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Some factors influencing the formation and in vitro drug release from matrix pellets prepared by extrusion/spheronization

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Abstract

A statistically designed experiment has been undertaken to evaluate the influence of formulation factors on the formation and drug release from pellets formed by the process of extrusion/spheronization. The influence of drug solubility, drug content, the quantity and type of release modifying agent and the quantity and type of filler on the process and properties was divided into two sections and the relationship indicated by canonical analysis, a multivariate analysis procedure. The first section considered the influence of the formulation variables on median pellet size, the steady-state extrusion force and the ratio of Avicel to water, while the second section considered the influence of the formulation variables on the in vitro drug release, as measured by the AUC and MDT of the percentage drug release time profile. The molecular weight of the polyethylene glycols was shown to be the main factor influencing the median pellet size and steady-state extrusion force. The water content required for good formulations was reduced significantly by the inclusion of polyethylene glycols, whereas the presence of glyceryl monostearate at differing levels did not influence the water level required. The analysis of the influence on drug release was not, however, so clear. Important factors appeared to be the drug solubility and choice of filler. The lower the drug solubility the larger the value of the AUC and MDT. Formulations containing barium sulphate have larger AUC and MDT values than those containing lactose. The presence of glyceryl monostearate or polyethylene glycol is not a factor significantly influencing drug release.

Keywords: Drug release; Drug solubility; Extrusion/spheronization; Glyceryl monostearate; Matrix pellet; Mean dissolution time; Polyethylene glycol; Steady-state extrusion force

1. Introduction

Several attempts have been made to modify drug release from multi-particulate oral dosage forms without the necessity of extending the process of production with a second step of film coating. Several authors have tried to achieve retardation by incorporating various hydrophobic materials into a basic formulation for pellets (e.g., Ghali et al., 1989). Such systems retard the penetration of aqueous fluids into the formulation and hence slow the rate of drug release.

Other workers have attempted to enhance release by the inclusion of polyethylene glycols and surfactants (Vervaet et al., 1994). Such systems, however, would only function if the presence of

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modifying agents did not interfere with the production processes. The preparation of pellets by extrusion/spheronization is not a process which can be used for all formulations. Hence, it is important to evaluate the factors which could affect both the ability to make spheres and the influence such factors would have on the drug release performance. The large number of possible factors indicates that a statistical multifactorial approach is appropriate. Factorial designs have been employed previously (Malinowski and Smith, 1975; Chariot et al., 1987; Pinto et al., 1992; Goskonda et al., 1994) but they are limited to univariate comparisons. The experimental design undertaken in this study provides a multivariate data material with single and cross effects between the different factors, hence canonical analysis was chosen to evaluate the influence of each single parameter and their interrelationships in the multivariate data.

2. Materials and methods

2.1. Materials

The following materials were obtained from the sources indicated:

2.1.1. Excipients

Avicel® PH 101 (FMC Corp., Ireland), glycerol monostearate (Pfaltz&Bauer Inc.), lactose (Sheffield Products, USA), barium sulphate (East Anglia Chemicals, Hadleigh, Ipswich, Suffolk, UK), polyglycol 3000 (Hoechst AG, Frankfurt/Main, Germany), polyglycol 6000 (Hoechst AG, Frankfurt/Main, Germany), polyglycol 10000 (Hoechst AG, Frankfurt/Main, Germany), polyglycol 20000 (Hoechst AG, Frankfurt/Main, Germany), polyglycol 35000 (Hoechst AG, Frankfurt/Main, Germany).

2.1.2. Drugs

Sodium salicylate (Merck AG, Darmstadt, Germany), propranolol HCl (BASF, Ludwigshafen, Germany), paracetamol (BDH, Poole, UK), theophylline (BASF, Ludwigshafen, Germany), indomethacin (Becpharm Ltd, Essex, UK).

2.1.3. Binding fluid

Freshly demineralised water was used as a liquid binder in the formulations. Freshly distilled water was used as a medium in the dissolution test.

