International Journal of Pharmaceutics, 102 (1994) 117–125

IJP 03357

Influence of granulation and compression process variables on flow rate of granules and on tablet properties, with special reference to weight variation

Pasi Merkku [a], Ann-Sophie Lindqvist [a], Kauko Leiviskä [b] and Jouko Yliruusi [a]

[a] *Pharmaceutical Technology Division, University of Helsinki, P.O. Box 15, FIN-00014 Helsinki (Finland) and* [b] *Control Engineering Laboratory, Department of Process Engineering, University of Oulu, Linnanmaa, FIN-90570 Oulu (Finland)*

(Received 14 May 1993)
(Accepted 30 June 1993)

Key words: Multilinear stepwise regression; 3^3 factorial design; Fluidized bed granulation; Inlet air temperature; Atomizing air pressure; Binder amount; Granule flow rate; Tablet properties

Summary

The influence of three independent fluidized bed granulation process variables (inlet air temperature, atomizing air pressure and binder solution amount) on the flow rate of granules and on the tablet properties was studied using the 3^3 factorial design. The dependence of the flow rate of granules, the tablet friability and the disintegration time of tablets on the fluidized bed granulation process variables was explained using the multilinear stepwise regression analysis. The flow time of the granules was affected by all three factors. The friability and the disintegration time of tablets were affected by the binder solution amount and the atomizing air pressure. The influence of inlet air temperature on the tablet responses was insignificant.

Introduction

Fluidized bed granulation is an important and extensively studied part of the tablet manufacture. The purpose of the process is mainly to increase the particle size and to improve the flowability of powders. Fluidized bed granulation itself is a complicated multivariate sub-process, with a large number of variables affecting the granule properties (Davies and Gloor, 1971; Aulton and Banks, 1978). Ultimately, these variables also affect many essential tablet properties. Several authors have shown the effects of process variables on the quality of granules and their compression properties (Rankell et al., 1964; Davies and Gloor, 1972; Gamlen et al., 1982; Veillard et al., 1982; Kocova El Arini and Polderman, 1983; Wan and Lim, 1990; De Jong, 1991). These studies did not, however, apply factorial designs together with the response surface methodology.

Some studies on the tablet compression process have used interesting factorial designs and regression analyses (Bos et al., 1991a,b; Gómez-Amoza, 1991). These authors used freely flowing, directly compressible tablet masses instead of pharmaceutical granules. However, there are still some papers in which the tablet properties have been explained on the basis of granulation pro-

Correspondence to: P. Merkku, Pharmaceutical Technology Division, University of Helsinki, P.O. Box 15, FIN-00014 Helsinki, Finland.

cess variables using factorial approaches. Timmins et al. (1992) have applied these techniques in studying the influence of high shear granulation process on tablets and Niskanen and Yliruusi (1992) in studying the effect of fluid bed granulation process variables on tablet properties. Quite limited factorial designs have been applied in these studies, however.

In the present paper, the influence of three independent fluidized bed granulation process variables (inlet air temperature, atomizing air pressure and binder solution amount) on the flow rate of granules and tablet properties was studied using the 3^3 factorial experimental design. The dependences were explained using correlation analysis and multilinear stepwise regression analysis.

Materials and Methods

Study design

The study followed a 3^3 factorial experimental design. The inlet air temperature (T), atomizing air pressure (p) and binder solution amount (m) were used as independent variables. The normalized factor levels of the independent variables are presented in Table 1. In the 2^3 factorial points the granulations were made in duplicate and in the center point in quadruplicate. The total number of batches was 38.

Preparation of granules

Batches (3 kg) of 80 mesh lactose α-monohydrate (DMV, Veghel, The Netherlands) were granulated using a 20% water dispersion of polyvinylpyrrolidone (Kollidon® K25, BASF, Germany). As a marker drug 2% of anhydrous theophylline (Ph. Eur.) was added to each batch to be granulated.

TABLE 1

Levels of independent variables

Variable	Factor levels			Dimension
	−1	0	+1	
Inlet air temperature (T)	40	50	60	(°C)
Atomizing air pressure (p)	1.0	1.5	2.0	(bar)
Binder solution amount (m)	150	300	450	(g)

The granules were prepared in an automated fluidized bed granulator (Glatt WSG 5, Glatt GmbH, Germany). The instrumentation and automation as well as the preparation of granules have been described previously (Merkku et al., 1992a,b, 1993a). After each granulation run the granules were sieved through a 2 mm sieve. The undersize fractions (< 2 mm) were used for flowability determinations and for tablet compression. The oversize fraction was always less than 3.1%.

