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Research paper

Optimization of an effervescent tablet formulation containing spray dried L-leucine and polyethylene glycol 6000 as lubricants using a central composite design

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Abstract

A rotatable central composite design is used to evaluate the effects of lubricants and compression force on the physical characteristics of effervescent tablets. Effervescent tablets lubricated with a combination of spray dried L-leucine and polyethylene glycol 6000 are prepared by direct compression and examined. Residual force, crushing strength and disintegration time are considered as response variables and related to the L-leucine and polyethylene glycol concentrations and to the compression force. The calculated models are used to assess the influence of the production factors on tablet properties. As increasing amounts of L-leucine, showing good lubricating properties, reduce the crushing strength and prolong tablet disintegration, the L-leucine concentration is kept at a low level. An optimum tablet formulation contains 2% L-leucine and 3% polyethylene glycol 6000. The tablets have a tensile strength of 0.47 MPa and disintegrate in less than 2 min. Predicted and experimental results are in agreement within a 95% CI.

Keywords: Effervescent tablets; Lubrication; L-Leucine; Polyethylene glycol 6000; Optimization; Spray drying; Rotatable central composite design

1. Introduction

Effervescent tablets provide several advantages over conventional oral solid dosage forms, although their production is associated with numerous problems [1–5]. One of the most critical problems is lubrication of the effervescent tablet formulation [2,5–9]. Although several authors have described the advantages of extrinsic lubrication and various punch coatings [2,5,9–14], none of these methods are as effective as the direct addition of a lubricant to the formulation. Substances for intrinsic lubrication in effervescent tablet formulations must have lipophilic properties, to provide a good lubrication, and hydrophilic properties, to form a clear solution of the disintegrated tablet [2,6–9]. The most effective lubricants known are the magnesium and calcium salts of fatty acids like stearic acid and arachnic acid, but as they are insoluble in water all of them yield cloudy solutions and a prolonged disintegration time. Since water-soluble materials provide poor lubrication properties, there are only a few non-toxic and tasteless substances resulting in sufficient lubrication and forming clear solutions, which are used in higher concentrations compared to the salts of fatty acids [3,5–9,15–18].

The studies of Röscheisen [6,19] on twenty different substances demonstrate that compounds of medium polarity are the most efficient lubricants for effervescent tablets. Fumaric acid and L-leucine are found suitable soluble materials

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providing adequate lubricating properties. The lubrication properties of water-soluble lubricants can be improved by spray drying [20]. Spray drying of L-leucine results in an increased efficiency [7], yielding more than 50% decreased residual and ejection forces in comparison to milled L-leucine. The combination of a large tablet diameter, relatively thin compacts and a lubricant with anti-binding properties results in weak tablets. Increasing the crushing strength and reducing the gliding friction within the die, polyethylene glycol as water-soluble lubricant and binder is investigated. However, the direct compression of these formulations results in adhesion to the punch faces and sticking occurs after compressing few tablets. As spray dried L-leucine shows an anti-adhesion effect as well as anti-binding properties a combination of polyethylene glycol and L-leucine is tested.

The best combination under conditions of competing objectives and interactive effects is often achieved by way of a costly and time consuming trial and error procedure. The resulting formulations are frequently not satisfactory and the separate quantification of effects is difficult [21, 22]. As the development of a pharmaceutical formulation and the associated process involves a number of variables, the advantages of a systematic approach using experimental design optimization techniques and chemometric data evaluation are obvious. Several methods of optimization are well documented in the literature, such as the Lagrangian method, simplex method and response surface methodology [21–35]. Response surface methodology is frequently employed and has the advantage over the Lagrangian method as it can handle many independent variables simultaneously [27,36]. Since linear and linear equations with interactions may be inappropriate, second order models which allow the fitting of an equation including quadratic terms are preferred. Second order response surface designs include Box–Behnken designs requiring three levels for each factor and central composite designs requiring five levels for each factor [37] allowing better estimation of terms of an order greater than one. Accordingly, we favour the latter design which is built upon the two-level factorial design by adding center and star points. The rotatable central composite design is widely employed for optimization problems [35,38–40] and has the advantage over the orthogonal design, that the variance of the predicted response is a function only of distance from the centroid irrespective of direction. Therefore, in these studies we apply a rotatable central composite design for the optimization of a standard effervescent tablet formulation, containing polyethylene glycol 6000 and spray dried L-leucine as lubricants. The aim of our work is to demonstrate the suitability of this approach for the development of an effervescent tablet formulation and to select an optimum formulation. The results for the determination of the most desirable concentration of both excipients and the optimum compression force are reported, the significant effects and interactions are identified and related to tablet properties.

