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RELEVANT PHENOMENA AND PROCESS PARAMETERS IN GRANULATION FOR MANUFACTURING OF PHARMACEUTICAL, NUTRACEUTICAL AND ZOOTECHNICAL PRODUCTS

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Abstract of the thesis

Wet granulation is a size enlargement process used in many fields, such as pharmaceutical, nutraceutical, zootecnichal, etc., due its ability to improve technological properties of the final product, compared to the powder form, and/or to realize suitable delivery systems for drug/functional molecules for oral administrations/food preparations and/or to produce intermediate processing products. In spite of its widespread use, economic importance and almost 50 years of research, granulates manufacture is still based on empirical approach. Moreover, phenomena involved in powders aggregation are not well understood, and thus it is difficult to successfully obtain a product with tailored features without extensive experimental tests.

In the scientific literature the approach to the granulation study is based on experimental tests, to investigate the impact of formulation and process variables on granules properties, or on modeling activities, to mathematically describe the involved phenomena. The two approaches, experimental and theoretical, are rarely applied together. In this study a novel integrate strategy of investigation was applied to elucidate the role of the phenomenological aspects, and their connection with the main operating parameters in granulation process, on the granules final properties, in order to develop physical-mathematical descriptions of the size enlargement unit operation, which can indubitably constitute a starting point for scale up purposes.

The first step of the Ph.D. research activity was the design and realization of a bench scale experimental set up, with the innovative feature of using an ultrasonic atomizer for spraying the wetting phase in order to improve its dispersion degree on the surface of powder bed. Four are the main sections composing the realized apparatus: feeding section, production section, stabilization section and separation section. For the preparation of granules, hydroxypropyl methylcellulose (*HPMC*) was used as powder model material due to its versatile properties. It is an easy to handle, available at low cost, odourless, hypoallergenic, biocompatible, and not toxic polymer, used as excipient in the formulation of hydrogel-based matrices in form of tablets or granules, in order to provide controlled release of oral solid dosage systems. Distilled water was used as binder phase. In the built configuration, the powder was placed in a low-shear granulator and agglomerated by spraying the binder phase. The produced wet granules were stabilized by dynamic drying in presence of a hot air flow, because the evaporation of the residual moisture slows down the degradation of the granules. The dry granules were separated by manual sieving with cutoff sizes from top to bottom as follows: 2 mm, 0.45 mm and a collection pan. Three granules fractions were obtained by the separation step: a fraction of "big scrap", i.e. particles with size larger than 2 mm, one of "small scrap", i.e. particles with size smaller than 0.45 mm, and one of "useful", i.e. particles with size between 0.45-2 mm. The range size 0.45-2 mm was considered as the fraction of interest being a size typical range of granules in the food, pharmaceutical and zootechnical fields. Finally, only the fraction of useful was subjected to characterization methods carried out adopting both the *ASTM* (American Society for Testing and Materials) standards and *ad hoc* innovative protocols. In particular, a new procedure for analysing the mechanical properties of granules, and an *ad hoc* built Dynamic Image Analysis (*DIA*) device, based on the free falling particle scheme, for monitoring the evolution of the *PSD* during the wet granulation process, were developed.

The experimental campaigns were planned by Design of Experiments (*DoEs*) approaches. A system with three process parameters (factors), i.e. impeller rotation speed (*rpm*), binder to powder ratio, and binder phase flow rate, each at three intensities (levels) was considered. Their impact on granules properties were assayed to find the best process operating conditions able to produce granules with tailored features, i.e. high product yield (% w/w of dry granules with size between 0.45 mm and 2 mm), low residual moisture content, and good flowability and compressibility properties. Under phenomenological point of view, it was observed that not all the combinations of parameter levels ensure good granulation. There are operating conditions, like low rpm with high binder phase flow rate and low binder to powder ratio, or, high rpm with lower binder phase flow rate and binder to powder ratio, which combined together can produce a high amount of granules with size lower than requested one (0.45-2 mm), i.e. failure of the aggregation phenomena. Others, like low rpm with high binder phase flow rate and high added binder phase amount, instead, can achieve clusters of powder and binder, i.e. over wetting phenomena, which is a condition to avoid. The best conditions of granulation were obtained with high rpm, high binder to powder ratio and low binder phase flow rate.