Preparation of tablets

The granule samples (400 g) were mixed with 0.5% of magnesium stearate (Ph. Eur.) for 5 min in a Turbula mixer (System Schatz, Willy A. Bachhofen, Switzerland). During storage (approx. 24 h) and compression the room temperature ranged from 20 to 27°C and the relative humidity from 35 to 43%. Tablets were compressed with an instrumented eccentric tablet press (Korsch-EK0, Erweka Apparatebau, Germany) using flat-faced (ϕ 9 mm) punches. The compression force was 10 kN and the target weight of tablets was 335 mg. During compression the upper and lower forces were measured in each batch from 10 tablets.

Flowability and angle of repose

The flowability of the granules was determined by a Flow-Time and Cone Angle Testing Instrument (PharmaTest PTG, PharmaTest, Germany) using three parallel measurements. The flowability was expressed as the flow time (s) for a 100 ml granule sample to flow through an 8 mm orifice. The instrument also gives the angle of repose by measuring the height of the granule pile, which is formed on a circular platform of a fixed diameter (ϕ 100 mm) in flow rate determination.

Tablet properties

Weight variation and radial crushing strength

The weight variation and the radial crushing strength were determined from 30 tablets using a laboratory scale (accuracy 0.1 mg) and a Schleuniger-2E Tablet Hardness Tester (Schleuniger and Co., Switzerland).

Friability The friability of the tablets was determined from about 6 g of tablets. After weighing the tablets were rotated in a Roche Friabilator for 5 min. The friability was expressed as percentage loss due to abrasion or fracture.

Disintegration time The disintegration time of the tablets was measured from six tablets according to the European Pharmacopoeia at 37 ± 1°C using pure water as medium liquid.

Statistical analyses

Correlation analysis Correlation analysis (Barlett chi-square statistics) was performed on the data presented in Table 2 using SYSTAT v. 5.0 (SYSTAT Inc., U.S.A.). The response variables were: flow rate of granules, standard deviation of flow rate, angle of repose, standard deviation of angle of repose, mean weight of tablets, standard deviation of mean weight, crushing strength, standard deviation of crushing strength, tablet friability, disintegration time of tablets, standard deviation of disintegration time, upper compression force, standard deviation of upper compression force, lower compression force, standard deviation of lower compression force and R value expressed as $R = F_{lp}/F_{up}$.

Regression analysis In previous papers, Merkku et al. (1993a,b) used multilinear stepwise regression analysis in studying the effects of three independent fluidized bed granulation process variables on the granule size and granule friability. In this study, regression models were developed for flow rate of granules, tablet friability and disintegration time of tablets.

The initial regression model for three independent variables used in the present study was as follows:

$$Y_1(T,p,m) = a_0 + a_1T + a_2p + a_3m + a_4Tp + a_5Tm + a_6pm + a_7T^2 + a_8p^2 + a_9m^2 + a_{10}Tpm \quad (1)$$

where $a_0,\ldots,a_{10}$ are the coefficients of a certain system. T, p and m denote the inlet air temperature, atomizing air pressure and binder solution amount, respectively.

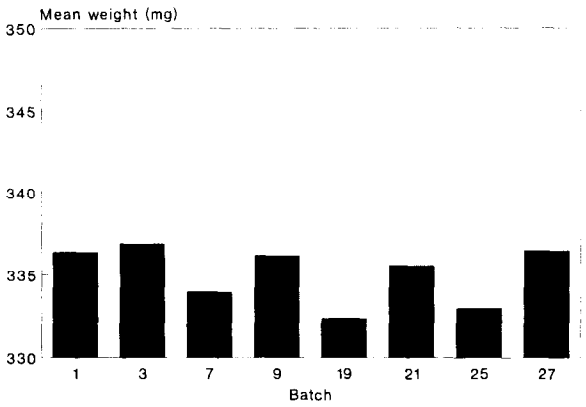


Fig. 1. Weight variation of tablets at the 2^3 factorial points.

Each term included in the final regression model was tested with the t-test. Only significant terms ($p < 0.05$) were included in the model. Before statistical analysis the independent variables were normalized to −1, 0 and +1. The statistical analyses and the generation of the regression models were performed using SYSTAT v. 5.0 (SYSTAT Inc., U.S.A.).

