/spheronisation can be achieved by adding an excipient to the formulation that has a greater or lesser deformability than microcrystalline cellulose (MCC), which is the basic spheronisation aid of most formulations. This must of course be achieved without losing the ability to form satisfactory pellets by the process. Lactose is an excipient that has been very often used in extrusion/spheronisation formulations and was shown by Bashaiwoldu et al (2004a, b) to increase the value of Young's modulus of pellets. The same workers also demonstrated that the addition of glyceryl mono-stearate (GMS) and the incorporation of ethanol into the binder liquid reduced the value of the Young's modulus of the pellets formed. Provided that the quantity of the ingredients added was within a limited range, the quantity of fluid required to produce satisfactory pellets was constant and therefore was not a factor in inducing changes in the properties of the pellets. The effect of wet mass composition on the surface tensile strength, overall pellet deformability and linear strain is less well studied in the literature. The aim of this work was to determine these effects using a factorial design approach.

Materials and Methods

Materials

The microcrystalline cellulose (MCC) used was Avicel PH-101 (batch number CA01148, FMC International, Little Island, and Cork, Ireland) and had a mean volume particle diameter of $54.80 \pm 0.54 \, \mu m$. It was used as received and incorporated as pelletisation enhancer. The lactose monohydrate (LM) used was SorboLac 400 (batch number 022-000405) having a mean volume particle diameter of $16.80 \pm 0.32 \, \mu m$ (MEGGLE GmbH: Wasserburg, Germany). The glyceryl monostearate (GMS) used was IMWITOR 900 Pulver (batch number 608-233; CONDIA Chemie GmbH, Witten, Germany) having a mean Ferret's diameter of $59.0 \pm 36.9 \, \mu m$. The liquid binders used were purified water made by reverse osmosis (USF-Elga; Elga Ltd, High Wycombe, UK) and ethanol (absolute alcohol; BDH GPR, Merck Ltd, Poole, UK), mixed with water in the ratio 1 part of ethanol to 7 parts of water by weight.

Preparation of pellets

The excipients (total weight 500 g) were blended in a planetary mixer (Model A200; Hobart LTD, London, UK) for 10 min. The liquid binder was added at a rate of approximately 50 mL min⁻¹. The mixing process was continued for further 15 min. The sides of the bowl and the stirrer were scraped every 5 min to detach the material adhering and to ensure a homogenous mixture. The wet mass was extruded using a ram extruder mounted in a mechanical press (Lloyd Instruments; MX50, Southampton, UK), which was fitted with a 50 kN load cell. About 100 g of the wet mass was first packed and manually consolidated in the stainless-steel barrel (2.5 cm i.d., approx. 20 cm long) fitted with a centrally

mounted die (1.0 mm diameter, 5.0 mm length (L/R = 10)), by inserting a stainles-steel piston. The crosshead positioned above the piston-barrel-die assembly was driven down at a constant speed, 200 mm min⁻¹, to extrude the wet mass. Approximately 40 g of the extrudate, at a time, was spheronised on a 12 cm diameter spheroniser (Model-120; G. B. Caleva Ltd, Sturminster Newton, Dorset, UK) fitted with a cross hatch grooved plate, for about 15 minutes at a speed of 1800 rev min⁻¹. The spheroniser was partially covered to limit the condensation of the binding liquid. The pellets were dried in a Laboratory Fluid Bed Drier (Model No. FBD/L70; PRL Engineering, Mostyn, Flintshire, UK). About 200 g of the pellets were dried at 60°C for 30 min to provide dry pellets.
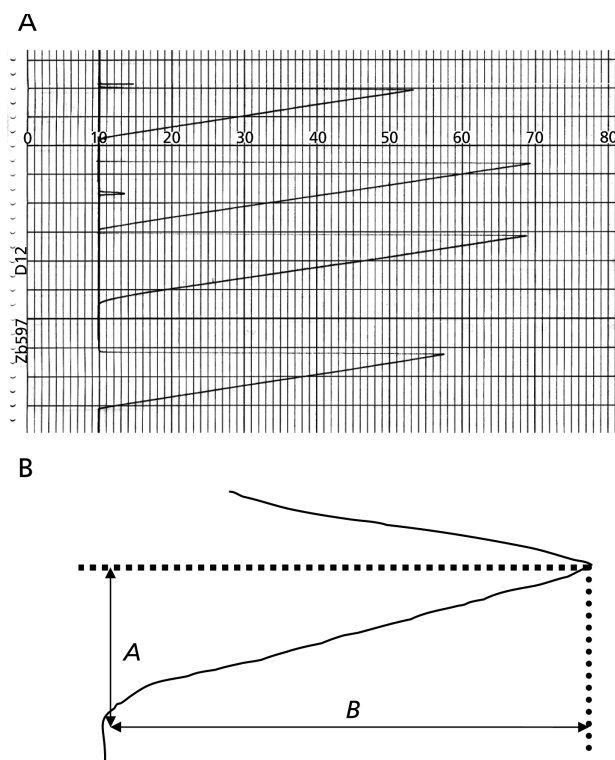
Properties of pellets

