Analele Universităţii din Craiova, seria Agricultură – Montanologie – Cadastru (Annals of the University of Craiova - Agriculture, Montanology, Cadastre Series) Vol. XLV 2015

THE OPTIMIZATION OF THE FORMULATION AND PRODUCTION BY EXTRUSION-SPHERONIZATION OF INERT PELLETS BASED ON MICROCRYSTALINE CELULOSE AND LACTOSE

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Keywords: pellets, extrusion, spheronization, design of experiments

ABSTRACT

The „design of experiment" approach to the manufacture of a product allows the simultaneous study of formulation and process variables that significantly influence the quality of a finished product, by performing only a limited number of experiments.
The aim of this study was to use design of experiment in order to optimize the laboratory-scale production by extrusion-spheronization of inert pellet cores consisting of a completely biodegradable, binary mixture of microcrystalline cellulose (MCC) and lactose (L). We have established the exact proportion of MCC, L and binder solution (a 2.5 % solution of polyvinylpyrrolidone, Kollidon $K_{29/32}$ in water) and process variables (spheronization time and speed) required for the production of pellets with desired, known, preset characteristics, such as size distribution, circularity and flow behavior.

INTRODUCTION

Pellets are small (0,5 – 2mm), free flowing, spherical shaped particles, with a wide array of uses, ranging from human and veterinary medicine to agriculture [1], fuel [2] and other industries [3]. Pelletization is an agglomeration process that converts fine powder blend of materials (drug(s) and excipients, in the case of pharmaceutical pellets) into small, free flowing, spherical units, referred to as pellet [4].

Currently, finished drug products are becoming more and more complex in terms of formulation and manufacturing techniques. Although modern scientific advances tend to resolve problems of the past, the development of new formulation solutions gives rise to new challenges, due to the fact that novel excipients often claim further studies. The manufacturing processes tend to evolve at a slower rate, as newly developed production equipment is not always a feasible solution for product manufacturers, due to high costs of equipment and their implementation.

A modern tool which comes to the aid of finished product manufacturers is represented by the experimental design approach. These experimental plans allow the simultaneous study of the impact of numerous formulation and process factors (variables) on the quality of the finished product. The most relevant benefit of experimental design is that, by performing only a limited number of experiments, it allows the manufacturer to obtain a product of high quality, by establishing the optimal compositions (formulations) and process conditions, in contrast to the time- and resource-consuming "trial-by-error" method that was previously employed [5].

The aim of this study was to optimize the laboratory-scale production by extrusion-spheronization of inert pellet cores consisting of a completely biodegradable, binary

mixture of microcrystalline cellulose (MCC), lactose (L). For this, we have established the proportion of microcrystalline cellulose (MCC), lactose (L) and binder solution (a 2.5 % solution of polyvinylpyrrolidone, Kollidon $K_{29/32}$ in water) and process variables (spheronization time and speed) required for the production of pellets with desired size distribution, circularity and flow characteristics. In this light, the word ”optimum” refers to the exact formulation and process conditions that lead to certain, desired and predictable characteristics of the inert pellets.

MATERIALS AND METHODS

In order to achieve the objective of the study, in the first stage, a selection of the excipients in the formulation of inert pellets was performed. Subsequently, an experimental plan and the independent and the dependent formulation and process variables were considered, then the actual experiments, suggested by the experimental plan, were performed. After the analysis of the quality of the experimental model chosen (the goodness of fit) and the analysis of the influence of the selected formulation and process factors on some quality characteristics (responses), considered as being significant for further processing of the pellets, the optimal formula and process conditions were determined.

1. The selection of the excipients in the formulation of the inert pellets

The function of the excipients included in the formulation of pellets is even more important when these are obtained by extrusion–spheronization [6].They facilitate the extrusion, convey a spherical shape to the wet pellets and also maintain their integrity.

Microcrystalline cellulose and lactose were chosen as excipients for the inert pellets.

2. Software

The optimization software Modde 8.0 (Umetrics, Sweden) was used for the fitting of the experimental data and the calculation of the coefficients and statistical indicators, in order to validate and evaluate the experimental design.