2.2. Mixing

Glyceryl monostearate (GMS) was ground in a mortar and pestle to remove coarse particles and passed through a 300 μm sieve. The polyethylene glycols (PEG) were ground in a small coffee grinder (Braun AG, Frankfurt, Germany) and passed through a 300 μm sieve. The dry powders (Avicel PH 101, drug, GMS, PEG and filler: total amount 195.0 g) were weighed (electronic balance Mettler PC 1616, Mettler Instrumente AG, Greifensee, Zürich, Switzerland) and then mixed for 10 min in a planetary mixer (Chef KN 201, Kenwood, Woking, UK). According to the required water/Avicel (W/A) ratio the corresponding amount of demineralised water (room temperature) was added. This blend was mixed for a further 10 min. The appropriate W/A ratio which gave the best pellets in terms of roundness was determined by trial and error.

2.3. Extrusion

The process of extrusion was carried out with a ram extruder system described by Harrison et al. (1987) attached to a Universal Testing Instrument (Lloyd MX 50, Lloyd Instruments, Southampton, UK).

The formulations were extruded through a die with a 1 mm diameter, 8 mm in length. The ram was lowered at a defined speed of 250 mm/min. The force displacement curves and the steady-state force values were recorded by computer, which received the output from the load cell of the instrument. These data were employed to assess the properties of the wet powder mass.

2.4. Spheronization

The resultant extrudate from three consecutive extrusions was placed on the 20.32 mm diameter radial cell plate of a spheroniser (Caleva, Sturminster Newton, Dorset, UK). This rotated at a

fixed speed of 1000 rpm. The duration of each spheronization depended on the properties of the extrudate. A spheronization time of 10 min proved sufficient for the formulations with GMS. However, the formulations with PEG required up to 30 min of spheronization to form satisfactory spheres. The spheres were dried at 45°C for 10–12 h.

2.5. Particle size analysis

The dried spheres were subjected to mechanical agitation by a sieve shaker for 10 min (Endecott test sieve shaker, Endecott Ltd, London, UK). The mesh diameters of the British Standard sieves followed a $\sqrt{2}$ progression between 500 and 2000 μm. The cumulative particle size distribution was plotted, from which the 50% value (median) was obtained.

2.6. Dissolution

Dissolution was undertaken by the USP paddle method, with a stirring rate of 100 rpm in 1000 ml of distilled water (Pharmatest, Hamburg, Germany). Dissolution tests were repeated six times for all formulations with 200 mg of pellets from the sieve fraction 1000–1400 μm. The samples collected were analysed by UV-Vis spectrophotometry (UV-Vis spectrophotometer,

Table 1
Statistical design

No.	D	LD (%)	L	LL (%)	LA (%)	F	FL (%)
1	D3	10	GMS	16	30	Lac	44
2	D3	10	GMS	16	40	Lac	34
3	D3	10	GMS	16	60	Lac	14
4	D3	10	GMS	16	74	Lac	0
5	D3	2	GMS	16	50	Lac	32
6	D3	5	GMS	16	50	Lac	29
7	D3	20	GMS	16	50	Lac	14
8	D3	34	GMS	16	50	Lac	0
9	D3	10	GMS	0	50	Lac	40
10	D3	10	GMS	8	50	Lac	32
11	D3	10	GMS	16	50	Lac	24
12 [a]	D3	10	GMS	24	50	Lac	16
13	D3	10	GMS	32	50	Lac	8
14	D1	10	GMS	16	50	Lac	24
15	D2	10	GMS	16	50	Lac	24
16	D4	10	GMS	16	50	Lac	24
17	D5	10	GMS	16	50	Lac	24
18	D3	10	GMS	16	50	BS	24
19	D1	10	GMS	16	50	BS	24
20	D2	10	GMS	16	50	BS	24
21	D4	10	GMS	16	50	BS	24
22	D5	10	GMS	16	50	BS	24
23	D3	10	PEG 3000	16	50	Lac	24
24	D3	10	PEG 6000	16	50	Lac	24
25	D3	10	PEG 10000	16	50	Lac	24
26	D3	10	PEG 20000	16	50	Lac	24
27	D3	10	PEG 35000	16	50	Lac	24