Results and Discussion

Correlation analysis

Flow rate

The results show that flow rate was a very effective parameter because it correlated ($p < 0.001$) very highly with the standard deviations of mean weight and upper and lower compression forces, and quite highly with the R value ($p < 0.005$). All these correlations are readily understood. If the granules do not flow freely into the die, there will be variation in weight and, most certainly, also in compression forces. An essential point here is that standard deviations of the compression forces can be used as a direct indicator of granule flow. This observation is more important because the flow time did not have any significant effect on the mean weight of the tablets.

TABLE 2

Flowability of granules and physical properties of tablets (T, inlet air temperature; p, atomizing air pressure; m, binder solution amount)

Batch	T	p	m	Flow rate (s)	SD	Angle of repose (°)	SD	Mean weight (mg)	SD	Crushing strength (N)	SD	Friability (%)	Disintegration time (min)	SD	F_{up}	SD	F_{lp}	SD	R
1_a	−1	−1	−1	12.0	0.1	32.0	0.3	336	1.0	44	4	3.5	7	2	10.2	0.14	9.47	0.13	0.927
1_b	−1	−1	−1	11.9	0.1	31.4	0.8	337	1.2	34	5	4.3	5	1	10.1	0.32	9.27	0.29	0.917
2	−1	−1	0	13.0	0.5	31.7	1.0	330	1.6	48	3	2.9	8	1	10.4	0.29	9.55	0.26	0.922
3_a	−1	−1	1	13.2	0.3	30.8	0.2	340	1.8	56	4	2.5	12	2	10.2	0.32	9.22	0.28	0.905
3_b	−1	−1	1	12.8	0.2	31.0	0.1	334	2.1	39	8	2.9	11	3	10.3	0.15	9.39	0.13	0.916
4	−1	0	−1	12.1	0.1	31.3	1.3	331	1.0	37	3	3.7	7	1	9.93	0.20	9.17	0.18	0.924
5	−1	0	0	12.1	0.2	31.2	0.4	333	1.3	56	2	2.5	10	1	9.87	0.13	9.10	0.13	0.922
6	−1	0	1	12.6	0.1	30.9	0.8	333	2.6	50	5	2.4	10	2	10.1	0.19	9.33	0.18	0.920
7_a	−1	1	−1	12.0	0.2	31.7	0.4	333	0.8	44	3	3.5	7	1	10.0	0.11	9.28	0.11	0.927
7_b	−1	1	−1	11.7	0.3	31.6	1.0	335	0.5	40	3	2.8	8	1	9.85	0.09	9.10	0.09	0.924
8	−1	1	0	11.8	0.1	31.6	0.7	332	0.7	50	2	3.0	10	2	9.81	0.11	9.10	0.11	0.927
9_a	−1	1	1	12.0	0.1	31.6	0.2	334	1.1	45	2	2.8	13	1	9.83	0.13	8.99	0.12	0.915