2. Materials and methods

2.1. Materials

The tablet ingredients used are Diamant Instant Sugar® (Krüger GmbH & Co. KG, Braunschweig, Germany), a direct compressible sucrose granulated with 0.25% dextrose syrup, coarse crystalline citric acid (E. Merck, Darmstadt, Germany) and sodium bicarbonate fine powder (Solvay-Alkali-GmbH, Rheinberg, Germany). Polyethylene glycol 6000 fine powder is supplied by Hoechst (Hoechst AG, Frankfurt, Germany). L-Leucine is purchased from Bayer (Bayer AG, Leverkusen, Germany) and spray dried as described below.

2.2. Spray drying

For spray drying a solution of 2.5% L-leucine in water is prepared. The solution is kept at a temperature of 80°C and spray dried in a Nubilosa spray dryer (Model LT-A, Nubilosa GmbH & Co. KG, Konstanz, Germany) at temperatures of 250–260°C for inlet air, 160–170°C for spraying and 60–70°C for outlet air, respectively. The low pressure air nozzle (three-component-nozzle, Hüttlin, Steinen, Germany) used has an inside diameter of 1.2 mm. A nozzle pressure of 0.6–0.7 bar, a microclimate of 0.1 bar and a spraying rate of 2.5 l/h are employed. Spray drying of L-leucine results in spherical hollow particles (Fig. 1), which are destroyed during compression. The little tiles of L-leucine yield good lubrication and prevent adhesion to the punch faces.

The influence of spray drying on the chemical stability of L-leucine is not monitored, since L-leucine and its solution are stable at high temperatures [41,42].

2.3. Tablet preparation

Tablets with a mass of 3 g are prepared on a single punch

Fig. 1. Scanning electron photomicrograph of a spray dried L-leucine particle.

tableting machine (EK II, Korsch Pressen GmbH, Berlin, Germany) using 25 mm bevelled edge tooling. The upper punch holder is instrumented with strain gauges (Type 3/120 XY11, Hottinger Baldwin Meßtechnik, Darmstadt, Germany) and the lower punch with a piezoelectric transducer (Type 9041, Kistler Corporation, Winterthur, Switzerland). Signal amplification is achieved by a Philips carrier wave measuring bridge (PR 9307 Philips, Kassel, Germany) for the strain gauges and a charge amplifier (Type 9007, Kistler Corporation, Winterthur, Switzerland) for the piezo transducer. The piezo instrumentation is used to record residual forces. The compression data are analysed using the Signalys software (Version 3.0, Data Systems, Marburg, Germany). To maintain the relative humidity during the tableting process at less than 15%, the compression area around the die table is insulated by two plastic cases. These cases are ventilated by compressed air with a relative humidity of 4%. An exact description of the plastic is given by Röscheisen [19]. The ventilation is started 1 h before tableting and continued during the process. The relative humidity is determined at room temperature with the Vaisala's indicator unit HMI 32 and the measurement probe HMP 35 (Vaisala, Helsinki, Finland).

The basic effervescent tablet formulation (batch size: 400 g) is kept constant during the experiments. By keeping x% lubricant the remaining amount is divided into 41% Diamant Instant Sugar®, 31% sodium bicarbonate and 28% citric acid. Sodium bicarbonate is passed through an 800 μm sieve. The lubricants are then sieved through a 315 μm sieve onto the other ingredients. Final mixing is carried out for 5 min in a Turbula mixer (Type T2C, Willy Bachofen AG, Basel, Switzerland) at 42 rpm. The relative humidity of the powder mixtures varies from 25 to 35%.

2.4. Uniformity of weight

The uniformity of weight is evaluated according to the European Pharmacopoeia.

2.5. Residual force

The residual force of six tablets in each batch is measured with the instrumentation described above to characterize the effectiveness of the lubricants. After compressing 15 tablets which are rejected the residual force of every third tablet is recorded. The residual force is read directly before the ejection peak which appears after 800 ms.