D, drug; LD, level of drug; L, type of release modifying agent; LL, level of release modifying agent; LA, level of Avicel; F, filler; FL level of filler; D1, indomethacin (solubility 0.04 g l^{-1}); D2, theophylline (solubility 8 g l^{-1}); D3, paracetamol (solubility 15 g l^{-1}); D4, propranolol HCl (solubility 50 g l^{-1}); D5, sodium salicylate (solubility 1000 g l^{-1}); Lac, lactose; BS, barium sulphate; GMS, glycerol monostearate; PEG, polyethylene glycol, number designates its molecular weight.

[a] Centre of gravity of the design.

model 554, Bodenseewerk Perkin-Elmer & Co. GmbH, Überlingen, Germany), measuring absorbance at the maximum wavelength of the drug.

2.7. Statistical plan

The formulations shown in Table 1 were chosen to form the statistical plan (different factors of the formulations = independent or influencing factors in the canonical analysis) according to a centre of gravity statistical design (Podczeck and Wenzel, 1990).

The level of the filling material (barium sulphate or lactose) was not integrated within the mathematical analysis because it represented the missing amount of material to make the formulation up to the 100% level and hence it could not be considered as a controlled variable. Canonical analysis as used by Podczeck et al. (1993) was chosen to analyse the results of the statistical design. In this analysis the calculation can only be based on numerical values for the influencing variables. The type of filler or release modifying agent is in the first instance non-quantitative and a code (dummy variable) had to be designed to transfer the qualitative property into a quantitative value. The use of dummy variables in canonical analysis has been described mathematically by Gaensslen and Schubö (1976). Hence, the different PEGs and the GMS were codified by their molecular weights for comparability (molecular weight of GMS: 358 g/mol). Barium sulphate and lactose were codified by their solubilities, to ensure the calculation could be undertaken (solubility of lactose: 200 g/l, and barium sulphate: 2.5×10^{-3} g/l (Merck Index, 1984).

Table 2
Steady-state extrusion force, water to Avicel ratio and median sphere diameter for the various formulations

No.	Median diameter (μm)	Steady-state extrusion force (kN)	Water/Avicel
1	1200	8.3	1.35
2	1200	10.0	1.12
3	1200	4.5	1.08
4	1210	7.2	1.12
5	1190	6.7	1.08
6	1180	7.0	1.12
7	1170	6.4	1.12
8	1165	7.2	1.20
9	1150	8.5	1.12
10	1190	7.2	1.15
11	1180	7.3	1.12
12	1200	6.8	1.08
13	1190	7.4	1.12
14	1190	8.4	1.10
15	1160	6.7	1.10
16	1180	8.2	1.00
17	1300	7.6	0.90
18	1270	3.6	1.20
19	1205	4.1	1.20
20	1210	3.8	1.20
21	1525	4.0	1.00
22	1310	4.6	0.90
23	1605	13.00	0.50
24	1730	14.40	0.55
25	1770	16.70	0.45
26	1855	21.70	0.50
27	1680	14.20	0.55

3. Results and discussion

Canonical analysis was applied to evaluate whether and to what extent the formulation (= independent or influencing factors, X) influences the processability of the extrusion-spheronization product and the drug release from the pellet in the dissolution test (= dependent or resultant factors, Y). As these are different properties of the formulation they were investigated separately, the dependent factors being divided into two sub-groups. On the one hand, the 'material properties' of the formulation were analysed, which are reflected in the steady-state force of the extrusion (SS force), the water/Avicel ratio of the formulation (W/A) and the median sphere size (50% value, MS). On the other, the characteristics of the dissolution profile were evaluated separately. Brockmeier et al. (1983) have proposed that an appropriate characterisation of the dissolution process can be provided by the area under the curve (AUC) of the dissolution as a function of time profile and the mean dissolution time (MDT).

