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RESEARCH ARTICLE

Relevance of air-to-liquid mass ratio effect on final granule properties of an Enalapril maleate formulation

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Abstract

Background: In the production of enalapril maleate tablets, the granulation process is the most crucial step. Numerous variables are known to influence the fluid bed granulation process and thus the final granule quality. In this study a novel descriptor for the nozzle parameter "air-to-liquid mass ratio" is presented. Granules manufacturing processes were designed by application of statistical experimental design.

Aim: The influence of the critical process parameter (CPP)—air-to-liquid mass ratio—on pharmaceutic properties of granules was studied. Air-to-liquid mass ratio can be considered as important variable influencing the droplet size of atomized liquid binder solution.

Results/Conclusion: A significant influence of air-to-liquid mass ratio on granule final particle size distribution was found. Increasing air-to-liquid mass ratio resulted in increased granules particle size distribution. Decreasing air-to-liquid mass ratio led to granules with reduced tapped density. Thus, it can be concluded that the parameter "air-to-liquid mass ratio" is a critical process parameter in the production of enalapril maleate granules.

Keywords: Enalapril maleate formulation; design of experiments, air-to-liquid mass ratio, fluid bed granulation, quality by design

Introduction

Granulation is a size-enlargement step of primary powder particles into free-flowing agglomerates[1], which can be performed by application of fluidized bed granulation. Fluidized bed granulation is an efficient spray granulation technology combining the process steps of blending, spraying, and drying. The straightforward principle of a fluidized bed process is an upward directed air stream passing through a heated powder bulk and shifting the powder bulk into a liquid-like state. Equilibrium between liquid supply and its evaporation plays an important role in fluidized bed granulation. When the equilibrium is shifted to the evaporation side, spray drying effects emerge due to high drying capacity of the process.

Knowledge about the entire granulation process and process parameter effects on final granule properties is needed for controlling the quality of the obtained product[2].

Fluidized bed granulation processes consist of multiple steps. Initially the solid powder mass is charged into the process container. After preheating of the powder mass the spraying of binder solution commences. The growth of granules is controlled by the fluid bed moisture content and the size of atomized binder solution droplets[3]. Dimension and shape of the droplets are influenced by the spraying rate and atomizing spray pressure. After all binder solution has been applied the drying step commences.

Several authors have studied the influence of air-to-liquid mass ratio onto granule characteristics like particle size distribution, but no evaluation using enalapril maleate formulation has been carried out, yet[4–7]. Enalapril maleate is a low-dose active pharmaceutical ingredient (API) known to have a narrow granulation and processing window. It is a white fine powder with poor flow and compaction properties. Enalapril maleate has turned out to behave challenging in terms of fluid bed processing for solid oral dosage forms[8].

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Air-to-liquid mass ratio as important parameter for granule properties

The air-to-liquid mass ratio [M_r] is defined by the ratio of the mass flow of spray air (M_a), given by the spray air pressure, to the liquid mass flow (M_L) of binder solution, given by the spraying rate[9]. The air-to-liquid mass ratio corresponds to the following equation:

$$M_r = M_a / M_L$$

Atomization of the liquid binder solution is controlled by the air-to-liquid mass ratio of the spray nozzle. Several authors reported that increasing spray air pressure and consequently increasing air-to-liquid mass ratio resulted in decreasing particle sizes[5,10–14], whereas others[15,16] found no effect of this parameter.

A linear correlation in logarithmic coordinates between air-to-liquid mass ratio and droplet size of an atomized binder solution has been reported by Schæfer and Worts[4]. They found that increasing the air-to-liquid mass ratio will result in decreasing droplet size of an atomized binder solution. This will increase the sputtering of the liquid binder solution in the solid powder bed during granulation, leading to a more homogenous distribution of liquid binder solution in the solid powder mass followed by the agglomeration of solid powder particles. It is thus hypothized that the described mechanism of granule growth will lead to increased final granule particle size distribution at higher air-to-liquid mass ratio.

The present granulation experiments have been performed to investigate the influence of the process parameter "air-to-liquid mass ratio" onto properties expressing granule quality such as particle size distribution, final granule residual moisture, and tapped density using enalapril as API. A statistical experimental design was used for the investigation of the granulation process. A factorial design plan incorporating four factors, varied over two levels and four center points was applied. The granulations were prepared according to the design plan.