2.6. Crushing strength

The crushing strength is determined using a Schleuniger hardness tester (Model 6D, Dr. K. Schleuniger, Solothurn, Switzerland) for ten tablets out of each batch which are selected at random. In the tables the crushing strength is additionally transformed into a tensile strength.

2.7. Disintegration time

The disintegration time of the tablets is determined according to the European Pharmacopoeia, stating a maximum disintegration time of 5 min for effervescent tablets. Six tablets from each batch are placed in 250 ml beakers, each containing 200 ml water (20 ± 1°C). The tablets are considered disintegrated when completely dispersed fragments are obtained and the liberation of gas stops.

2.8. Storage of tablets

Tablets are stored for 7 days in polypropylene tubes with drying seals before the crushing strength and the disintegration time are measured.

2.9. Experimental design

For the optimization of the effervescent tablet formulation, a randomized rotatable central composite design is employed for three independent factors, the concentration of L-leucine (x_1), the concentration of polyethylene glycol 6000 (x_2) and the compression force (x_3). The dependent response variables measured are residual force, crushing strength and disintegration time. The formulations are listed in Table 1 in coded form. The experiments are conducted in random sequence. The transformation to physical units is summarized in Table 2. Center points are repeated three times (formulations nos. 15–17 in Table 1) in order to evaluate the experimental error.

2.10. Data evaluation

Data evaluation is done using stepwise multivariate linear

Table 1

Coded central composite experimental design for three factors

Formulation no.	x_1	x_2	x_3
1	−1	−1	−1
2	1	−1	−1
3	−1	1	−1
4	1	1	−1
5	−1	−1	1
6	1	−1	1
7	−1	1	1
8	1	1	1
9	$-\alpha$	0	0
10	α	0	0
11	0	$-\alpha$	0
12	0	α	0
13	0	0	$-\alpha$
14	0	0	α
15	0	0	0
16	0	0	0
17	0	0	0

Table 2

Factor levels applied in the optimization

Factor	Factor level X				
	$-\alpha$	−1	0	1	α
x_1 L-Leucine (%)	1.81	4.0	7.0	10.0	12.19
x_2 PEG 6000 (%)	1.81	4.0	7.0	10.0	12.19
x_3 Compression force (kN)	18.4	29.0	43.5	58.0	68.6

regression analysis [43]. The model predictor equations are estimated for each dependent variable separately. The general type of predictor equation resulting from a three level experimental design is a second-order polynomial in the following form:

$$y_i = b_0 + b_1 . x_1 + b_2 . x_2 + b_3 . x_3 + b_{12} . x_1 . x_2 + b_{13} . x_1 . x_3 + b_{23} . x_2 . x_3 + b_{11} . x_1^2 + b_{22} . x_2^2 + b_{33} . x_3^2 + e_i, \quad (1)$$

where b_0 is an intercept term, $b_1 \ldots b_{33}$ represent estimates of the original unknown regression parameters, $x_1 \ldots x_3$ are the independent variables and e_i is the residual error for variable y_i. Higher interactions are not included, because no effect is expected from these interactions. Using forward-selection and backward-elimination to model building, the significant factors in the equations are selected for each dependent variable. To test whether the terms add significantly to the regression model the F-ratio is calculated and compared to the critical F-value. The probability of each coefficient being equal to zero is examined with the Student's t-test. All tests are performed at a 95% ($\alpha = 0.05$) level of significance. To examine the effect of the intercept term the regression is calculated (i) with included intercept and (ii) without intercept. The model with significantly increased R^2 and increased model sum of squares is preferred. In the final model equations, only the significant factors are included. The adequacy of the final regression models is assessed by analysis of variance (ANOVA), performing the lack of fit (LOF) and goodness of fit (GOF) tests. The model is considered adequate, when the regression shows no lack of fit.

Validation of the model equations is done by independent measurements obtained from tablets produced at factor levels not used in the previous experiments. In this study the models are validated by preparing and testing the following three predicted formulations:

- 2.5% L-leucine, 2.5% polyethylene glycol 6000, 42.0 kN
- 6.0% L-leucine, 8.0% polyethylene glycol 6000, 27.6 kN
- 11.0% L-leucine, 11.0% polyethylene glycol 6000, 38.5 kN

Statistical analyses are performed using Statgraphics® Plus for Windows™ (Version 1.4, Statistical Graphics, Rockville, Maryland). The diagrams are generated using Excel™ (Version 5.0, Microsoft, Unterschleissheim, Germany).