The independent variables chosen for this statistical design varied widely and were unrelated to each other. This fact is a basic requirement for the applicability of the canonical analysis, The results used in the first part of the analysis are given in Table 2.

3.1. Pellet formation

The median size of the pellets was expected to be mainly dependent on the kind and quantity of the release modifying filler, as well as on the amount of microcrystalline cellulose. For reasons of a subsequent treatment, it is important to produce a median size which is suitable for other procedures. A size of about 1.0–1.4 mm has been proposed to be optimal. It has been suggested that a steady-state force between 3 and 8 kN should be aimed at for the extrusion process using this type of extruder (Bains et al., 1991). As this target is not always being reached, this study was expected to detect the variables which exert the greatest influence on the SS force. The W/A ratio defines the quantity of water in the formulation. It was expected to be mainly dependent on the solubility of the drug and the excipients.

Looking at the results of the canonical analysis, the Wilks test Λ (multivariate test of significance) indicates significantly a global interdependence between the influencing (X) and the dependent (Y) variables ($\Lambda = 0.080$; approx. $F = 4.11$, $f_1 = 18$, $f_2 = 51$).

The values of the canonical correlations clearly prove that the canonical variables provide a certain content of information (0.851, 0.724, 0.625). For the dependent variables the extracting measuring value $g^2_{\times|u}$ is 1.00. This indicates that the investigations were well balanced and can lead to a complete canonical solution.

The values of the measures of redundance indicate to which extent the varying values of Y can be explained by the independent variables. The value of 57.2% ($g^2_{y|u} = 0.572$) signifies that the dependent variables must have been influenced by quite a number of further internal or external factors which have not been studied.

Comparing the interranging communalities, it can be seen that each dependent variable was influenced. However, the effect on the SS force was slightly more significant than that on the other variables ($d^2_{\text{ss-force}|U} = 0.65$ m, $d^2_{W/A|U} = 0.54$, $d^2_{MS|U} = 0.54$).

In investigating the cause of these effects, it was detected from the interranging communalities that the main influencing factors are the molecular weight of PEG/GMS ($d^2_{\times|v} = 0.56$) and the solubility of the filler lactose or barium sulphate ($d^2_{\times|v} = 0.69$). The influences caused by the solubility of the drug ($d^2_{\times|v} = 0.23$) and the microcrystalline cellulose ($d^2_{\times|v} = 0.15$) were less distinct but still existed. No influence can be explained by the level of drug ($d^2_{\times|v} = 0.03$) or the level of PEG or GMS ($d^2_{\times|v} = 0.01$).

Comparing the values of the canonical correlations, a particular classification of the single effects caused by the influences above can be obtained. The molecular weight of the polyglycols or the GMS was shown to represent the most decisive factor in determining the median particle size. By increasing the molecular weight of the polyglycols a parallel increase of the median size can be observed up to a molecular weight of

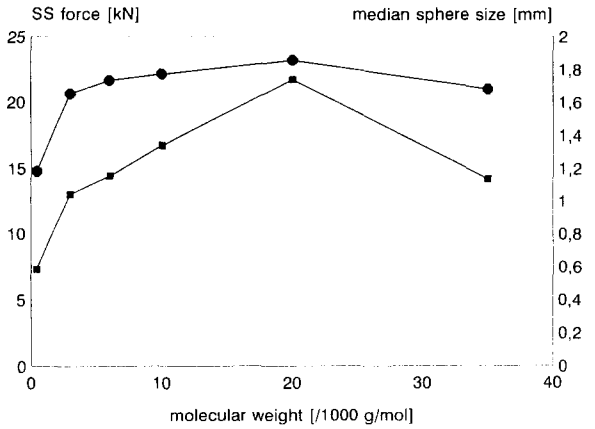

Fig. 1. Influence of the molecular weight of the release modifying agent on the median pellet size (●) and steady-state extrusion force (■).