Materials and methods

Materials

Enalapril maleate (USP grade) was obtained from Andenex-Chemie (Braunschweig, Germany). Lactose monohydrate was purchased as Granulac® 200 (Meggle, Wasserburg, Germany). The granule formulation consists of 2% API, 84.5% Lactose monohydrate, 11% Maize starch, and 1.5% Sodium hydrogen carbonate. The API was incorporated in the liquid binder solution enabling homogeneous distribution of the low-dose API. In addition to the API, the granulation liquid binder solution consists of sodium hydrogen carbonate dissolved in purified water. The latter was added to prevent hydrolysis of the enalapril maleate prodrug into enalaprilate, the *in vivo* active moiety.

Instrumentation

The fluid bed granulations were performed in a Hüttlin Unilab® (Hüttlin GmbH, Schopfheim, Germany). A near infrared (NIR) spectrometer model X-One® (NIR Online GmbH, Walldorf, Germany) was used for continuously monitoring the inline moisture content during the granulation process. In Figure 1, the mounting of the NIR spectrometer on the product container of the fluidized bed granulator is shown.

The special design of the Unilab® fluidized bed granulator, which implements the efficient air distribution plate DiskJet® allows the installation of the NIR device directly on the product container without the risk of blocking the window with product dust. The granules are fluidized in a uniform and harmonized way so that the product cleans the NIR window itself continuously during the process. The equipment for inline moisture analysis with NIR spectroscopy needs to be calibrated initially. The calibration setup and accuracy test for application of NIR spectroscopy using the enalapril maleate formulation has been communicated in a previous paper[8]. By use of inline NIR spectroscopy, a continuous control of the fluid bed granulation process is possible. This idea is in line with American Food and Drug Administration's (FDA) Process Analytical Technology (PAT) guideline[17].

Particle size measurements were performed using QicPic (Sympatec GmbH, Pulverhaus, Germany). The measuring principle of QicPic is a high-speed picture analysis sensor technology. The samples were measured using air as medium and were prepared by dispersion. The dispersion pressure was 200 kPa. The result reported was a mean of 3 independent measurements.

Software

Development and creation of the experimental design as well as analysis and fitting of the models to experimental data have been performed using the software MODDE 9 (Umetrics AB, Sweden).

Granulation procedure

The starting powder mass was suck into the fluid bed after the product container had been preheated. Mixing took place until the desired product temperature of 38°C was reached. This took about 10 min after which the spraying of granulation binder liquid commenced. The

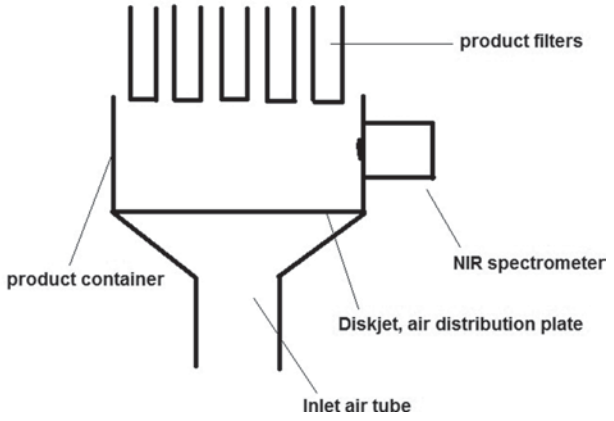

Figure 1. Installation of the NIR spectrometer directly on the product container of the Unilab fluidized bed granulator.

process conditions are presented in Table 1. The studied variables besides the derived air-to-liquid mass ratio were inlet air volume, inlet air temperature, and spraying rate. The range of the variables was determined based on preliminary experiments.

The experimental design matrix is presented in Table 2. The design used in the present experiment was a randomized factorial design with quadruplicate center point runs (batches N6, N13, N15, and N16) to ensure the repeatability of the process. The experiment matrix was built using MODDE 9. The inlet air relative humidity during the experiments was not included in the design as it was an uncontrollable variable.

Table 3 shows the dependent response variables that summarize most important granule properties.

Results and discussion

Influence of air-to-liquid mass ratio on final granule particle size distribution (PSD)

Granules were characterized physically by their mean diameter and granule size distribution. Evaluation of granule size distribution was performed by analyzing the particle mass diameters d10, d50, and d90.

