OPTIMIZATION OF A FLUID BED GRANULATION PROCESS FOR AN ORAL FORMULATION THROUGH THE "DESIGN OF EXPERIMENT" (D.O.E.) APPROACH

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Introduction and Setting of the study.

The application of the design of experiments (DoE) is not only a valuable methodological tool for the optimization of manufacturing processes, but more often a requirement by the regulatory bodies and control authorities to encourage and implement at the companies the "Quality by Design". DoE is the methodology to explore critical parameters (Critical Process Parameters, CPPs) that characterize a process through a multivariable analysis, and that returns as output the magnitude of the correlation between the different parameters of the process and the end result of the process itself. This tool then, not only is able to maximize results through the correct setting of the parameters (productivity and efficiency), but is also able to predict the reciprocal interactions between the possible combinations of parameters quality attributes (Critical Quality Attributes , CQAs) of the finished product.

In the specific case shown, it has been investigated a process of fluid-bed granulation of a formulated effervescent mix. The potentially critical parameters have been identified through a pre-development study and the output to monitor have been defined in order to characterize the efficiency and quality of the process.

For the study, it was used a pilot plant, consisting of a fluid bed granulator PAG (images 1 and 2), operating with a batch size of 2 kg.

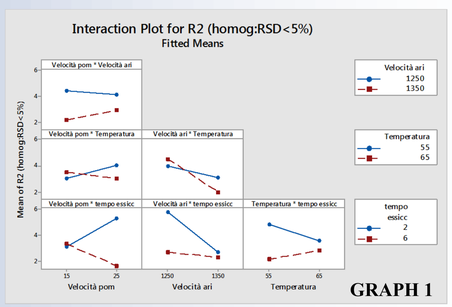
The CPPs studied were: rate of delivery of the binder solution, speed of inlet air in the system, the temperature of the air entering into the system and the drying time. Each parameter was varied between two extreme values chosen on the basis of a preliminary study.

TEST	Rate pump (RPM)	Rate inlet air (RPM)	Temp inlet air (°C)	Drying time (mins)	4,75% <Av assay<5,25%	Omog (RSD <5%)	Ass1-MeanAss <5%	Ass12-MeanAss <5%	Ass3-MeanAss <5%	Ass4-MeanAss <5%	Ass5-MeanAss <5%	% Water smp1 <4%	% Water smp2 <4%	% Water smp3 <4%	% Water smp4 <4%	% Water smp5 <4%	Measn-Water % / batch <4%
1	15	1350	55	6	4.59	3.1	4.4	3.9	1.6	0.5	0.6	1.6	1.7	1.5	1.7	1.6	1.63
2	25	1350	65	3	5.21	2.2	2.2	1.9	0.7	3.3	0.1	2.0	2.6	2.0	2.5	2.5	2.31
3	15	1350	65	3	4.92	1.5	1.0	0.9	2.3	1.0	1.1	1.9	1.4	1.3	1.4	3.4	1.88
4	15	1350	55	3	4.76	1.9	1.1	2.6	0.7	0.6	2.4	1.8	5.1	2.0	1.9	1.7	2.49
5	25	1250	65	6	4.78	1.9	0.8	2.2	0.0	1.2	2.6	1.9	1.8	1.8	1.9	1.5	1.79
6	25	1350	55	6	4.82	1.7	1.1	1.7	0.6	1.9	1.8	2.3	2.1	2.5	2.4	1.7	2.20
7	15	1350	65	6	4.13	3.0	3.6	3.5	1.3	2.6	1.2	1.2	1.1	1.2	1.3	1.2	1.18
8	25	1350	55	3	5.01	4.9	1.7	4.4	5.3	6.6	1.3	3.3	2.4	3.0	2.8	3.1	2.91
9	25	1250	55	6	5.15	1.6	0.1	0.8	2.8	1.0	1.1	2.7	2.5	3.0	3.2	3.0	2.85
10	15	1250	55	3	4.95	4.5	5.4	3.4	5.8	1.8	2.1	1.6	1.5	1.9	1.8	1.9	1.74
11	15	1250	55	6	4.93	2.4	2.5	3.8	0.2	0.6	1.6	1.6	1.5	1.5	1.5	1.5	1.53
12	25	1350	65	6	5.14	1.6	1.3	1.8	1.1	2.0	0.3	1.9	2.7	2.4	2.6	1.7	2.23
13	25	1250	55	3	5.40	5.5	1.2	0.7	6.8	0.2	8.6	4.1	3.1	2.9	2.5	2.2	2.95
14	15	1250	65	3	5.22	5.0	2.7	0.5	3.3	8.5	3.1	1.6	1.6	1.5	1.4	1.5	1.53
15	25	1250	65	3	5.36	5.1	5.7	1.1	7.7	2.9	0.2	5.8	6.5	4.7	7.3	5.8	6.03
16	15	1250	65	6	4.86	5.0	5.4	7.6	1.7	0.8	3.1	1.3	1.2	1.3	1.0	1.0	1.14