20000 g/mol. A sudden decrease follows at a molecular weight of 35000 (see Fig. 1). There was a similar maximum in the median pellet diameter at a PEG molecular weight of 20000 (see Fig. 1). There is a significant increase in size of those pellets containing any of the grades of PEG (see Fig. 1).

In addition to the objective assessment by canonical analysis, a subjective evaluation of the processability of polyglycol formulations was obtained during the extrusion-spheronization process. The wet powder mass with incorporated polyglycols proved to be slightly sticky. This property was constantly shown in all five formulations, although it seems to be generally independent of the water content. The behaviour of these masses was not very satisfactory as they tended to adhere to the plate of the spheroniser. Therefore, its grooves were blocked and the material was transported from pellet to pellet via the plate. Thus, the whole principle of the spheronization, i.e., the rolling movement of particles along the grooves of the plate, became ineffective. The result is reflected in pellets which are definitely larger than the optimal size (1.0–1.4 mm) and have a wide particle size range. Moreover, they failed to produce spherical granules, as they gave a product of varying degrees of roundness.

An experiment was undertaken to investigate whether there is a relationship between the water content and the 'stickiness' of the mass. The W/A ratio was decreased until the mass did not adhere to the plate. The resultant dumb-bells proved that this approach to improving the properties of the wet powder mass was not possible.

Comparing the interranging communalities (canonical analysis), the molecular weight of the polyglycols/GMS seems to exert the greatest influence on the SS force, followed by a still significant effect by the solubility of the filler (lactose/barium sulphate). Although there is a slight influence by the solubility of the drug on the W/A ratio, the molar mass of the GMS/PEG proved to be the most decisive factor for the required content of water in the formulation. This fact is clearly demonstrated by the canonical analysis. While the necessary water content increased from PEG 3000 to 6000, an unexpected decrease in the water content used appeared between PEG 6000 and 10000. Then the W/A ratio increased again for PEG 35000. Only about half the amount of water was required to form satisfactory spheres in the presence of the PEGs. The addition of PEG to the system could result in large hydration shells being associated with the powdered PEG which are so strongly bound that water is not available to pass into the microcrystalline cellulose structure. This results in sufficient external water to lubricate the extrusion process, but fails to soften the mass, hence the

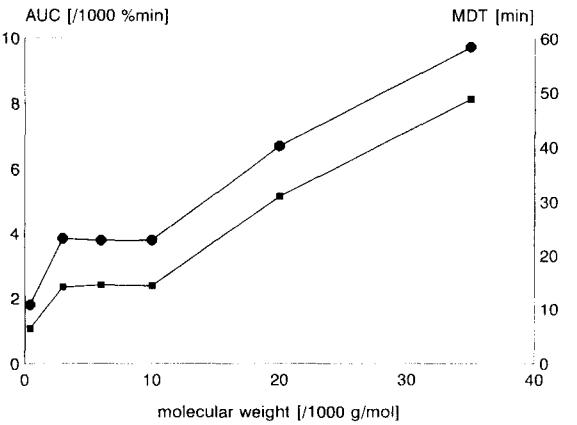

Fig. 2. Influence of the molecular weight of the release modifying agent on the AUC of % dissolution time curve (■) and MDT (●).

steady-state extrusion forces are higher than for formulations containing glyceryl monostearate. The presence of varying quantities of GMS in the formulation (Expts 9–13) did not change the water/Avicel ratio significantly. It was the presence of fillers which had a more noticeable effect.

The canonical analysis only considers the molecular weight of the release modifying agent but not its hydrophilicity or hydrophobicity. This influencing factor which could not be quantified might have provided a further explanation for a relation between the independent variables and the W/A ratio.

3.2. *In vitro drug release*

The drug release in the dissolution test was described by the following dependent variables: AUC (area under the curve); MDT (mean dissolution time).