In Figure 2 contour plots demonstrating the relationship between the air-to-liquid mass ratio and the spraying rate are shown; in the third dimension the d10- (Figure 2A), d50- (Figure 2B), and d90 particle size distributions (Figure 2C) are depicted.

The d10 granule particle size distribution (Figure 2A) represents the fines in the measured sample. The fines are defined as particles of size less than 60μm (blue to yellow curves). From blue curves to red curves the particle sizes within the d10 distribution are increasing from 35μm (blue) to 65μm (red). Particle sizes within the d10 distribution are increasing with increasing air-to-liquid mass ratio and with increasing spraying rate. The dependency of the d10 distribution from air-to-liquid mass ratio and spraying rate is not linear. At low spray rates (35 g/min), the influence of both parameters i.e. air-to-liquid mass ratio and spraying rate onto the agglomeration mechanism of small particles is low due to spray drying effect. At high spray rates both parameters become important since wetting of the fine particles and their agglomeration can be controlled by the volume of liquid binder added as well as by the droplet size of liquid binder solution, which is correlated to the air-to-liquid mass ratio.

Table 1. Process variables and levels.

Variables	Symbol	Levels		
		−1	Centre	+1
Inlet air volume (m^3h)	InAir	140	170	200
Inlet air temperature (kJ)	Temp	35	50	65
Spraying rate (g/min)	Spray	30	45	60
Air-to-liqud mass ratio	Ratio	1.29	4.54	7.74

Table 3. Dependent response variables.

Response variables	Symbol
d10 final granule	d10
d50 final granule	d50
d90 final granule	d90
Residual moisture final granule	resM
Maximum moisture during granulation	maxM
Tapped density	tapD

Table 2. Experimental design matrix.

Exp. name	Run order	Inlet air volume	Spraying rate	Air-to-liquid mass ratio	Inlet air temperature
Nl	6	200	60	7.74	65
N2	15	140	60	1.29	35
N3	20	140	30	7.74	65
N4	1	140	30	1.29	65
N5	13	140	30	129	35
N6	2	170	45	4.54	50
N7	4	140	60	7.74	35
N8	16	200	60	129	65
N9	9	200	60	1.29	35
N10	3	140	30	7.74	35
N11	17	140	60	1.29	65
N12	10	200	60	7.74	35
N13	11	170	45	4.54	50
N14	19	200	30	7.74	65
N15	5	170	45	4.54	50
N16	18	170	45	4.54	50
N17	8	140	60	7.74	65
N18	7	200	30	1.29	35
N19	12	200	30	1.29	65
N20	14	203	30	7.74	35

The agglomeration mechanism of the very fine particles is controlled by nucleation; this is an additional explanation for the nonlinear dependency compared to d50 distribution (Figure 2B). Nucleation is to be regarded as primary stage of particle enlargement. In this elementary phase of particle growth few primary particles are representing the fines. In Figure 2A, the influence of air-to-liquid mass ratio is decreasing with increasing spraying rate; keeping in mind that air-to-liquid mass ratio is allied to the droplet size of an atomized binder solution. Within the growth regime of fine particles (d10 < 65µm) at high humidity ≅ high spraying rate (60 g/min) the droplet size of the atomized binder solution becomes less relevant as fine particles anyway can relatively easy agglomerate—due to their low mass rather weak binding forces are necessary to build agglomerates. As described by Sastry et al.[18], the nucleation is characterized by a change of mass and number of nuclei as a function of time, therefore nucleation is a time-controlled nonlinear enlargement of particles.

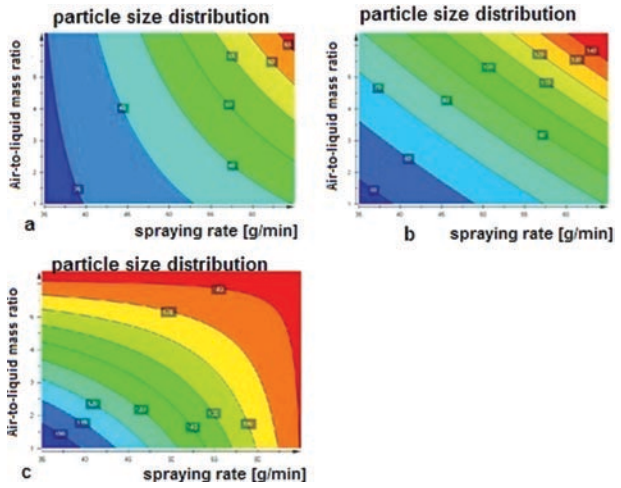

Figure 2. Contour plots of the effect of air-to-liquid mass ratio (y-axix) and spraying rate (x-axis) onto granule particle size distribution. The d10 (a), d50 (b), and d90 (c) values are given in micrometer and are shown as numbers in the plot. The contour levels are plotted as curves; the area between the curves is color coded to indicate interpolated values of the respective particle size distribution.

