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ORIGINAL ARTICLE

Optimization of fluid bed formulations of metoprolol granules and tablets using an experimental design

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Abstract

Background: The granulation process of a metoprolol tartrate (very difficult to process active pharmaceutical ingredient) formulation in laboratory scale fluid bed equipment was studied. *Aim*: To study the influence of two formulation factors and three process parameters on the characteristics of the granules and subsequently of the tablets, in the case of fluid bed granulating of a powder mix containing metoprolol tartrate. *Method*: In order to study the influence of formulation factors (binder solution concentration and the silicon dioxide ratio) and process factors (atomizing pressure, the length of the final drying phase, and the inlet air temperature) on the technological and pharmaceutical properties of granules and tablets, a fractional factorial experimental design resolution V+ with five factors and two levels was used. *Results:* A high atomizing pressure allows us to obtain fine granules with large poly-dispersion index and granules with high tapped and untapped density, tablets with short disintegration time, short mean dissolution time, and a high percentage metoprolol tartrate release in the first 15 minutes. A lower concentration of binder solution allows us to obtain granules with very good flow properties, tablets which have no tendency to stick on the set punch of tabletting machine and no capping. The final drying time of granules has an influence only on the granule's relative humidity and tapped and untapped density, without any influence on the granules flow properties. *Conclusions*: The practical experimental results from the formulation processed in optimal working conditions were close to the predicted ones by Modde 6.0 software.

Key words: *Experimental design; fluid bed granulation; metoprolol tartrate; optimization; resolution V*

Introduction

Metoprolol is a cardioselective beta-blocker, and it is used in the management of hypertension, angina pectoris cardiac arrhythmias myocardial infarction, and heart failure[1]. Metoprolol tartrate is a white crystalline powder, with very poor flow and compaction properties due its low bulk density, electrostatic charge, and sticking tendency and by consequence a very difficult active pharmaceutical ingredient (API) to work with[2]. Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. The main reasons of granulation are to improve the flow properties of a powder mix, to improve the compaction characteristics of a powder mix, and to prevent segregation of the constituents of a powder mix. The fluidized bed technology makes possible to prepare granules efficiently[3].

Fluid bed granulation is a size-enlargement step in the production of tablets in the pharmaceutical industry. During size-enlargement, adhesive forces such van der Wals forces and the formation of bridges become effective. The granulation process in the fluidized bed is however a complex process, because there are many parameters that can influence it. Therefore, knowledge about the effect of the granulation process is necessary for controlling the process[4].

During the fluid bed granulation process, the granulation liquid is sprayed in the powder fluid bed, and the particles are blended with the relatively free binder, producing porous conglomerations. The growth of granules is controlled first by the fluid bed moisture content and by the dimension of binder solution drops. The moisture content depends on the equilibrium between moistening and evaporation. Moistening is controlled by the liquid

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atomization rate through nozzle. Evaporation is influenced mainly by the inlet air temperature and humidity. The dimensions of the binder solution drops are influenced by the binder solution concentration, the position of the solution spraying nozzle, the solution spray rate, and the atomization pressure[5,6].

In the last years, much effort has been taken to investigate the effect of the formulation and process parameters on granules properties[7–11,23,24] and to find optimum condition in preparing solid dosage forms[12], but there has been no studies about metoprolol tartrat granulation, a very difficult API processing in solid dosage forms, due to its very low bulk density, electrostatic charge, agglomeration, and sticking tendency during handling.

The purpose of this study was to define the optimum parameters setting so that they would obtain metoprolol tartrate immediate release tablets, via fluid bed granulation, with best pharmacotechnical properties. To perform the study, a fractional experimental design was used, by means of which the influence of two formulation factors (binder solution concentration and the silicon dioxide ratio) and of three technological parameters (the atomization pressure, the length of the drying phase, and the inlet air temperature) on both the technological and pharmaceutical properties of granules and of resultant tablets obtained after compressing the granules have been studied.

Material and methods

Materials

Metoprolol tartrate (Microsin, Bucharest, Romania), polyvinylpyrolidone—PVP K 30 (BASF, Ludwigshafen, Germany), lactose monohydrate 200 mesh (Meggle, Wasserburg, Germany), sodium starch glycolate—Vivastar (JRS Pharma, Rosenberg, Germany), Microcrystalline cellulose PH102 (JRS), magnesium stearate (Merck, Darmstadt, Germania), silicon dioxide—Aerosil 200 (Degussa, Darmstadt, Germany), and distilled water.

Apparatus

Fluid bed granulator Strea 1 (Aeromatic AG, Bubendorf, Switzerland), tablet press EK-0 (Korsch, Berlin, Germany), mass volumetric test apparatus SVM (Erweka, Heusenstamm, Germany), DIN sieve set (VEB MLW, Leipzig, Germany), tablet hardness test apparatus Monsanto (Monsanto, Modena, Italy), tablet disintegration test apparatus ZT 2 (Erweka), dissolution apparatus PT-DT7 (PharmaTest, Hainburg, Germany), spectrophotometer UV-Vis V530 (Jasco, Tokyo, Japan), and humidity balance MB 45 (Ohaus, Pine Brook, NJ, USA).