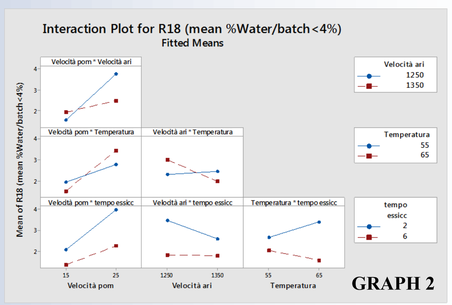
Data processing– Interaction Plots

The 16 granules obtained were analyzed with respect to the critical quality attributes selected. The CQAs considered were: appearance, loss on dry, percentage assay , homogeneity of the assay. The data accumulated in the experimental tests were processed using the software (Minitab17, graphs 1, 2 and 3). Here is a summary of the results collected:

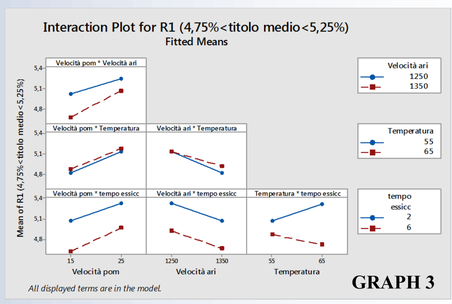
the homogeneity of the granulate is strongly dependent on the speed of the air flow inside the fluid bed granulator, during the first phase of the granulation process and the drying time, while it is less influenced by the speed of the pump and the temperature of 'incoming air. The optimization of the process in a predictive way led to the conclusion that an air fan speed of 1500-1750rpm and a drying time of at least 6 minutes allow the obtaining of a product with all the required features and with a probability level enough high to consider the process robust in terms of reproducibility and reliability.



GRAPH 1



GRAPH 2



GRAPH 3

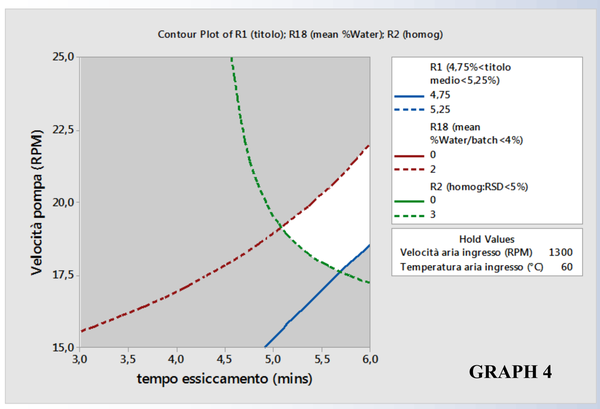
IMAGE 1

IMAGE 2

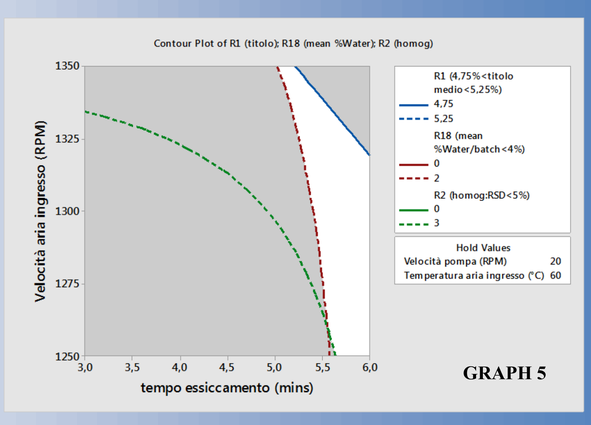
Data processing- Contour plots

Homogeneity-water content-assay combination and predictive optimization of the process

Charts 4 and 5 are each a prediction of the surface in which is possible to meet with greater probability the combination water-homogeneity-assay in the desired specifications, by varying a couple of parameters, while the remaining couple of parameters has been set to a median value of the target range. The calculation was restricted to the parameters that most influence the CQAs, namely the drying time, the air fan speed at the entrance and the pump speed. The calculation has been optimized for a water content < 2%, and for homogeneity expressed as a% RSD between < 3%. The feasibility region is white, while in gray are highlightned the regions of non-feasibility.