The d50 granule particle size distribution (mean particle distribution, Figure 2B) is defined by the size range from 60µm to 140µm (blue to orange curves). Figure 2B shows that the particle sizes within the d50 distribution are increasing with increasing air-to-liquid mass ratio and with increasing spraying rate. The dependency of the d50 distribution on air-to-liquid mass ratio and spraying rate is almost linear.

From blue to red curves, the particle sizes within the d90 distribution (Figure 2C) are increasing from 100µm (blue) to 180µm (red). The d90 granule particle size distribution represents the coarse part of the measured particles in the sample. The region of coarse particles is defined as agglomerates larger than 140µm (green to red curves). Again, the particle sizes increase within the d90 distribution with increasing air-to-liquid mass ratio and spraying rate, respectively. The dependency of the d90 distribution from air-to-liquid mass ratio and spraying rate again is nonlinear but has an inverse curve progression as compared to the d10 contour plot (Figure 2A). The reason for the different shapes of the curves for d10 distribution (Figure 2A) and d90 distribution (Figure 2C)

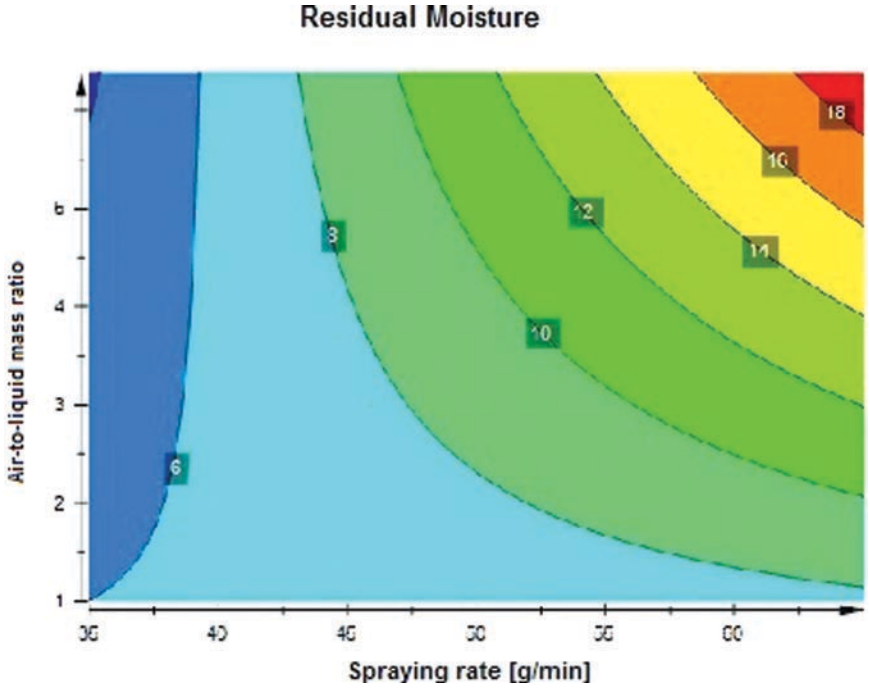

Figure 3. Contour plot of the effect of air-to-liquid mass ratio (y-axis) and spraying rate (x-axis) onto granules residual moisture. The contour levels are plotted as curves; the area between the curves is color coded to indicate interpolated values of the respective residual moisture. The numbers which are shown in the plot represent the corresponding residual moisture in % water content.