3. Experimental design

A D-Optimal experimental design plan, based on a polynomial equation II (quadratic), was selected.

The final objective of this stage of the study was to model the response surfaces (to identify which are the formulation and process factors that have the highest impact on the characteristics of the pellets), thus providing a deeper understanding of how these responses are affected by the independent variables and to perform predictions, such as the identification and optimization of the functionality ranges of the independent variables (formulation and process variables).

The experimental plan included 5 independent variables (formulation- and process-related) and 3 dependent variables (also called responses). The independent variables were the percentages of microcrystalline cellulose (commercial grade Avicel PH 101, FMC Biopolymer, Ireland), respectively of lactose and of the binder solution (aqueous solution 2.5% of polyvinyl pyrrolidone Kollidon K29 / 32) used to prepare the damp mass to be extruded, the spheronization speed (rpm) and spheronization time (minutes). The selected dependent variables, evaluated as responses of the experimental plan, were the pellet fraction remaining on the 0.8 mm sieve after sieving of the resulting pellets, the circularity of the pellets and the Hausner ratio. The factor list is presented below.

Table no. 1

List of independent variables (formulation and process parameters)

Name (Abrev.), Unit	Type	Use	Settings	MLR Scale	PLS Scale
Spheronization time (Dur), min	Quantitative	Controlled	2 to 5	Orthogonal	Unit Variance
Spheronization speed (Vit), rpm	Quantitative	Controlled	500 to 1000	Orthogonal	Unit Variance
MCC, Fraction	Formulation	Controlled	0.25 to 0.4	None	Unit Variance
L, Fraction	Filler	Controlled		Orthogonal	Unit Variance
Binder (Lia), Fraction	Formulation	Controlled	0.35 to 0.5	None	Unit Variance

The number of experiments generated for the experimental model used was 28, according to the experimental design matrix shown in the following table.

Table no. 2

Experimental design matrix

Exp. code	***Order***	***Independent variables***				
		Process factors (Spheronization parameters)		**Formulation factors**		
		Dur	**Vit**	**MCC**	**L**	**Lia**
N1	8	2	500	0.25	0.4	0.35
N2	19	5	1000	0.25	0.4	0.35
N3	20	2	500	0.4	0.25	0.35
N4	17	2	500	0.25	0.25	0.5
N5	24	5	500	0.25	0.25	0.5
N6	4	2	1000	0.25	0.25	0.5
N7	23	5	500	0.4	0.1	0.5
N8	1	2	1000	0.4	0.1	0.5
N9	27	2	1000	0.4	0.2	0.4
N10	22	2	1000	0.3	0.35	0.35
N11	25	2	833	0.25	0.4	0.35
N12	21	2	666	0.4	0.1	0.5
N13	9	5	500	0.35	0.3	0.35
N14	10	5	1000	0.4	0.15	0.45
N15	26	5	1000	0.35	0.15	0.5
N16	28	5	833	0.25	0.25	0.5
N17	2	5	666	0.4	0.25	0.35
N18	6	4	500	0.25	0.4	0.35
N19	12	3	500	0.4	0.1	0.5
N20	15	4	1000	0.25	0.25	0.5
N21	5	3	1000	0.4	0.25	0.35
N22	13	4	1000	0.4	0.25	0.35
N23	16	3.5	500	0.32	0.25	0.42

				5		5
N24	14	3.5	750	0.25	0.325	0.425
N25	11	3.5	750	0.325	0.175	0.5
N26	3	3.5	750	0.325	0.25	0.425
N27	18	3.5	750	0.325	0.25	0.425
N28	7	3.5	750	0.325	0.25	0.425

3. Performing the experiments included in the matrix of the experimental plan

Performing the experiments involved two stages, namely the preparation of the inert pellets corresponding to the generated formulations, in the conditions imposed by the matrix, and, respectively, the quality control of the resulting inert pellets for the selected parameters (assessment of the responses).

