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Optimization of poorly compactable drug tablets manufactured by direct compression using the mixture experimental design

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Abstract

The poor flowability and bad compressibility characteristics of paracetamol are well known. As a result, the production of paracetamol tablets is almost exclusively by wet granulation, a disadvantageous method when compared to direct compression. The development of a new tablet formulation is still based on a large number of experiments and often relies merely on the experience of the analyst. The purpose of this study was to apply experimental design methodology (DOE) to the development and optimization of tablet formulations containing high amounts of paracetamol (more than 70%) and manufactured by direct compression. Nineteen formulations, screened by DOE methodology, were produced with different proportions of Microcel® 102, Kollydon® VA 64, Flowlac®, Kollydon® CL 30, PEG 4000, Aerosil®, and magnesium stearate. Tablet properties, except friability, were in accordance with the USP 28th ed. requirements. These results were used to generate plots for optimization, mainly for friability. The physical–chemical data found from the optimized formulation were very close to those from the regression analysis, demonstrating that the mixture project is a great tool for the research and development of new formulations.

Keywords: Paracetamol; Tablets; Mixture experimental design; Response surface methodology; Direct compression

1. Introduction

Paracetamol is a drug widely used in therapeutics for its analgesic and antipyretic properties. Usually it is formulated in tablets containing 300–500 mg of drug. Paracetamol exhibits poor compression ability, low flowability and its tablets show a tendency to cap (Hong-Guang and Ru-Hua, 1995; Yu et al., 1988). The poor compaction behavior of paracetamol and its reduced plastic deformation have been explained in terms of the crystal structure of the material, which is based on a monoclinic crystal system (Jivraj et al., 2000; Nichols and Framptom, 1998). Due to these characteristics the production of paracetamol tablets is almost exclusively by wet granulation.

The advantages of direct compression are well known: fewer processing stages, elimination of heat and moisture effects, increase of productivity and reduction of the final cost of the product. Furthermore, direct compression is considered an appropriate process for hygroscopic and thermo-sensitive substances (Jivraj et al., 2000; Beyer et al., 2001). A serious limitation of this technique is the use of more than 30% of the drug in the formulation, mainly for drugs that present low flowability and segregation (Jivraj et al., 2000). Regarding to the manufacturability, a good flowability of the blend, i.e., the dry mixture of excipients and drug, is critical for the compression of the tablets in terms of dissolution, friability and content uniformity.

Some attempts have been made to modify the properties of paracetamol crystals using different crystallization techniques in order to improve the compaction properties of unmodified crystals (Fachaux et al., 1995; Di Martino et al., 1996; Abdelillah et al., 1995). However, the most common limitations of these methods were the relatively high solvent content remaining in the final agglomerates even after drying, the high temperature required, besides the strict control over atmosphere and time (Garekani et al., 2000a,b).

Alternatively, a number of manufacturers have prepared paracetamol powders for direct compression. These materials have good compressibility, but all these paracetamols for direct compression are mixtures of paracetamol with either starch,

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carboxymethylcelulose, pregelatinized starch, PVP or gelatin. Above all, their dissolution rates are sometimes lower than those of conventional paracetamol and they are not 'pure paracetamol' according to the official monographs.

Nowadays, most of the experimentation on tablet formulation development is still performed by changing the levels of each variable (factor) at a time, in an unsystematic way, keeping all other variables constant in order to study the effects of that specific variable on the selected response or to find the optimal conditions of a complete system. This methodology is based on large number of experiments and often relies merely on the experience of the analyst (Kincl et al., 2005).

Statistical experimental design, also called design of experiments (DOE), is a well-established concept for planning and execution of informative experiments. DOE can be used in many applications. An important type of DOE application refers to the preparation and modification of mixtures. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture (Eriksson et al., 1998).

In DOE approach, process variables are first 'screened' to determine which are important to the outcome (excipient type, percentage, mixture time, etc.). Next step is the 'optimization', when the best settings for the important variables are determined. In particular, response surface methodologies have been successfully applied in both drug discovery and development (Gooding, 2004). Advances in supporting software, automated synthesis instrumentation, and high-throughput analytical techniques have led to the broader adoption of this approach in pharmaceutical discovery and chemical development laboratories (Congreve and Jamieson, 2002).

Taking into account the limitations and challenges in developing direct compressed tablet formulations containing over than 30% of a poorly compactable drug with low flowability, we applied mixture experiments, as described by Cornell (1990). In this methodology, the study of the ingredient effect on some measurable characteristics of the blend (or response) is an attempt to find the formulation (or formulations) that produce the 'best' response (Cornell, 1990).