Experimental design

To perform the study, a fractional experimental design (resolution V+) with five factors and three levels was used[13,14,22]. The independent variables (formulation and process variables) are shown in Table 1. The experimental design matrix is presented in Table 2. The dependent variables (characteristics of granules and tablets) are presented in Table 3.

Software

Construction of the experimental design, computation of coefficients, statistical parameters, and fitting of the experimental data to assess the results have been performed using Modde 6.0 optimization program, Umetrics[14].

Granules preparation

Granulation process was performed in a fluid bed granulator (Aeromatic AG). The working conditions are presented in Table 4. After ending the atomization of the

Table 1. Independent variables (formulation and process variables).

		Levels		
Variables	Symbol	−1	0	1
Atomizing pressure (bar)	X_1	0.5	1	1.5
Binder solution concentration (%)	X_2	5	10	15
Drying time (min)	X_3	30	45	60
Inlet air temperature (°C)	X_4	50	60	70
Silicon dioxide ratio (%)	X_5	1	2	3

Table 2. The matrix of the experimental design.

Nr exp	Run order	X_1	X_2	X_3	X_4	X_5
N1	1	0.5	5	30	50	3
N2	7	1.5	5	30	50	1
N3	19	0.5	15	30	50	1
N4	14	1.5	15	30	50	3
N5	9	0.5	5	60	50	1
N6	11	1.5	5	60	50	3
N7	18	0.5	15	60	50	3
N8	4	1.5	15	60	50	1
N9	10	0.5	5	30	70	1
N10	12	1.5	5	30	70	3
N11	13	0.5	15	30	70	3
N12	17	1.5	15	30	70	1
N13	6	0.5	5	60	70	3
N14	5	1.5	5	60	70	1
N15	16	0.5	15	60	70	1
N16	3	1.5	15	60	70	3
N17	15	1	10	45	60	2
N18	8	1	10	45	60	2

X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

Table 3. Dependent variables.

Technological properties of granules	Symbol
Granules mean diameter (μm)	Y_1
Granules polydispersion index (%)	Y_2
Untapped density	Y_3
Tapped density	Y_4
Carr index	Y_5
Hausner ratio	Y_6
Relative humidity (%)	Y_7
Technological and pharmaceutical properties of tablets	
Sticking behavior	Y_8
Capping behavior	Y_9
Disintegration time (minutes)	Y_{10}
Mean dissolution time (minutes)	Y_{11}
% released at 15 minutes	Y_{12}
% released at 30 minutes	Y_{13}
Crushing strength (kN)	Y_{14}

Table 4. Working conditions.

Parameters	Value
Method (type)	Top spray
Charge load (g)	180
Duration of dry mixing (minutes)	1
Nozzle diameter (minutes)	0.8
Spaying rate (g/minute)[a]	5–15
Atomizing pressure[a]	0,5–1
Spraying time (minute)	5–21
Inlet air temperature (°C)	50–60
Outlet air temperature (°C)	30–33
Fan air (m^3/minute)	4–5
Drying temperature, (°C)	60
Bag filter shaking time (seconds)	7
Duration of final drying (minutes)[a]	30–60

[a]variable, depending on the experimental design matrix.

binder solution, the granules were dried for variable periods of time (according to the experimental design matrix) in the same apparatus at 60°C.

Tablets preparation

To prepare immediate release tablets with metoprolol tartrate, compression of the obtained granules was achieved by an eccentric tablet press Korsch EK-0 (Korsch, Berlin, Germany). The tablet press was equipped with a 10 mm diameter standard concave round punches and dies. The compression force was adjusted to 20 ± 3 kN and the average mass of the compressed tablets was fixed at 360 mg.

Determination of the dependent variables (the results)

For granules, mean diameter and granules polydispersion index determination were sieved using a set of sieves with different apertures (100, 200, 300, 400, 500, and 600 μm). Granules mean diameter (*Md*) and granules polydispersion index (*P.I.*) were calculated according to Equations (1) and (2):

$$Md = \frac{\sum n_{i^*} \times X_i}{N} \tag{1}$$

$$P.I. = \pm \frac{\mathrm{SD}}{Md} \times 100, \tag{2}$$

where N is frequency and SD is standard deviation.

Determination of untapped density, tapped density, Carr index, and Hausner ratio of the granules were performed according to well-known methods described in literature[15]. All analysis were measured in duplicate, reporting the average.

The humidity of the granules was determined by using humidity balance Ohaus MB 45. Approximately 2 mg of sample was placed into a sample pan and dried at 80°C until the weight change was less than 0.02% over 10 minutes and the percent of mass loss was calculated. The sticking and capping behavior of the tablets was evaluated by using a scale from 1 to 3 (1, no sticking/capping; 2, a small sticking/capping tendency; and 3, high sticking/capping tendency). Determination of the tablets disintegration time was performed according to the official method from the European Pharmacopoeia, Ed 6[16]. Hardness of tablets was determined by using Monsanto hardness tester[17].