9_b	−1	1	1	12.2	0.1	31.8	0.4	338	1.0	50	2	2.3	12	2	10.3	0.12	9.53	0.10	0.928
10	0	−1	−1	12.1	0.3	32.8	0.2	328	1.2	29	5	4.2	4	1	9.87	0.14	9.05	0.13	0.918
11	0	−1	0	12.3	0.3	32.1	0.8	331	2.1	37	5	3.7	6	1	9.84	0.36	9.09	0.33	0.923
12	0	−1	1	12.7	0.1	32.1	0.1	330	2.0	48	3	2.8	12	1	9.85	0.11	9.11	0.11	0.925
13	0	0	−1	11.8	0.3	31.6	0.1	335	1.0	39	4	3.7	9	2	9.89	0.06	9.17	0.05	0.926
14_a	0	0	0	11.7	0.2	31.2	0.5	335	0.8	44	3	2.8	10	2	10.1	0.10	9.50	0.09	0.937
14_b	0	0	0	11.7	0.2	31.8	0.1	330	2.7	49	4	2.8	10	3	9.89	0.14	8.97	0.12	0.907
14_c	0	0	0	11.5	0.1	32.0	0.6	333	1.7	48	3	2.7	11	2	10.2	0.09	9.46	0.08	0.925
14_d	0	0	0	11.9	0.2	31.9	0.4	336	0.9	55	3	2.5	11	1	9.88	0.09	9.18	0.08	0.929
15	0	0	1	11.7	0.1	31.2	0.4	333	0.8	40	3	2.9	11	1	10.1	0.09	9.45	0.09	0.932
16	0	1	−1	11.8	0.2	31.3	0.6	335	0.7	36	4	3.2	7	0	10.3	0.09	9.61	0.08	0.930
17	0	1	0	12.0	0.2	31.8	0.1	335	0.7	43	4	2.7	11	1	10.3	0.15	9.58	0.15	0.934
18	0	1	1	11.7	0.1	30.9	0.9	336	1.2	40	4	2.8	11	1	9.78	0.10	9.14	0.08	0.934
19_a	1	−1	−1	11.8	0.1	31.7	0.5	334	1.4	38	4	3.5	8	1	10.0	0.19	9.23	0.18	0.920
19_b	1	−1	−1	12.0	0.1	32.3	0.7	331	1.6	34	6	3.1	7	2	9.89	0.11	9.12	0.10	0.922
20	1	−1	0	12.9	0.5	31.8	0.5	340	3.3	51	5	2.8	8	2	9.71	0.23	8.97	0.21	0.923
21_a	1	−1	1	12.7	0.3	31.1	0.9	334	1.8	45	3	3.0	10	3	9.84	0.30	9.03	0.27	0.917
21_b	1	−1	1	12.9	0.4	33.0	0.5	337	2.7	47	5	2.4	12	1	9.81	0.28	9.03	0.26	0.920
22	1	0	−1	11.6	0.1	31.3	0.7	333	0.6	34	7	3.8	6	0	9.87	0.14	9.15	0.11	0.927
23	1	0	0	11.8	0.1	31.6	0.2	331	2.0	41	8	3.2	8	2	9.89	0.09	9.17	0.09	0.927
24	1	0	1	12.0	0.1	31.6	0.2	328	2.9	45	5	3.8	13	1	10.2	0.18	9.41	0.17	0.923
25_a	1	1	−1	11.7	0.1	32.1	0.3	332	2.6	37	5	3.7	7	2	9.96	0.16	9.21	0.14	0.924
25_b	1	1	−1	11.8	0.2	32.0	0.6	335	0.7	45	3	2.9	7	2	9.92	0.13	9.16	0.12	0.923
26	1	1	0	12.0	0.1	31.9	0.1	332	1.5	43	3	3.0	10	1	9.86	0.10	9.06	0.10	0.919
27_a	1	1	1	12.4	0.1	32.9	0.9	342	2.8	64	4	2.0	14	2	10.3	0.15	9.30	0.14	0.906
27_b	1	1	1	11.8	0.1	32.0	0.4	331	1.6	39	3	1.2	13	1	10.1	0.12	9.34	0.12	0.925