2. Materials and methods

2.1. Materials

The following raw materials were used: Aerosil® (Blanver), Magnesium estearate (Aspen Farmacêutica), Flowlac® (Meggle), Kollydon® VA 64 (Basf), Kollydon® CL 30 (Basf), Microcel® 102 (Colorcon), paracetamol (Huzhou Konch Pharmaceutical Co. Ltd.) and polietilenoglicol (PEG) 4000 (Synth). All other reagents were of analytical grade. Paracetamol (>99%) was used as standard in quantitative determinations.

2.2. Preparation of paracetamol tablets

Seven constituents, Microcel® 102 (X_1), Kollydon® VA 64 (X_2), Flowlac® (X_3), Kollydon® CL 30 (X_4), PEG 4000 (X_5), Aerosil® (X_6), magnesium estearate (X_7), were mixed according to mixture design, with multiple constraints on the component proportions, using fixed intervals, as stated in Tables 1 and 2. The total amount of excipients was maintained at 200 mg, and the paracetamol content was 500 mg. The coordinates of the 19 design points for the constrained were generated and randomly arranged by Design-Expert® software and the respective tablet formulations are described in Table 3.

Table 1
Variables and intervals selected to perform the mixture design

Variables in total excipient	Level	
	Low	High
X_1 = fraction of Microcel® 102	0.50	0.875
X_2 = fraction of Kollydon® VA 64	0.10	0.250
X_3 = fraction of Flowlac®	0.00	0.250
X_4 = fraction of Kollydon® CL 30	0.00	0.100
X_5 = fraction of PEG 4000	0.00	0.100
X_6 = fraction of Aerosil®	0.00	0.030
X_7 = fraction of magnesium	0.005	0.025

The amount of paracetamol was fixed at 500 mg. The amount of total excipients was fixed at 200 mg. $X_1 + X_2 + X_3 + \cdots + X_7 = 100\%$ of the mixture design ($\sum X = 1$).

Drug and excipients were weighted and mixed in a biconical mixer (Pharmatest), for 25 min. Tablets were produced in a single-punch tablet press (Fabbe), with a compression force of 3000 kg. Flat-faced tablets with a diameter of 12 mm were obtained.

2.3. Powder properties

The water content of samples was determined in a Gehaka, IV2002 analyser, until the sample achieved constant mass. The mass difference was considered as being the water content.

The repose angle was measured according to the fixed-funnel method (Prista et al., 1995). The end of a funnel was placed 2 cm above a flat base. Powder (around 2.5 g, depending on the bulk density of the material) was filled into the funnel, so that after releasing it out of the funnel the top of the resulting cone reached the end of the funnel. From the height of the cone (h) and its diameter at the base (d) the angle at the base, the angle of repose (α) was determined (each result reported is a calculated average of three measurements):

$$\tan \alpha = 2h/d \quad (1)$$

where α is the angle of repose (°), h the height of the cone formed by the powder (mm) and d is the diameter of the cone (mm).

For the determination of bulk and tap densities, an appropriate amount of the sample was poured in a 100 mL tared graduated cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density (ρ_{bulk}) according to the mass/volume ratio. For tap density (ρ_{tap}), the cylinder was tapped 1225 times, until volume was constant, using a Logan TAP-2 tap density analyzer. The compressibility (Prista et al., 1995; Lachman et al., 2001; Velasco et al., 1995) was calculated using the equation:

$$\%\ \text{of compressibility} = [(\rho_{tap} - \rho_{bulk})/\rho_{tap}] \times 100 \quad (2)$$

Table 2
DOE parameter settings including ingredients, and proportion (%) in the mixture of excipients

Run	Microcel® 102 (X_1)	Kollydon® VA 64 (X_2)	Flowlac® (X_3)	Kollydon® CL 30 (X_4)	PEG 4000 (X_5)	Aerosil® (X_6)	Magnesium stearate (X_7)
1	0.578	0.166	0.125	0.050	0.050	0.016	0.015
2	0.610	0.250	0.000	0.000	0.100	0.030	0.005
3	0.500	0.250	0.245	0.000	0.000	0.000	0.005
4	0.500	0.250	0.250	0.100	0.100	0.000	0.025
5	0.595	0.250	0.000	0.100	0.000	0.030	0.025
6	0.500	0.100	0.245	0.000	0.100	0.030	0.025
7	0.875	0.100	0.000	0.000	0.000	0.000	0.025
8	0.578	0.166	0.125	0.050	0.050	0.016	0.015
9	0.500	0.100	0.245	0.100	0.000	0.030	0.025
10	0.525	0.100	0.250	0.000	0.100	0.000	0.025
11	0.865	0.100	0.000	0.000	0.000	0.030	0.005
12	0.595	0.250	0.000	0.000	0.100	0.030	0.025
13	0.578	0.166	0.125	0.050	0.050	0.016	0.015
14	0.500	0.250	0.245	0.000	0.000	0.000	0.005
15	0.695	0.100	0.000	0.100	0.100	0.000	0.005
16	0.578	0.166	0.125	0.050	0.050	0.016	0.015
17	0.695	0.100	0.000	0.100	0.100	0.000	0.005
18	0.515	0.100	0.250	0.100	0.000	0.030	0.005
19	0.578	0.166	0.125	0.050	0.050	0.016	0.015