3. Results and discussion

The tablets obtained of all formulas are found to obey the pharmacopoeial requirements regarding the uniformity of weight. The values of residual force, crushing strength and disintegration time of the 17 experiments are listed in Table 3. These responses are used to generate model equations for the three dependent variables. The model equations are validated by preparing and testing three new formulations. First, the estimated models for the response variables are discussed separately. Second, an optimum formulation is determined by a multivariate approach.

3.1. Residual force

A low residual force indicates good lubrication. All tablet formulations show good lubrication properties. The regression parameters and ANOVA results, including lack of fit and goodness of fit tests are shown in Table 4. The residual force is influenced by all of the factors analyzed and can be described by Eq. (2):

$$F_{Res} = 7.37 . F_C - 0.366 . x_{Leu} . F_C - 0.176 . x_{PEG} . F_C \text{ (N)} \quad (2)$$

F_{Res} (N) corresponds to the residual force; F_C is the compression force (kN); x_{Leu} and x_{PEG} are the fractions of L-leucine (%) and polyethylene glycol (%), respectively. In Eq. (2) and the following equations (Eqs. (3)–(5)) the factors F_C, x_{Leu} and x_{PEG} are divided by their respective units. The correlation between measured data and predicted values is shown in Fig. 2a).

Since it is not feasible to represent the influence of three parameters on the response in one diagram the response is plotted as a function of each variable in Fig. 3. In this diagram, the factor levels are normalized according to the following equation:

$$N = \frac{x - X_{-1}}{X_1 - X_{-1}} \times 100\% \quad (3)$$

where N is the normalized factor level given in % of the factor range, x is the unnormalized factor level, X_{-1} and X_1 correspond to the lowest and highest factor levels, respec-

Table 3

Measured values of residual force, crushing strength and disintegration time of the 17 calibration and 3 validation experiments

No.	Experiment	%L-leucine	% PEG 6000	Compression force (kN)	Residual force (N)	Crushing strength (N)	Tensile strength (MPa)	Disintegration time (s)
1	13	4	4	28.14	153	21.4	0.13	270
2	7	10	4	28.86	65	12.6	0.07	930
3	11	4	10	29.49	137	55.0	0.33	155
4	10	10	10	29.86	80	24.5	0.15	925
5	12	4	4	59.27	335	44.9	0.27	185
6	2	10	4	60.00	148	21.3	0.13	910
7	17	4	10	58.54	214	74.6	0.45	170
8	4	10	10	55.53	150	27.0	0.17	940
9	5	7	1.81	42.23	207	25.8	0.15	400
10	15	7	12.19	44.29	102	43.8	0.26	562
11	8	7	7	17.82	54	15.8	0.09	535
12	16	7	7	68.60	227	47.3	0.29	410
13	1	1.81	7	42.95	253	69.9	0.41	95
14	3	12.19	7	42.36	91	19.4	0.11	1260
Center points								
15	9	7	7	43.23	150	36.5	0.23	483
16	6	7	7	42.89	138	37.0	0.22	530
17	14	7	7	44.10	153	31.8	0.20	490
Validation data								
18		2.5	2.5	42.0	279	40.2	0.24	110
19		6	8	27.6	101	37.2	0.07	400
20		11	11	38.5	87	16.9	0.10	1260

tively (cf. Table 2). The lines in Fig. 3 correspond to a variation of each factor from 0 to 100% with the other variables held constant at the 50% level. As expected, the residual force increases with increasing compression force. Comparison of the gradients shows that compression force has the highest influence on this response. The residual force can be reduced by the addition of L-leucine and polyethylene glycol. As shown in Fig. 3, the residual force is