These two parameters have been proposed to provide good characterisation of the dissolution profile (Brockmeier et al., 1983). The results are presented in Table 3. Looking at the statistical analysis the Wilks test again indicates a significant interdependence between the independent (X) and dependent (Y) variables ($\Lambda = 0.087$, approx. $F = 56.67$, $f_1 = 12$, $f_2 = 284$).

The values of the canonical correlations (0.953, 0.216) demonstrate that the canonical values contain a certain amount of information. However, the content is not as dominant in information as in the analysis of the extrusion process. The existence of a complete canonical solution is clearly shown by the extracting measure value ($g^2_{\times|u} = 1.000$).

In this analysis the measures of redundance indicate that not more than 32.1% of the values of the dependent variables can be explained by the canonical variables of X (i.e., the influencing

Table 3
Area under the % drug dissolved time profile for and mean dissolution time after various formulations (results are the mean and standard deviation of six replicates)

No.	Area under dissolution curve (% min)	Mean dissolution time (min)
1	1103.0 ± 33.2	10.78 ± 0.26
2	1098.6 ± 26.4	10.68 ± 0.23
3	1505.0 ± 19.6	15.08 ± 0.26
4	2135.2 ± 148.5	21.53 ± 1.37
5	675.4 ± 20.2	6.59 ± 0.12
6	783.6 ± 23.4	7.67 ± 0.25
7	1886.7 ± 22.1	18.22 ± 0.20
8	3612.8 ± 202.6	36.24 ± 1.51
9	1072.7 ± 30.9	10.58 ± 0.34
10	1295.9 ± 24.6	12.47 ± 0.17
11	1068.7 ± 32.3	10.78 ± 0.28
12	1172.6 ± 54.1	11.61 ± 0.53
13	1534.5 ± 44.8	15.47 ± 0.28
14	> 30000.0	> 300.0
15	2244.2 ± 43.8	23.60 ± 0.34
16	826.3 ± 48.9	7.97 ± 0.36
17	425.6 ± 14.1	4.40 ± 0.14
18	14989.8 ± 74.9	119.30 ± 0.16
19	> 30000.0	> 300.0
20	14758.1 ± 53.3	121.00 ± 0.22
21	1121.5 ± 59.9	74.43 ± 0.15
22	5610.7 ± 15.2	38.22 ± 0.09
23	2352.7 ± 20.6	23.11 ± 0.13
24	2412.4 ± 12.9	22.74 ± 0.03
25	2395.5 ± 10.5	22.81 ± 0.03
26	5158.2 ± 42.8	40.18 ± 0.04
27	8126.6 ± 52.7	58.35 ± 0.08

factors). This result is obviously not very satisfactory and other factors need to be identified. Comparing the values of the interranging communalities ($d^2_{AUC|u} = 0.39$, $d^2_{MDT|u} = 0.26$), it can be ascertained that the parameters of the dissolution test are being influenced by the independent variables, although this influence is not as distinct as expected. The univariate F tests show that, concerning the whole dissolution test, the solubility of the lactose/barium sulphate proved to be the main influencing factor ($(d^2_{\times|v} = 0.71)$. This is not surprising because the filler content of at least 24% can dominate most of the formulations. The high solubility of the lactose provides the possibility of highly porous spheres during the dissolution process, which allows the drug substances to be released quickly. On the other hand, barium sulphate is insoluble, and hence the dissolution process is prolonged by the retention of the shape of the pellets. The AUC was highly influenced by the solubility of the drug, by the molecular weights of GMS/PEG and the solubility of the lactose or barium sulphate. In this assessment of the influencing factors, the conclusion can be drawn that the molecular weight of GMS/PEG indeed influences the drug release (see Fig. 2), but neither the presence nor the percentage content of these ingredients in the formulation has an effect. The absence of the effect of GMS corresponds to the results of melt pelletization reported by Thomsen et al. (1994). The presence of PEG does not enhance drug release. The analysis of variance shows, however, that by decreasing the solubility of the filling material (lactose to barium sulphate) the drug release can be significantly prolonged. As far as the dissolution of the drug is concerned, one can detect that the drug release from the pellets is also delayed by decreasing the solubility of the drug (see Fig. 4). The solubility of the lactose or barium sulphate again was detected to cause the greatest effect on the value of the mean dissolution time, followed by the solubility of the drug.

