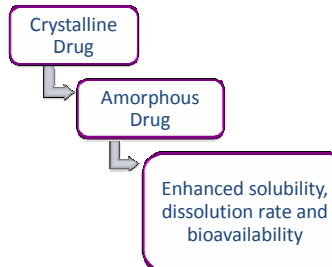


INTRODUCTION

Paroxetine, gabapentin 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 range, 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) of these particles by hot-stage microscopy and laser diffraction.



METHODS

Preparation of the samples: Ball Milling

Particles were obtained using a planetary ball mill (PM 100 CM, Retsch) operated in different conditions: time of milling – 1,5,10, 30 and 60 min; speed of the mill – 100, 400, 650 rpm; size of the spheres used – 0,1;1;3 mm; dry or wet milling, presence or absence of Tween 60, as a surfactant.

Observation and measurement of the milled particles: Hot Stage microscopy

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).

Measurement of the milled particles: Laser diffractometry

The size and shape of olanzapine, paroxetine and gabapentin particles were determined by 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 AND DISCUSSION

The size of particles (laser diffractometry and microscopic analysis) decreases with the milling time for both dry and wet milling, for all drugs. For **OLANZAPINE** wet milling seemed to be more effective in size reduction than dry milling. Although 30 and 60min (at 650rpm) are the best conditions (Fig. 1), there was a particle size reduction to almost 50%, after 10min milling at 650rpm. Both microscopy and laser diffractometry measurements showed that when wet milling was considered the most effective amount of water was 2,5mL for all speeds (10min milling). Microscopy showed for **PAROXETINE** and **GABAPENTIN** a reduction of 40% (minimum size achieved - 21µm) and 16% (minimum size achieved - 23µm), respectively in the dry milling for 30 or 60min, at 650rpm. Microscopical observation of the raw materials and milled particles of the three drugs always shows a crystalline form (Fig. 2). As the milling time increases, the particles got smaller and the crystals were damaged and seem to continue in the crystalline form.

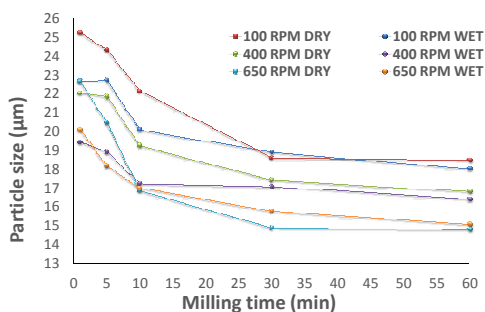


Fig 1: Influence of milling time on Olanzapine particle size (Microscopic analysis)

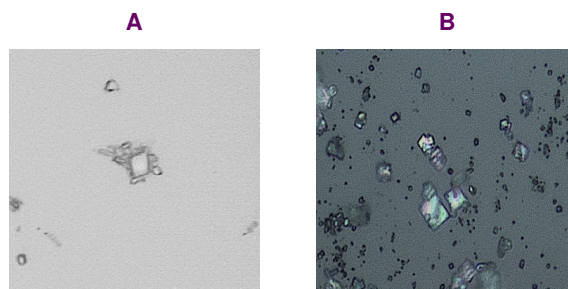


Fig 2: A) Olanzapine raw material **B)** Olanzapine milled particles (650rpm, wet) (Microscopic analysis; magnification 20x)

CONCLUSION

The minimum size achieved was on the micrometer range and the milled particles of the three drugs seem to remain 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. In future studies, different processing conditions, such as higher speed and/or milling time, or other size reduction technique (solvent evaporation, should thus be considered.

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ACKNOWLEDGEMENT

Fundação para a Ciência e a Tecnologia (PTDC/DTP-FTO/1057/2012) is acknowledged for funding.