Dissolution studies

The dissolution studies were performed according to the method from the USP 31: dissolution medium, simulated gastric fluid without enzyme; volume, 900 mL, apparatus, 1 (basket method); agitation, 100 rpm (USP 2008). One tablet (equivalents at 100 mg metoprolol tartrate) was put into a vessel with 900 mL dissolution media. At specific time intervals, 2 mL solutions were withdrawn, immediately filtered through a 0.45 μm filter and the drug concentration was assayed spectrofot ometrical UV at 275 nm

Mean dissolution time was calculated according to the Equation (3). For each formulation, the dissolution studies were performed thrice.

$$\mathrm{TMD} = \frac{\sum_{j}^{n} \frac{t_j + t_{j+1}}{2} \times \%D}{\sum_{j}^{n} \%D}, \tag{3}$$

where: n is the number of time points, t_j time point, and $\%\ D$ – the mean percent of drug dissolved.

Results and discussions

Experimental design analysis. summary of fit

To study the influence of the formulation factors on the properties of the resulted granules and tables, an experimental design with five factors and two levels was used. The matrix of the experimental design is shown in Table 2. The matrix of the results that were obtained is presented in Table 5.

To fit the experimental data with chosen experimental design and for the calculation of the statistical parameters, the statistical module from Modde 6 software was used. To check the validity of the experimental design, the following statistical parameters were determined: R^2, Q^2, and ANOVA test. R^2 represents the fraction of variation of the response explained by the model and Q^2 represents the fraction of variation of the response that can be predicted by the model. Both R^2 and Q^2 values are numbers, between 0 and 1. Values close to 1 for both R^2 and Q^2 indicate a very good model with excellent predictive power. R^2 and Q^2 provide the best summary of fitting the model[13].

The results obtained after the fitting and the statistical parameters calculation using data obtained from the experimental design are shown in Figure 1. The results fit well for Y_1–Y_9; Y_{11}, Y_{12}, responses and are satisfactory for Y_{10}, Y_{13}, Y_{14} responses.

ANOVA (analysis of variance) test shows whether the variance of the results is determined by modifications of the formulation factors or represents a variance determined by experimental errors (Eriksson, 2000). The results of ANOVA test show that the experimental data obtained for Y_1–Y_{14} responses were good P for model was lower than 0.05 and P for residual was greater than 0.05) for all responses.

Analysis of the influence of formulation factors on the granules properties

Analysis of the influence of formulation factors on the granules mean diameter and granules polydispersion index

Granules may be characterized physically by the mean diameter and granule size distribution. Evaluation of granule size distribution is performed by determining granules polydispersing index versus granules mean diameter[18,19]. Very good quality granules have a granule size distribution within a restricted range, which is a minimum polydispersion index.

Only the atomizing pressure (X_1) has significant influence on mean diameter, the increase of atomization pressure causes the decrease of mean

Table 5. Matrix of the results.

Exp name	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9	Y_{10}	Y_{11}	Y_{12}	Y_{13}	Y_{14}
N1	422.45	40.31	0.381	0.406	6.12	1.065	1.70	1.0	1.0	7.0	11.2	72.7	100.4	8.0
N2	193.82	61.71	0.463	0.492	5.83	1.062	1.47	3.0	1.0	7.0	8.7	82.7	101.7	7.0
N3	305.14	45.35	0.352	0.384	8.40	1.092	1.20	3.0	1.0	7.0	11.3	69.7	101.8	7.0
N4	235.31	45.06	0.405	0.479	15.56	1.184	1.60	2.0	2.0	5.0	9.1	80.7	102.8	7.0
N5	454.74	35.51	0.389	0.403	3.33	1.03	0.91	1.0	1.0	7.0	9.6	74.7	102.4	7.0
N6	190.1	58.78	0.442	0.484	8.64	1.095	1.21	3.0	1.0	7.0	9.0	76.9	99.7	7.0
N7	296.33	41.17	0.358	0.387	7.50	1.081	1.70	2.0	1.0	7.0	9.6	71.5	96.0	8.0
N8	236.58	39.47	0.446	0.544	18.07	1.221	1.30	2.0	2.0	5.0	10.2	70.0	101.6	8.0
N9	334.97	34.65	0.312	0.339	8.00	1.087	1.54	1.5	1.0	8.0	11.3	70.2	101.0	7.0
N10	285.31	45.21	0.388	0.411	5.78	1.061	0.92	1.0	1.0	6.0	9.4	81.1	104.6	7.0
N11	386.77	51.25	0.054	0.066	19.25	1.238	1.81	3.0	2.0	7.0	9.6	83.0	93.3	7.0
N12	237.21	37.72	0.403	0.449	10.26	1.114	1.36	2.0	1.0	5.0	8.6	81.0	103.1	7.0
N13	280.55	37.68	0.339	0.366	7.20	1.078	1.58	1.0	1.5	6.0	9.0	78.9	105.1	7.0
N14	278.13	45.22	0.394	0.422	6.67	1.071	1.32	1.5	1.0	7.0	6.4	98.8	98.1	8.0
N15	389.44	51.43	0.537	0.675	20.33	1.255	1.05	3.0	2.0	7.0	6.5	77.0	98.1	7.0
N16	224.45	39.31	0.403	0.442	8.80	1.096	1.08	2.0	2.0	5.0	7.1	85.8	95.8	7.0
N17	271.37	47.5	0.328	0.349	9.00	1.094	1.40	1.0	1.5	5.0	8.6	82.8	95.7	7.0
N18	295.8	45.31	0.368	0.322	7.20	1.078	1.21	1.5	1.0	6.0	9.0	84.3	92.7	7.0

Y_1, granules mean diameter; Y_2, granules polydispersion index; Y_3, untapped density; Y_4, tapped density; Y_5, Carr index; Y_6, Hausner ratio; Y_7, relative humidity; Y_8, sticking behavior; Y_9, capping behavior; Y_{10}, disintegration time; Y_{11}, mean dissolution time; Y_{12}, % released at 15 minutes; Y_{13}, % released at 30 minutes; Y_{14}, crushing strength.

