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The influence of type and quantity of model drug on the extrusion/spheronization of mixtures with microcrystalline cellulose
I. Extrusion parameters

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Abstract

Five model drugs, (methyl, propyl and butyl paraben, 4-hydroxybenzoic acid and propyl gallate), similar in their chemical structure were mixed with microcrystalline cellulose and water in different proportions and forced through a ram extruder. The overall water movement was measured by the difference between the initial water in the formulation and the water content in the plug remaining after extrusion was completed. The differences in theoretical and practical volume occupancy of the materials inside the barrel were calculated to look for trapped air inside the barrel. The steady-state extrusion force for each formulation was recorded. All five materials demonstrated differences in behaviour during extrusion. The relationship between each of the three properties measured and both the drug-load and initial water content was examined, to establish the potential relationship that existed between the differences due to the drug models. The five drug models were divided into two sub-groups, when examining the way that they underwent extrusion. Methyl, propyl and butyl paraben formed one group while 4-hydroxybenzoic acid and propyl gallate formed the other group. Within the former group the relationship between steady-state extrusion force and the percentage of drug and water present tended to be lower than those in the latter group. For the former group these relationships were non-linear.

Keywords: Extrusion; Microcrystalline cellulose; Model drugs; Water retention

1. Introduction

Neither the ability to present a drug as a pellet formulation by the process of extrusion/spheronization, nor the range of level of incorporation, are as yet predictable from a knowledge of the physiochemical properties of the drug (Newton, 1996). Formulations are generally based on trial and error. For a restricted series of theophylline derivations (Hileman et al. 1997) established that it was possible to predict the quantity of water required to produce an 'optimum'

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formulation from the solubility of the drug, although their definition of optimum was questionable. Lustig-Gustafsson et al. (1999) have shown that for a wider range of compounds (whose solubility ranged over three decades) mixed with an equal quantity of microcrystalline cellulose, the quantity of water required to produce a good formulation was related to the solubility of the model drug. For a range of drugs mixed with 20% of a spheronizing grade of MCC, Jover et al. (1996) found again that water solubility was an important determinant of the water content required to produce a 'good' formulation.

Water and microcrystalline cellulose therefore are very important features of extrusion/spheronization formulations. The combination ensures that the wet powder mass has the appropriate consistency to ensure a product is formed. The two important stages of the process where 'consistency' is involved are the stages of extrusion and spheronization. The latter process involves chopping the extrudate into appropriate lengths, followed by shaping these 'chopped' lengths into round pellets. The former process can be undertaken by several methods, all of which involve forcing the wet mass through an orifice of restricted dimensions. The force necessary to achieve this depends on the consistency of the mass, the dimensions of the orifice (diameter and length) and the rate at which the process is undertaken. The ability to describe the consistency of a wet powder mass, which can be successfully extruded to form smooth surface uniform extrudate, has been described by Harrison et al. (1985, 1987) and Raines et al. (1990) using capillary rheometry. Such an approach is time-consuming and also does not consider the potential for assessment of the water migration tendencies of the wet powder mass.

As an alternative method of screening formulations with ranging contents of water, microcrystalline cellulose and drug type, an approach has been adopted which considers the relative water content of the plug after the wet powder mass has been extruded using a ram extruder under standard conditions, and the force necessary to push the mass through the die.

Such an approach is employed here to attempt to relate drug properties to the processability of product. This first paper considers the extrusion process.

2. Materials and methods

The following five materials of similar chemical structure were chosen as drug models: (1) methyl paraben lot: M20225; (2) propyl paraben lot: P7822; (3) butyl paraben lot: N433; (4) *p*-hydroxybenzoic acid lot: 401251; and (5) propyl gallate 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 Feret diameter is here defined as the average of 36 Feret diameters obtained from the same particle in 5° steps around it. A total of 512 particles from each material were studied in this way. The number average values are given in Table 1.

Binary mixes of microcrystalline cellulose (Avicel PH-101 lot: 6521, FMC Corporation

Table 1
Number average particle size, standard deviation, and apparent particle density of model drug samples

Material	Number average particle size (μm)	Standard deviation (μm)	Apparent particle density (g/cm^2)
4-*para*-Hydroxybenzoic acid	27.9	14.03	1.46
Methyl paraben	26.6	19.72	1.36
Butyl paraben	44.1	29.97	1.23
Propyl paraben	24.8	14.26	1.27
Propyl gallate	31.7	18.08	1.35