British Standard sieves (Endecotts Ltd, London, UK) were used to obtain pellets of the size fraction between 1.0 mm and 1.18 mm diameter. The pellets were spherical in shape as judged from their aspect ratio and shape factor as described by Podczeck et al (1999), the latter value always being larger than 0.6. To determine the values, 100 pellets were placed on a black slide and analysed with a Seescan image analyser (Solitaire 512; Seescan, Cambridge, UK) connected to a black and white camera (CCD-4 miniature video camera module; Rengo, Toyohashi, Japan) and zoom lens (18-108/2.5 Olympus, Hamburg, Germany). The imaging conditions and procedures as outlined by Podczeck et al (1999) were followed, using a pixel value of 22–24 μm/pixel.

The mechanical strength of 30 pellets from each batch was determined as the crushing load needed to break the pellets using a CT-5 (Engineering systems, Nottingham, UK). The speed of the upper mobile platen fitted with 5 kg-load cell (load cell resolution ± 0.001 kg) was set at 1 mm min⁻¹. For the brittle pellets, the platen returned back automatically when a significant drop in the load was observed due to sudden crack propagation. For the non-brittle pellets, however, the force increased linearly up to a first maximum, then dropped slightly and rose again until final pellet fracture. The first maximum was noted on the force/time graph (Servogor-120; J. M. Instruments, Kent, UK) and the first peak was recorded as the breaking load. The surface tensile strength $\sigma_{t(s)}$ was derived from the crushing force and pellet diameter using the equation by Shipway & Hutchings (1993):

$$\sigma_{t(s)} = 0.4 F_0 / \pi R^2 \tag{1}$$

where F_0 = breaking load (N) and R = pellet radius (m).

During the diametral compression of the pellets, load/time profiles (kg min⁻¹) were obtained (Figure 1A). By determining the horizontal distance of the load/time profile (distance A in Figure 1B, given in min) to that of the platen displacement (given in mm min⁻¹), and converting the load (distance B in Figure 1B, given in mm) to force (using the output from the CT–5, given in kg, multiplied by 9.81 m s⁻² to convert to N), a force/displacement profile was produced. Two different measurements were made from this curve. Firstly, the inverse of the slope of the force/displacement curve was determined

A

B

Figure 1 Load/time profiles as obtained for pellets during the diametral compression test (A) and evaluation of the profile to obtain the mechanical properties of the pellets (B). By determining the horizontal distance of the load/time profile (distance *A*, given in min) to that of the platen displacement (given in mm min^{-1}), and converting the load (distance *B*, given in mm) to force (using the output from the CT–5, given in kg, multiplied by 9.81 m s^{-2} to convert to N), a force/displacement profile can be obtained.

from the initial point where the platen started to exert pressure on the pellet up to the maximum load at which the pellets failed in tension (i.e. B/A, see Figure 1B). The average of 30 samples from each batch was taken as the deformability of the pellets. Secondly, from the unidirectional decrease in the dimension of the pellet along the direction of the compressing force (i.e. distance A in Figure 1B), linear strain or shrinkage was determined as a ratio of decrease in height of the pellets before they broke to their original height.

Results and Discussion

To determine the influence of individual components of a mixture (e.g. of powders) on properties of a formulation is a difficult task. Formulations are usually designed so that the total amount of ingredients is 100%. However, this means that by varying the concentration of one of the components, all, or at least one other, component concentration(s) will automatically change also. The use of factorial designs hence becomes restricted, as the assessment of the effects by means of analysis of variance will not be possible under consideration of all variables due to this inter-variable correlation. Armstrong (2006) recommends considering whether one of the variables could be in excess of the others. If the other variables are changed to a small degree only in each

formulation, then it might be possible to neglect the excess variable, "as its proportion will show little change" (Armstrong 2006). The same author then recommends in these situations treating the remaining factors using standard factorial designs. However, the general problem that is faced here is that the excess variable (e.g., a tablet filler) should be completely inert and should have no effect on the process, whatever its level.