Paracetamol amount was fixed at 500 mg; the mixture of total excipient was fixed at 200 mg; each run composition was random and arranged according to screening model provided by the Design-Expert® software.

where ρ_{bulk} is the bulk density (g/mL) and ρ_{tap} is the tap density (g/mL).

2.4. Tablet properties

The tablet properties were examined according to the USP 28th ed. specifications. The hardness of tablets was measured using a Nova Ética 298 hardness tester. Each hardness value reported is a calculated average of ten measurements. The disintegration time was measured in purified water at $37 \pm 0.5\,^{\circ}C$, in an Ética 301 AC apparatus, using disks. Each disintegration time reported is a calculated average of six determinations. The average tablet weight was determined weighting 20 tablets individually using an analytical balance (Sartorius, model BL 2105). Tablet friability was calculated as the percentage weight loss of 20 tablets after 100 rotations in an Ética H3CR friabilator.

The paracetamol content was determined using an in-house validated spectrophotometric procedure in a Bechman Coulter DU640 spectrophotometer (HMSO, 2005).

Dissolution of paracetamol from tablets was measured according to the USP 28th ed. paddle method, at a paddle speed of 50 rpm, in 900 mL of pH 5.8 buffer solution at $37 \pm 0.5\,^{\circ}C$, using a Hanson Research SR-6 dissolution tester. The paracetamol concentration of each sample ($n = 6$) was spec-

Table 3
Tablet compositions (mg)

Formulation	Microcel® 102	Kollydon® VA 64	Flowlac®	Kollydon® CL 30	PEG 400	Aerosil®	Magnesium stearate	Total weight
1	115.50	33.24	24.94	10.06	10.06	3.14	3.08	700.02
2	123.00	50.00	0.00	0.00	20.00	6.00	1.00	700.00
3	100.00	50.00	49.00	0.00	0.00	0.00	1.00	700.00
4	100.00	50.00	5.00	20.00	20.00	0.00	5.00	700.00
5	119.00	50.00	0.00	20.00	0.00	6.00	5.00	700.00
6	100.00	20.00	49.00	0.00	20.00	6.00	5.00	700.00
7	175.00	20.00	0.00	0.00	0.00	0.00	5.00	700.00
8	115.50	33.24	24.94	10.06	10.06	3.14	3.08	700.02
9	100.00	20.00	49.00	20.00	0.00	6.00	5.00	700.00
10	105.00	20.00	50.00	0.00	20.00	0.00	5.00	700.00
11	173.00	20.00	0.00	0.00	0.00	6.00	1.00	700.00
12	119.00	50.00	0.00	0.00	20.00	6.00	5.00	700.00
13	115.50	33.24	24.94	10.06	10.06	3.14	3.08	700.02
14	100.00	50.00	49.00	0.00	0.00	0.00	1.00	700.00
15	139.00	20.00	0.00	20.00	20.00	0.00	1.00	700.00
16	115.50	33.24	24.94	10.06	10.06	3.14	3.08	700.02
17	139.00	20.00	0.00	20.00	20.00	0.00	1.00	700.00
18	103.00	20.00	50.00	20.00	0.00	6.00	1.00	700.00
19	115.50	33.24	24.94	10.06	10.06	3.14	3.08	700.02

The content of paracetamol for all formulations was 500.00 mg.

trophotometrically determined at 244 nm (Bechman Coulter, DU640).

2.5. Data analysis

Design-Expert® software was used to model the shape of the surfaces. The best-fitting mathematical model was selected based on the comparisons of several statistical parameters including the determination coefficient (R^2), the adjusted determination coefficient (adj-R^2) and the F-value provided by analysis of variance (ANOVA). All responses providing a significant F-value originated response surfaces.