a. The preparation of the inert pellets by extrusion–spheronization

The preparation steps were the homogenization of dry powders (in a cubic blender), the wetting the powder with a binder solution (in a cubic mixer), the extrusion (in a Extruder Model 25, Caleva Process Solutions Ltd., UK, equipped with a mesh sieve 1.2 mm), the spheronization (in a Spheronizer Model 120, Caleva Process Solutions Ltd., UK, the friction plate 120 mm in diameter, with square indentations 3 x 3 mm and a depth of the grooves of 1 mm), the drying the pellets at 40° C (in an oven EU / BE 200-800).

b. The determination of the selected dependent variables

The determinations were made, where appropriate, according to compendial methods (pellet size distribution, bulk and tapped density) [7, 8] or by methods described in the literature (circularity of the pellets) [9].

Particle size distribution

The parameter was determined by the sifting and sorting method [7, 8].

Pellet circularity

The parameter was determined using a Visioscan® 98 VC apparatus (Courage + Khazakha GmbH, Germany), with an image magnification of 30X. The recorded images of the pellets were then processed using the ImageJ software (National Institute for Health, U.S.A.), in order to calculate the value of circularity of the photographed shapes.

Determination of Hausner ratio

The Hausner ratio was calculated using the values of bulk and tapped density [7], determined by using a Vankel Tap Density Tester, on weighed samples of pellets with a size between 0.8 and 1.18 mm.

RESULTS AND DISCUSSIONS

1. Response matrix

The response (dependent variables) matrix is shown in the following table.

Table no. 3

Response matrix

Exp. code	***Circularity***	***Fraction on 0.8 mm sieve***	***Hausner ratio***
N1	0.6758	89.1165	1.1066
N2	0.8434	0.0947	1.0673
N3	0.5666	89.3168	1.0921
N4	–	0	–
N5	–	0	–
N6	–	0	–
N7	0.5811	29.2264	1.0606
N8	0.7049	32.6442	1.1000
N9	0.6816	89.0080	1.1194
N10	0.6355	69.1749	1.0454
N11	0.7316	36.2006	1.0143
N12	0.7442	12.6761	1.0526
N13	0.4058	92.9607	1.0859
N14	0.8135	51.8301	1.1090
N15	–	0	–
N16	0.9264	0.0678	1.0337
N17	0.6099	89.1997	1.0169
N18	0.6586	87.2247	1.1441
N19	0.6197	25.6682	1.1172
N20	–	0	–
N21	0.6746	90.8136	1.1206
N22	0.6793	89.4348	1.0969
N23	0.5884	71.7444	1.1060
N24	–	0	–
N25	–	0	–
N26	0.7546	47.7890	1.0565
N27	0.6898	49.6813	1.0458
N28	0.6898	37.6866	1.0334

The analysis of the obtained data revealed that the distribution of pellet size varies widely, depending on the formulation and processing conditions.

The pellet circularity values recorded is also distributed within a wide range (between the maximum value of 0.9264, obtained for the N16 experiment and the minimal value of 0.4058, corresponding to the pellets obtained in the N13 experiment). It is estimated that circularity values above 0.7 suggests that the pellets are acceptably spherical [6].

All experimental formulations of pellets were characterized by Hausner ratio values of less than 1.2, which indicates a weak cohesion between the pellets and freely flowing characteristics.

2. Data fit and validation of the experimental plan

Data fit was performed for a confidence interval of 95%, using the PLS (Partial Least Squares) method. The validation of the experimental plan was performed by demonstrating two criteria: model fit and dependency curves.

a. Model validation

Experiments N4, N5, N6, N 15, N 20, N 24 and N25 have led to clumps of pellets, with considerably higher sizes than the 1.18 mm sieve openings. Because the D-Optimal model allows the exclusion experiments for which the combination of levels of factors has resulted in unacceptable results, as well as an irregular experimental range, these experiments were excluded from fitting experimental data to validate the plan [10].

The results obtained by fitting the experimental data to the model and the interpretation of the calculated statistical parameters are shown in the following figure.