Table 1 shows a set of eight formulations, forming the basis for an extrusion/spheronisation experiment to test what effect a small change of the excess variable, here MCC, has on the outcome of a 2^2-factorial designed experiment. The difference between the MCC concentrations in blocks 1 and 2, each of which forms an independent 2^2-factorial design, is between 90 g and 125 g (i.e. between 18 and 25%). The maximum concentrations reached for LM and GMS are 16.7% (i.e. in total these two components never make up more than $^1/_3$ of the total formulation). It is not clear what Armstrong (2006) meant by "considerable excess," but it would appear as though a maximum ratio of $^2/_3$ excess to $^1/_3$ influence factor components in the mixture should meet his suggestions.

The design shown in Table 1 was repeated (i.e. in the first run water was used as binder liquid, whereas in the second run a water–ethanol mixture (7:1) was utilised). The experiments as outlined in Table 1 form an envelope in which the system MCC–LM–GMS works with the same amount of liquid in the formulation. To establish the accurate limits of this envelope would not be possible by factorial design because of the complex and critical nature of the process. All pellets were spherical in shape with an aspect ratio well below 1.1 and a shape factor well above 0.6 (the critical level as defined by Podczeck et al 1999), and in each batch more than 90% of the pellets were found in the target size fraction (here 1–1.18 mm). The results for the mechanical strength of the pellets are listed in Table 2.

Table 3 summarises the results from the analysis of variance performed for each 2^2-factorial design, considering the surface tensile strength, pellet deformability and linear strain in turn as response variables. In no case was a significant

Table 1 Factorial designed experiments to elucidate the effect of glyceryl monostearate (GMS) and lactose monohydrate (LM) concentration on the mechanical properties of pellets made by extrusion/spheronisation

Block	Concentration (in parts)		
	LM	GMS	(MCC = excess)
1	1	1	8
1	2	1	8
1	1	2	8
1	2	2	8
2	1	1	9
2	2	1	9
2	1	2	9
2	2	2	9

Each block forms one 2^2-design, which has been repeated with two different binder liquids (i.e. water and water/ethanol) and the two blocks differ in the level of the excess variable (i.e. the spheronisation aid microcrystalline cellulose, here used to bulk up the formulations to a defined weight).

Table 2   Results for surface tensile strength, pellet deformability and linear strain of pellets of 1–1.18 mm size fraction

| Block/Formulation	Tensile strength (MPa)	Deformability (kN m^{-1})	Linear strain (%)
Binder liquid = water			
1/1	4.85 ± 0.96	102.4 ± 11.9	10.17 ± 1.92
1/2	4.69 ± 0.71	96.4 ± 13.5	10.64 ± 2.27
1/3	3.42 ± 0.76	80.7 ± 10.2	9.19 ± 2.22
1/4	3.37 ± 0.73	80.2 ± 13.2	9.11 ± 1.94
2/1	4.00 ± 0.76	86.4 ± 11.0	9.94 ± 1.60
2/2	3.11 ± 0.61	78.1 ± 12.2	8.79 ± 1.95
2/3	2.77 ± 0.57	75.5 ± 11.4	7.91 ± 1.43
2/4	2.71 ± 0.46	79.3 ± 9.3	7.40 ± 1.43
Binder liquid = water/ethanol			
1/1	3.28 ± 0.51	77.8 ± 11.6	9.16 ± 1.59
1/2	2.73 ± 0.40	73.5 ± 7.9	7.98 ± 1.24
1/3	2.61 ± 0.39	68.5 ± 6.2	8.17 ± 1.34
1/4	2.28 ± 0.38	61.8 ± 9.6	7.95 ± 1.13
2/1	2.77 ± 0.43	73.0 ± 9.8	8.24 ± 1.57
2/2	1.91 ± 0.23	57.2 ± 7.3	7.30 ± 1.15
2/3	1.93 ± 0.34	59.4 ± 7.3	7.03 ± 1.42
2/4	2.14 ± 0.34	64.6 ± 8.4	7.17 ± 1.42

Data are means ± s.d.

