Research paper

Effects of different milling techniques on the layered double hydroxides final properties

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ABSTRACT

Layered double hydroxides (LDHs) find many applications in the pharmaceutical field. Often, the synthetic product requires a suitable grinding procedure before starting any type of manufacturing process. Choosing the appropriate grinding procedure is important; it must reduce the particle size without modifying the LDH's native layered structure and crystal morphology. Using the LDH MgAl-NO_3 as model sample, the aim of this paper was to investigate the influence of three common grinding procedures: knife mill, ball mill and jet mill, on particles size, morphology, specific surface area, crystallinity and flow character. Results highlighted that the jet milling procedure is the most appropriate method to induce particle size reduction while maintaining the original MgAl-NO_3 features.

1. Introduction

The layered double hydroxides (LDH) find many applications in different fields such as catalysis (Debecker et al., 2009), wastewater treatment (Pshinko et al., 2011), drug delivery, cosmetic, etc. Specifically, in the pharmaceutical sector, they are employed as (i) host materials for poorly soluble active pharmaceutical ingredients (APIs) (Perioli and Pagano, 2012; Perioli et al., 2013), (ii) drug delivery systems (Carretero and Pozo, 2009; Costantino et al., 2008; De Sousa et al., 2013; Rives et al., 2014) and (iii) rheological agents for topical formulations (Lee et al., 2009; Perioli and Pagano, 2016). With regard to the pharmaceutical field, the particular layered structure is suitable for interesting intercalation reactions that give rise to inorganic-organic hybrids, in which the API (guest) is stored in molecular form in the interlayer nanospaces of LDH (host). When this inorganic-organic hybrid is put in contact with biological fluids, the inorganic structure is able to trigger the drug release, modifying their biopharmaceutical performances with considerable advantages (Perioli and Pagano, 2012; Rives et al., 2014). LDH are multi-functional materials, which are also of great interest as excipients and functional ingredients for oral and topical formulations.

In oral formulations, LDH can enhance powder flowability thanks to its glidant-like properties (Perioli et al., 2012), while as a topical formulation it can act as rheological (Perioli and Pagano, 2016) and texturizing agent (Albiston et al., 1996).

The physical properties of LDH influence the final characteristics of the formulations in which is incorporated; particular attention must therefore be directed to its particle size. This parameter in fact controls many aspects of the formulation, concerning both, manufacturing, and the quality and performances of the final product. Particle size plays an important role in conditioning the mixing and blending of LDH's into other powders, and therefore the homogeneity, stability and flowability of the final blend (Yu, 2008). Moreover, the particle size is a relevant parameter, especially when LDH is incorporated in semisolid topical formulations intended for skin application (Choy et al., 2007). In fact, such products must possess specific requirements such as homogeneity, good extrusion from the packaging, good spreadability and no abrasive effect during their application on the skin. As far as the final product's quality and performances are concerned instead, particle size plays an important role in conditioning drug release rate and kinetics (Perioli et al., 2011).

Several synthetic methods have been developed in order to control LDH size and morphologies, among them should be worthy of names nucleation and crystal growth methods (Choy et al., 2002; Xu et al., 2006; Rives et al., 2006) and precipitation inside the water pool of reverse micellae (O'Hare et al., 2007; Bellezza et al., 2009) that allow to obtain particles with nanometric dimensions. However, the solids during drying step give as at-times large aggregates of micrometric dimensions. As a matter of fact, the search for methodologies, applicable also to classical synthetic methods, able to give particles with

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controlled dimensions and to be used in a widespread and effective manner at industrial level is still open. One solution to the formation of large aggregates could be to pulverize them by grinding methods, in order to have a powder suitable for formulation manufacturing.

There exist several grinding methods differing by the type of force applied to induce particle fracturing (breaking). These methods can be categorized as four types: impact (e.g. jet milling), attrition (e.g. ball mill), knife (e.g. knife cutter milling) and direct-pressure (e.g. roll mills) (Troy, 2005; Wennerstrum et al., 2002). The choice of the appropriate technique depends on the characteristics of the material that must be grinded; it is important to consider the material's properties as hardness, heat sensitivity, hygroscopicity, etc. (Wennerstrum et al., 2002).

Taking into account all these aspects it is necessary to find an appropriate procedure to preserve all the native product features (morphology, lamellar structure, etc.) during the grinding process. Moreover, this procedure must afford a free-flowing material with uniform particle size.

With this goal in mind, three commonly used milling techniques were examined. The LDH $[Mg_{0.63}Al_{0.37}(OH)_2]$ $(NO_3)_{0.37}·0.4·H_2O$ (henceforth called MgAl) was chosen as anionic lamellar clay model because of its widespread usage as filler, excipient, carrier and anionic exchanger (Del Hoyo, 2007). All the samples obtained were carefully analyzed in order to evaluate the effect of the selected grinding procedures on final dimensions, morphology, specific surface area, crystallinity and flowability.

2. Materials and methods

2.1. Chemicals

$Mg(NO_3)_2·6·H_2O$, and $Al(NO_3)_3·9·H_2O$ were purchased from Fluka. Deionized water was obtained from a reverse osmosis based Milli Q System (Millipore). Other reagent grade chemicals and solvents were used without further purification.

