Sizing and morphology analysis of milled olanzapine, paroxetine and gabapentin particles using hot stage microscopy and laser diffractometry

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Introduction: Paroxetine, gabapentine and olanzapine are drugs used in mental disorders (e.g. epilepsy, aggressive behaviour, schizophrenic and bipolar dysfunctions), very often in prolonged, life-long, therapies. However, since these drugs are poorly water soluble and exist in several polymorphic forms, they exhibit remarkably different clinical outcomes (1). Amorphization is a strategy used over the last decade to enhance the water solubility of drugs (2), in contrast with previous strategies of crystal engineering. Amorphization can be achieved by reducing the particle size to the nanometric scale, using a milling ball technique (3). The goal of the present work is to obtain amorphous particles of the three drugs, using different milling conditions, and characterize (size and morphology) these particles by hot-stage microscopy and laser diffraction.

Materials and Methods: Particles were obtained using a planetary ball mill (PM 100 CM, Retsch) operated in different conditions (time of milling, speed of the mill, size of the spheres used, dry or wet milling, presence or absence of Tween 60, as a surfactant). The size and shape of olanzapine, paroxetine and gabapentin particles were determined by microscopy (Olympus BX51, Japan, fitted with polarized light and a heating stage, Linkam THMS350V, UK) and laser diffractometry (Mastersizer 2000, Malvern, equipped with a Hydro 2000S sample dispersion unit). Particle size and size distribution were determined using the manufacturers' (Olympus and Malvern) software.

Results: The size of particles (laser diffractometry and microscopic analyses) decreased with the milling time for both dry and wet milling, for all drugs. For olanzapine, dry milling seemed to be more effective in size reduction than wet (water) milling for all the rotations tested (100, 250, 400, 650rpm). Milling (dry and wet) of the other drugs, for 10 min, either at 400 or 650 rpm, resulted in a particle size reduction to almost 50%. When wet milling was considered the most effective amount of water was 2,5mL for all speeds (10min milling). Results have also shown that the most effective diameter of the milling spheres was 3mm diameter, for both dry and wet milling. Microscopy has shown for paroxetine and gabapentin a reduction in the size of particles of 40 and 16%, respectively (dry milling for 30 or 60min, at 650rpm).

Discussion and Conclusions: The minimum size achieved was on the micrometer scale and the milled particles of all the drugs remained in the crystalline state. In fact, the longest milling time tested (60min) and/or the highest mill speed considered (650rpm) in these preliminary studies were not sufficient to attain particles in the nanometer range, nor the amorphous state for the three drugs. In future studies, different processing conditions, such as higher speed and milling time, should thus be considered.

References:

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