Table 3   Results of the analysis of variance performed for each block of experiments and for each binder liquid used

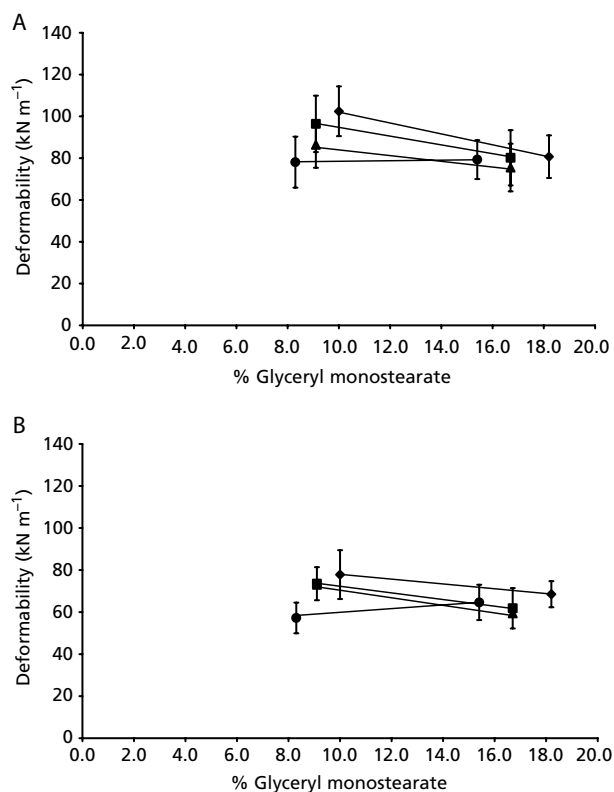| Binder liquid		Water		Water/ethanol	
Block		1	2	1	2
Surface tensile strength					
Glyceryl monostearate	F	**9.272**	**5.363**	3.144	2.440
	P	0.016	0.049	(0.114)	(0.157)
Lactose monohydrate	F	1.0	1.822	3.272	2.339
	P	(0.914)	(0.214)	(0.108)	(0.165)
Interaction	F	1.0	1.391	1.0	**7.240**
	P	(0.819)	(0.272)	(0.548)	0.027
Deformability					
Glyceryl monostearate	F	**7.157**	1.0	4.039	1.0
	P	0.028	(0.468)	(0.079)	(0.534)
Lactose monohydrate	F	1.0	1.0	1.108	1.234
	P	(0.659)	(0.733)	(0.323)	(0.299)
Interaction	F	1.0	1.0	1.0	4.843
	P	(0.708)	(0.370)	(0.824)	(0.059)
Linear strain					
Glyceryl monostearate	F	1.077	1.306	1.0	1.0
	P	(0.330)	(0.286)	(0.529)	(0.524)
Lactose monohydrate	F	1.0	1.0	1.0	1.0
	P	(0.877)	(0.382)	(0.392)	(0.479)
Interaction	F	1.0	1.0	1.0	1.0
	P	(0.825)	(0.361)	(0.553)	(0.635)

Data provided are the F-value and the probability value P for rejection of the Null hypothesis. The latter value is given in brackets if the effect was not significant with $P > 0.05$, whereas the former value is provided in bold for a significant result. (n.b., while numerically the F-ratio can become less than 1.0 due to large variability in the data, the F-distribution is only defined between 1 and infinity. Hence, values that have been computed to be less than 1.0 are listed as 1.0 in the table.)

effect found for the linear strain, and thus this variable will not be discussed further. Also, in all cases, the LM level was found not to be a significant influence factor.