Table 2
Composition of the different formulations

Formulation code	Parts by weight			% Water of total weight	% Drug of solid	MCC:water ratio
	Drug	MCC	Water			
B	5	5	7	41.18	50.00	1:1.4
H	7	5	7	36.84	58.33	1:1.4
I	8	5	7	35.00	61.54	1:1.4
J	10	5	7	31.82	66.67	1:1.4
U	12	5	7	29.17	70.59	1:1.4
Y	14	5	7	26.92	73.68	1:1.4
C	5	5	8	44.44	50.00	1:1.6
K	7	5	8	40.00	58.33	1:1.6
L	8	5	8	38.10	61.54	1:1.6
M	10	5	8	34.78	66.67	1:1.6
T	12	5	8	32.00	70.59	1:1.6
X	14	5	8	29.63	73.68	1:1.6
D	5	5	9	47.37	50.00	1:1.8
N	7	5	9	42.86	58.33	1:1.8
O	8	5	9	40.91	61.54	1:1.8
P	10	5	9	37.50	66.67	1:1.8
V	12	5	9	34.62	70.59	1:1.8
Z	14	5	9	32.14	73.68	1:1.8
E	5	5	10	50.00	50.00	1:2.0
Q	7	5	10	45.45	58.33	1:2.0
R	8	5	10	43.48	61.54	1:2.0
S	10	5	10	40.00	66.67	1:2.0
W	12	5	10	37.04	70.59	1:2.0
A	14	5	10	34.48	73.68	1:2.0

Cork, Ireland) and each of the model drugs in different ratios as listed in Table 2, were mixed using a planetary mixer, (model N50, Hobart, London, UK) for 5 min. To each type of binary mix, water was added in amounts listed in Table 2 to make a wet mass and mixed for an additional 10 min. The wet mass was allowed to stand in a sealed container for at least 12 h, to allow water equilibrium to take place. The wet mass was then fed into a hardened steel barrel (2.54 cm internal diameter and approximately 20 cm in length), which was fitted with a hardened steel die 4 mm in length, 1mm in diameter. The barrel was filled in successive portions and the wet mass inside the barrel was hand compacted by placing a 2 kg weight on a Perspex piston inserted into the barrel. A hardened piston fitted with a Teflon washer was inserted into the barrel and placed under the load cell of a mechanical press (Lloyds MX50, Southampton, UK). The material inside the barrel was extruded at 200 mm/min. The steady-state extrusion force described by Harrison et al. (1987) was recorded.

2.1. Overall water migration

The overall water migration was evaluated by weighing and drying the plug remaining at the end of extrusion at 60° overnight using an oven with fan (Hotbox size 1, Gallenkamp, London, UK). The difference between the initial water content in the formulation and the water content inside the remaining plug was calculated.

2.2. Volume occupancy

The volume of the compacted wet mixture at the point when the steady-state force (i.e. when the first extrudate comes out of the die) was compared to the theoretical volume of the pow-

ders and water. By comparing the actual volume of the mixture and the volume of the powders and water, it is possible to estimate if there is air present in the sample within the barrel. Jerwanska et al. (1995), using a 10 mm die, found that all the air escaped downward from the die and upward from the gap between the piston and the barrel before reaching the steady-state force. Air trapped inside the barrel during extrusion would appear as small air bubbles and can affect the extrusion process by causing uneven distribution of water, changes in the force profile, rough extrudates, etc. The apparent particle density of the powders was measured using an air comparison pyconometer (model: 930, Beckman Ltd., Irvine, CA). Each material was measured five times and the average of the values was calculated and used as the material's density.

The volume of the compacted mixture was calculated using the following equation:

$$V_{\text{compact}} = (D_{\text{ss}} - D_{\text{end}} + H_{\text{plug}})\pi r^2 \quad (1)$$

where D_{ss} is the displacement of piston upon reaching the steady-state force (measured from the extrusion profile); D_{end} is the displacement of piston at the end of extrusion (measured from the extrusion profile); H_{plug} is the height of the remaining plug and r is the radius of barrel (1.27 cm).

Both displacement variables were obtained from the force–displacement profile. The theoretical density of the mixtures of powders and water was calculated using the following equation:

$$D_{\text{theoretical}} = (D_{\text{m}}P_{\text{m}} + D_{\text{Av}}P_{\text{Av}} + P_{\text{w}}) \quad (2)$$

where D_{m} is the density of the material tested; P_{m} are the parts of material tested in the mixture; D_{Av} is the density of Avicel; P_{Av} are the parts of Avicel in the mixture; P_{w} are the parts of water in the mixture (water density was assumed to be 1.0 g/cm^3).

