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EXTRUSION OF AN EFFERVESCENT GRANULATION WITH A TWIN SCREW EXTRUDER, BAKER PERKINS MPF 50 D

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ABSTRACT

Anhydrous citric acid and sodium bicarbonate were granulated with ethanol in an extruder.

The load on the motor, the dwell time, the fraction above 1.00 mm and below 0.125 mm of unmilled granulation, the geometric mean diameter by weight and the carbon dioxide content of the milled granulation were influenced by all these process variables: powder flow rate, ethanol concentration, screw speed, die restriction and screw configuration. However, the impact of powder flow rate, ethanol concentration and

screw speed was partly of an interaction type, except in the case of motorload. As the response variables showed significant interactions, the dependence on the process variables was complex.

The temperature of the extrudate was affected by screw configuration, die plate and ethanol concentration without any interactions.

Regarding the output, this variable was influenced by screw configuration and by an interaction between ethanol concentration and die plate.

INTRODUCTION

Pharmaceutical granulations are normally produced in different types of mixers, although extruders are sometimes used.[1]

The effervescent granulation is composed of anhydrous citric acid and sodium bicarbonate. Dehydrated alcohol is used as the granulating liquid. A portion of the citric acid is dissolved during the massing and functions as a binder. After drying and milling, the granulation is mixed with other components and compressed to effervescent tablets.

The effervescent granulation is normally produced in a planetary mixer by batchwise operation. As continuous operation might bring advantages, such a production technique was tested. The co-rotating twin screw extruder was assumed to be a suitable piece of equipment, as it had recently been tested for production of paracetamol extrudates[2]. So, the operating conditions of the extruder were examined in relation to the production of the effervescent granulation.

MATERIALS AND METHODS

Materials

The granulation is composed of 2/3 anhydrous citric acid and 1/3 sodium bicarbonate; see Table 1. Dehydrated alcohol is the granulating liquid. All the raw materials are of Ph.Eur. quality.

Extruder

The twin screw extruder[3] was used as a 15:1 extruder, which means that the powder inlet port was at a distance, from the exit of the extruder, of 15 extruder diameters. Both powders were added from separate feeders[4] into the inlet port.

TABLE 1

Powder Characteristics

Substance	Geometric mean diameter by weight, μm	Geometric standard deviation
Anhydrous citric acid	600	1.3
Sodium bicarbonate	115	1.5

The powder flow rates from the feeders at different settings were tested by weighing the powder fed during 6 min. Besides, samples from both feeders were taken for 4.8 s every 0.5 min for 30 min and weighed in order to obtain an idea of the variation in the powder flow rate at low and high powder-flow levels.

Ethanol was pumped through a nozzle in the extruder barrel.

The ethanol flow rates at different settings were tested by means of weighing the liquid obtained from 6 min of pumping.

Tests were performed either without restriction plates or with a strand die of 1.4-mm thickness with 3-mm holes occupying 32.5% of the total area.

Two different screw configurations composed of feeding, mixing and discharge zones were tested, representing a medium and a low intensity of agitation.

The extruder barrel was cooled with water to a temperature of 25° C during all the tests.

Experiments

The influence of the following process variables was investigated: powder flow rate (P); ethanol flow rate, which was expressed as ethanol concentration as a percentage on a dry-weight basis (E); rotation rate of agitator shafts or screw speed (S); restriction or die plates (D); and screw configuration (C).

2^3 factorial experiments with centre points were performed for each of the four combinations of screw configuration and die plate/no die plate, Table 2. The experiments in the centre points were replicated once. Five of the experiments concerning medium screw configuration were also replicated once. The centre points were only used for variance estimation.

The actual levels of the independent variables are supplied in Table 3.

Granulation

Each granulation experiment was run for 30 min.

During operation, the influence on the following response variables was examined: load of drive motor (LOAD); temperature of the extruded mass (TEMP); dwell time (TIME); output (OUTP); granule fraction above 1.00 mm (>1MM) and below 0.125 mm (<0.125MM) of dried and unmilled granulation; geometric mean diameter by weight (MDGW) and carbon dioxide content (CO_2) of dried and milled granulation.

The load on the drive motor was read from the display at 15 and 30 min.

The temperature of the extruded mass was checked at 15 and 30 min by means of immediately measuring the stable temperature of a small heap sampled just below the outlet of the extruder, with a Pt-100 resistance element[5].