In comparison with the AUC the MDT is more influenced by the initial slope of the dissolution profile than by the whole dissolution concentration. Hence, the influence of the type of release modifying agent on the initial drug release is not so distinct. However, the whole dissolution profile is related to the type of release modifying agent employed (see Fig. 2).

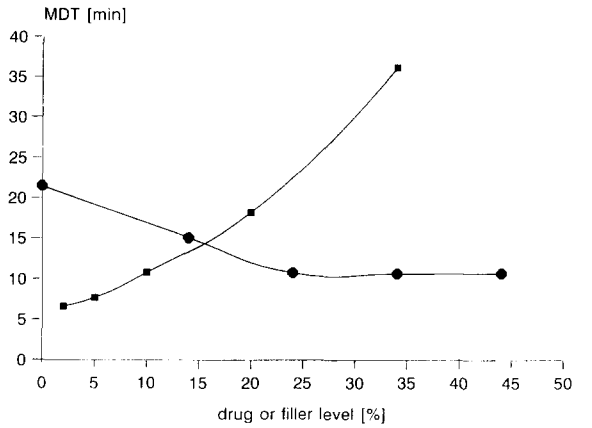

Fig. 3. Influence of drug solubility on the MDT of pellet formulations containing lactose (■) and barium sulphate (●) as the filler.

The influence of the proportion of drug in the formulation on the in vitro dissolution was also found to be significant. As the proportion of the drug increased, the MDT increased (see Fig. 3). This is surprising as it would be expected that the smaller the amount of drug present, the easier it would be to inhibit the release by the presence of glyceryl monostearate. The change in content of lactose was not analysed, as the levels are not independently controlled. Nevertheless, the re-

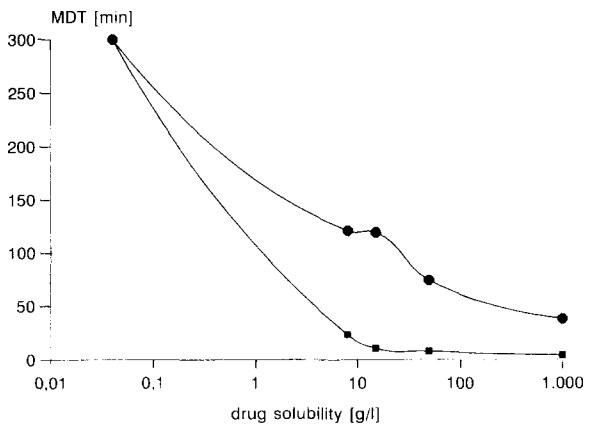

Fig. 4. Influence of the proportion of the drug (paracetamol) (■) and the filler (lactose) (●) on the MDT of pellet formulations.

sults in Fig. 3 illustrate that there is little to be gained by increased lactose content above the central level of 24%, but there is a slight reduction in release below this average level.

4. Conclusion

The statistical design of the experiments has been able to isolate some of the important factors involved in the preparation of matrix pellets by the process of extrusion/spheronization. The incorporation of up to 32% of glyceryl monostearate into the formulation was possible without adversely affecting the extrusion force required or the median pellet size. Addition of a range of molecular weight PEG, however, increased the extrusion force and median pellet size, a maximum in both occurring at a molecular weight of 20 000. A considerably smaller quantity of water was required to prepare formulations containing PEG. The in vitro dissolution was influenced mainly by drug solubility and whether the filler was the soluble lactose or the insoluble barium sulphate. There was a slight dependence of drug release on the molecular weight of the PEG; the higher the molecular weight the higher the MDT.

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