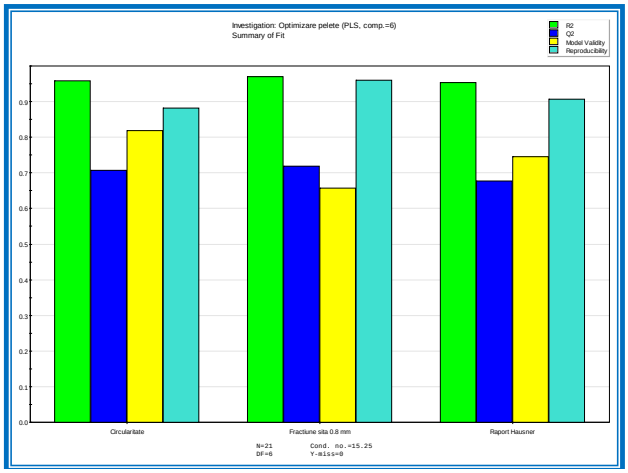


Figure 1. The results obtained in data fit for the Circularity, Fraction 0.8 mm sieve and Hausner ratio responses

The selected model is consistent with the experimental data. For all responses considered, values of R2 greater than 0.95, and good values of Q2 (around 0.7) were obtained, indicating a good capacity of prediction of the selected experimental model. In addition, high values for the model validity and reproducibility were obtained for all replicates.

b. Dependency curves

The graphs of the residual curves of the observed responses function of the expected responses indicate a satisfactory alignment of data points on the regression line and a satisfactory fit of the data with the selected model.

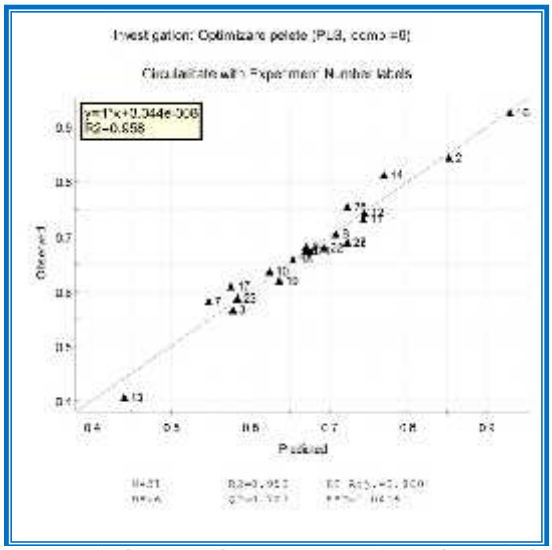


Figure 2. The residual curve of observed responses function of the estimated responses for the „Circularity” response

In conclusion, the analysis of the quality of fit based on the statistic parameters R^2 and Q^2 and on the dependency curves show a good fit of the model.

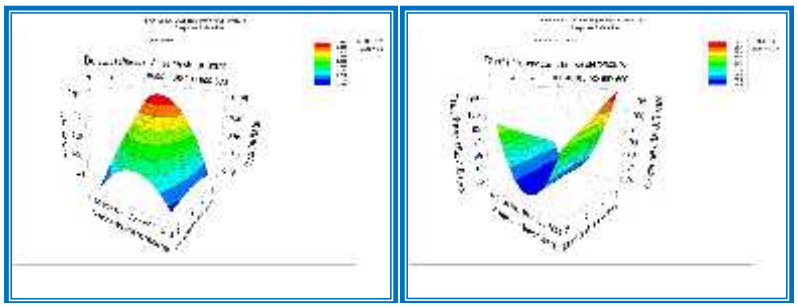
3. Analysis of the influence of formulation and technological factors on the characteristics of the pellets

By taking into account the extent to which the formulation and process factors have influenced the monitored responses (roundness, dimensions and flow characteristics), it was possible to establish a hierarchy of the importance of independent variables. The method of ranking the importance of responses is based on the coefficients of the equation used for fitting the experimental design and on the response surface analysis.