TABLE 2

Experimental Design of Each Screw Configuration

Test No	Factors and factor level				Factor combination
	P	E	S	D	
1	-1	-1	-1	-1	(1)
2	1	-1	-1	-1	a
3	-1	1	-1	-1	b
4	1	1	-1	-1	ab
5	-1	-1	1	-1	c
6	1	-1	1	-1	ac
7	-1	1	1	-1	bc
8	1	1	1	-1	abc
9	-1	-1	-1	1	d
10	1	-1	-1	1	ad
11	-1	1	-1	1	bd
12	1	1	-1	1	abd
13	-1	-1	1	1	cd
14	1	-1	1	1	acd
15	-1	1	1	1	bcd
16	1	1	1	1	abcd
17	0	0	0	-1	0-1
18	0	0	0	1	0+1

TABLE 3

Process Variables and Factor Levels for Each Screw Configuration

	Process variable	Factor levels -1	0	1
P	Powder flow rate, kg/h	60	75	90
E	Ethanol concentration, %	5.5	7.0	8.5
S	Screw rate, rpm	260	350	440
D	Restriction plate	No	-	Yes
C	Screw configuration, agitation type	Low	-	Medium

A rough estimate of the dwell time was obtained by adding a small amount of colour, approximately 1 g of patent blue[6], in the inlet port and measuring the time until it reached the outlet.

The extrudate was collected in a bucket from the exit port during 3 min and weighed. The output was calculated as a percentage of the theoretical discharge rate.

Samples were drawn after 20 min for sieve analysis. These samples were dried in ventilated drying ovens[7], for 7 h at room temperature and 7 h at 60°C. The whole sample intended for sieve analysis of unmilled granulation, approximately 100 g, was sieved for 10 min through sieves measuring 1.00, 0.500 and 0.125 mm[8].

The larger sample for sieve analysis of milled granulation, approximately 3 kg, was comminuted through a 1.0 mm screen in a granulating machine[9]. Then it was reduced to a sample of approximately 100 g by means of regular sampling from the granulation stream flowing through a tablet machine hopper. Sieve analyses were performed through sieves measuring 0.710, 0.500, 0.250 and 0.125 mm, and the duration of the sieving process was 10 min.

The carbon dioxide content was measured with the help of a gravimetric method. CO_2 was expelled from the granulate and adsorbed on Ascarite granules[10].

Statistical analysis

The influence of the process variables on each of the response variables was tested by analysis of variance with all interaction terms included. Besides, the interdependence of the response variables was tested by means of stepwise regression. For each response variable, the other response variables together with all the process variables (including their interactions) were used as independent variables. No table for the stepwise regression is reproduced in this article. Correlation coefficients between the response variables were calculated.

RESULTS AND DISCUSSION

Extruder

The variation in the powder flow rate during the short time intervals differed between the feeders. With regard to the original feeder of the extruder, the variation was about ± 3%, while the variation of the second feeder - a temporary loan - was approximately ± 10%. In spite of this large variation, we were obliged to use the second feeder.

Statistical analysis

When studying the influence of many factors, there is always a risk that factors without effect on the response still happen to become significant. To avoid this source of error, effects were considered significant only at $P<0.01$.

Since the estimated main effects and interactions are, by and large, uncorrelated, the results of the analysis of variance are quite straight-forward. Besides the analysis of variance, correlation coefficients and stepwise-regression models were also calculated in order to describe the interdependences of the response variables. On the basis of the stepwise regression, we may derive information about the influence on a response variable exercised by the other response variables, once the effect of the most important process variables and their interactions has been compensated for. The response variables, however, are in part strongly correlated, which is why the conclusions from the correlation coefficients and the stepwise regression will not always be the same. For example, it could be that even if one variable is highly correlated with another, the former is not significant in a regression model where other variables are included, too. It should be stressed that various problems may occur in the stepwise procedure; these results should therefore be cautiously interpreted.

<u>Tests with the two screw configurations</u>

As the screws convey the material forward, it is heated by a combination of transferred and frictionally generated heat.[11] Through the addition of ethanol, the mixture becomes a viscous liquid in the extruder channel. If there is a restriction at the end of the channel, a positive pressure gradient will be established. This will cause some of the granulation to flow in the opposite direction.

The results of the experiments are summarized in Table 4, regarding the medium intensity agitation, and in Table 5, with reference to the low intensity type of screw configuration.

The load on the motor and the temperature of the extrudate were the same at 15 and 30 min and the values normally deviated from those that were present at the start. This indicates that normal operating conditions are attained within 15 min. In Tables 4 and 5, only the 15-min values are supplied.

The variation found in the replicated tests was reasonable.