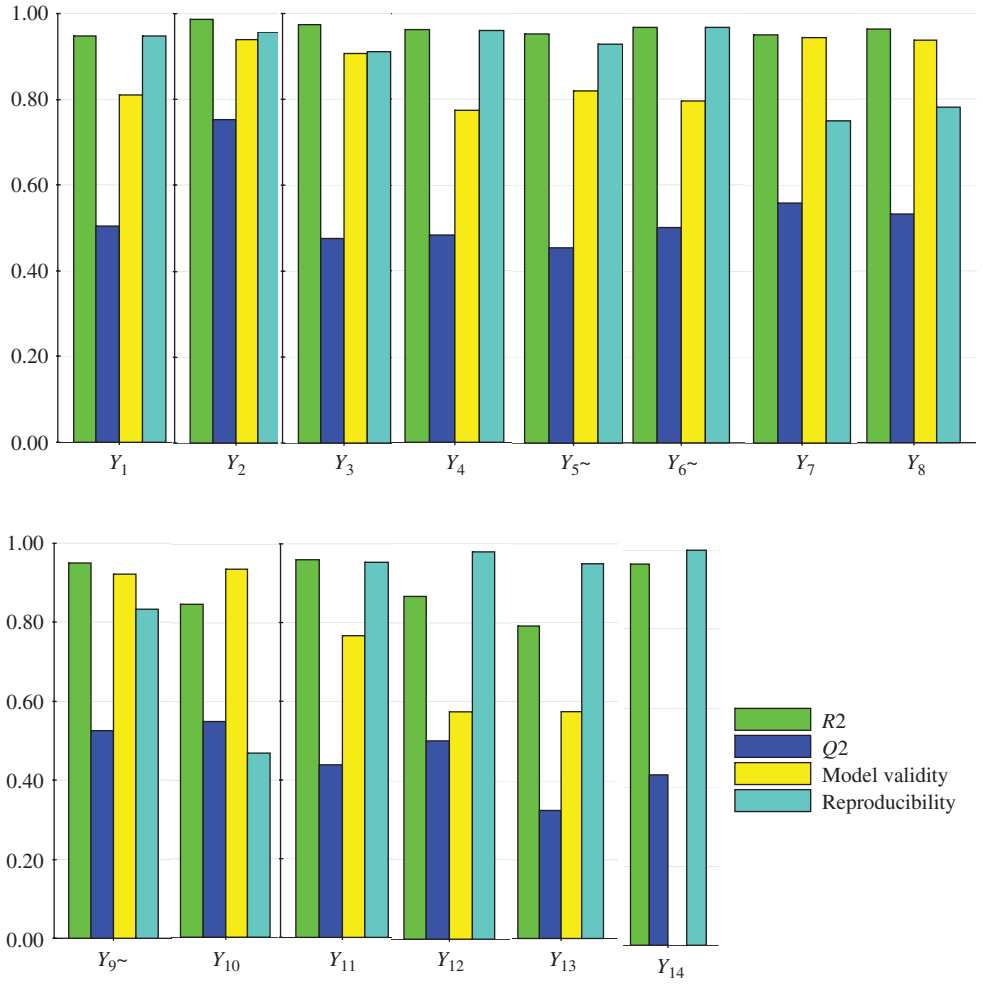

Figure 1. The fitting of the experimental data with the chosen model. Y_1, granules mean diameter; Y_2, granules polydispersion index; Y_3, untapped density; Y_4, tapped density; Y_5, Carr index; Y_6, Hausner ratio; Y_7, relative humidity; Y_8, sticking behavior; Y_9, capping behavior; Y_{10}, disintegration time; Y_{11}, mean dissolution time; Y_{12}, % released at 15 minutes; Y_{13}, % released at 30 minutes; Y_{14}, crushing strength.

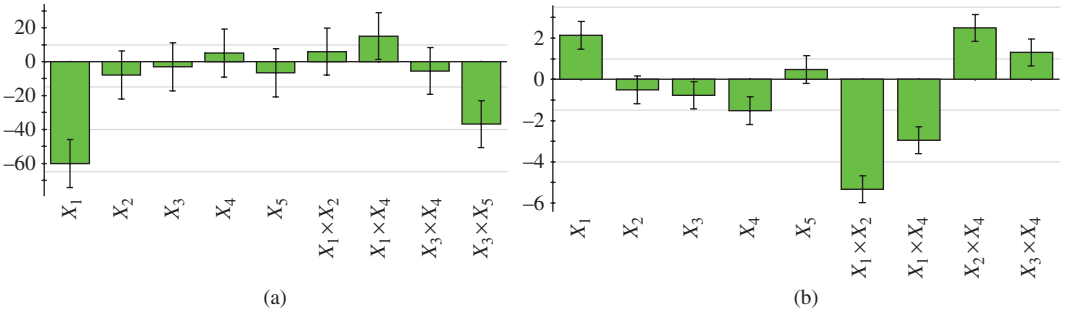

Figure 2. The influence of formulation factors on the granules mean diameter Y_1 (a) and on granules polydispersion index Y_2 (b). X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

diameter (Y_1) (Figure 2a). The liquid droplet size produced by nozzle depends mainly on the atomizing air pressure, spray rate, and nozzle diameter. The nozzle produced smaller liquid droplet at high atomizing air pressure which results in fine granules and granules with lower mean diameter, respectively. The results are in concordance with other studies[4,20]. The other factors have little influence on mean diameter.