Weight variation

The standard deviation of the tablet weight had the highest correlations with the above mentioned flow rate and, surprisingly, with the R value ($p < 0.001$). The other high correlations ($p < 0.02$) were in the following descending order: standard deviations of compression force, disintegration time and crushing strength. The results here suggest that the R value as well as the standard deviations of the compression force may be useful in studying and minimizing the weight variation. Naturally, this observation will require furher studies with other materials. When a larger amount of binder was used, the mean tablet weight was larger irrespective of the atomizing air pressure and inlet air temperature (Fig. 1). This is obviously due to the higher density of the granules.

Crushing strength

The crushing strength of the tablets showed two very high – but quite trivial – dependences on the friability and disintegration time ($p < 0.001$). It was also observed that the crushing strength increased with increasing binder amount (Fig. 2) irrespective of the inlet air temperature and atomizing air pressure. According to the analysis of variance, the binder amount was the only factor that affected the crushing strength of tablets (Table 3). This means that the use of a large amount of binder yields a larger number of bondings between the particles and, consequently harder granules and tablets.

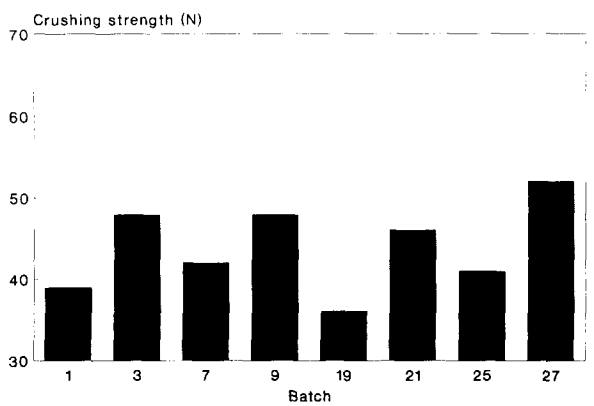


Fig. 2. Crushing strength of tablets at the 2^3 factorial points.

TABLE 3

Summary of the analysis of variance

Source	Flow rate	Friability	Disintegration time	Crushing strength
T	[c]	–	–	–
p	[a]	–	[a]	–
m	[a]	[a]	[a]	[c]
$T \cdot p$	–	–	–	–
$T \cdot m$	–	–	–	–
$p \cdot m$	[c]	–	–	–
$T \cdot p \cdot m$	–	–	[c]	–

Level of significance [a] $p < 0.001$, [b] $p < 0.01$ and [c] $p < 0.05$. (–) Difference between the probability values is insignificant ($p > 0.05$).

R value

The R value had the next highest correlations (in descending order): standard deviation of mean weight, flow rate, standard deviations of the upper and lower forces and lower compression force.

It is once again suggested that especially the standard deviations of the compression forces can be used as an indicator of granule flow. The standard deviations of the compression forces and the R value may be useful parameters in indicating weight variation, although additional studies with other materials will be required to show the general usefulness of these parameters. It should be noted that the upper force alone was not able to explain the granule flow.

Regression models

Regression models were generated by using all (total 38) experimental points. The final regression models had the following forms:

Flow rate of granules

$$Y_2(T,p,m) = 0.204T^2 + 0.270p^2 - 0.170pm - 0.285p + 0.246m + 11.77 \quad (2)$$

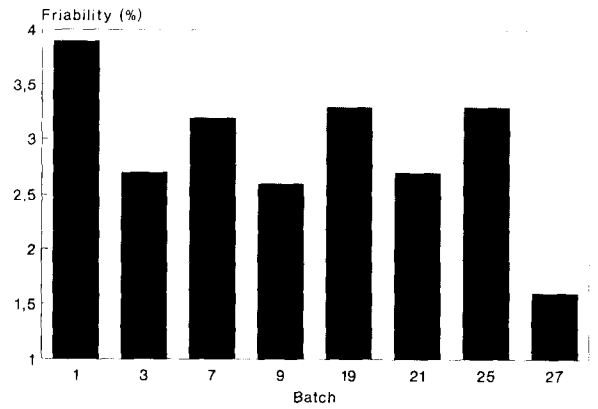


Fig. 3. Tablet friability at the 2^3 factorial points.

where $Y_2(T,p,m)$ is the flow rate, T denotes the inlet air temperature, p is the atomizing air pressure and m represents the binder amount. The squared multiple regression coefficient of the model was 0.751. The model showed directly that the flow time of granules was non-linearly dependent on the inlet air temperature and pressure.

The three-dimensional surface plots (Fig. 5a–c) have been drawn on the basis of the model by assigning a constant value to one of the variables T, p or m using Graftool v. 3.3 (Graphical Analysis System, 3-D Visions Corp., U.S.A.).

Effect of temperature The inlet air temperature did not have any clear effect on the flow rate of the granules. The most important factors were the atomizing air pressure and the binder solution amount (Table 3). The shape of the response surface is in each level similar, with approximately the same maxima and minima. The best flowing granules were obtained when a small amount of binder (150 g) was used (Fig. 5a). The effect of atomizing air pressure was more complicated. A change from 1.0 to 1.7 bar decreased, but a change from 1.7 to 2.0 bar increased the flow rate. At higher pressures the proportion of better wetting droplets evidently increases significantly, and larger granules with longer flow time are formed.

Effect of atomizing air pressure The atomizing air pressure had only a slight effect on the flow rate of the granules. The response surface had a parabolic structure in each level. Again, the fastest flowing granules were achieved when a small amount of binder (150 g) was used (Fig. 5b). A change in temperature from 40 to 50°C decreased, but a change from 50 to 60°C increased the flow rate. The decrease might be due to the changes in viscosity of the binder solution and to drying of the binder droplets. The flow rate increased at higher temperatures, which might be due to an increase in the amount of low viscous, better wetting droplets.