TABLE 4

Results of Screw Configuration of Medium Agitation Type

No	Factor combination	Load, %	Temperature of extrudate, C	Dwell time, s	Output, %	Unmilled granulation Fraction >1.00 mm,%	Unmilled granulation Fraction <0.125 mm,%	Milled granulation Mean diameter, um	Milled granulation CO , %
1	0+1	20	41	15	96.0	95.6	1.3	390	12.2
2	0-1	17	40	12	93.5	85.8	2.5	380	13.0
3	abc	13	35	12	92.2	74.7	3.8	450	14.0
4	acd	21	44	12	94.8	92.9	2.4	370	12.6
5	c	12	36	10	93.2	88.8	1.6	390	12.5
6	bd	19	39	18	95.2	91.6	2.3	405	12.9
7	d	24	40	17	93.2	69.5	4.9	370	11.4
8	0-1	16	34	12	92.2	86.6	3.1	390	13.0
12	0+1	18	35	14.5	94.7	92.9	2.6	420	12.4
13	ab	16	32	16	92.2	49.2	5.2	510	14.1
14	ad	34	40	18.5	92.7	87.2	4.2	400	13.0
15	cd	14	38	12.5	93.2	89.8	3.3	410	11.0
16	abcd	8	30	11	94.2	77.3	5.2	450	14.7
17	d	23	40	17	93.2	79.5	4.9	420	10.7
18	a	32	36	16.5	94.8	90.7	3.6	350	12.3
19	ab	14	31	15.5	93.2	44.8	5.6	500	13.8
20	b	18	33	16.5	92.2	69.2	6.1	420	13.5
21	ac	18	41	11	92.7	92.5	2.3	370	12.9
22	bc	5	26	6.5	95.2	79.0	1.8	610	15.0
23	(1)	19	34	9.5	93.2	64.2	4.5	450	12.9
24	b	16	34	16	93.7	70.2	6.2	420	13.0
28	abd	18	34	17.5	93.2	78.1	8.0	390	13.5
29	0+1	19	40	15	96.0	91.1	3.8	380	12.1
33	abd	20	37	17.5	94.2	85.4	5.6	395	13.5
34	bc	5	26	8.5	92.2	80.2	1.6	610	14.6
35	bcd	5	28	9.5	96.8	90.4	1.8	455	15.0

TABLE 5

Results of Screw Configuration of Low Agitation Type

No	Factor combination	Load, %	Temperature, °C Extrudate	Dwell time, s	Output, %	Unmilled granulation Fraction >1.00 mm,%	Unmilled granulation Fraction <0.125 mm,%	Milled granulation Mean diameter, μm	Milled granulation CO_2 %
40	acd	8	35	4.2	95.8	64.3	4.8	550	13.5
41	ab	4	24	4.8	97.3	39.9	2.9	675	16.1
42	c	5	24	4.8	98.0	19.1	2.8	565	16.0
43	0+1	6	30	4.8	98.4	85.1	2.4	510	14.2
44	0-1	4	25	4.0	98.4	35.8	1.6	745	15.1
45	0+1	6	28	4.8	98.4	84.1	3.0	490	14.5
46	bcd	4	26	4.2	96.8	92.5	2.6	470	14.3
47	(1)	4	25	4.5	98.0	17.6	2.8	565	16.4
48	cd	6	32	4.2	98.0	45.2	5.6	465	15.2
49	b	4	23	5.5	98.3	63.7	1.4	780	15.1
50	bd	5	26	5.5	98.3	87.7	2.3	500	15.0
51	abcd	5	26	4.2	98.3	92.5	1.8	500	14.9
52	bc	4	24	4.0	92.2	75.1	1.2	710	16.1
53	abd	5	27	6.0	96.3	93.1	1.6	530	15.1
54	0-1	5	25	4.0	97.2	29.1	2.1	650	16.2
59	d	7	32	5.4	98.0	53.8	5.5	500	14.4

TABLE 6

Analysis of Variance

Response variable	Significant main effects and interactions	
	$P \leq 0.001$	$0.001 < P \leq 0.01$
LOAD	P,E,S,C	D
	PC,EC,SC	PE,PES,PESC
TEMP	E,D,C	-
TIME	P,S,D,C	
	PC,ES,ED,SD,SC,DC	PE,PS,PD
	PES,PDC,ESC,EDC,SDC	PED,PEC,ESD
	PESD,PESC	PEDC,PESDC
OUTP	C	ED
>1MM	E,S,D,C	
	PE,EC,SD,DC,EDC	PD,PDC,PESD,PESC
<0.125MM	EC	S,D,C
		PE,ED,SC
MDGW	E,D,C	
	ED,DC	PESDC
CO_2	E,D,C	
	ED,EC	DC,PDC,ESC,
		PEDC