The atomizing pressure (X_1) and the inlet air temperature (X_4) have a significant influence on granules polydispersion index. Increasing the atomizing pressure (X_1) leads to the increase of the granules polydispersion index (Y_2), and increasing the inlet air temperature (X_4) leads to narrow granules polydispersion index (Y_2). In the same time, some significant interaction between studied factors was found: $X_1 \times X_2$ (atomizing pressure—binder solution concentration), $X_1 \times X_4$ (atomizing pressure—inlet air temperature), $X_2 \times X_4$ (atomizing pressure—inlet air temperature), and $X_4 \times X_4$ (drying time—inlet air temperature) (Figure 2b).

An increase in the atomizing pressure leads to smaller granules and more broadly dispersed.

Analysis of the influence of formulation factors on the granules untapped and tapped density

Granules may be characterized physically also by the untapped density and tapped density. Evaluation of these parameters is important to assess the flowability and compressibility properties of the granules[15].

We observed that the increase of atomizing pressure (X_1) and drying time (X_3) leads to an increase in density (both untapped and tapped) while the increase of inlet air temperature leads to a decrease of density (both untapped and tapped) (Figure 3a and b). The explanation is that an increase of the atomizing pressure and drying time leads to a denser granule by the spatial configuration of the obtained granules, more precisely a favorable alignment of the granules in bulk.

Analysis of the influence of formulation factors on the granule flow properties (Carr index and Hausner ratio)

Granulation is designated to improve the flow properties of powder mix[3]. To characterize granules flow properties the, Carr index and Hausner ratio were determined. The most important factor that has influence on granules flow properties is binder solution concentration (X_2). The increase of binder solution concentration (X_2) leads to an increase in both Carr index and Hausner ratio, that means poorer compressibility and flowability of the powder. A small influence has inlet air temperature (X_4), the increase of inlet air temperature leads also to an increase in both Carr index and Hausner ratio (Figure 4a and b).

There is also a strong interaction between the atomizing pressure and inlet air temperature (X_4) ($X_1 \times X_4$), increasing atomizing pressure in the same time with

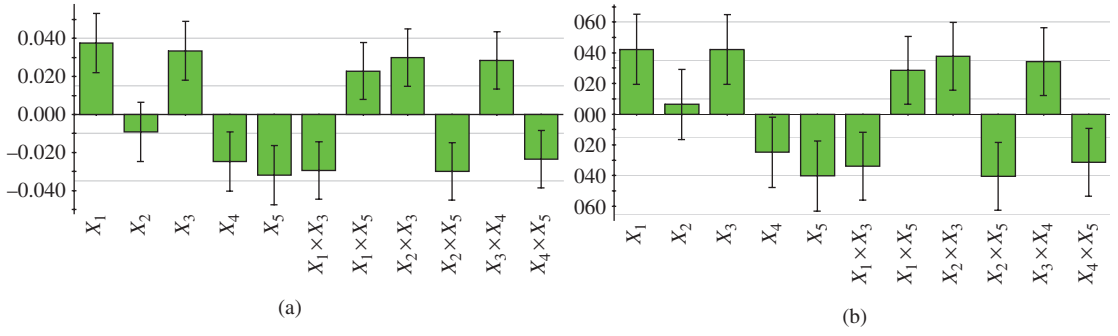

Figure 3. The influence of formulation factors on the untapped density Y_3 (a) and tapped density Y_4 (b) of the granules. X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

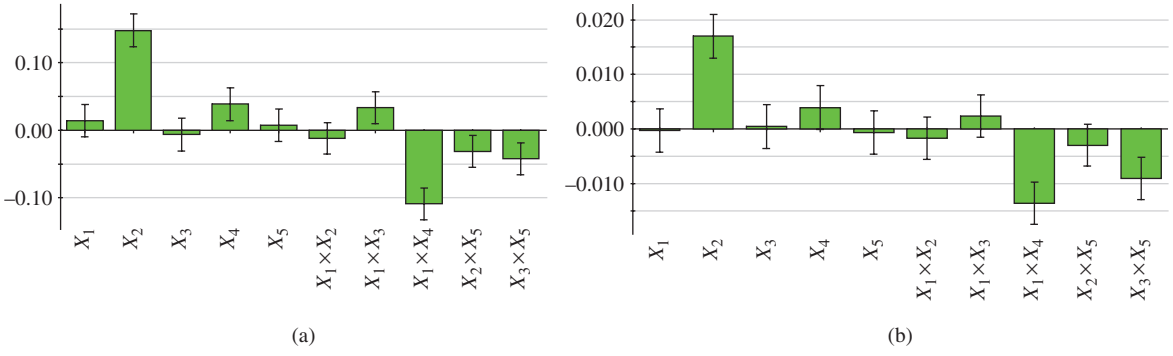

Figure 4. The influence of the formulation factors on Carr index Y_5 (a) and Hausner ratio Y_6 (b). X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