3. Results and discussion

The flowability of a powder is a behavioral characterization of its ability to flow, and its vital importance in the production of tablets is well documented in the literature (Hong-Guang and Ru-Hua, 1995; Jivraj et al., 2000; Prista et al., 1995). The powder flowability was evaluated by the angle of repose and percentage of compressibility, smaller values of both parameters indicating better flowability. The flowability data for the formulations are shown in Table 4. The angle of repose of powders without Aerosil® (formulations 3, 4, 7, 10, 14, 15 and 17) presented high levels of repose angles (42.90–48.10°), in contrast to those containing this lubricant combined to magnesium stearate (formulations 1, 2, 5, 6, 8, 9, 11, 12, 13, 16, 18 and 19 presented repose angles from 10.73° to 18.87°). The compressibility index for the powders containing only magnesium stearate as lubricant are also significantly higher than for those with Aerosil®. These results support the fact that we could not obtain tablets from blends with higher repose angle and higher compressibility because they exhibited relatively poor flow and they were not able to produce uniformity on supplying powder to the die cavity of the tablet machine. This fact suggests that Aerosil® is an indispensable constituent in the tablet formulations.

The water content of each formulation is shown in Table 4. The amount of water in the blends varied from 1.50 to 2.87%. These results were within suggested limits (between 1.5 and 3.0%) for tablets produced by direct compression (Prista et al., 1995).

Table 4
Experimental values of repose angle, compressibility and water content of each blend

Blend	Repose angle (°)	Compressibility (%)	Water content (%)
1	20.93	30.49	2.38
2	18.87	27.49	2.40
3	43.87	31.46	2.35
4	45.80	35.91	2.35
5	12.23	30.65	2.87
6	10.73	30.75	2.45
7	42.90	33.25	2.25
8	16.97	30.45	1.79
9	16.90	29.97	2.50
10	39.67	33.82	1.54
11	14.07	30.05	2.51
12	14.60	30.46	2.15
13	16.43	31.34	1.50
14	45.43	34.12	2.25
15	43.77	35.35	2.19
16	18.00	29.66	1.97
17	48.10	34.43	2.15
18	16.93	30.09	1.65
19	21.37	30.21	2.05

The mechanical strength of pharmaceutical compacts is defined as the force required to fracture a specimen across its diameter, which is usually reported as ‘tablet hardness’ in the pharmaceutical industry. Pharmaceutical compacts are required to have sufficient mechanical strength to withstand handling yet remaining bioavailable. The hardness data were considered acceptable for direct compression formulations. As shown in Table 5, they varied from 5.5 to 11.1 kgf.

The time of disintegration ranged from 1.8 to 8.0 min and the results met the HMSO (2005), which states the limit for uncoated tablets at 15 min (Table 5).

The maximum official weight variation for tablets heavier than 250 mg is 5%, therefore, all formulations met the USP 28th ed. specifications. The results of weight variation are shown in Table 5.

Based on the USP 28th ed. specifications, all formulations met the requirement of not less than 85% of drug dissolved in 30 min (Table 5).

Table 5
Average tablet weight, hardness, friability, paracetamol content, disintegration time and percentage of drug dissolved of each tablet formulation

Formulation	Weight (mg)	Hardness (kgf)	Friability (%)	Paracetamol content (%)	Disintegration time (min)	Dissolution (%)
1	695.8	9.8	3.24	98.0	1.9	92.0
2	693.7	11.1	0.55	99.0	5.0	91.4
5	675.7	7.4	8.35	97.5	1.8	87.9
6	699.0	6.1	9.96	98.6	6.9	92.2
8	704.7	7.2	6.16	96.6	4.7	93.1
9	696.1	5.5	11.74	98.6	8.0	92.3
11	678.0	7.4	4.60	97.2	4.4	92.8
12	687.4	7.1	9.38	103.0	2.2	87.4
13	704.7	6.0	6.86	100.9	2.1	95.1
16	719.4	6.4	3.99	100.5	2.4	95.6
18	714.5	8.3	5.96	98.7	3.4	93.0
19	706.9	6.1	5.06	100.5	3.2	94.0

Omitted runs (formulations 3, 4, 7, 10, 14, 15, and 17) where not compressed as a result of bad feeding during the filling of tablets dies.

Paracetamol tablet content ranged from 96.6 to 103.0%, in accordance with the HMSO (2005) specification (95–105%).

A maximum friability of not more than 1.0% of weight is considered acceptable for tablets (US Pharmacopeia XXVIII, 2005). Only formulation 2 presented friability in accordance with official specification (0.55%). The use of flat punches, theoretically, reduces the tendency to cap. However, tablets of all formulations presented lamination, except formulations 2, 17 and 18, demonstrating the poor plastic characteristics of paracetamol.

3.1. Analysis of data and evaluation of models

According to Eriksson et al. (1998), screening is used in the beginning of the experimental procedure for investigating large numbers of factors aiming to reveal the most important among them. Optimization is applied for finding a factor combination matching an optimal response profile. The design supporting a linear model is useful when the experimental objective is screening, whereas, the design supporting quadratic or special cubic models are relevant for optimization. The coordinate system for the mixture problem is called a simplex coordinate system. With three components the coordinate can be plotted on a triangular graph (Cornell, 1990).