Figures 2A and 2B compare the effect of changing the GMS level on the surface tensile strength of the pellets. Using water as binder liquid (Figure 2A), an increase in GMS concentration decreases the surface tensile strength of the pellets. It can clearly be seen that the effect is less pronounced in block 2 (i.e. for the 2^2-factorial design using a larger quantity of spheronisation aid (MCC)). Also, although the interaction term was statistically not significant (Table 3), the effect depends to some degree on the LM concentration for the block 2 experimental design. This indicates how complex these formulations are. However, if the liquid binder is exchanged (i.e. 1 part of ethanol is added to 7 parts of water (w/w)) the surface tensile strength appears no longer to depend on the two formulation components as such. However, as before, the amount of the excess variable MCC has an effect on the outcome of the statistical analysis. As can be seen from Table 3 and Figure 2B, there is an interaction between GMS and LM in block 2 (i.e. at high LM concentrations the surface tensile strength does not change, whereas at
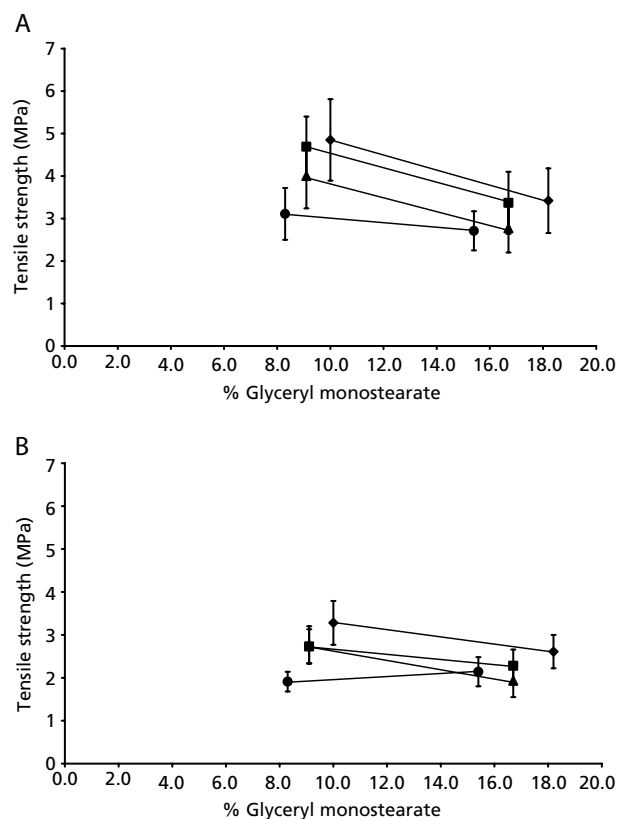
Figure 2   Graphical presentation of the effect of glyceryl monostearate on the surface tensile strength of pellets, as derived from factorial designed experiments. A. Binder liquid = water. B. Binder liquid = water/ethanol (7:1 w/w). Experimental block 1 (lower concentration of excess variable; see Table 1): ◆ low level of lactose monohydrate; ■ high level of lactose monohydrate. Experimental block 2 (higher concentration of excess variable; see Table 1): ▲ low level of lactose monohydrate; ● high level of lactose monohydrate.

Figure 3 Graphical presentation of the effect of glyceryl monostearate on the deformability of pellets, as derived from factorial designed experiments. A. Binder liquid=water. B. Binder liquid=water/ethanol (7:1 w/w). Experimental block 1 (lower concentration of excess variable; see Table 1): ◆ low level of lactose monohydrate; ■ high level of lactose monohydrate. Experimental block 2 (higher concentration of excess variable; see Table 1): ▲ low level of lactose monohydrate; ● high level of lactose monohydrate.

low concentrations of LM the surface tensile strength decreases again with an increase in GMS concentration).

Figures 3A and 3B compare the effect of changing the MGS level on the deformability of the pellets for high and low levels of LM and experimental blocks 1 and 2. The pellet deformability is given in kN m^{-1} (i.e. an increase in the value signifies a decrease in pellet deformability). As can be seen from Table 3 and Figure 3, only one significant effect appears to exist (i.e. an increase in pellet deformability with increase in GMS concentration in block 1, which is the 2^2-factorial design with the lower concentration of the excess variable MCC in the formulations).

The vast amount of non-significant relationships demonstrates the domineering role of the spheronising aid MCC for the success of the process and the formulation properties. However, the few significant findings indicate the limitations of statistical evaluations of mixtures, where an excess variable has been excluded from the considerations. The binder liquid used to form the wet mass has been shown to be a very important parameter, and an overall comparison of the formulations has demonstrated this to be a significant finding ($F=11.94$ and 17.42, and $P=0.004$ and 0.001, for surface

tensile strength and pellet deformability, respectively). The addition of ethanol to the water used reduces the degree of swelling of MCC and thus prevents full plasticisation of the wet mass. As a result the pellets are more fragile and limited in their strength.

Conclusion

The results have demonstrated that the spheronisation aid used, microcrystalline cellulose, is the domineering factor in most mechanical properties studied, except for the surface tensile strength, which decreased significantly with an increase in glyceryl monostearate concentration. The change in binder liquid from water to a water/ethanol mixture further changed the behaviour of the systems significantly. The assumption of an excess variable being less critical for the statistical outcome of a factorial experiment has not been found feasible for the systems studied.

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