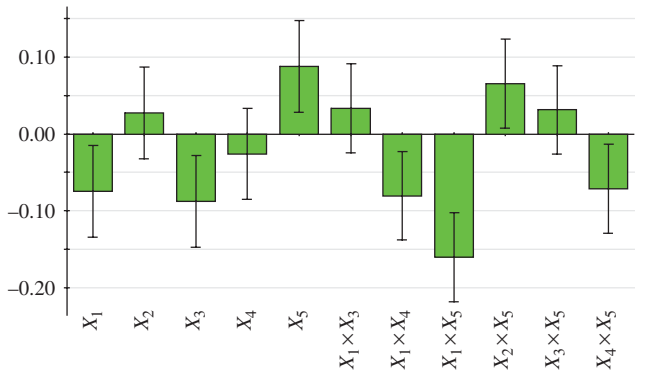

Figure 5. The influence of the formulation factors on granules relative humidity Y_7. X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

increasing inlet air temperature leads to granules with better compressibility and flowability properties.

Analysis of the influence of formulation factors on the granule relative humidity

We observed that the increase of atomizing pressure (X_1) and drying time (X_3) leads to a decrease in relative humidity of the granules. These aspects are related to the mean diameter of granules (high atomizing pressure conduct to obtain fine granules) and the equilibrium between the internal water content of the granule and the moisture in the surrounding area (Figure 5).

Analysis the influence of formulation factors on the pharmaceutical and technological tablets properties

The quality of the granules may also be evaluated directly by analyzing pharmaceutical and technological characteristics performed on them or by determining the properties of the tablets that were obtained from these granules[15,18].

Analysis of the influence of formulation factors on the sticking and capping behavior of the tablets

The most important factor that has an influence on the sticking tendency is binder solution concentration (X_2). An increase of binder solution concentration from 5% to 15% leads to obtaining tablets that have the tendency to stick (Figure 6a) on the metallic parts of the machine (punch and die) and also have capping tendency (Figure 6b). In the same time, there are some important interactions between studied factors with influence on sticking behavior of the tablets, increasing the binder solution concentration in the same time with inlet air temperature (interaction $X_2 \times X_4$) led to tablets with sticking tendency (Figure 6a) but increasing the atomizing pressure in the same time with binder solution concentration (interaction $X_1 \times X_2$) or increasing the binder atomizing pressure in the same time with inlet air temperature (interaction $X_1 \times X_4$) led to tablets with low sticking tendency (Figure 6a).

The most important factor that has an influence on capping behavior of the tablets is binder solution concentration (X_2) (Figure 6b). An increase of binder solution concentration from 5% to 15% leads to obtain tablets that have capping tendency. There are some important interactions between studied factors with influence on capping behavior of the tablets. Increasing the atomizing pressure in the same time with inlet air temperature (interaction $X_1 \times X_4$) and increasing drying time in the same time with silicone dioxide ratio (interaction $X_3 \times X_5$) led to tablets without capping tendency (Figure 6b). This observation conducts to the conclusion that high capping tendency is related with bonded granules, wet inside or high humidity of powder mix for tabletting.

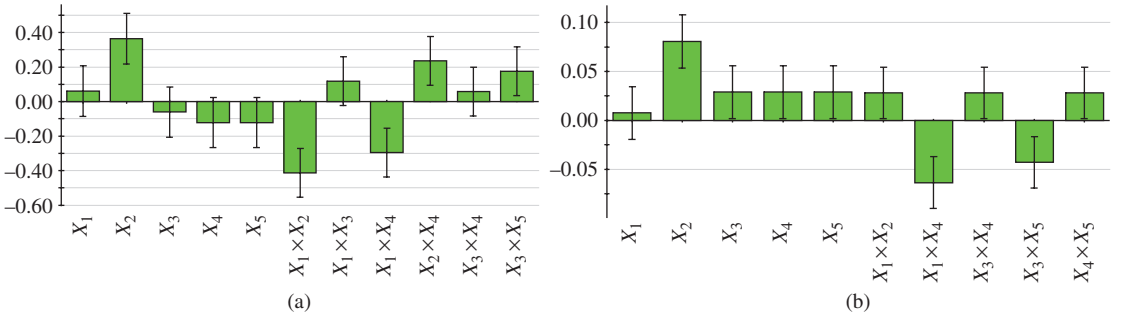

Figure 6. The influence of the formulation factors on the sticking Y_8 (a) and capping behavior Y_9 (b). X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

Analysis of the influence of formulation factors on the tablets disintegration time and tablets crushing strength

All studied formulations had good disintegration time behavior; in all cases the disintegration time was shorter that 15 minutes. The studied factors that have influence on disintegration time are atomizing pressure (X_1) and binder solution concentration (X_2). The increase of the atomizing pressure (X_1) and binder solution concentration (X_2) leads to tablets with shorter disintegration time. There is also a strong interactions between these tow factors ($X_1 \times X_2$) with the same effect (Figure 7a). The high atomizing pressure is favorable to obtain fine and less bonded granules that may conduct a rapid disintegration of the tablet.