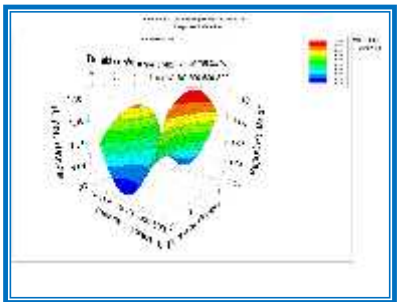
The conclusions of this study allow the determination of the optimum values for the formulation and processing parameter, consistent with its objectives.

The analysis of the formulation and technological factors (the independent variables) was realized by tracking three-dimensional representation of the response surfaces. Thus, it is possible to predict and select the "best conditions" that lead to a certain response. The graphs below are a three-dimensional rendering of the surface areas of the expected responses.

It was found that the highest values of circularity (0.939) can be obtained for minimum levels of the MCC variable (0.25) and maximum binder (0.5). In the case of the „Fraction 0.8 mm sieve” response, the maximum expected values (highest yield of the process) are obtained for maximum MCC (0.4) and minimum Binder (0.35), in the conditions of the longest spheronization time considered (5 minutes) and at slow speed. High values of the „Hausner ratio” parameter can be predicted, regardless of formulation factors, if the processing is performed under an average spheronization duration (3.5 minutes) or extreme levels of spheronization speed (500 rpm or 1000 rpm). The lowest values are obtained for minimum and maximum spheronization speeds.



a. MCC = 0.25, Binder = 0.5 ***i. MCC = 0.4, Binder = 0.35***



b. MCC = 0.325, Binder = 0.5

Figure 3. Response surfaces of the dependent variables „Circularity” (a), „Fraction 0.8 mm sieve” (i), „Hausner ratio” (b)

4. The determination of the optimal formulation

The optimal formula was established after data fitting and the evaluation of the experimental results included in the experimental matrix using the tool "Optimizer", thus

identifying an experimental field, limited by the values imposed on the factors and by the criteria set for the responses – the pharmacotechnical characteristics of the pellets: to maximize the value for the parameter „Circularity" (thus obtaining more spherical pellets), to maximize value for the parameter „Fraction 0.8 mm sieve" (the highest possible yield of the process that leads to pellets with a size between 0 8 mm and 1.18 mm) and the lowest possible value for the „Hausner ratio" (a value of less than 1.2 indicating a good flow of its pellets).

During optimization, various combinations were generated for the assigned values of the independent variables (factors), the optimizer running a number of iterations for each combination. After running the optimizer, the combination of independent variables corresponding to corresponding to the optimal responses was selected, the experiment conditions with the highest number of iterations (334). The following combination of levels for independent variables was considered to be corresponding to the optimal formula:

Table no. 4

Levels of the formulation and process variables corresponding to the optimal characteristics of the inert pellets

Independent variables	Levels for the optimal formula
Spheronization time	2
Spheronization speed	871.964
MCC	0.4
L	0.25
Binder	0.35

The formula selected as the final result of the optimization process was prepared and tested in order to establish consistency with the prediction. The values obtained in the evaluation of the pellet characteristics were very close to the ones predicted by the model.

Table no. 5

Practical results vs. theoretical (calculated) results

Parameter	***Theoretical***	***Practical***
Circularity	0.69	0.71
Fraction 0.8 mm sieve	79.8	89.24
Hausner ratio	1.06	1.08

CONCLUSIONS

The experimental design that was applied made possible the identification of the optimal formulation and technological parameters considered as independent variables, by imposing certain criteria for the responses (the characteristics of the resulting pellets).

The formula selected as the final result of the optimization process was prepared and tested in order to establish consistency with the prediction. The recorded values of the dependent variables were very close to those predicted by the model, which indicates the adequacy of mathematical models applied for each of the responses. The findings allowed the optimum formulation and processing parameters to be established, consistent with the objectives considered in the beginning of the study.

AKNOWLEDGMENT

The work has been funded by the "Tineri Cercetători" Programme 2013-2015 financed by the University of Medicine and Pharmacy „Carol Davila", Research contract no. 28326 / 04.11.2013.

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