Effect of binder solution amount The amount of binder solution affected significantly the flow rate of granules at high inlet air temperatures and at low atomizing air pressure. The response surface is highly curved (Fig. 5c) due to the quadratic terms of T and p.

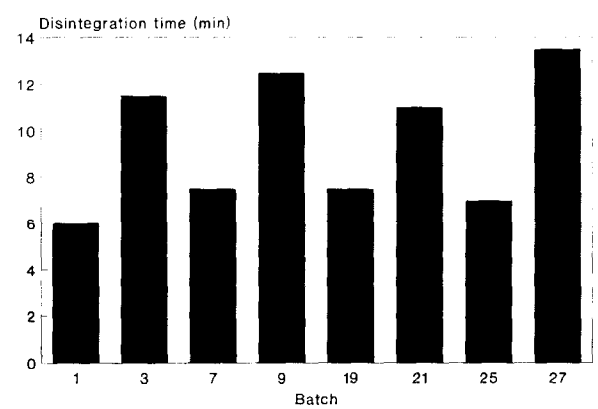


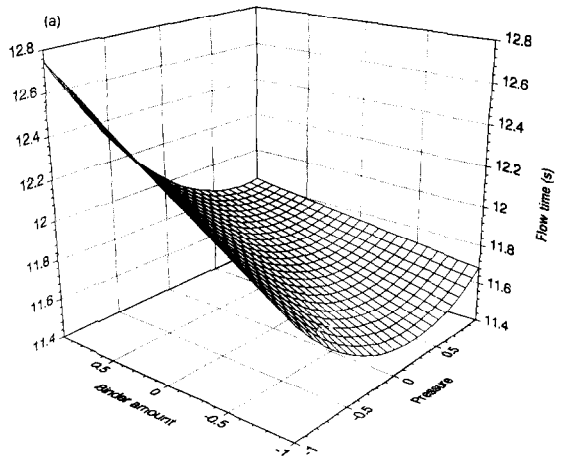
Fig. 4. Disintegration time of tablets at the 2^3 factorial points.

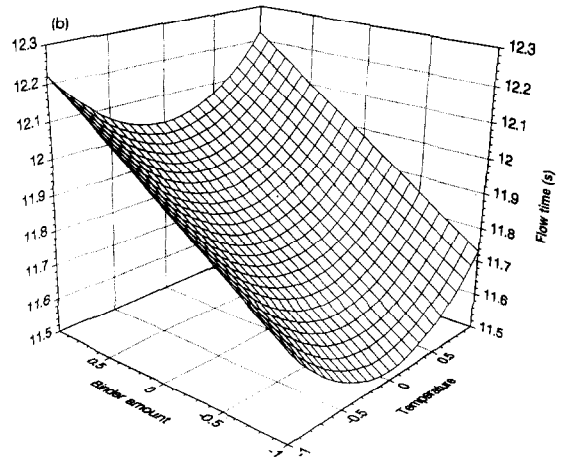
Friability of tablets

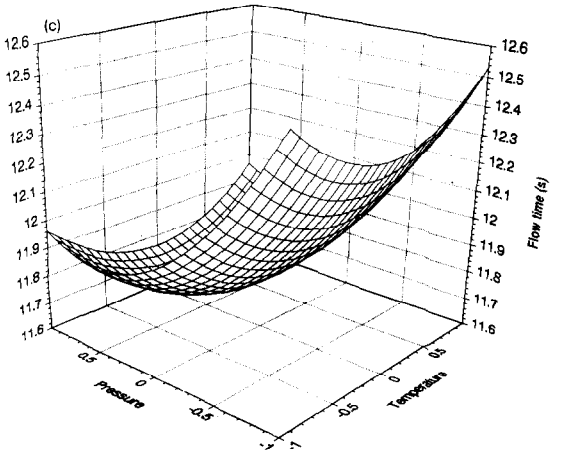
$$Y_3(p,m) = -0.219p - 0.465m + 3.008 \qquad (3)$$

where $Y_3(p,m)$ is the friability of tablets. The squared multiple regression coefficient was now only 0.495.