A crushing strength of 4 kg-force determined with Monsanto hardness tester is considered to be minimum for a satisfactory tablet[17]. The obtained results show that all the formulations had very good crushing strength; all the values were greater that 6 kg-force (more 50% that minimum) and were in a very narrow and stable interval. From data analysis results, it is shown that tablets crushing strength is influenced only by drying time (X_3) and inlet air temperature (X_4). The increase of the final drying time (X_3) leads to increasing the crushing strength of tablets and the increase of the inlet air temperature leads to obtaining tablets with lower crushing strength (Figure 7b).

Analysis of the influence of formulation factors on the active substance release from tablets

The results of the dissolution studies of metoprolol tartrate from tablets are shown in Figure 8. With all the experiments performed, the tablets complied with dissolution requirements of USP 31 (more than 75% dissolved in 30 minutes)[21].

To evaluate the influence of studied factors on the release of metoprolol tartrate from tablets, the following parameters were determinated: mean dissolution time

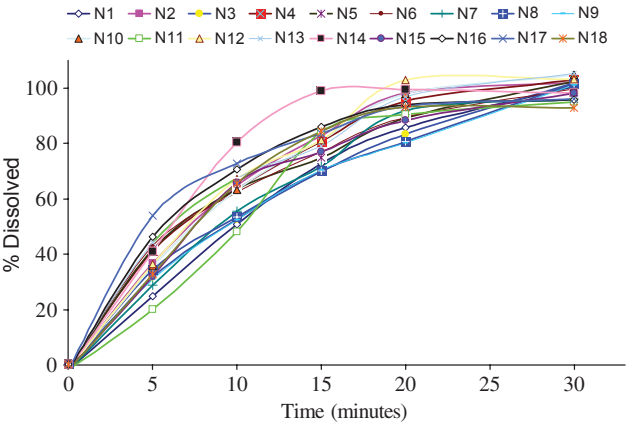

Figure 8. The results obtained at evaluation in vitro metoprolol tartrate release form formulations N_1-N_{18}. N_1-N_{18} formulation perfomed according with experimental design matrix (Table 2).

Y_{11}, percent released at 15 minutes Y_{12}, and percent released at 30 minutes Y_{13}. The influence of formulation factors on metoprolol tartrate release from tablets are shown in Figure 9. According to the obtained results, the studied factors have influenced only the mean dissolution time Y_{11} and percent released at 15 minutes Y_{12}, and no influence on percent released at 30 minutes Y_{13}. Atomizing pressure (X_1), drying time (X_3), and inlet air temperature (X_4) have a strong influence on the release of metoprolol tartrate from tablets. High atomizing pressure, long final drying time, and high inlet air temperature allow to obtain tablets with shorter mean dissolution time and high percent metoprolol tartrate released at 15 minutes (Figure 9a and b). The binder solution concentration has no influence on drug release form tablets. There was no correlation between formulation factors and percent metoprolol tartrate released at 30 minutes, a high standard deviation for all factors that cross the 0 line implies that all studied factors have no significant influence on this response. This finding can be explained by high percent release of metoprolol tartrate, nearly 100%, in all the cases.

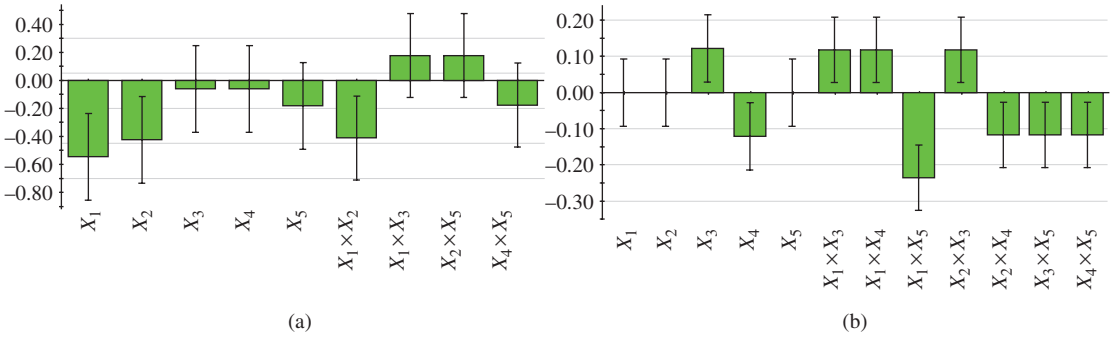

Figure 7. The influence of the formulation factors on the disintegration time Y_{10} (a) and on crushing strength Y_{14} (b). X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