In the first phase, we constructed a screening design for investigating the influence of each factor (ingredient of the excipient) in the responses (tablets and powder characteristics). With seven factors, the lead number of experiments $N = 19$ was suggested by the Design-Expert® software, and runs were randomly set. After producing and analyzing the formulations, physical–chemical responses were applied to fit the appropriate model (linear or quadratic). The model was tested for goodness of fit (R^2) and analysis of variance (ANOVA) was applied to verify the adequacy of the regression model in terms of a lack-of-fit test. This test implies that the residual response sum of squares is separated into the components model error and pure error, and their significances were obtained by an F-test (Table 6). Each response was investigated regarding to outliers and it was found that all points were placed in a normal distribution (data not showed).

Response contours diagrams illustrating model equations and showing the effects of excipients on paracetamol tablets/powder characteristics were created to interpret the mixture region (Figs. 1 and 2). In the response surface, each factor (pure mixture component) is represented in a corner of an equilateral triangle; each point within this triangle refers to a different proportion of components in the mixture. The maximum percentage of each ingredient considered by the regression is placed at the corresponding corner while the minimum is positioned at the middle of the opposite side of the triangle.

In Figs. 1 and 2, four variables (ingredients) were fixed at their average compositions while the other three were placed at the corners of the triangle. Centroid (the center of the triangle) represents the mixture in equal parts. In this study, the centroid was replicated five times to determine reproducibility and detect non-linear responses. The lighter shaded regions showed in the figures refer to areas not applied in the regressions, due to the restrictions fixed according to Table 1.

It was found that for water and paracetamol contents, linear or quadratic models were not significant as presented in Table 6. Consequently, variations on the excipient composition had no influence on the water and paracetamol contents. In general, linear model is the most appropriate to the mixture design since the relations between the ingredients of mixture are showed by directly proportional responses. In addition, linear model is less complex than other models. Probably, an important factor on the water content formulations was paracetamol humidity, since it represents 70% of the content of all formulations. Paracetamol tablet content was not influenced by the excipient composition possibly because its percentage was maintained constant in all formulations.

Repose angle (RA) showed to be affected by the excipient composition (linear and quadratic models were significant). From regression data of the linear model it was obtained the equation:

$$\mathrm{RA} = 42.91X_1 + 44.95X_2 + 40.39X_3 + 46.65X_4 + 42.78X_5 - 341.13X_6 - 14.39X_7 \quad (3)$$

This equation shows negative values for Aerosil® (X_6) and magnesium stearate (X_7), demonstrating their negative effect on the repose angle. The covered experimental region is depicted in Fig. 1A. As seen, this region is a two dimensional simplex, in which three excipients (Aerosil®, Microcell®, and magnesium stearate) were placed at the corners (vertices) while other

Table 6
Analysis of variance of the linear and quadratic models for the responses (physical–chemical characteristics)

Model	Repose angle	Compressibility	Water content	Weight	Hardness	Friability	Paracetamol content	Disintegration	Dissolution
Linear	Sig	Sig	Not-sig	Sig	Sig	Sig	Sot-sig	Sig	Sig
R^2	0.8741	0.7726	0.3053	0.8328	0.8207	0.9005	0.4005	0.8767	0.8246
Adj-R^2	0.8111	0.6588	−0.0420	0.6301	0.6055	0.7810	−0.3189	0.7287	0.6140
F value	13.88	6.79	0.88	4.12	3.81	7.54	0.56	5.92	3.92
Quadratic	Sig	Sig	Not-sig	Not-sig	Not-sig	Sig	Not-sig	Sig	Not-sig
R^2	0.9912	0.9397	0.8124	0.8421	0.8332	0.9185	0.6068	0.8903	0.8445
Adj-R^2	0.9735	0.8191	0.4371	0.5659	0.5414	0.7759	−0.0814	0.6984	0.5725
F value	56.19	7.79	2.16	3.05	2.86	6.44	0.88	4.64	3.10

Sig = significant, Not-sig = not significant.

