THE INFLUENCE OF SOME CHARACTERISTICS OF RANITIDINE HYDROCHLORIDE ON THE FORMING AND PREPARATION OF THE TABLETS

POSTOLACHE LILIANA*[1,2], ONUŢĂ ALEXANDRU-EVLAMPIE[2,3]

[1]*Faculty of Pharmacy, University of Medicine and Pharmacy "Gr. T. Popa", Str. Universităţii nr. 16, 700115 Iasi, Romania*
[2]*Antibiotice S.A., Str. Valea Lupului nr. 1, 707410, Iassy, Romania*
[3]*Faculty of Automation and Computer Science, Technical University "Gheorghe Asachi"of Iasi, Str. Prof, Dr. Doc. Demetrius Mangeron, nr. 27, 70005, Iasi, Romania*
**corresponding author: liliana_postolache@yahoo.com*

Abstract

The physical behavior of pharmaceutical solid forms is determined by the raw materials characteristics used in their manufacture. These must come only from authorized sources. When the raw materials are coming from different sources they may not have identical properties in the formula. It is important to know the properties of the active pharmaceutical ingredient (API), individually and in combination with the excipients, within the formula.

The aim of this study was to evaluate the influence of API's characteristics, from different producers, on the behavior of some ranitidine tablets, obtained by dry granulation.

The statistical method for data processing consisted in the multivariate linear regression analysis (Partial Least Squares – PLS). Its implementation was performed using Modde 9.0 Umetrics Suedia software.

The results have shown that in order to avoid the additional costs of technology re-optimization and technological flow sheet revalidation in the case of changing the API supplier, we should re-evaluate it, in the context of formula and of the authorized production process.

Rezumat

Comportamentul fizic al formelor farmaceutice solide orale este determinat de caracteristicile materiilor prime utilizate în fabricaţia lor.

Acestea trebuie să provină numai de la producătorii autorizaţi. Dacă provin din surse diferite pot să nu aibă proprietăţi identice în formulă. Este foarte importantă cunoaşterea proprietăţilor principiului activ, individual şi în combinaţie cu excipienţii din formulă.

Obiectivul acestui studiu a fost evaluarea influenţei caracteristicilor principiului activ, provenit de la producători diferiţi, asupra comportamentului unor comprimate cu ranitidină, obţinute prin granulare uscată.

Metoda statistică de prelucrare a datelor a constat în analiza regresională multivariată (*Partial Least Squares* – PLS), iar implementarea acesteia s-a realizat cu ajutorul softului *Modde 9.0 Umetrics Suedia*.

Rezultatele studiului au arătat că pentru a evita costurile adiţionale cu reoptimizarea tehnologiei şi revalidarea procesului tehnologic în cazul schimbării furnizorului de principiu activ, acesta din urmă trebuie reevaluat în contextul formulei şi a procesului de fabricaţie autorizat.

Keywords: ranitidine hydrochloride**,** linear regression, tablets, independent variable, friability.

Introduction

The production of medicines is accomplished according to an authorized formula, through validated processes on qualified equipments, using raw materials from authorized sources. Thus, the obtained medicines are characterized by stability, uniformity and therapeutical efficiency. The raw materials must be acquisitioned only from approved suppliers, mentioned in the relevant specification [1,4]. When the raw materials come from different sources, they may not have identical properties in the formula. For this reason, it is very important to know the API's properties (API – active pharmaceutical ingredient), individually and in combination with the excipients in the formula. Changing the API supplier can be initiated only after a comparative analysis of the quality of this new source with the authorized source [2]. The flowing of the powders is usually determined by the particles sizes, the distribution of the particles sizes and their formula. The high differences between particles sizes may lead to segregation during the production. Unlike the particles with regulated shape (almost spherical), the unregulated shape of the particles determines weak flowing properties [3]. Therefore, the different density and granulometry of API, may lead to different results in terms of powders flow and tablets characteristics, depending on the formulation.

The aim of this study was the evaluation of the influence of API's characteristics, coming from different producers, on the behavior of some ranitidine tablets, obtained by dry granulation.

To understand the phenomenon a multivariate linear regression analysis was used to allow the setting of some quantitative equations between the independent variables (factors) and dependent variables (responses): the Partial Least Squares – PLS [5].

Materials and Methods

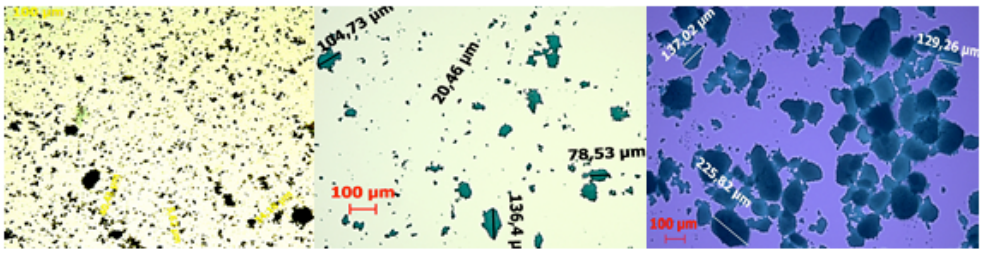
Materials

In this study ranitidine hydrochloride (the polymorph form I) with different granulometric distribution, from three different producers was used (table I and figure 1).