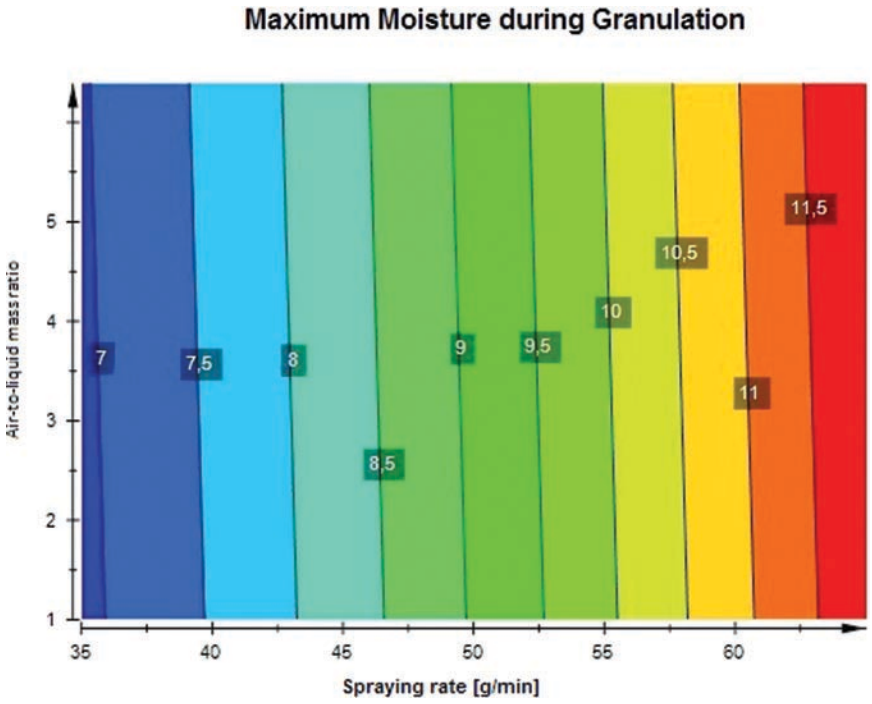

Figure 4. Contour plot of the effect of air-to-liquid mass ratio (y-axis) and spraying rate (x-axis) onto granules maximum moisture during granulation. The contour levels are plotted as curves; the area between the curves is color coded to indicate interpolated values of the respective residual moisture. The numbers which are shown in the plot represent the corresponding maximum moisture in % water content.

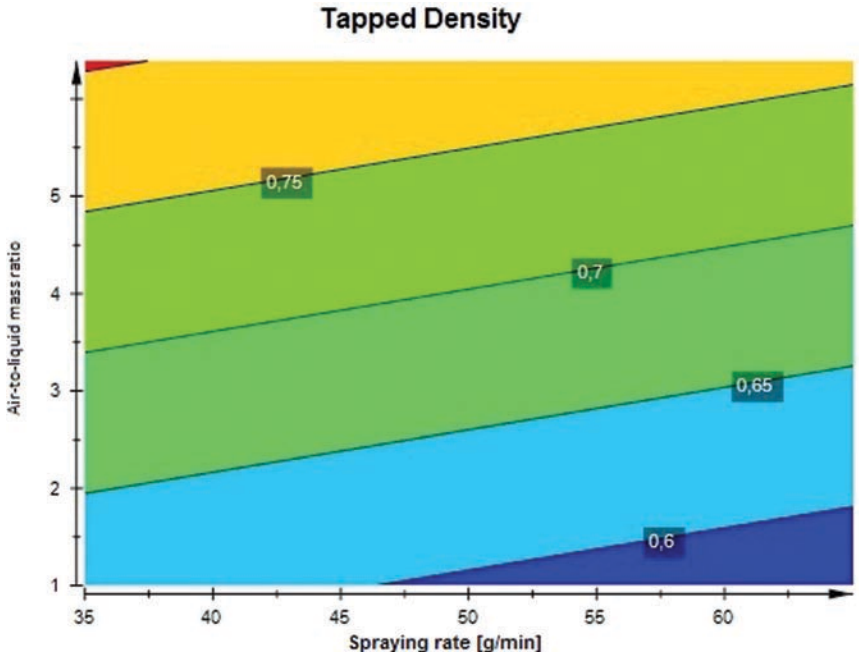

Figure 5. Contour plot of the effect of air-to-liquid mass ratio (y-axis) and spraying rate (x-axis) onto granule tapped density. The contour levels are plotted as curves; the area between the curves is color coded to indicate interpolated values of the respective tapped density. The numbers which are shown in the plot represent the corresponding tapped density in g/ml.

is that the growth mechanism for fine particles compared to coarse particles is different. The agglomeration mechanism of the coarse particles is controlled by secondary agglomeration mechanism (ball growth)[18]. In the secondary agglomeration stage, the particles reach a size where further growth is only possible by adhesion of smaller particles onto larger particles. The ball growth mechanism is inhomogeneous and controlled by irregular growth because of the limited number of very large particles in the granular material. Thus, for the very large particles a tendency is observed that the influence of the air-to-liquid mass ratio i.e. the droplet size of the binder liquid becomes negligible and likewise the influence of the spraying rate becomes dominant. For very large

particles, the studied range of the air-to-liquid mass ratio i.e. the correlated droplet size of the atomized binder liquid is not huge enough for overall wetting and consecutively agglomeration. The wetting and agglomeration of very large particles is then only controllable by increasing volume of added binder liquid = increasing spraying rate.