Using the value calculated by the previous equation ($D_{\text{theoretical}}$), the theoretical volume of the mixture could be calculated using this equation:

$$V_{\text{theoretical}} = (W_{\text{full}} - W_{\text{empty}})/D_{\text{theoretical}} \quad (3)$$

where W_{full} is the Weight of the barrel filled with the mixture and W_{empty} is the weight of the empty barrel.

2.3. Steady-state extrusion force calculation

Using a computer program the average steady-state extrusion force was calculated from the point at the beginning of extrusion to its completion at the beginning of the forced flow stage, if this occurred.

2.4. Data analysis

The data collected was analysed using ANOVA to examine the way the three measured properties changed with a change in the water-to-MCC ratio and the amount of drug in the formulation. The former was used to standardise the measure of fluid needed by the formulation.

3. Results and discussion

Although each of the different formulations was processed, with some formulations no results were recorded. This happened when the 20 kN load cell limit was reached before extrusion started as in these cases, the mass possessed insufficient plasticity to extrude. Thus, below an initial water content of 29.6%, for 4-hydroxybenzoic acid and below 32.00% for propyl gallate, the mixture would not extrude.

3.1. Volume occupancy

For all materials, except propyl gallate, small differences in volumes were recorded, which can be explained as experimental error. Therefore, these volume differences can be neglected and allow the conclusion that no air is present in the barrel during extrusion (as reported by Jerwanska et al., 1995). With propyl gallate, the volume differences were consistently higher than with the other materials. This could be due to variable particle shape influencing the way the material is packed.

3.2. Overall water migration

The difference between the water content in the remaining plug after extrusion and the water orig-

inally added to the mixture (moisture differences) can give an idea of the extent of water movement occurring in the barrel during extrusion. Harrison et al. (1985), Fielden et al. (1989), Baert et al. (1992) and Tomer and Newton (1999a) reported the phenomenon that water could move faster than solids in the extrusion process. A negative value in the following results means that the plug was drier than the original formulation. The extent of the difference between the two water contents is related to the overall amount of water movement occurring during the extrusion process. The results analysed by ANOVA (SPSS 10.0 Woking, UK) are presented in Table 3. All three factors, type of drug, quantity of drug and the MCC to water ratio are significant, but so are the two factor interactions. Thus the MCC to water ratio is only significant in conjunction with the type of drug. The percentage of drug present interacts with the type of drug and in general it would appear that the type of drug is more important than the quantity present in the mixture (the value of mean square (drug) > mean square (% drug)).

Because of these interactions it is useful to treat each drug separately. The results for the difference in water level between the initial water content and the water in the plug, for each type of drug for different proportions of drug are illustrated in Fig. 1a–e. For 4-hydroxybenzoic acid (Fig. 1a) as the percentage of water in the initial wet mass increases, there is a greater difference between the initial water content and the plug water content, as the initial water content increases and the drug content increases. All the results lie on one continuous curve. This result is what one would expect. In general, as the proportion of MCC in a formulation increases, the water holding capacity could be expected to increase. This material was not identified as having the smallest moisture retention capacity (MRC) when studied by a centrifugation technique (Tomer and Newton, 1999b) but did have a higher water mobility level when evaluated by collection of the extrudate (Tomer and Newton, 1999a).

When a CH_3 group is added to the basic parahydroxybenzoic acid molecule, the shape of the initial water/water difference graph changes. The differences are smaller and now, the difference decreases as the proportion of water in the formulation increases and above approximately 35% initial water content, as the proportion of MCC in the formulation increases. Below 35% initial water content, there is a tendency to follow a reverse of this pattern for the two formulations containing the lowest MCC levels. Adding further methyl groups to give butyl and propyl paraben, the curve clearly divides into two regions at about 40% initial water content, with an increase in difference in water level below the initial water content and a decease in difference in water content above this value (Fig. 1c,d). Propyl gallate shows a similar change in behaviour at about 40%

Table 3
Analysis of variance of the difference in water between initial water level and water remaining in plug for type of drug, % of drug and the MCC to water ratio

Source	Type III sum of squares	Degree of freedom	Mean square	*F*	Sig.
Corrected model	2500.468	59	42.381	7.593	0.000
Intercept	6044.231	1	6044.231	1082.947	0.000
CF1 (% of drug)	101.189	5	20.238	3.626	0.006
CF2 (MCC:water)	6.357	3	2.119	0.380	0.768
CF3 (type of drug)	919.915	4	229.979	41.205	0.000
CF1*CF2	75.211	15	5.014	0.898	0.570
CF1*CF3	959.586	20	47.979	8.596	0.000
CF2*CF3	438.210	12	36.517	6.543	0.000
Error	334.877	60	5.581		
Total	8879.576	120			
Corrected total	2835.345	119			