The model Y_3 shows directly that the inlet air temperature did not affect the tablet friability. The factor m was clearly the most dominating factor (Table 3). In this case, the response surface is very stable without local maxima and minima. When a high binder amount (450 g) and a high atomizing air pressure (2 bar) were used, the tablets had the lowest friability percentage (Figs 3 and 6). The most friable tablets were achieved with a low binder amount (150 g) and a low







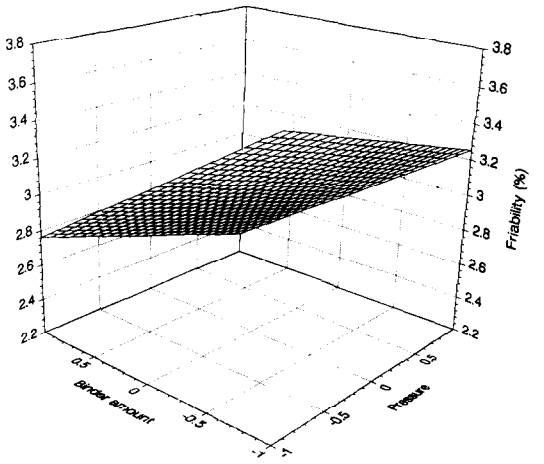


Fig. 6. Dependence of tablet friability on binder amount and atomizing air pressure.

atomizing air pressure (1 bar). This might be due to the large droplet size which causes improper wetting of powder particles. The friability percentage decreased when the binder solution amount was large irrespective of the inlet air temperature and atomizing air pressure (Fig. 3). This may be due to the good wetting of the mass. Model Y_3 has a rather low squared multiple R. It is expected that the use a greater number of friability determinations would increase the squared multiple regression coefficient. This should be tested in the future.

Disintegration time

$$Y_4(p,m) = 0.769p + 2.500m + 9.368 \qquad (4)$$

where $Y_4(p,m)$ is the disintegration time of tablets. The squared multiple regression coefficient was 0.784.

This model showed again that the inlet air temperature did not affect the tablet response. Factors m and p were the most important (Table 3). The response surface is also very stable in this

Fig. 5. (a) Effect of inlet air temperature (50°C) on the flow time of granules. (b) Effect of atomizing air pressure (1.5 bar) on the flow time of granules. (c) Effect of binder amount (300 g) on the flow time of granules.

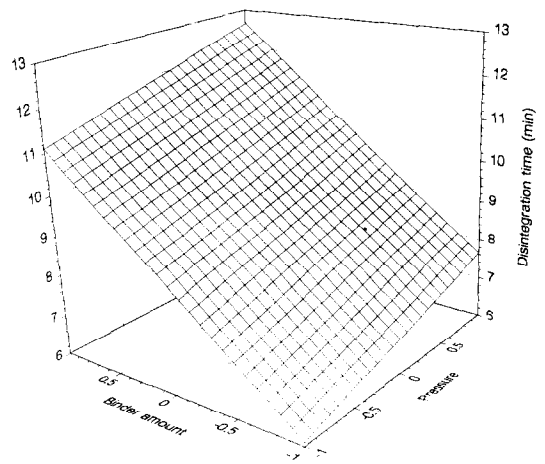


Fig. 7. Dependence of disintegration time on binder amount and atomizing air pressure.

case (Fig. 7). The disintegration time increases systematically with increasing binder amount (Fig. 4). The effect of atomizing air pressure is similar (Fig. 7). When a high atomizing air pressure with a large amount of binder is used, the smaller droplets form more bondings between the powder particles and produce harder granules and tablets. These results agree with the friability results.

This study proved that the flow rate of granules was quite well explained by the independent variables. The development of regression models for the tablet responses was more complicated. The inlet air temperature did not affect the tablet responses. It can be concluded that tablet compression is a robust process, which hinders most of the effects of independent granulation process variables as also suggested by Niskanen and Yliruusi (1992). However, the disintegration time of tablets was still reasonably well explained by the regression model.

Acknowledgements

This study was supported by the Technology Development Centre in Finland (TEKES) and the Finnish pharmaceutical industry (Huhtamäki, Leiras and Orion Corporation, Orion-Farmos Pharmaceuticals). The authors wish to thank Osmo Antikainen, M.Sc. (Eng.), Jaana-Liisa Aro, B.Sc. (Pharm.), and Tanja Laaksonen, laboratory assistant, for technical assistance. Financial support from the Jenny and Antti Wihuri Foundation is acknowledged.

References

Aulton, M. and Banks, M., The factors affecting fluidised bed granulation. *Manuf. Chem.*, 49 (1978) 50–56.