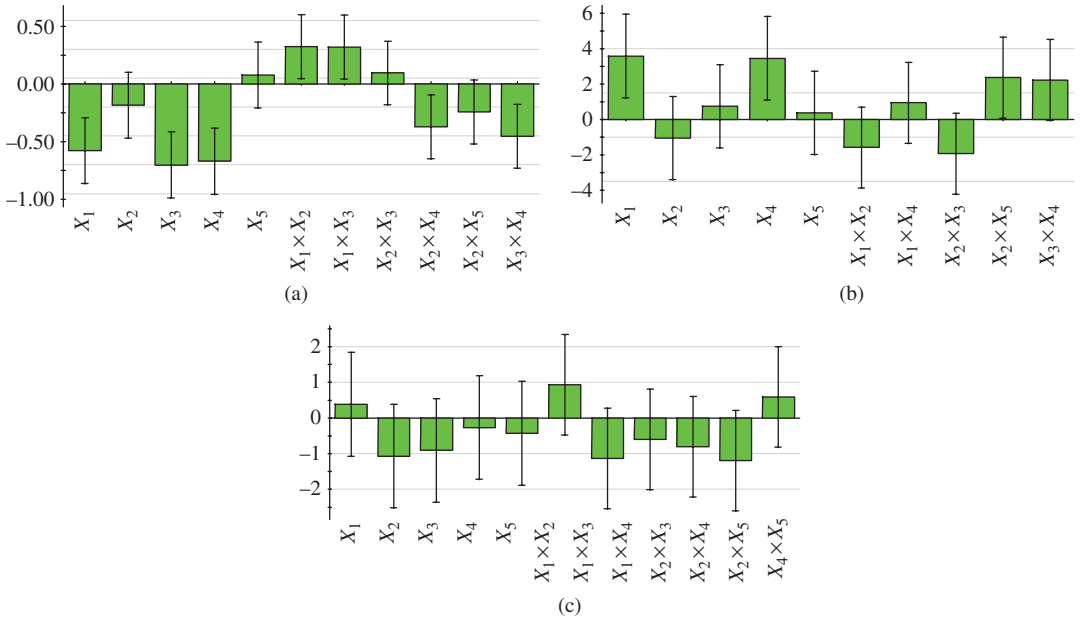

Figure 9. The influence of the formulation factors on the mean dissolution time Y_{11} (a), % released at 15 minutes Y_{12} (b), and % released at 30 minutes Y_{13} (c). X_1, atomizing pressure; X_2, binder solution concentration; X_3, drying time; X_4, inlet air temperature; X_5, silicon dioxide ratio.

Table 6. The optimum formula.

Independent variable	Symbol	Level settings
Atomizing pressure (bar)	X_1	1.5
Binder solution concentration (%)	X_2	9.0
Drying time (minutes)	X_3	31.46
Inlet Air Temperature (°C)	X_4	70
Silicon dioxide ratio (%)	X_5	2

Table 7. The optimum formula—results.

Responses	Symbol	Predicted	Obtained
Granules mean diameter (μm)	Y_1	264.918	260.2
Granules polydispersion index (%)	Y_2	42.292	41.137
Untapped density	Y_3	0.365	0.364
Tapped density	Y_4	0.398	0.402
Carr index	Y_5	8.291	9.452
Hausner ratio	Y_6	1.090	1.104
Relative humidity	Y_7	1.21	1.19
Sticking behavior	Y_8	1.429	1
Capping behavior	Y_9	0.994	1
Disintegration time (minutes)	Y_{10}	5.748	6
Mean dissolution time	Y_{11}	8.631	9
% released at 15 minutes	Y_{12}	84.574	82.12
% released at 30 minutes	Y_{13}	102.342	100.20
Crushing strength (kgf)	Y_{14}	7.029	7

Optimum formula determination

Using the optimization module from Modde 6.0 software and ideal value for the responses, the theoretical optimum processing conditions were determined (Table 6). The results (predicted ones with Modde 6.0 software and practical obtained) are presented in Table 7. The practical values obtained for the optimum formula were close to the predicted results by the experimental design (Table 7).

Conclusions

We have studied the influence of two formulation factors and three process parameters on the characteristics of the granules and subsequently of the tablets, in the case of fluid bed granulating of a powder mix containing metoprolol tartrate, a very difficult processing API.

The most important influence on granules properties have atomizing pressure and binder solution concentration. A high atomizing pressure allows obtaining fine granules with large polydispersion index and granules with high tapped and untapped density, tablets with short disintegration time, short mean dissolution time, and high percent metoprolol tartrate release in first 15 minutes. A lower concentration of binder solution allows obtaining granules with very good flow properties and tablets that have no tendency to stick to the metallic parts of the machine or to capping. The binder solution concentration used has no influence on drug release from tablets. The final drying time of granule has influenced only the relative humidity and tapped and untapped density without any

influence on the flow properties of the granules. Inlet air temperature has an influence only on tapped and untapped density of granules, a high inlet air temperature allows to obtain granules with lower tapped and untapped density. The influence of inlet air temperature on the other granules and tablet properties is nonsignificant. The influence of the ratio of silicon dioxide is nonsignificant on tablets properties.

The influences of the formulation and process variables are very important to assess a robust fluid bed granulation process and to establish the critical parameters for the process to properly control it. Experiments performed according to the experimental designs allow the performing in deep study of the formulation and processing factors which have an influence on the technological and pharmaceutical properties of the granules and on the resulted tablets, respectively, and the establishment of optimal working conditions.

Moreover, the optimum processing condition and conclusions from experimental design analysis performed in this work suggest that they can be a valid tool for scaling—up the fluid bed granulation process.

Declaration of interest: The authors report no conflicts of interest.

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