Influence of air-to-liquid mass ratio on granule residual moisture

Granules were characterized by the amount of residual moisture because residual moisture may have an influence on subsequent process steps i.e. tableting[8].

In Figure 3 the air-to-liquid mass ratio and the spraying rate are plotted versus the granule residual moisture. It becomes obvious that the spraying rate plays an essential role. The graph shows that at low spraying rates from 35 to 50 g/min and likewise low air-to-liquid mass ratio the influence of spraying rate is negligible. This observation can be explained by the existence of a spray drying effect at low spraying rate.

At low air-to-liquid mass ratios the droplets are large. Increasing droplet surface area by an increase in the air-to-liquid mass ratio, results in a higher evaporation rate. In this case, much less binder solution is available for particle agglomeration and granule growth. Factors that improve the degree of atomization i.e. increasing spray air pressure will increase the evaporation rate[19]. Only at higher air-to-liquid mass ratios a higher spraying rate leads to increased granule residual moisture.

Influence of air-to-liquid mass ratio on granule maximum moisture during process

Not only residual moisture but also the maximum moisture during the granulation process has a high impact on tableting[8]. Therefore, the influence of air-to-liquid mass ratio on granule maximum moisture during granulation has also been studied (Figure 4).

In Figure 4 the relationship between the air-to-liquid mass ratio, the spraying rate and the granule maximum moisture during granulation is shown. It can be seen that the influence of air-to-liquid mass ratio onto granules maximum moisture during the process is negligible. The increase of the spraying rate on the other hand causes an increase in maximum moisture. The maximum moisture content depends on the equilibrium between moistening and evaporation. At a certain spraying rate, the moistening exceeds evaporation and can result in caking of the powder bed through overwetting. This spraying rate is known as critical spraying rate[20].

Influence of air-to-liquid mass ratio on granule tapped density

Evaluation of the tapped density is important to assess the flowability and compressibility properties of granules[21].

In Figure 5 the influence of the air-to-liquid mass ratio and the spraying rate on the tapped density is shown. Increasing air-to-liquid mass ratio and decreasing spraying rate lead to increased tapped density due to fine particles obtained with these parameter settings. Figure 6 shows a cartoon of different ways of bulk alignment of granule particles.

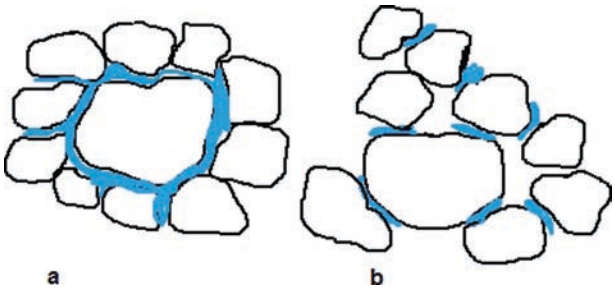

Figure 6. Bulk alignment of granule particles. (A) The alignment of denser granules with low porosity. (B) The alignment of bulky granules with more hollow space.

Increasing atomizing spray air pressure give denser granules probably due to lower granule porosity and a more favorable alignment (Figure 6A) of the granules compared to the bulky alignment of granules encountering partial surface moistening (Figure 6B).

Conclusions

The present study confirms that the atomization of the binder liquid clearly affects granule particle attributes. An increase in atomizing spray pressure and an increase in air-to-liquid mass ratio lowers the droplet size of liquid binder solution, which leads to a larger granule size for the presented enalapril maleate formulation. This novel description of the relationship between the examined droplet sizes and the final granule size of enalapril maleate granules was investigated by granulation experiments. When enalapril maleate granules with a desired d50-value between 100 and 140 µm have to be produced, then the nozzle air-to-liquid mass ratio must be set at high level. When granules with a desired d50-value between 80 and 120 µm should be obtained, then the air-to-liquid mass ratio must be set at a lower level. For producing granules with desired residual moisture of 6.5%, the spraying rate of the liquid binder solution is of negligible importance when the nozzle air-to-liquid mass ratio is controlled. This means that the way of atomization of binder liquid is of central importance in operating the fluid bed when processing an enalapril maleate formulation. The results of the present study imply that air-to-liquid mass ratio can be used to control granule particle attributes by maintaining other parameters constant.

