Study for the transformation of Terazosin tablets manufacturing process, from wet granulation to Moisture - Activated Dry Granulation (MADG)

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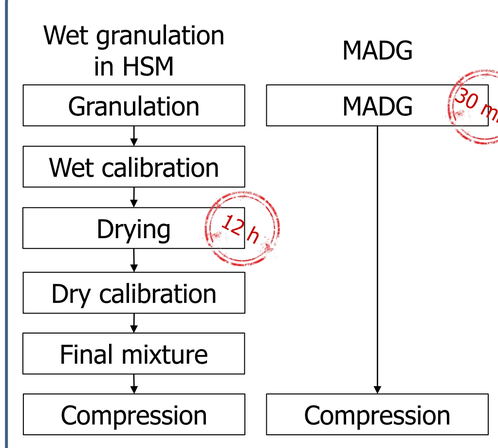
INTRODUCTION

The Moisture-Activated Dry Granulation technique (MADG) is a one-pot process, performed in High Shear Mixer, aimed to prepare the granulate using a small amount of granulating liquid (water).

The MADG process includes two major stages:

1. *Agglomeration stage:* API, fillers and binder are mixed to obtain a uniform mixture. During mixing, a small amount of water (1-4%) is sprayed onto the powder, thus moistening the binder and making it tacky, forming small and spherical agglomerates.
2. *Moisture-distribution and absorption stage:* moisture absorbents (microcrystalline cellulose, silicon dioxide) pick up moisture from the agglomerates and redistribute moisture within the mixture. The process continues with the addition of a disintegrant and then a lubricant, each followed by mixing.

The final granulate has a narrow particle size distribution and a low residual moisture content, making it suitable for the following tableting process.[1]



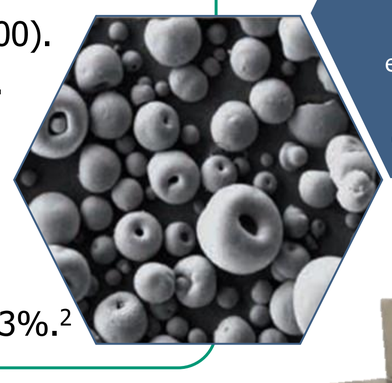
AIM OF THE WORK

The aim of this work was the application of MADG to the Terazosin 5 mg tablets manufacturing process, currently carried out by wet granulation.

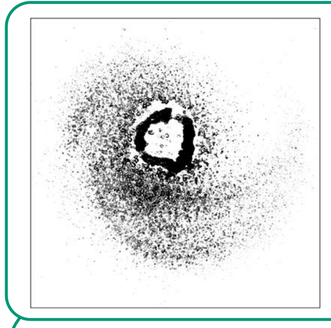
The goal was to simplify the process by eliminating the drying phase, traditionally performed in a static oven (49°C, 12 h), leading to an energy-saving process.

MATERIALS

- Terazosin Hydrochloride Dihydrate.
- Lactose Monohydrate (Granulac 200).
- Microcrystalline cellulose (Avicel PH 200).
- Polyvinylpyrrolidone K-30 (PVP K-30).
- Silicon dioxide (Aeroperl 300).
- Magnesium stearate.
- Crospovidone Cross-Linked (PVP CL).
- Purified Water (PW).
- Sunset Yellow 23%, Blue Indigotine 13%.[2]



Aeroperl 300: the high adsorption capacity due to mesopores (2-50 nm) and their high volume (1,5-1,9 ml/g) makes it an effective excipient for replacing physical drying in wet granulation process.



Preliminary investigation to determine the best conditions of ***spraying water***:

- Nozzle n. 3
- Tube diameter Ø 1,6 mm
- Speed 55 rpm
- Flow 14,55 g/min

METHODS

Quality by Design (QbD):

- **Quality Target Product Profile (QTPP)** from the commercial product.
- **Risk analysis** to select DoE's factors.
- **Design of Experiments (DoE)**:

  1° DoE AGG -*Custom Design* reduced with *D-optimal*; Factors: 3-7% PVP K-30, 1-4% PW, 300-400 RPM Impeller speed, Use of chopper (yes or no); Responses: LOD MA, Flow, Flow Speed, D_a , D_t , CI.

  2° DoE 02 -*Central Composite Design* with axial point external to the faces and with centroids; Factors: 1-2,5% PW, 0,5-1,33 % Aeroperl 300, 4-12 min Massing time; Responses: LOD MA, Flow, Flow Speed, D_a , D_t , CI.

Granulate's characterization: particle size distribution, Loss On Drying, bulk density, tapped density, Carr Index, flow properties, speed flow, angle of repose, compaction study, test di Wells.

Tablets manufacturing: tablets were produced using a rotary tablet press equipped by oblong punches, with a score line on one side, measuring 10 x 5 mm and had a convex shape with a cup radius 5 mm. In-Process Control (IPC): weight, thickness and hardness.

Tablet's characterization: uniformity of content (UV-Vis), uniformity of mass, friability, disintegration test, dissolution test.