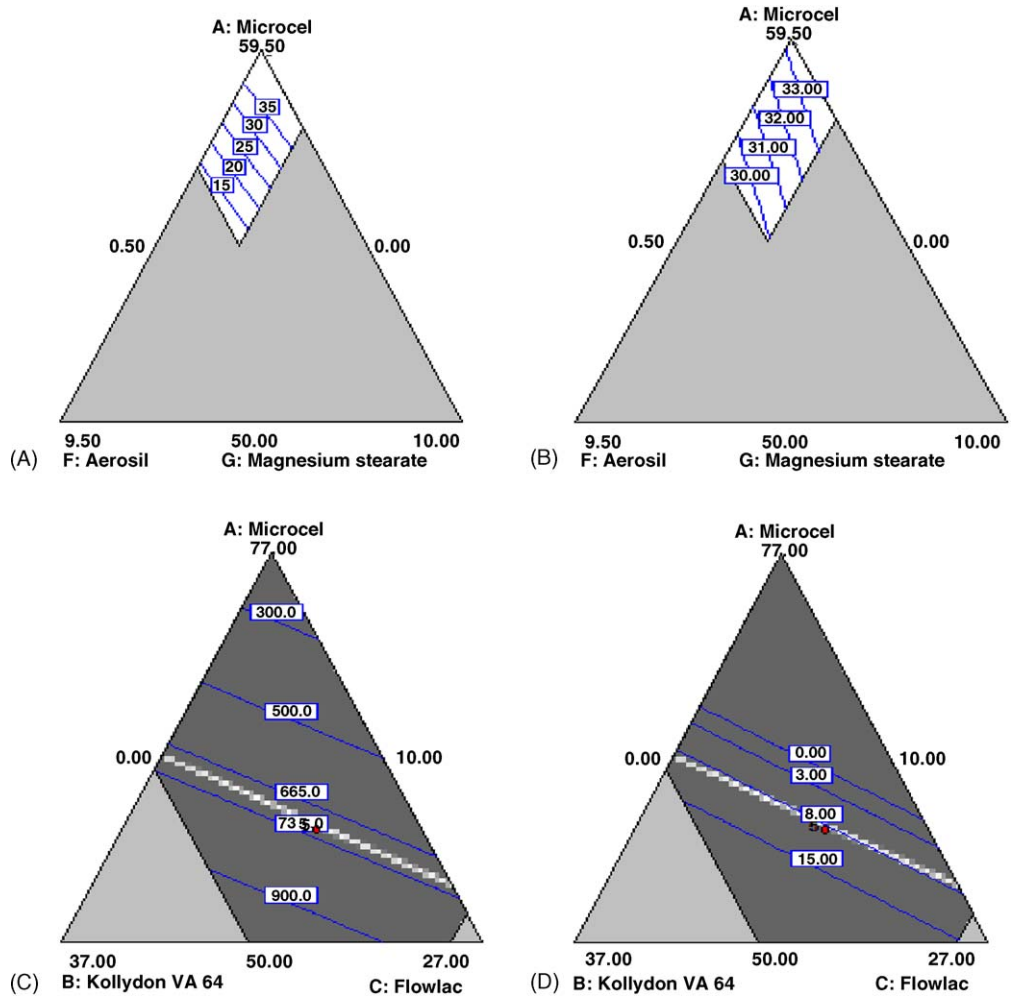

Fig. 1. Triangular-dimensional contours diagrams illustrating effects of excipients on paracetamol tablets/powder characteristics. (A) Repose angle; (B) compressibility (both with fixed values of Kollydon® VA 64 at 17.50%, Flowlac® at 12.50%, Kollydon® CL at 5.00%, and PEG at 5.00%); (C) weight; (D) hardness (both with fixed values of Kollydon® CL at 5.00%, PEG at 5.00%, Aerosil® at 1.50%, and magnesium stearate at 1.50%).

materials were fixed (Kollydon® VA 64 at 17.50%, Flowlac® at 12.50%, Kollydon® CL at 5.00% and PEG at 5.00%). In Fig. 1A, Microcel® percentage varied from 59.50% (maximum percentage selected and placed at the corner) to 50% (minimum percentage of the regression showed in the middle of the opposite side of the triangle). Equally, Aerosil® percentage ranged from 9.5 to 0.0%, and magnesium stearate, from 10.0 to 0.50%. The clear area in the top represents the repose angle data varying from 15° to 35°: the repose angle is reduced with the increasing of Aerosil®.

Linear significant model was also obtained for compressibility (C), and the equation calculated from the regression data was:

$$C = 32.99X_1 + 31.85X_2 + 32.39X_3 + 37.19X_4 + 44.63X_5 - 22.56X_6 + 48.33X_7 \quad (4)$$

This equation shows a negative value to Aerosil® (X_6) and confirms the effect of this lubricant on improving flowability by reducing compressibility. Fig. 1B – constructed similarly to Fig. 1A – illustrates this fact by showing decreasing values of compressibility with the increasing of Aerosil®. These finding concurred with the results of previous studies which reported that Aerosil® is a suitable glidant for direct compression formulations (Lachman et al., 2001; Velasco et al., 1995).