Declaration of interest

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References

1. Lipsanen T, Antikainen O, Räikkönen H, Airaksinen S, Yliruusi J. (2007). Novel description of a design space for fluidised bed granulation. Int J Pharm, 345:101–107.

2. Schæfer T, Worts O. (1977). Control of fluidized bed granulation I: Effects of spray angle, nozzle height and starting materials on granule size and size distribution. Arch Pharm Chem Sci Ed, 5:51–60.
3. Rambali B, Baert L, Thoné D, Massart DL. (2001). Using experimental design to optimize the process parameters in fluidized bed granulation. Drug Dev Ind Pharm, 27:47–55.
4. Schæfer T, Worts O. (1977). Control of fluidized bed granulation II: Estimation of droplet size of atomized binder solutions. Arch Pharm Chem Sci Ed, 5:178–193.
5. Schæfer T, Worts O. (1978). Control of fluidized bed granulation IV: Effects of binder solution on granule size and size distribution. Arch Pharm Chem Sci Ed, 6:14–25.
6. Schæfer T, Worts O. (1978). Control of fluidized bed granulation III: Effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. Arch Pharm Chem Sci Ed, 6: 1–13.
7. Zank J, Kind M, Schlünder EU. (2001). Particle growth and droplet deposition in fluidised bed granulation. Powder Techn, 120:76–81.
8. Hartung A, Knoell M, Schmidt U, Langguth P. (2011). Role of continuous moisture profile monitoring by inline NIR spectroscopy during fluid bed granulation of an Enalapril formulation. Drug Dev Ind Pharm, 37:274–280.
9. Gretzinger J, Marshall WR. (1961). Characteristics of pneumatic Atomization. AIChE, 7:312–318.
10. Davies WL, Gloor WT Jr. (1972). Batch production of pharmaceutical granulations in a fluidized bed. II. Effects of various binders and their concentrations on granulations and compressed tablets. J Pharm Sci, 61:618–622.
11. Gupte AR. (1973). Das Granulieren in der Wirbelschicht. Pharm Ind, 35:17–20.
12. Davies WL, Gloor WT Jr. (1971). Batch production of pharmaceutical granulations in a fluidized bed. I. Effects of process variables on physical properties of final granulation. J Pharm Sci, 60:1869–1874.
13. Rankell AS, Scott MW, Lieberman HA, Chow FS, Battista JV. (1964). Continuous Production of Tablet Granulations in a Fluidized Bed II. Operation and Performance of Equipment. J Pharm Sci, 53:320–324.
14. Thurn U. (1970). Dissertation: Mischen, Granulieren und Trocknen pharmazeutischer Grundstoffe in heterogenen Wirbelschichten. ETH Zürich.
15. Ormos Z, Pataki K, Csukas B. (1973). Studies on Granulation in a fluidized bed III. Calculation of the feed rate of granulating Liquid. Hung J Ind Chem, 1:463–474.
16. Ormos Z, Pataki K. (1979). Studies on Granulation in a fluidized bed VIII. Effect of the raw material initial particle size upon granule formation. Hung J Ind Chem, 7:105–116.
17. US Food and Drug Administration. (2003). PAT- A framework for innovative pharmaceutical development, manufacturing and quality assurance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidan-ces/ucm070305.pdf
18. Sastry KVS, Fuerstenau DW. (1973). Mechanism of Agglomerate Growth in green Pelletization. Powder Techn, 7:97–105.
19. Scott MW, Lieberman HA, Rankell AS, Battista J. (1964). Continuous Production of Tablet Granulations in a Fluidized Bed I. Theory and Design Considerations. J Pharm Sci, 53:314–319.
20. Hu X, Cunningham J, Winstead D. (2008). Understanding and predicting bed humidity in fluidized bed granulation. J Pharm Sci, 97:1564–1577.
21. Parikh DM. (2005). Handbook of pharmaceutical granulation technology. New York, London: Taylor&Francis Group, 513–534.