Table I

Raw materials used in formulations

Active ingredient and excipients	Function	Manufacturer
Ranitidine hydrochloride	API-active pharmaceutical ingredient	U'Quifa, Spain – encoded S1
		Shasun, India – encoded S2
		Neuland, India – encoded S3
Microcristalline cellulose (Vivapur®type 102)	Filler and binder	JRS Pharma, Germany
Sodium starch glycolate (Vivastar®)	Disintegrant	JRS Pharma, Germany
Colloidal silicon dioxide (Aerosil®200)	Glidant	Degussa, Germany
Magnesium stearate	Lubricant	Union Derivan SA, Spania



S1 S2 S3

Figure 1

Appearance of particles of API

Methods

Within the studies, the dry granulation method was used and three formula were established (encoded FI, FII, FIII), with a different percentual composition for excipients with filler and disintegrant role (table II).

Table II

The qualitative composition for the formulations

Raw materials (%)	FI	FII	FIII
Ranitidine hydrochloride	56	56	56
Microcristalline cellulose	41	39	37
Sodium starch glycolate	1	3	5
Colloidal silicon dioxide	1	1	1
Magnesium stearate	1	1	1

Ranitidine hydrochloride was homogenized with microcrystalline cellulose 102 in a 60 Liters V homogenizer (15 minutes at 7 rpm). The obtained mixtures were compacted on dry granulator, Alexanderwerk, in similar functioning conditions (1.25 mm sieve, 3 mm foliole thickness), excepting the compaction pressure: 25 bar, 37.5 bar and 50 bar. The resulted granules were homogenized with sodium starch glycolate and colloidal silicon dioxide (5 minutes at 7 rpm) and lubricated with magnesium stearate (3 minutes at 7 rpm).

The samples from the lubricated granules were taken to determine the Hausser and Carr index and the repose angle (Erweka ST 12 tester).

The final compositions were compressed on a rotary press with a 10 kN tabletting force and 14 rpm rotation speed. Biconvex round shape tablet tooling with a 9 mm diameter was used. The average weight of a tablet was 300 mg. Tablets physical properties were measured on 20 tablets for friability (Vankel AG 104 friabilator) and 6 tablets for the disintegration time (Hanson Research QC 21 tester).

The experimental plan was generated by using Modde 9.0 Umetrics software through the variation of three formulations and process factors (independent variables) on three levels (table III).

Table III

Independent variables and their levels of variation

Independent variables	Abbreviation	Units	Type	Levels of variation
Sort of API	API	-	Qualitative	S1 / S2 / S3
Disintegrant	Dis	%	Multilevel	1 / 3 / 5
Compaction pressure	Pres	bars	Multilevel	25 / 37,5 / 50

As dependent variable a series of characteristics of lubricated product and tablets was studied (table IV).

Table IV

Dependent variables and their admissibility limits

Dependent variables	Abbreviation	Units	Values	
			min	max
Haussner index	IndH	-	1,2	1,3
Carr index	IndC	%	16	28
Angle of repose	Angle	degrees	-	30
Disintegration time	DesT	min	-	15
Friability	Friab	%	-	1

Results and Discussion

In order to establish the factorial plan of type 3^3 there were necessary 27 experimental determinations (table V).

For the model validation the statistical parameters R^2 and Q^2 were calculated, the variance was determined (ANOVA test) and the dependence curves of the observed values according to the model estimated values were drawn. The obtained results indicated the experimental data fitting with the chosen model and a good capacity of plan prediction.

Table V

The matrix of the experimental plan

Exp. No.	Exp. Name	Run Order	API	Dis	Pres	IndH	IndC	Angle	DesT	Friab
1	N1	14	S1	1	25	1,277	21,674	29,9	7,5	0,042
2	N2	5	S2	1	25	1,333	24,645	36,0	10,6	0,404
3	N3	2	S3	1	25	1,330	25,388	29,8	8,2	0,071
4	N4	27	S1	3	25	1,284	22,585	30,7	7,2	0,008
5	N5	7	S2	3	25	1,316	23,329	31,02	9,1	0,285
6	N6	16	S3	3	25	1,331	25,542	29,5	8,8	0,047
7	N7	15	S1	5	25	1,291	23,496	31,4	6,8	0,058
8	N8	10	S2	5	25	1,298	22,013	26,5	7,7	0,167
9	N9	3	S3	5	25	1,331	25,697	29,1	9,3	0,024
10	N10	4	S1	1	37,5	1,258	19,753	28,4	6,8	0,091
11	N11	11	S2	1	37,5	1,325	23,841	34,9	10,0	0,407
12	N12	20	S3	1	37,5	1,335	25,841	30,4	8,6	0,074
13	N13	12	S1	3	37,5	1,269	21,124	29,2	6,6	0,033
14	N14	23	S2	3	37,5	1,311	22,868	30,3	8,7	0,281
15	N15	21	S3	3	37,5	1,340	26,338	30,2	9,3	0,043
16	N16	6	S1	5	37,5	1,280	22,260	30,1	6,5	0,024
17	N17	18	S2	5	37,5	1,297	21,895	25,6	7,4	0,155
18	N18	17	S3	5	37,5	1,344	26,835	29,9	10,0	0,013
19	N19	29	S1	1	50	1,239	17,831	26,9	6,1	0,139
20	N20	22	S2	1	50	1,316	23,036	33,9	9,5	0,411
21	N21	25	S3	1	50	1,340	26,293	31,0	8,9	0,077
22	N22	28	S1	3	50	1,254	19,427	27,8	6,1	0,075
23	N23	13	S2	3	50	1,307	22,406	29,3	8,3	0,277
24	N24	19	S3	3	50	1,349	27,133	30,9	9,8	0,041
25	N25	26	S1	5	50	1,268	21,024	28,8	6,1	0,011
26	N26	9	S2	5	50	1,297	21,776	24,8	7,2	0,143
27	N27	8	S3	5	50	1,357	27,793	30,7	10,7	0,003
28	N28	1	S1	3	37,5	1,269	21,125	29,2	6,6	0,039
29	N29	30	S1	3	37,5	1,271	21,314	29,4	6,6	0,042
30	N30	24	S1	3	37,5	1,275	21,658	29,9	6,9	0,065