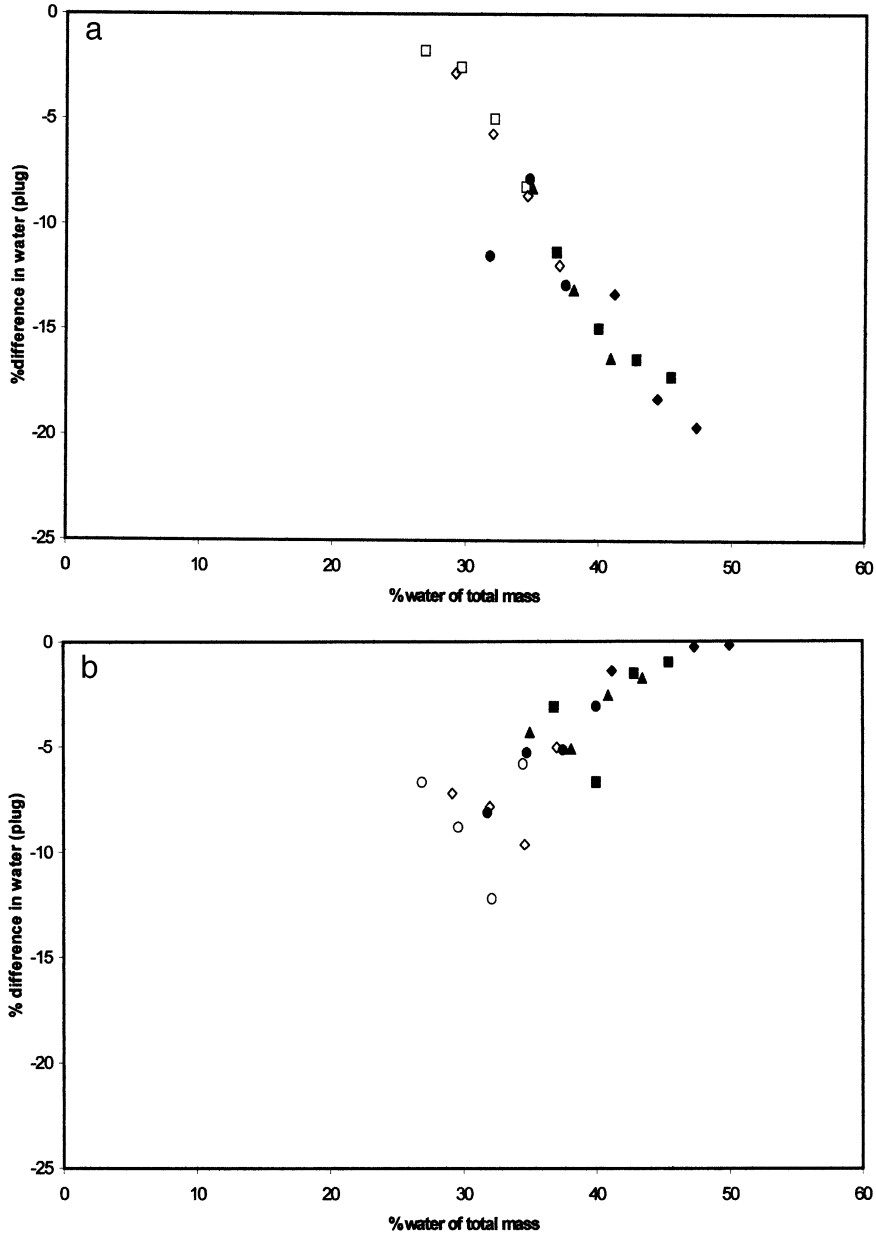


Fig. 1. Difference in water between the initial wet mass and the final plug for (a) 4-*para*-hydroxybenzoic acid, (b) methyl paraben, (c) propyl paraben, (d) butyl paraben, (e) propyl gallate as a function of the % water in the total mass. □ = 50%, ◇ = 58.33%, ● = 61.54%, ▲ = 66.67%, ■ = 70.59%, ◆ = 73.68% of model drug.

initial water content (Fig. 1e). The propyl gallate gave the highest MRC values when tested by the centrifuge technique (Tomer and Newton 1999b). The reason for this maximum in the percentage of difference is at the moment not clear.