Regarding the load on the motor, this was significantly influenced by all the five process variables, but screw configuration had the most important influence. The medium agitation type configuration increased the response. There were a lot of interactions, too; see Table 6. The power consumption of the motor, or the motorload, depends on the rate of extrusion[11]; the influence of the screw speed was hence expected. The power requirement also depends on the viscosity of the viscous fluid in plasticating extruders. Therefore, both the ethanol concentration and the powder flow rate are expected to produce an effect. Because both the screw configuration and the die plate will cause a pressure gradient in the channel, these two factors are expected to influence the load, too. As the factor levels are normalized to -1, 0 and +1, the magnitude of the coefficients in Table 7 will directly indicate the degree of influence of the process variables. The sign in front of the coefficient indicates whether the response is increasing or decreasing. As for the dependence on the other response variables, dwell time and temperature turned out to be the most important both according to stepwise regression and the correlation analyses. Higher values of both variables increased the load.

The temperature of the extrudate was influenced by screw configuration, die plate and ethanol concentration; see Table 6. Medium agitation type configuration increased the response; so did die plate, although not so distinctly. Increasing ethanol concentration reduced the temperature. There were no interactions. A dependence on all the factors is expected, but as ethanol reduces the friction between the powder particles in the channel, this may weaken the impact of powder flow rate and screw speed. Besides, as the temperature is measured outside the extruder, evaporation of some solvent may affect the results. Mean diameter, load and CO_2 content were the

TABLE 7

Stepwise Regression. Model and Standard Deviation (s).

Model*			s
LOAD	=	11.2+1.6P-2.7E-2.8S+0.84D+5.9C-0.94PE+1.2PC-1.7EC-2.6SC+0.84PES+0.66PESC	1.16
TEMP	=	31.2-2.7E+1.9D+4.1C	2.20
OUTP	=	95.2-1.6C+0.68ED	1.02
>1MM	=	68.6+7.5E+3.4S+11.3D+12.5C-4.8PE-0.22PS+2.1PD-11.5EC-2.7SD-6.2DC-2.4PDC+2.7EDC-1.9PESD+1.8PESC	3.23
<0.125MM	=	3.30-0.46S+0.37D+0.37C+0.40PE-0.44ED+0.64EC-0.45SC	0.64
MDGW	=	497+35E-41D-68C-28ED+25DC+18PESDC	28.6
CO_2	=	14.2+0.43E-0.52D-1.0C+0.36ED+0.45EC+0.32DC+0.23PDC+0.24ESC-0.28PEDC	0.41

* The model of TIME was very complex. Therefore it is not represented in the table.

most important of the other response variables both according to the stepwise regression and the correlation coefficient analysis. Higher values of mean diameter and carbon dioxide reduced the temperature, while higher load values increased the response.

The determination of residence-time distribution is laborious. Therefore, a simpler test was used which gave a rough estimate of the dwell time. This time was very short, less than approximately 6 s in the case of the low intensity configuration; see Table 5. All the colour was emptied from the extruder within a minute. In respect of medium intensity screw configuration, the dwell time was also short, less than 20 s; see Table 4. The colour left the outlet port within a few minutes. All the process variables had an impact on the dwell time, but the influence of the ethanol concentration was weaker and of an interaction type; see Table 6. The screw configuration of the medium intensity type, and die plate,increased the response, while an increased screw speed decreased the dwell time. The impact of the powder flow rate produced opposite effects in relation to the two screw configurations. It is to be expected that the dwell time is affected by all the process variables. When no die restriction is used, there ought to be no pressure gradients in the channel, and the screw speed should be the dominating factor. Temperature has an important influence according to the correlation analysis, see Table 8, but not according to the stepwise analysis. This could probably be explained by the fact that other process variables can take its place as explanatory variables. Otherwise load and CO_2 content affected the dwell time, too.

The output of an isothermal extruder with a uniform screw is directly proportional to the speed of rotation of the screw[11]. However, because of the possibility of effecting a holdback by a kneading paddle configuration, the throughput rate is not necessarily proportional to the rotor speed in the case of twin screw extruders[12]. The output was affected by screw configuration and by a weaker interaction between ethanol concentration and die plate; see Table 6. A larger output was obtained with the configuration of the mild agitation type. The correlation coefficients did not reveal large correlations. Still, they were significant for some response variables; see Table 8.