where: API – active pharmaceutical ingredient; DIS – disintegrant; Pres – compaction pressure; IndH – Haussuer Index; IndC – Carr Index; Angle – angle of repose; DesT – disintegration time; Friab – friability.

The evaluation of the studied factors and the interactions between them on the responses was achieved by analyzing the equations coefficients used to fit the experimental data, presented as histograms (figure 2).

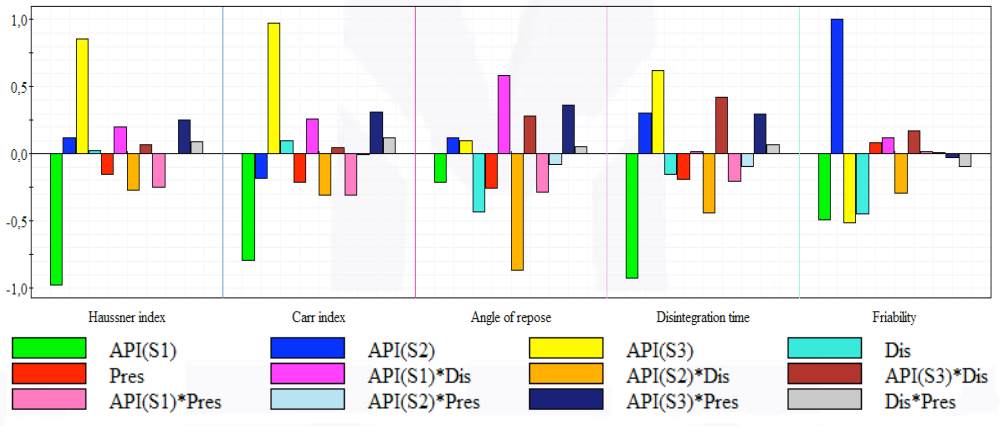


Figure 2
The influence of independent factors on the responses

It was observed that S1 and the interaction S1*Pres have significantly influenced the studied properties. The increase of the compaction pressure favored the flow of the lubricated products and the tablets disintegration.

The physical behavior of samples with S2 depended by the S2*Dis interaction. Increasing the percentage of disintegrate determined the reduction of all studied values. The sample with S2 and 5% disintegrate presented the smallest repose angle.

The S3 source didn't influence the flowing factors and tablets disintegration (the error bar for standard deviation passed 0 for all mentioned factors). For the formula FIII, higher compaction pressures ensured the best tablets friability.

Conclusions

From the statistical analysis of the obtained data resulted that an API from different producers may determine different pharmaco-technical properties for the powders and tablets for which it is used, according to its characteristics, formula and process parameters. In order to prevent the additional costs with the technological re-optimization and technological flow revalidation, the behavior of a new source must be evaluated in the context of the formula and the authorized manufacturing process.

References

1. ***Materii prime, Capitolul 5 Fabricaţia, Ghid privind Buna Practică de Fabricaţie pentru Medicamentele de uz Uman, Bucureşti, 2009, 48-49
2. Ahjel S., Lupuliasa D., Directly Compressible Adjuvants – A Pharmaceutical Approach, *Farmacia*, 2008, 56(6), 591-599.
3. Hancock B., Colvin J., Mullarney M., The Relative Densities of Pharmaceutical Powders, Blend, Dry Granulations, and Immediate Reales Tablets, *Pharm. Technol.,* 2003, 64-80.
4. Bodea M., Tomuţă I., Leucuţa S., Identification of critical formulation variables for obtaining metoprolol tartrate mini-tablets, *Farmacia*, 2010, 58(6), 719-727**.**
5. MODDE 9, Software for Design of Experiments and Optimization, User's Guide and Tutorial, Umetrics AB, Umea, 2010.

Manuscript received: March 23rd 2011