Linear model was achieved for friability (F) and the Eq. (5) was calculated:

$$F = 19.79X_1 + 408.12X_2 + 260.74X_3 - 577.21X_4 - 578.69X_5 - 180.25X_6 - 180.31X_7 \quad (5)$$

This equation and the triangular-dimensional contours diagram (Fig. 2A) show that higher proportions of Microcel® (X_1), Kollydon® VA 64 (X_2) and Flowlac® (X_3) promoted higher friability on tablets. This model showed to be inappropriate to describe the effect of these materials on friability since they were expected to act as binders. Possibly, it resulted from the fact that we had few reliable values of friabilility because, in most formulations, tablets have broken during the test. In this Fig. 2A, there is a narrow region (clear line) – with certain compositions – that corresponds to the official specified limits for friability. It is important to remember that the figures show a particular part

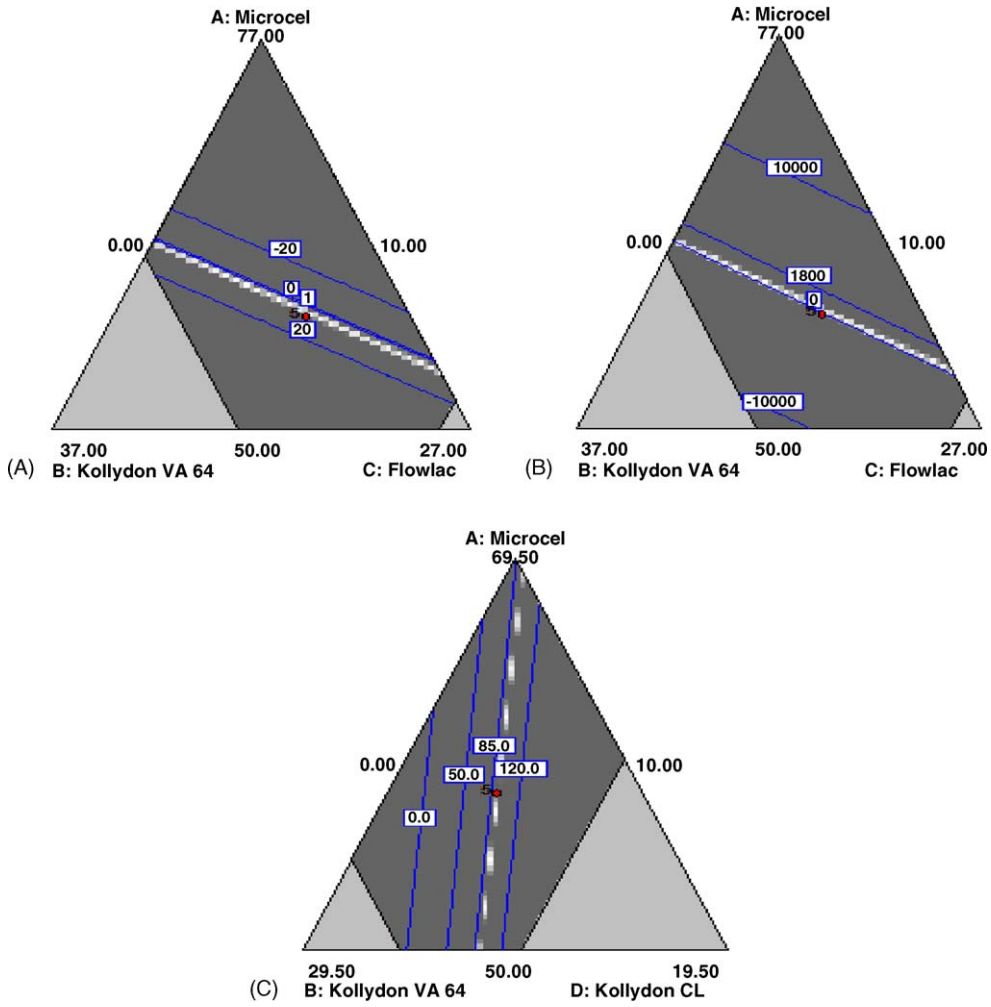

Fig. 2. Triangular-dimensional contours diagrams illustrating the effects of excipients on paracetamol tablets characteristics. (A) Friability; (B) disintegration (both with fixed values of Kollydon® CL at 5.00%, PEG at 5.00%, Aerosil® at 1.50%, and magnesium stearate at 1.50%); (C) dissolution (fixed values of Flowlac® at 12.50%, PEG at 5.00%, Aerosil® at 1.50%, and magnesium stearate at 1.50%).

of the mixture analysis, differently from the Design Expert® software, where the figures are interactive, and it is possible to change the fixed components to the variable ones, as well as their percentages. In this case (Fig. 2A), percentages of Microcel® varied from 77.00 to 50.00%, Flowlac® from 27.00 to 0.00% and Kollydon® VA 64, from 37.00 to 10.00%, while Kollydon® CL, PEG, Aerosil®, and magnesium stearate were fixed at their average percentages (5.00, 5.00, 1.50 and 1.50%, respectively).