The fraction above 1.00 mm of unmilled granulation, which is a suitable indicator of the granulation process, was influenced by all the five process variables, although the impact of the powder flow rate was difficult to interpret; see Table 6. As there were interactions, these indicate that the effect of the process variables is complex and cannot be studied by varying one factor at a time. It is to be expected that the properties of the unmilled granulation are influenced by all the process variables, as the amount of solvent and the agitation are very important regarding traditional agglomeration[13]. The carbon dioxide content, the fine fraction of unmilled granulation and the mean diameter of the milled granulation influenced the coarse fraction of the unmilled granulation according to the stepwise regression. All three variables reduced the coarse fraction. The correlation coefficients did not reveal large correla-

TABLE 8

Correlation Coefficients between Response Variables

Response variables	Correlation coefficient							
	LOAD	TEMP	TIME	OUTP	>1MM	<0.125MM	MDGW	CO_2
LOAD	1	0.84	0.88	-0.59	0.45	0.37	-0.73	-0.78
TEMP	0.84	1	0.74	-0.54	0.54	0.34	-0.83	-0.87
TIME	0.88	0.74	1	-0.65	0.46	0.44	-0.70	-0.73
OUTP	-0.59	-0.54	-0.65	1	-0.35	-0.27	0.43	0.55
>1MM	0.45	0.54	0.46	-0.35	1	-0.14	-0.58	-0.65
<0.125MM	0.37	0.34	0.44	-0.27	-0.14	1	-0.37	-0.30
MDGW	-0.73	-0.83	-0.70	0.43	-0.58	-0.37	1	0.73
CO_2	-0.78	-0.87	-0.73	0.55	-0.65	-0.30	0.73	1

$P < 0.001$ for correlation coefficient $\geqslant 0.476$
$0.001 \leqslant P < 0.01$ for correlation coefficient between 0.381 and 0.476

tions; still, they were significant for some response variables.

Regarding the fraction below 0.125 mm of the unmilled granulation, which is also a suitable indicator of the agglomeration process, this parameter was significantly affected by all the process variables, too. The impact of the powder flow rate is not quite convincing. However, the influence of ethanol concentration and powder flow rate was of an interaction type; see Table 6. This fine granule fraction was affected by the mean diameter of the milled granulation according to the stepwise regression.

The mean diameter of the milled granulation was influenced by screw configuration, ethanol concentration and die plate and some interactions involving powder flow rate and to a minor extent also screw speed; see Table 6. Medium screw configuration and die plate reduced the diameter, while the response grew with increasing ethanol concentration. As the milling process will influence the mean diameter, too, it is expected that some of the process variables will disappear as unimportant with reference to this response variable. According to the stepwise regression, the mean diameter was influenced by temperature and by the fine and coarse granule fractions of unmilled granulation. All three variables reduced the response. Temperature, load, dwell time and carbon dioxide content constitute important influences according to the correlation coefficients; see Table 8.

The carbon dioxide content of the granulation was affected by all the process variables, too, although powder flow rate and screw speed exerted their influences via interactions; see Table 6. However, the influence of the screw speed was inconsiderable. The screw configuration of medium agitation type and die plate reduced the carbon dioxide content, while the response - with some exceptions - increased with a higher ethanol concentration. As the theoretical carbon dioxide content of the powder mixture is 17.5%, there was a decomposition of sodium bicarbonate in all the tests. The decomposition was lower with the low intensity agitation; see Tables 4 and 5. Decomposition of sodium bicarbonate will occur because of the heat generated in the extruder. But there may also be a decomposition from the interaction between the acid and the bicarbonate. Effects from die restriction, screw configuration and ethanol concentration are therefore expected. The influence from screw speed and powder flow rate was not unexpected. As for the dependence on the other response variables, temperature, coarse granule fraction and load are the most important ones according to the stepwise regression analysis. Higher values of these three variables reduced the response. According to the correlation coefficients, temperature, load, dwell time and mean diameter will affect the carbon dioxide content; see Table 8.

CONCLUSIONS

The following response variables were affected by all the process variables: load on motor, dwell time, coarse and fine fractions of unmilled granulation, mean diameter of milled granulation and carbon dioxide content. The dependence on the process variables was complex; the effect produced by a variable depends on the respective levels of the other variables.

Regarding the temperature of the extrudate, this response variable was influenced by screw configuration, die plate and ethanol concentration without any interactions.

Screw configuration and an interaction between ethanol concentration and die plate affected the output.

The screw configuration was the dominating process variable with regard to most of the tested response variables.

Mathematical models were fitted.

The dependence between the response variables was tested, and temperature influenced load, mean granule diameter and carbon dioxide content. Load affected temperature and dwell time.

It is possible to produce the effervescent granulation with the extruder, if suitable levels are selected for the process variables.

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