2.2. Layered double hydroxide synthesis

The MgAl-NO₃, having the predicted formula $[Mg_{0.63}Al_{0.37}(OH)_2]$ $(NO_3)_{0.37}·0.4·H_2O$ was synthesized using the urea method (Costantino et al., 1998), obtaining the carbonate form. Subsequently, it was converted into its nitrate form by titration (Bish, 1980). It was then dispersed in a NaNO₃ solution (0.1 Mol/L) and titrated by a HNO₃ solution (0.1 Mol/L) by means of an automatic titrator (Titralab VIT 90 Video Titrator Radiometer, Copenhagen, Denmark) operating at pH stat mode, at pH = 5.

2.3. Particle size reduction techniques

- Ball milling was performed through a ball mill KM (capacity 1 L) attached to its drive unit (AR 400) via the ERWEKA Universal Gear provided by porcelain balls with diameters in the range of 20 to 50 mm. 60% of the grinding jar (rotation speed 50 rpm) volume was filled with grinding balls and MgAl powder. During the grinding, powder samples were taken at 10, 30 and 60 min.
- Knife milling was made by GRINDOMIX GM 300 Retsch (Düsseldorf, Germany) equipped by four sharp stainless steel blades. The sample was milled working at 2000 rpm for 10 min, motor power 1.1 kW.
- The jet milled product was prepared by IMS Micronizzazioni s.r.l. (Milano, Italy). In this case size reduction is the result of the high-velocity collisions between particles of the process material itself. The sample is introduced in a chamber by means of a high speed jet of compressed air or inert gas. This is responsible for the impact of particles into each other and their consequent size reduction. Experimental runs were carried out by spiral jet mill Micronette MD100 (Nuova Guseo – Villanova sull'Arda, Italy). The solid was delivered at a constant feed rate by a screw feeder. After being

dropped into the injector cone, it was accelerated and fed into the milling chamber (loading speed 22 g/min) through a Venturi injector. The gas used for grinding was pressurized nitrogen, to avoid risks of dust explosion. Pressure reducing valves allowed adjusting the grinding and the feeding pressure within a precision of 0.1 bar.

2.4. Sieving analysis

The sieve analysis was performed using a sieve shaker Octagon 200 (Endecotts Ltd., London, UK) on sieves of mesh sizes: 2.33 mm, 1 mm, 710 μm, 280 μm;180 μm 149 μm and 105 μm.

2.5. Single particle optical sensing analysis

An Accusizer C770 (PSS Inc., Santa Barbara, CA) with the SPOS technique "Single Particle Optical Sensing" was used to determine the size distribution of the different samples of grinded MgAl analyses were performed in triplicate and sizes were expressed as cumulative volume distributions.

D10, D50 and D90 are defined as the size values corresponding to cumulative distributions at 10%, 50% and 90%, respectively. These represent the particle sizes, below which 10%, 50% and 90%, respectively, of the samples' particles lie.

2.6. Scanning electron microscopy analysis (SEM)

SEM micrographs were taken with FE-SEM LEO 1525 Zeiss - LEO Electron Microscopy Inc., One Zeiss Drive (Thornwood, NY). The samples were by deposition of the powder on the stab under nitrogen flow. The raw powder was not sifted and the dispersion was not sonicated. Before observation, the samples were sputtered and coated with chromium for 5 min under an argon atmosphere.

2.7. Nitrogen adsorption–desorption isotherms

Nitrogen adsorption–desorption isotherms were determined with a Micromeritics ASAP 2010 instrument at $-196.15\,°C$ on the samples outgassed for 48 h at room temperature. The specific surface area was calculated with the Brunauer, Emmett, and Teller (B.E.T.) method (Brunauer et al., 1938).

The calculation of the mesopore size volume was performed by Barrett, Joyner, Halenda method (BJH) (Barrett et al., 1951).

2.8. X-ray analysis

Powder X-ray diffraction patterns (PXRD) of powders were collected with a Philips X'Pert PRO MPD diffractometer operating at 40 kV and 40 mA, with a step size 0.03° 2theta, and step scan 40 s, using Cu Kα radiation and an X'Celerator detector.

2.9. Flow properties determination

Flow properties of the grinded MgAl were determined by Carr's compressibility index (Carr, 1965) and Hausner's ratio (Hausner, 1967), as prescribed by European Pharmacopoeia (Ph. Eur. 9.0 Ed.). Such procedure consists of the determination of the apparent volume before and after powder settling, by using a tap density instrument (ERWEKA GmbH SVM 101/201, Heusenstamm Germany). A weighted amount of sample was introduced in a dried graduated cylinder (250 mL) occupying a volume between 150 and 250 mL. The volume measured before settling is the bulk volume (V_0). The sample was submitted to successive tapping (10, 500 and 1250 times), and the corresponding volumes were measured (V_{10}, V_{500}, and V_{1250}); V_{1250} represents the settled volume (V_f). The measurements were taken in triplicate, each result represents an average of three measurements and the error was expressed as standard deviation (SD). The Carr's compressibility index (CI) was