Bos, C.E., Bolhuis, G.K., Lerk, C.F., De Boer, J.H., Duineveld, C.A.A., Smilde, A.K. and Doornbos, D.A., The use of a factorial design to evaluate the physical stability of tablets prepared by direct compression: I. A new approach based on the relative change in tablet parameters. *Eur. J. Pharm. Biopharm.*, 37 (1991a) 204–209.

Bos, C.E., Bolhuis, G.K., Lerk, C.F., De Boer, J.H., Duineveld, C.A.A., Smilde, A.K. and Doornbos, D.A., The use of a factorial design to evaluate the physical stability of tablets prepared by direct compression: II. Selection of excipients suitable for use under tropical conditions. *Eur. J. Pharm. Biopharm.*, 37 (1991b) 210–215.

Davies, W.L. and Gloor, W.T., Jr, Batch production of pharmaceutical granulations in a fluidized bed: I. Effects of process variables on physical properties of final granulation. *J. Pharm. Sci.*, 60 (1971) 1869–1874.

Davies, W.L. and Gloor, W.T., Jr, Batch production of pharmaceutical granulations in a fluidized bed: II. Effects of various binders and their concentrations on granulations and compressed tablets. *J. Pharm. Sci.*, 61 (1972) 618–622.

De Jong, J.A.H., Tablet properties as a function of the properties of granules made in a fluidized bed process. *Powder Technol.*, 65 (1991) 293–303.

Gamlen, M.J., Seager, H. and Warrack, J.K., The structure and tablet properties of paracetamol granules prepared in a fluidized bed and by wet massing. *Int. J. Pharm. Tech. Prod. Mfr*, 3 (1982) 108–114.

Gómez-Amoza, J.L., Hernández, B., Landín, M., Pérez-Marcos, B., Souto, C., Concheiro, A. and Martinez-Pacheco, R., Influence of compression force and polymer type on the physical, structural and drug-release characteristics of methylcellulose-based tablets. *Eur. J. Pharm. Biopharm.*, 37 (1991) 142–146.

Kocova El Arini, S. and Polderman, J., Some factors influencing the properties of tablets made from fluid-bed granulations. *Drugs Made Ger.*, 26 (1983) 205–211.

Merkku, P. and Yliruusi, J., Use of 3^3 factorial design and multilinear stepwise regression analysis in studying the fluidized bed granulation process: I. *Eur. J. Pharm. Biopharm.*, 39 (1993a) 75–81.

Merkku, P., Antikainen, O. and Yliruusi, J., Use of 3^3 factorial design and multilinear stepwise regression analysis in studying the fluidized bed granulation process: II. *Eur. J. Pharm. Biopharm.*, 39 (1993b) 112–116.

Merkku, P., Yliruusi, J. and Hellén, L., Testing of an automated laboratory scale fluidized bed granulator using different bed loads. *Acta Pharm. Fenn.*, 101 (1992b) 173–180.

Merkku, P., Yliruusi, J., Kaukonen, A., Hellén, L. and Kristoffersson, E., The use of an automated fluidised bed granulator in pharmaceutical process research. *Proc. 11th Pharm. Technol. Conf., Manchester*, 2 (1992a) pp. 227–259.

Niskanen, T. and Yliruusi, J., Evaluation of the effects of two independent granulation process variables on tablet properties. *Acta Pharm. Nord.*, 4 (1992) 253–257.

Rankell, A.S., Scott, M.W., Lieberman, H.A., Chow, F.S. and Battista, J.V., Continuous production of tablet granulations in a fluidized bed: II. Operation and performance of equipment. *J. Pharm. Sci.*, 53 (1964) 320–324.

Timmins P., Delargy, A.M., Minchom, C.M. and Howard, J.R. Influence of some process variables on product properties for a hydrophilic matrix controlled release tablet. *Eur. J. Pharm. Biopharm.*, 38 (1992) 113–118.

Wan, L.S.C. and Lim, K.S., Compaction characteristics of fluidized bed lactose granules with different modes of addition of binder. *STP Pharm.*, 6 (1990) 624–628.

Veillard, M., Bentejac, R., Puisieux, F. and Duchene, D., A study of granule structure: Effects of the method of manufacture and effects of granule structure on compressibility into tablet form. *Int. J. Pharm. Tech. Prod. Mfr*, 3 (1982) 100–107.