Table 4

Summary of regression and ANOVA results

Factor	Coefficient	SD	t	P[a]	R^2[b]	Variation	SS[c]	d.f.[d]	MS[e]	F	F_{crit}	Decision
Residual force												
F_C	7.37	0.48	15.5	0.00	0.9850	Model	4.93×10^5	3	1.64×10^5	306	3.34	GOF[f]
$x_{Leu} \times F_C$	–0.366	0.046	–7.91	0.00		Residual	7.51×10^3	14	537			Positive
$x_{PEG} \times F_C$	–0.176	0.046	–3.82	0.00		Lack of fit	7.39×10^3	12	615	9.77	19.4	LOF[g]
						Pure experimental	126	2	63			Negative
						Total	5.00×10^5	17				
Crushing strength												
F_C	0.964	0.175	5.52	0.00	0.9924	Model	2.68×10^4	6	4.47×10^3	239	3.09	GOF
x_{Leu}	–3.934	1.192	–3.30	0.01		Residual	206	11	18.7			Positive
x_{PEG}	6.336	1.022	6.20	0.00		Lack of fit	189	9	21.0	2.66	19.4	
$x_{Leu} \times F_C$	–0.065	0.025	–2.60	0.02		Pure experimental	16.5	2	8.23			LOF
$x_{Leu} \times x_{PEG}$	–0.536	0.141	–3.79	0.00		Total	2.70×10^4	17				Negative
x_{Leu}^2	0.411	0.118	3.47	0.00								
Disintegration time												
Intercept	73	21	3.45	0.00	0.9801	Model	1.80×10^6	1	1.80×10^6	737	4.54	GOF
x_{Leu}^2	8.35	0.31	27.16	0.00		Residual	3.67×10^4	15	2.45×10^3			Positive
						Lack of fit	4.96×10^3	3	1.66×10^3	0.63	3.49	LOF
						Pure experimental	3.17×10^4	12	2.64×10^3			Negative
						Total	1.84×10^6	16				

[a]Probability level for each t-value, for $P \leq 0.05$ the term significantly differs from 0.
[b]Correlation coefficient R^2.
[c]Sum of squares.
[d]d.f., degrees of freedom.
[e]Mean squares.
[f]GOF, goodness of fit.
[g]LOF, lack of fit.

more influenced by L-leucine compared to polyethylene glycol.

3.2. Crushing strength

For the determination of the crushing strength, two different model equations result using forward-selection and backward-elimination for model building. The forward-selection leads to a simple regression model, which is easy to explain, but does not show good results for the R^2, the model sum of squares and the correlation between predicted and measured data. Using backward-elimination the following second-order polynomial results:

$$F_{Crush} = 0.964 . F_C - 3.934 . x_{Leu} + 6.336 . x_{PEG} - 0.065 . x_{Leu} . F_C - 0.536 . x_{Leu} . x_{PEG} + 0.411 . x_{Leu}^2 \text{ (N)} \quad (4)$$

F_{Crush} corresponds to the crushing strength (N). Again, the exact regression parameters and ANOVA results are given in Table 4. The correlation predicted values vs. measured data is depicted in Fig. 2b).

Each of the three parameters influences the value of the crushing strength. L-Leucine is included as a single factor, an interaction and a quadratic term. For the optimization, this is an important result although this behaviour is not straightforward to explain. Nevertheless, the model showing good results for the R^2, the model sum of squares and the correlation predicted values versus measured data is preferred.

Fig. 4 shows the isoresponse curves calculated according to Eq. (4) at three different compression force levels. In addition, Eq. (4) and Fig. 4 show that the crushing strength can be increased by increasing the polyethylene glycol concentration and the compression force. This is expected due to the binding properties of polyethylene glycol. L-Leucine, on the other hand, shows negative influence on the tablet hardness, which is expected as it exhibits anti-binding properties. As a consequence, the concentration of L-leucine should be kept at a low level. For an effervescent tablet of 25 mm diameter a crushing strength of at least 60 N is desired.