GRAPH 4

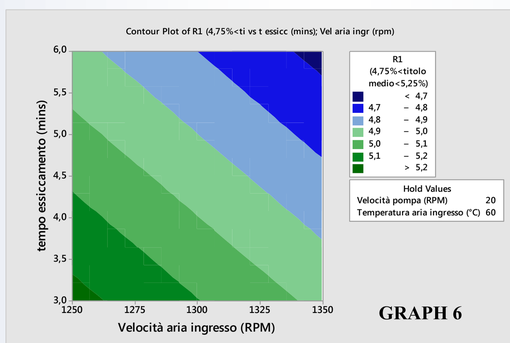


GRAPH 5

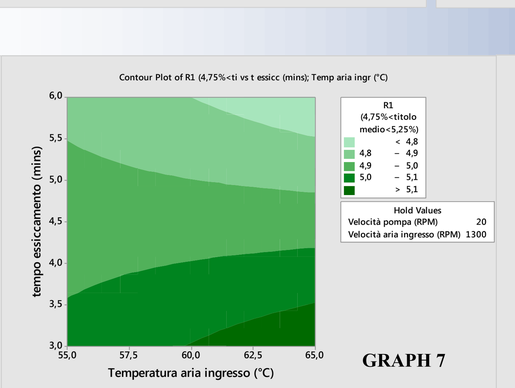
Data processing- Contour plots

Mean percentage Assay

The graphs 6-11 give a prediction of the values of mean percentage assay by the variation of couples of parameters. The distribution of mean percentage assays in each graph appears to be fairly uniform, outlining considerable area for maneuver on the parameters analyzed from time to time, as long as it remains in the central part of the chart. From a multidimensional point of view, these graphs represent a prediction of the surfaces of mean percentage assays with respect to the variation of a couple of parameters, while the remaining couple is set at the median values of the ranges explored. Even this graphical representation confirms the interpretation of previous data.



GRAPH 6



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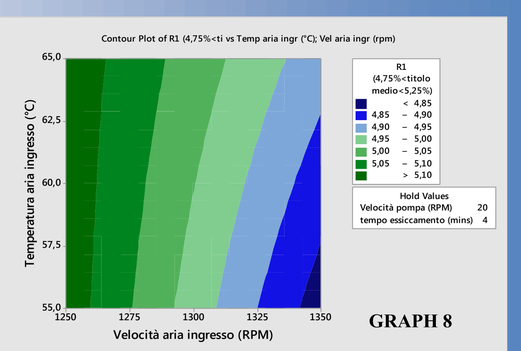

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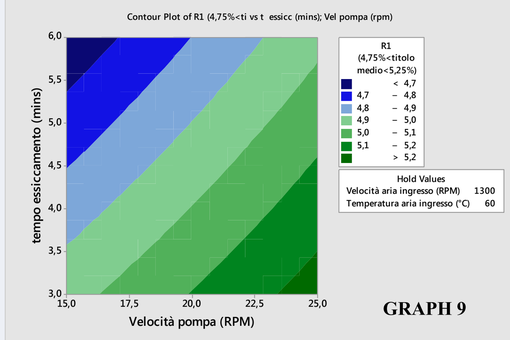
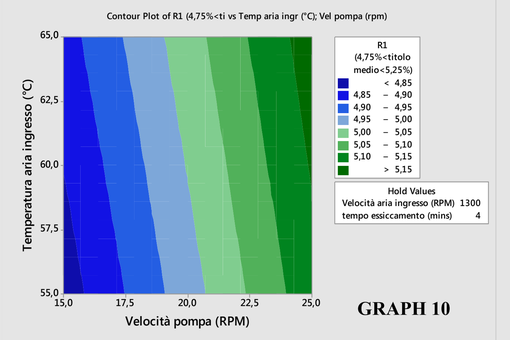
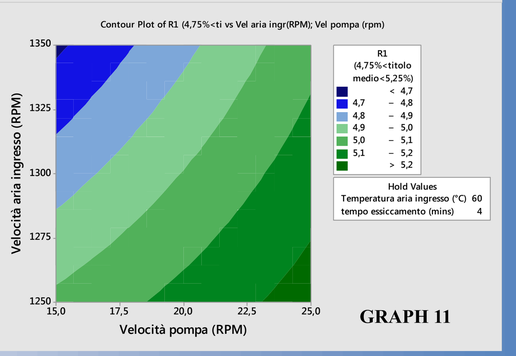


GRAPH 9



GRAPH 10



GRAPH 11

References

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2. *ICH (2008b) Pharmaceutical Development Q8(R1)*
3. *ICH (2008c) Pharmaceutical Development Q8(R1), annex*
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5. *Fluid bed Technology: Overview and Parameters for Process Selection. Saurabh Srivastava1, Garima Mishra. Review Article. International Journal of Pharmaceutical Sciences and Drug Research 2010; 2(4):* ***236-246***

Conclusions

This study represented an initial exploration of the granulation process by setting a DoE-scale laboratory. Despite the hypothesis of problems related to the geometry of the apparatus of granulation laboratory and to the intrinsic characteristics of the powders in the mixture, the tests have not shown in the complex too many critical OOS. The work done and the conclusions obtained from the laboratory study have been the starting point for the task of scaling up and validation of the process on an industrial scale with 112 kg batch size. Despite the differences in plant and mass of powder processed, the validity of the considerations that emerged from the DoE has been confirmed by the analytical results of several industrial lots, performed by varying each time the critical parameters studied.

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