3.3. Extrusion force

The results for the steady-state extrusion force, which occurs when the formulations were extruded under standard conditions, were analysed

by multiple regression analysis (SPSS Version 10.0, SPSS, Woking, UK). The best fit model for the relationship between the steady-state extrusion force as a function of the percentage of drug and the MCC to water ratio were derived and these dimensional representations are presented in Fig. 2a–e, over the range of observed experimental values. There is a curvilinear relationship when the model drug was 4-hydroxybenzoic acid (Fig. 2a), the force increasing rapidly as the proportion of solid drug increases and the proportion of water present decreases. This contrasts sharply with the representations for methyl, butyl and propyl *para*-hydroxybenzoic acid. Here the force

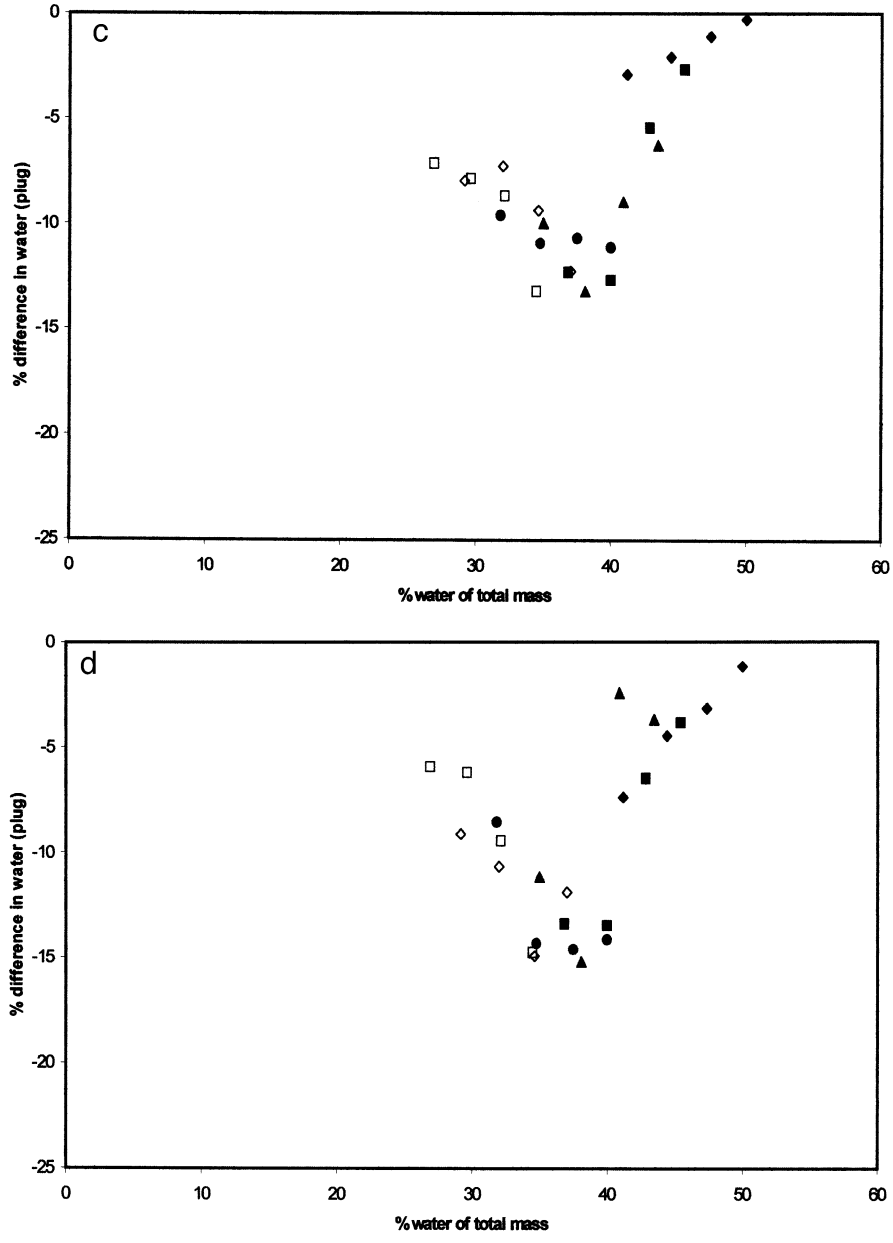


Fig. 1. (*Continued*)