To fully understanding the behaviour of *HPMC* granules as active ingredient delivery systems, the intensities of process parameters, which are found to give the better product yield, were used in the production of loaded granules. In particular, the effect of three formulation variables, i.e. molecule payload,

molecule solubility and binder type, on physical and mechanical properties of granules were investigated and, moreover, analysis of release mechanisms were speculated. A hydrophilic compound, vitamin B12, and a lipophilic one, vitamin D2, were employed as model molecules. First of all, the best loading method in *HPMC* granules for the hydrophilic molecule, vitamin B12 (payload 1 % w/w), was investigated. Vitamin B12 was incorporated in the *HPMC* granules by two different loading methods: according to the method 1, the vitamin B12 was dissolved in the liquid binder phase (here the binder phase was a solution of distilled water and vitamin B12); according to the method 2, the vitamin B12 was pre-mixed with *HPMC* powders (here the powder was a mixture of *HPMC* and vitamin B12). It was observed that the loading method type does not influence the granules flowability properties and the product yield, however, a better dispersion of vitamin B12 inside the *HPMC* polymer matrix was achieved by using the method 1, perhaps for the uniform spraying of B12 together with the binder phase. Thus, by exploiting the most successful method 1, two different payloads of vitamin B12 and vitamin D2 (1 % and 2.3 % w/w) were assayed. Due to lipophilic properties of the D2, a binder phase made by a solution of ethanol and water with a 75/25 v/v ratio was used to produce vitamin D2 loaded *HPMC* granules. Results showed that the use of ethanol in the binder phase reduces the product yield and leads to the formation of granules with less defined shape, smaller mean size, less hard structure and worse flowability. Moreover, the presence of ethanol induces a slightly faster polymer erosion respect to granules obtained by using only water. The increase of payload both for the hydrophilic and lipophilic molecule leads to the formation of granules with a harder and more compact structure. The vitamins solubility influences their release mechanism: diffusion for the hydrophilic molecule (at 3 hours the vitamin B12 was fully released, regardless of the payload and of the *HPMC* erosion rate) and erosion for the lipophilic one (at 3 hours the amount of vitamin D2 released was similar to the amount of eroded *HPMC*).

Due to the relevance of size distributions in practical uses of granulates (the process yield is based on this parameter), hardware and software of a *DIA*-device for *PSD* analysis were designed, developed, tested and then used to perform studies on the growing of the powder agglomerates during the process. *PSD* measurements were used to obtain a basic understand of the phenomenological aspects for optimize the key process parameters, i.e.: process time, impeller rotation speed and binder phase flow rate. The process parameters optimization was carried out by Response Surface Methodology (*RSM*) and using the granulation yield (% w/w of wet granules within the size range 2-10 mm) as the main variable of interest. It was observed that the agglomeration, breakage and nucleation phenomena occur simultaneously in the granulator, with the predominance of the agglomeration during the binder addition phase, later balanced by the breakage phenomenon. Thanks to this initial phenomenological analysis, process time was optimized. Response surface studies indicated that the interaction between the impeller rotation speed and the binder flow rate influences the granulation yield (and in general the granules *PSDs*), especially at high rpm.

Agglomeration, breakage and nucleation phenomena experimentally observed by *PSDs* analysis were mathematically described by using the Population Balance Equations (*PBEs*) approach. *PBEs* were discretized in 60 classes, ranging from 60 to 20000 μm with a geometrical progression of $2^{1/6}$, therefore, the resulting model was a system of 60 Ordinary Differential Equations (*ODEs*), one for each class, which was implemented and solved numerically by MATLAB® 2014b software. Suitable mathematical functions to describe phenomena and parameters were selected from literature or purposely developed in this work. In particular, three models with increasing complexity were considered: a pure agglomeration model that disregards all the other phenomena; an agglomeration and breakage model; a complete model with agglomeration, breakage and nucleation. The different modeling structures were then validated by comparison with experimental data. As overall result, it was observed that a pure agglomeration model overestimates the granules formation and, despite the presence of the breakage factor improves the model capabilities, the best matching with experimental evidences was obtained using the complete model, which takes into account also the nucleation phenomena. Achieved results prove that the developed modeling structures respond to physical observed phenomena.