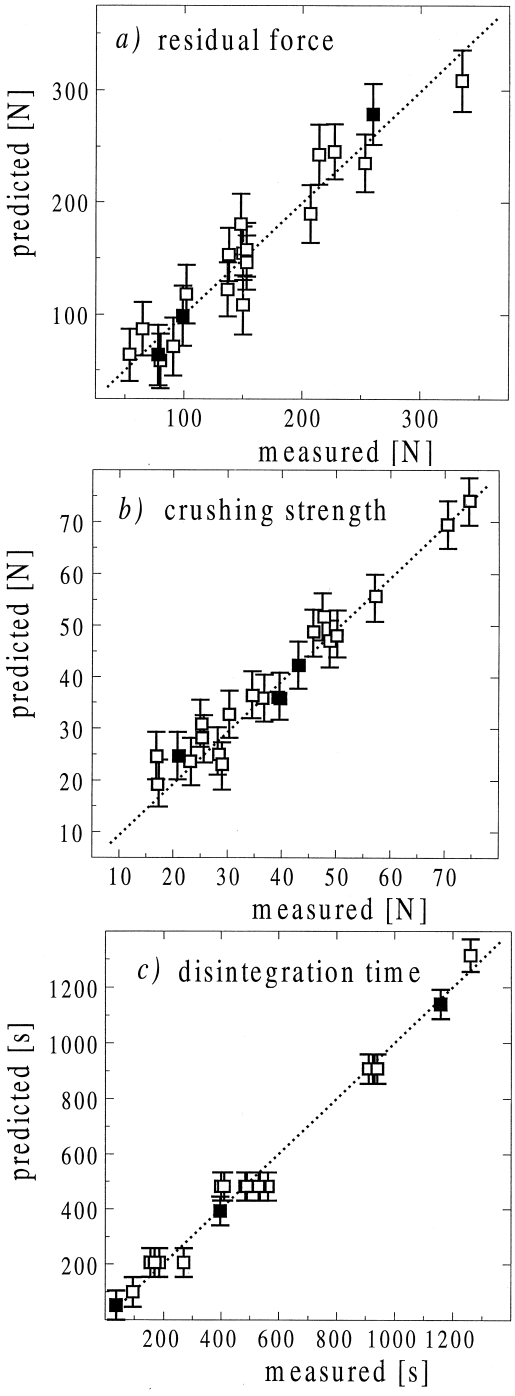

Fig. 2. Correlation between measured data and predicted values. (a) Residual force, (b) crushing strength, (c) disintegration time. The dotted line indicates ideal correlation. The hollow squares correspond to the calibration data. The solid squares mark the validation experiments. The error bars indicate the respective standard deviations of the predicted values.

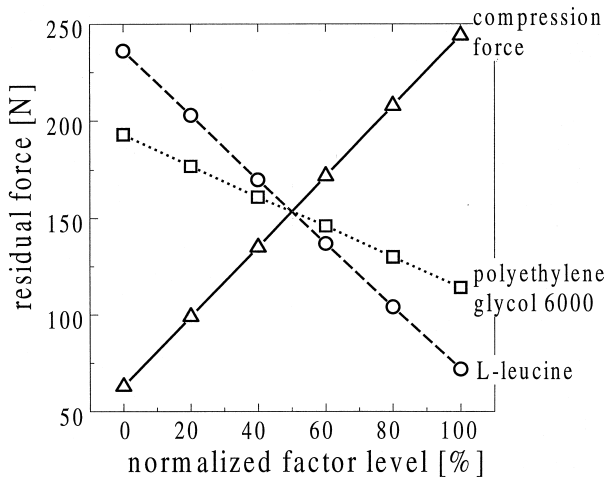

Fig. 3. Residual force function of each independent variable.

3.3. Disintegration time

The measured data are consistent with the following model equation:

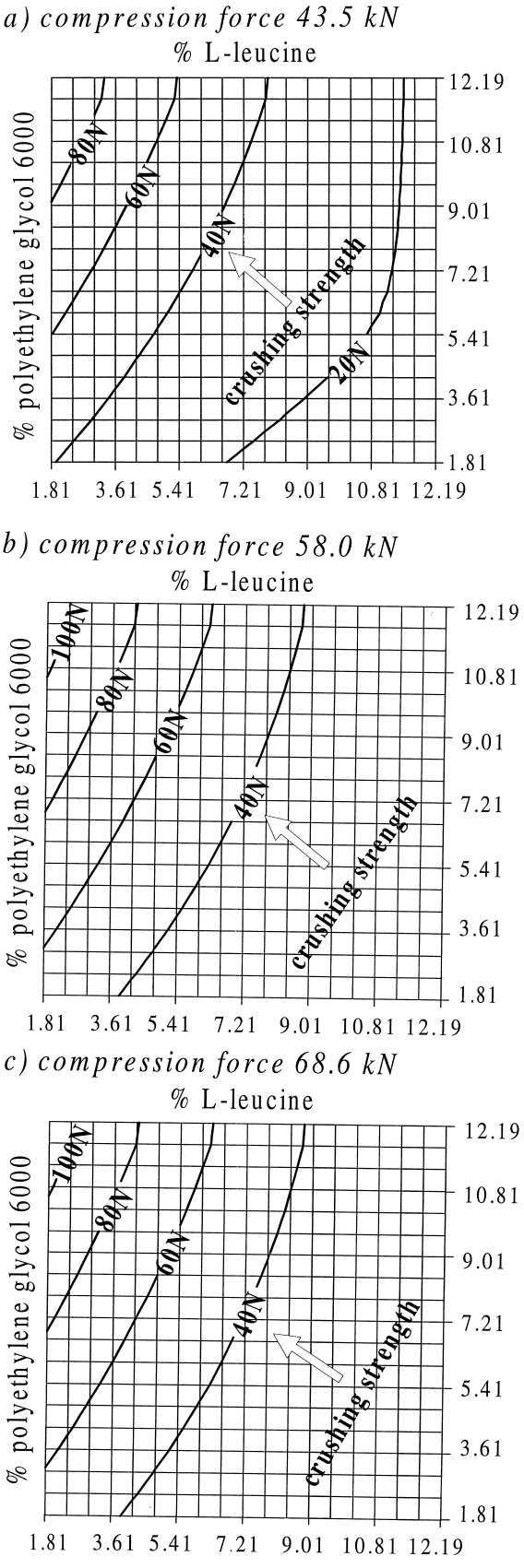

Fig. 4. Effect of L-leucine and polyethylene glycol concentration on crushing strength.

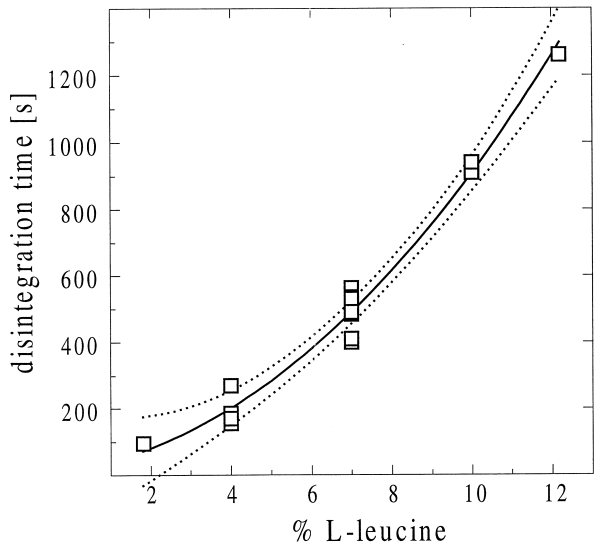

Fig. 5. Effect of L-leucine concentration on tablet disintegration time. The dotted lines indicate the 95% confidence limit of the response function.

$$t_{Dis} = 73 + 8.35 x_{Leu}^2 \text{ (s)} \quad (5)$$

Here, t_{Dis} corresponds to the disintegration time given in seconds. The correlation between predicted values and measured data is indicated by the hollow squares in Fig. 2c). According to the model, the disintegration time is a function of the concentration of L-leucine only. Other effects are not significant within a 5% error probability. As is depicted by the plot of Eq. (5) in Fig. 5, the amino acid significantly increases tablet disintegration time. This is due to the fact that L-leucine is the most lipophilic substance among all excipients used. Thus, the calculated model confirms the expected effects.

The European Pharmacopoeia specifies a disintegration time of less than 5 min for effervescent tablets. According to Eq. (5) the content of L-leucine should not exceed 5% to comply with this condition. Therefore, a low concentration of L-leucine is advantageous for both crushing strength and disintegration time.

In general higher compression forces result in tablets with higher density and longer disintegration times. On the contrary effervescent tablets with increased density have prolonged floating times and an increased contact time of the tablet surface with the immersion fluid. For this reason no influence of the compression force on disintegration times of tablets can be observed.

3.4. Validation of the model equations

The models are validated by three formulations (cf. Section 2.9) that are selected to be at factor levels different from those used in the central composite design. The results are included in Fig. 2 and indicated by the solid squares. The error bars in Fig. 2 correspond to the respective standard deviation of the prediction. The figure clearly shows, that the measured data are within the 95% confidence intervals

Table 5

Optimum tablet formulation in comparison to a tablet formulation containing 5% L-leucine

Compression force (kN)	Response variable	2% L-leucine + 3% PEG 6000		5% L-leucine
		Predicted	Experimental	Experimental
68.6	Residual force (N)	419	510	575
	Crushing strength (N)	67	76 (tensile strength: 0.47 MPa)	26 (tensile strength: 0.16 MPa)
	Disintegration time (s)	106	99	320
58	Residual force (N)	354	437	415
	Crushing strength (N)	58	64 (tensile strength: 0.40 MPa)	22 (tensile strength: 0.13 MPa)
	Disintegration time (s)	106	103	368

of the predicted values for all response variables. Therefore, the model equations may be used to describe the real dependencies and are applied in the following prediction of an optimum parameter set for tablet production.