RESULTS

DoE AGG – Screening of process parameters

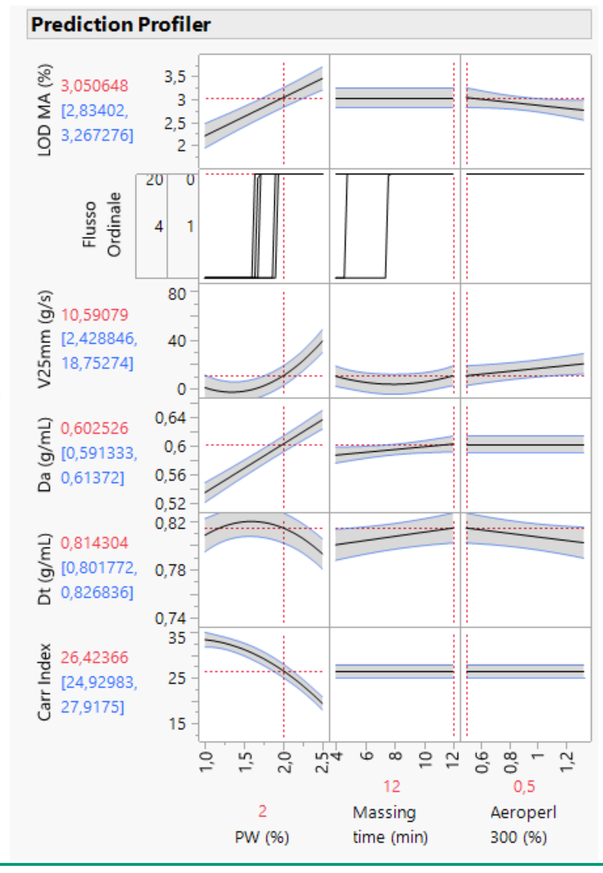
✓ The amount of water (% PW) and its quadratic interaction were the factors that mostly significantly influenced the investigates responses.

× The amount of PVP K-30 (% PVP) was significant only for some responses.

× Impeller speed and Use of chopper were not statistically significant for any of the investigated responses.

DoE 02 – Definition of the Proven Acceptable Range

- For amount of ***water*** > 2% excellent Flow values (4 mm) were obtained. However, for lower water %, the probability of the response exceeding 20 mm increases, with a huge worsening of the response. The effect of water was also evident in all other response.
- An increment in ***massing time*** increased the probability of obtaining a lower flow, while its effect on the other responses was less evident.
- The effect of the amount of ***Aeroperl 300*** was minimal.

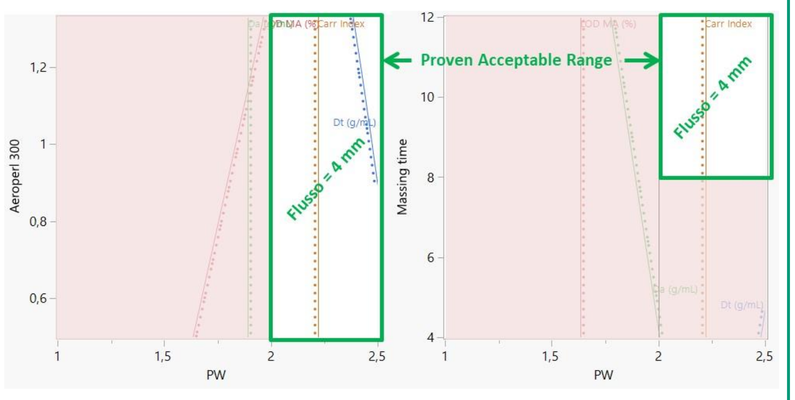


Prediction models verified

Results of experimental tests suggested that the granulate must have a Flow of 4 mm to obtain tablets with good mass and content uniformity. Prediction models showed that a **Flow of 4 mm** was obtained under the following conditions:

• Amount of water	2 – 2,5 %
• Massing time	8 – 12 min
• Amount of Aeroperl 300	0,5 – 1,33 %

Proven Acceptable Range



Optimal operating condition:

• Amount of water	2 %
• Massing time	12 min
• Amount of Aeroperl 300	0,5 %

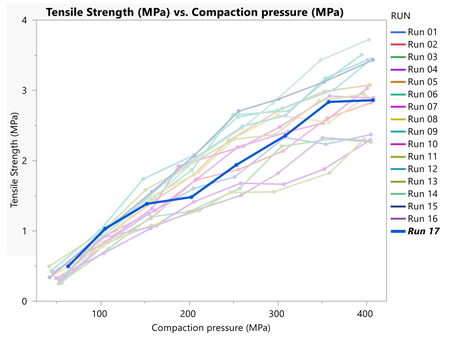
Characterization of the optimized tablets

Experimental results:

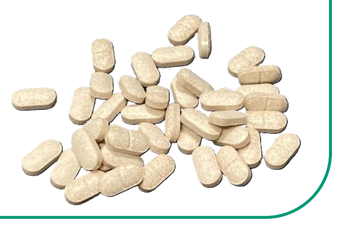
Friability	0,26 %
Disintegration	2,52 min
Uniformity of mass	148,50 mg
Dissolution test	99 – 103 %

Specification limits:

Friability	0,5 %
Disintegration	<15 min
Uniformity of mass	148,50 mg ±7,5 %
Dissolution test	>80% in 30 min



Optimal condition verified



CONCLUSIONS

1. Tablets' quality for the uniformity of mass and uniformity of content are related to flow properties.
2. It was possible to construct models capable of providing accurate predictions for the responses: Flow, LOD MA, Flow, D_a , D_t , CI.
3. The optimal operating condition was identified within the Proven Acceptable Range.
4. MADG method resulted applicable for Terazosin tablets manufacturing process: the quality of the final product meets the QTPP specifications.

References:

[1]Ullah et. al., Pharmaceutical Technology 33(11): 62–70 (2009).

[2]Ullah et. al., Pharmaceutical Technology 33(12): 42–49 (2009).

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