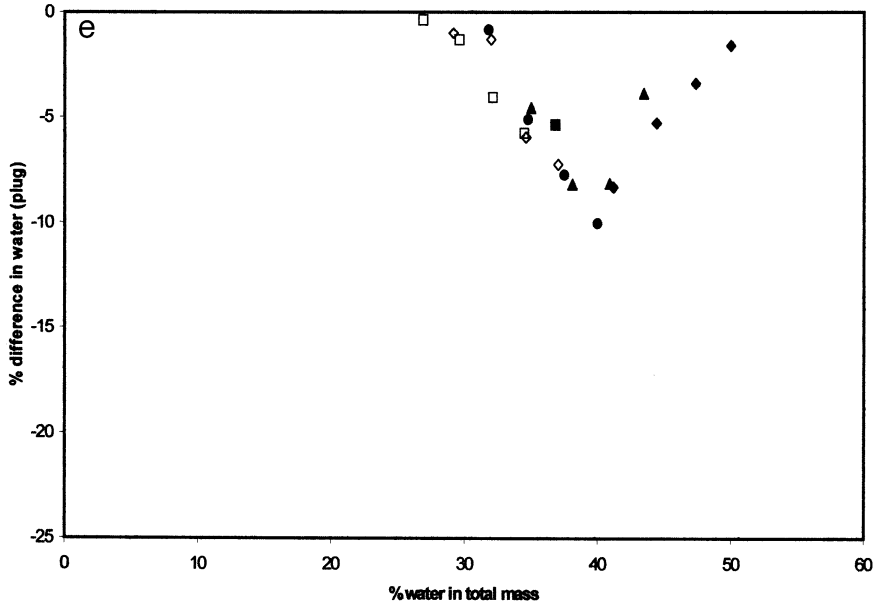
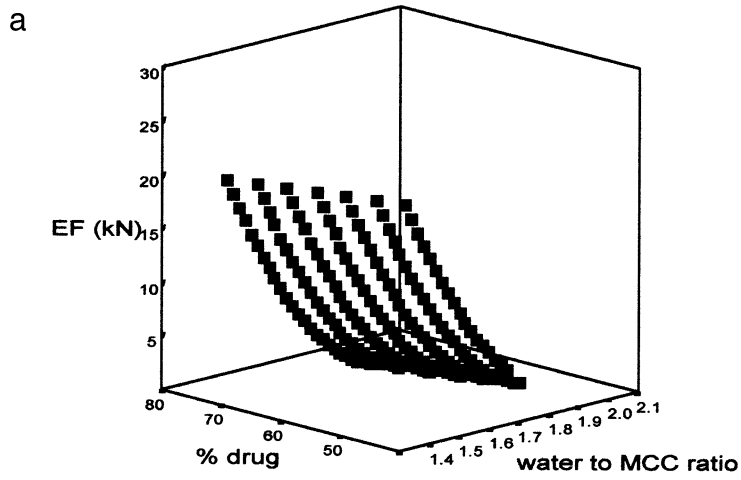


Fig. 1. (*Continued*)

does increase with the proportion for drug and reduction in water level, but not so dramatically and in an approximately linear manner (Fig. 2b–d). There is a slight tendency for curvature of the response surface with the results for propyl *para*-hydroxy benzoate, but as with the other two esters, the forces are relatively low. With propyl gallate however, the forces are again high, especially at high drug levels and the response surface is curved (Fig. 2e). Here there is not only the interaction between the percentage of drug and the water content but also a second order effect for both these terms, that for water level having a high coefficient. The high sensitivity of the extrusion force for 4-hydroxy benzoic acid and propyl gallate formulations contrasts sharply with the way these two sets of formulations respond in terms of water movement when extruding. The 4-hydroxybenzoic acid shows an increase in water difference as the initial quantity of water in the formulation increases and the drug content decreases, resulting in water level differences in excess of 15%. In contrast propyl gallate never shows a water difference exceeding 13% and also shows differences that decrease with water content and increase with MCC content.

The question arises as to what is the source of these differences in the model drugs. The model drugs are similar in their mean particle size ranging from 24.8 to 44.1 μm. It would be surprising if these small changes in particle size could provide a potential explanation. The material with the highest sensitivity to water content is 4-hydroxybenzoic acid, which has a water solubility of 1 in 125 g, which is more than twice that of propyl gallate (1 in 286 g), 16 times that of methyl paraben (1 in 2000 g) and 42 times that of butyl paraben (1 in 6500 g). While these differences are quite large, even at the lowest drug load, and the highest water level, only 1.6% of the 4 *para*-hydroxybenzoic acid would dissolve at equilibrium. Hence it is unlikely that the differences in extrusion behaviour could be due to the gross physical loss of solid particles due to dissolution. The 4-hydroxybenzate and propyl gallate have similar values for total solubility parameter 27.60 and 27.29 $MPa^{1/2}$, respectively (Tomer and Newton, 1999b). They do have very different dispersion solubility components (17.18 and 13.54 $MPa^{1/2}$, respectively), and different hydrogen bonding solubility components (17.48 and 21.20 $MPa^{1/2}$, respectively). Thus there are similarities and