3.5. Selection of optimum parameters

In order to find the level of each independent variable that will lead to a tablet formulation with optimum properties, a simple exhaustive grid search is performed within the range of the central composite design. This is justified because (i) the parameter range of the design is selected to include the whole range of virtually interesting excipient concentrations and technically applicable compression forces; and (ii) because the three dimensional factor space ensures a very fast and easy to perform calculation. Therefore, the regression equations for each response variable are combined, the calculated response values of every combination are sorted on size and compared. Target parameters are a crushing strength of at least 60 N, a disintegration time of at most 100 s and a minimum level of lubricant addition. A residual force of 500 N is considered acceptable.

Due to the fact that the model equations and the calculated response surfaces demonstrate that a good lubrication is competing with a short disintegration time and a high crushing strength, this is not a trivial problem because of the additional requirement that the excipient concentration should be kept at a minimum level. Since interaction terms are significant for at least two response variables, a mere inspection of the response surfaces is to be considered with caution because one of the three variables must be held constant for the generation of the two dimensional surfaces.

From the grid search, an optimum parameter set specifying 2% L-leucine and 3% polyethylene glycol 6000 is selected as the best formulation and a compression force of 68.6 kN is chosen. To prove the validity of the prediction, the formulation is compressed at two force levels (58 and 68.6 kN) and tested in the same manner as described above. Table 5 comprises the experimental results and the predicted values for the various responses in comparison to a tablet formulation containing 5% L-leucine. The two target parameters, i.e. crushing strength and disintegration time, are predicted correctly. Since the residual force is affected with a large measurement error, the experimental results are higher than the predicted values.

The effervescent tablets lubricated with a combination of L-leucine and polyethylene glycol 6000 exhibit increased values of crushing strength. Tablets containing 5% L-leucine as sole lubricant are weak and show three times prolonged disintegration time. For both tablet formulations the lubrication is sufficient as demonstrated by their respective values of residual force (cf. Table 5). For the optimum formulation compressed at 68.6 kN a residual force of 510 N is measured which decreases to 437 N for the lower compression force level of 58 kN. It has been shown elsewhere [6,20] that at a compression force of 58 kN a formulation containing 5% sodium stearate as lubricant shows a residual force of 134 N, a formulation lubricated with 5% sodium benzoate gives a value of 412 N and for a formulation including 5% ground adipic acid a residual force of 770 N is measured. These substances are used as lubricants for effervescent tablets, but sodium stearate, being water-insoluble, does not form a clear solution after tablet disintegration. The tablets compressed with sodium benzoate show a crushing strength of only 41 N (tensile strength: 0.25 MPa) and their solution has a soapy taste. Since in this study the measured residual force of 437 N is in-between this range (134–770 N) and the tablets show a sufficient crushing strength and yield a clear solution, it is obvious that a combination of L-leucine and polyethylene glycol 6000 is advantageous.

4. Conclusions

The central composite design is demonstrated to be a useful method in the characterization of the effects of variables and process parameters in the development of an effervescent tablet formulation. Simple response surface models describing the influence of L-leucine, polyethylene glycol 6000 and compression force on lubrication, crushing strength and disintegration time are established and used to predict an optimum formulation given a minimum limit for the crushing strength and a maximum limit for the disintegration time. The predicted and the experimental data

are found to be in good agreement. As L-leucine, polyethylene glycol 6000 and compression force show opposing effects on the responses, an optimum combination comprising of 2% L-leucine and 3% polyethylene glycol 6000 is compressed at 68.6 kN. This formulation shows a residual force of 510 N and provides tablets with a crushing strength of 76 N (tensile strength: 0.47 MPa) that disintegrate in less than 2 min. The work presented clearly demonstrates the usefulness of an experimental design approach for a fast and reliable formulation design.

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