The equation obtained from the linear model to average tablet weight (AW) was:

$$\mathrm{AW} = 770.12X_1 + 2289.42X_2 + 1726.02X_3 - 1475.46X_4 - 1446.82X_5 - 442.76X_6 + 601.75X_7 \quad (6)$$

By this equation, Microcel® (X_1), Kollydon® VA 64 (X_2) and magnesium stearate (X_7) increase average tablet weight, while the other materials decrease it. Fig. 1C shows a clear narrow region on the triangle where the average weight meets official specifications (between 665 and 735 mg).

The equations calculated for hardness (H), disintegration (Dsg), and dissolution (Dss), according to linear model, were:

$$H = 12.11X_1 + 1117.90X_2 + 72.94X_3 - 136.54X_4 - 131.89X_5 - 49.34X_6 - 33.66X_7 \quad (7)$$

$$\mathrm{Dsg} = -2760.15X_1 - 61692.83X_2 - 38310.15X_3 + 85869.95X_4 + 85785.02X_5 + 37071.01X_6 - 6606.46X_7 \quad (8)$$

$$\mathrm{Dss} = 77.62X_1 - 358.06X_2 - 183.08X_3 + 730.16X_4 + 725.63X_5 + 277.47X_6 - 8.99X_7 \quad (9)$$

Equations from regression data of the linear model (Eqs. (3)–(9)). RA: repose angle; C: compressibility; F: friability; AW: average table weight; H: hardness; Dsg: disintegration; Dss: dissolution. X_1: Microcel®; X_2: Kollydon® VA 64; X_3: Flowlac®; X_4: Kollydon® CL; X_5: PEG 4000; X_6: Aerosil®; X_7: magnesium stearate.

Table 7
Prediction of a new experiment with the optimized formulation, based on the DOE model

Ingredient	mg/tablet
Paracetamol	500.0
Microcel® 102	123.9
Kollydon® VA 64	50.0
Kollydon® CL 30	4.0
Polyethylene glycol 4000	16.4
Aerosil®	4.7
Magnesium stearate	1.0

Prediction was given with 95% confidence limits. Total desirability of responses was 62% (0.62).

According to the linear model, hardness was positively affected by Microcel® (X_1), Kollydon® VA 64 (X_2), and Flowlac® (X_3)—and negatively affected by Kollydon® CL (X_4) (crospovidone), PEG 4000 (X_5), Aerosil® (X_6) and magnesium stearate (X_7). In contrast, Fig. 1D shows higher hardness values as Microcel® percentage decreases from 77.00 to 50.00%. It is explained since, for hardness, the X_2 coefficient in Eq. (7), H was significantly higher than others, indicating the prevalent influence from Kollydon® VA 64 (X_2), while other ingredients showed relative low influence on hardness.

The linear equation for disintegration evidenced positive effect of Microcel® (X_1), Kollydon® VA 64 (X_2), and Flowlac® (X_3) on the disintegration time and negative one for Kollidon® CL. The latter excipient is a disintegrant and it should have reduced the time for tablet disintegration. On the other side, Kollidon® CL has increased paracetamol dissolution (Eq. (8)). Fig. 2B and C show higher tablet disintegration and paracetamol dissolution values as Microcel® decreases. Disintegration also depended on Flowlac® increasing.

Based on the fitted regression models, optimal factor settings were selected by Design-Expert® in order to identify experimental settings in which all desirabilities were met as well as possible. An optimum formulation was generated by the software, which has been produced and analyzed. The composition of this optimized tablet is described in Table 7. The predicted and observed results for the optimized tablet formulation are described in Table 8. As seen, the model predicted well all responses, even for paracetamol and water content, which models were not significant.

With the aid of this design it was possible to meet all the official specifications, demonstrating that the experimental planning of mixture can supply trustworthy results, reducing the spent time and the number of experiments.

Table 8
Predicted and observed responses (physical–chemical data) from optimized tablet formulation

Test	Predicted	Observed
Compressibility (%)	32.0	29.8
Water content (%)	2.3	2.1
Repose angle (°)	21	18
Weight variation (mg)	700.0	724.1
Hardness (kgf)	11.2	16.0
Friability (%)	1.03	0.91
Paracetamol content (%)	99.7	97.4
Disintegration (min)	2.3	2.6
Dissolution (%)	91.9	92.0

4. Conclusions

An optimized formulation of tablets by direct compression was found to paracetamol, a powder with a well-known bad flowability and poor compactability. A formulation containing 70% of the drug was produced without previous paracetamol treatment and by using conventional raw material and equipments. Design and analysis of experiments were used as good tools to obtain the optimal formulation, which showed good flowability, no lamination and that also met all official pharmaceutical specifications.

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