EF = 94.787 - 2.844xD -40.389xW - 0.988xDxW
+0.028xDxD



EF = 7.659 + 0.139xD - 7.638xW

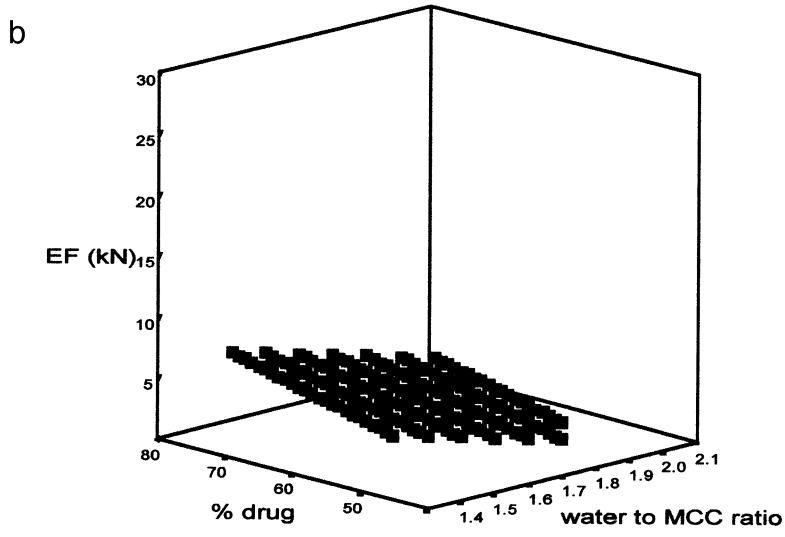
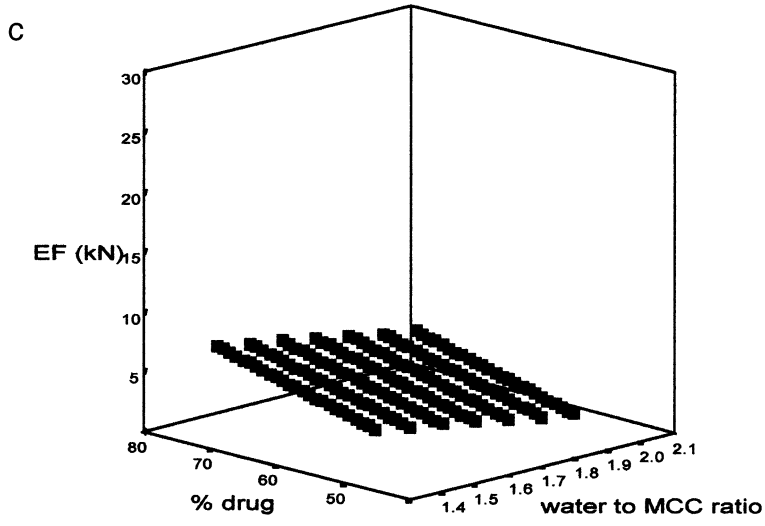


Fig. 2. Extrusion force (E_F, in kN) as a function of the % of drug (D) in the dry formulation and the water to MCC ratio (W) for (a) 4-parahydroxy benzoic acid (RMS deviation, residual analysis 20.04%), (b) methyl paraben (RMS 16.39%), (c) propyl paraben (RMS 23.03%), (d) butyl paraben (RMS 36.96%), (e) propyl gallate (RMS 16.85%).

EF = 3.240 + 0.149xD - 4.984xW

c



EF = -40.296 + 1.000xD + 19.017xW
- 463xDxW

d

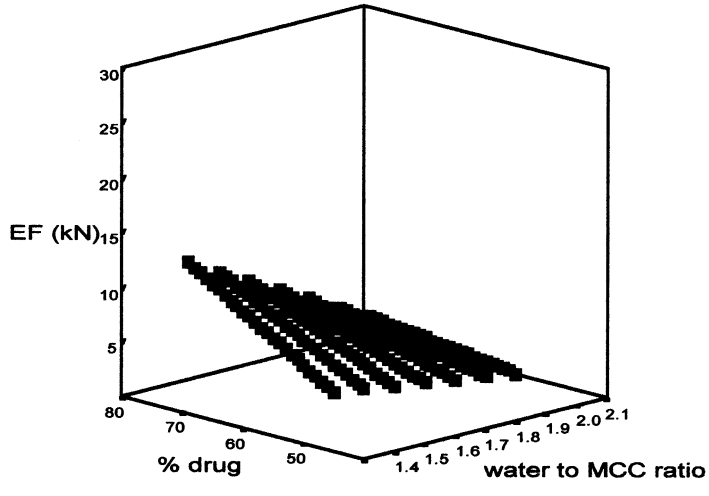


Fig. 2. (*Continued*)

EF = 77.495 - 1.334xD - 40.389xW - 0.988xDxW
+ 0.030xDxD + 24.365xWxW

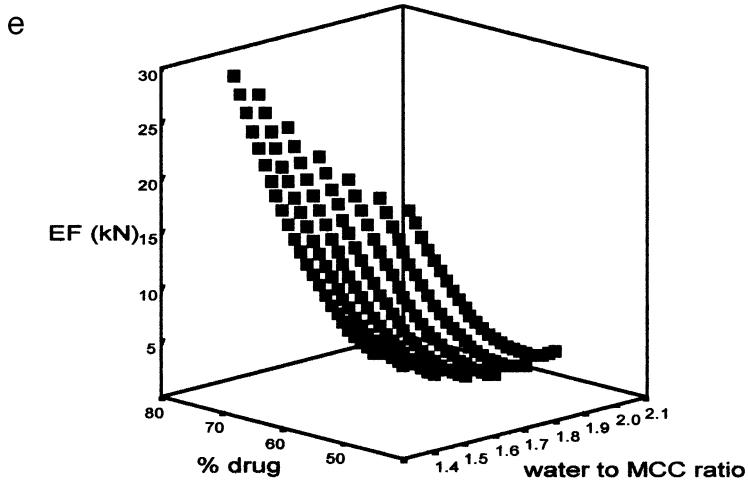


Fig. 2. (*Continued*)

differences and as yet no physico–chemical prediction can be provided.

4. Conclusions

The way both the water content and the drug load on the formulation affect the extrusion parameters was found to be different between the five drug-models. In spite of their similar properties and similar molecular structure, the materials behaved differently during extrusion. The systems divided into two groups; the parabens (methyl, propyl and butyl paraben) which behaved similarly, and propyl gallate and 4-HBA, which had similarities in terms of extrusion force effects but totally different behaviour in terms of water retention under the conditions of extrusion. In agreement with past publications, no air was found present in the extrusion barrel during extrusion, in the exception of propyl gallate, which recorded small volume differences, for which no explanation could be found at this stage.

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References

Baert, L., Remon, J.P., Knight, P., Newton, J.M., 1992. A comparison between the extrusion forces and sphere quality of a gravity feed extruder and a ram extruder. Int. J. Pharm. 86, 187–192.

Fielden, K.E., Newton, J.M., Rowe, R.C., 1989. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. J. Pharm. Pharmacol. 41, 217–221.

Harrison, P.J., Newton, J.M., Rowe, R.C., 1985. Flow defects in wet powder mass extrusion. J. Pharm. Pharmacol. 37, 81–83.

Harrison, P.J., Newton, J.M., Rowe, R.C., 1987. The application of capillary rheometry to the extrusion of wet powder masses. Int. J. Pharm. 35, 235–242.

Hileman, G.A., Upadrashta, S.M., Nean, S.H., 1997. Drug solubility effects on predicting optimum conditions for extrusion and spheronization of pellets. Pharm. Dev. Technol. 2, 43–52.

Jerwanska, E., Alderborn, G., Newton, J.M., Nystrom, C., 1995. The effect of water content on the porosity and liquid saturation of extruded cylinders. Int. J. Pharm. 121, 65–71.

Jover, I., Podczeck, F., Newton, J.M., 1996. Evaluation, by a statistically designed experiment of an experimental grade of microcrystalline cellulose, Avicel 955 as a technology to aid the production of pellets with high drug loading. J. Pharm. Sci. 85, 700–705.

Lustig-Gustafsson, C., Kaur Johal, H., Podczeck, F., Newton, J.M., 1999. The influence of water content and drug solubility on the formulation of pellets by extrusion/spheronization. Eur. J. Pharm. Sci. 8, 147–152.

Newton, J.M., 1996. Spheronization. In: Swarbrick, J.E., Boylan, J.C. (Eds.), Encyclopedia of Pharmaceutical Technology, vol. 14. Marcel Dekker, New York, pp. 187–205.

Raines, C.L., Newton, J.M., Rowe, R.C., 1990. Extrusion of microcrystalline cellulose formulations. In: Barter, R.E. (Ed.), Rheology of Food, Pharmaceutical and Biological Materials with General Rheology. Elsevier Applied Science, Barking, UK, pp. 248–257.

Tomer, G., Newton, J.M., 1999a. Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions. Int. J. Pharm. 182, 71–77.

Tomer, G., Newton, J.M., 1999b. A centrifuge technique for the evaluation of the extent of water movement in wet powder masses. Int. J. Pharm. 188, 31–38.