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Evaluating the effects of processing parameters on budesonide nanocrystals prepared by nanomilling.

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SUMMARY

The aim of this study was to optimise processing parameters in the preparation of budesonide nanocrystals by a miniature media milling process performed. Using Polysorbate 80 as the surfactant choice of stabilizer, the effect of milling bead size, milling time and stabilizer concentration on budesonide particle size was determined. Particle size decreased with smaller milling bead size and longer milling time. However, no significant further decrease was seen after milling past 6 hours. Increasing Polysorbate 80 concentration led to an increase in budesonide particle size. Future direction will incorporate stability study with the screening of optimal stabilizer choice.

INTRODUCTION

Inhaled glucocorticoids are one of the most important groups of drugs used in the treatment of pulmonary diseases. Due to their poor aqueous solubility, suspension formulations are widely marketed dosage forms, e.g., budesonide inhalation suspension (Pulmicort Respules®, Astrazeneca, UK) available commercially for nebulized delivery. However, limited dissolution and rapid mucociliary clearance are amongst the drawbacks reported for nebulized microsuspensions (Knoch 2005). Nanocrystal formulations are increasingly being used as a strategy to overcome these drawbacks. The reduction in particle size offers increased saturation, and improved solubility and dissolution rate in comparison to the microsuspension.

In this study, budesonide nanocrystals were prepared using a miniature media milling process. Particle size obtained from this process depend on processing parameters. Furthermore, the physical stability of the milled suspension depends on the presence of stabilizers to mitigate aggregation and/or Ostwald ripening. Therefore, the aim was to optimise parameters such as milling bead size, milling time, and stabilizer concentration, and determine their effect on budesonide nanocrystal size using polysorbate 80 as the stabilizer (as per Pulmicort Respules®).

MATERIALS AND METHODS

Nanocrystals of budesonide were prepared using a milling process previously described, (Gregori 2016) with modifications. The system consists of four magnetic stir bars (12 x 6 mm), 0.2 g of budesonide, and 4 mL of 0.5, 1, or 2% of Polysorbate 80 (Croda) placed in a 7 mL vial with 8 g of Yttria stabilized zirconia beads (Chemco Advance Materials, China) of sizes 0.1 – 0.15, 0.2 – 0.3, or 0.3 -0.4 mm. The system was stirred at 1500 rpm for 24 hours with sampling of the supernatant at 1, 2, 3, 4, 6, and 24 hours. Then, particle size distribution and polydispersity index (PDI) were determined by

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dynamic light scattering (Malvern Zetasizer Nanoseries, Malvern Instruments, UK).

RESULTS AND DISCUSSION

Firstly, the effect of milling bead size on budesonide particle size was determined, (Figure 1A). The smaller bead size (0.1 – 0.15 mm) produced the smallest particle size of 171.4 nm after milling for 24 hours, compared to the larger bead size (0.2 – 0.4 mm) producing particle size of 303.8 nm. This can be attributed to the faster movement of the smaller beads compared to larger beads, more energy per collision, and therefore, faster breakage of the drug particle during the milling process. However, it took 24 hours of milling to achieve a uniform distribution and PDI value of 0.15, whereas milling with bead size 0.2 – 0.3 produced the same PDI after only 4 hours with particle size 464.8 nm. Although, the smaller beads were more effective in achieving a smaller particle size, they were not the most efficient.

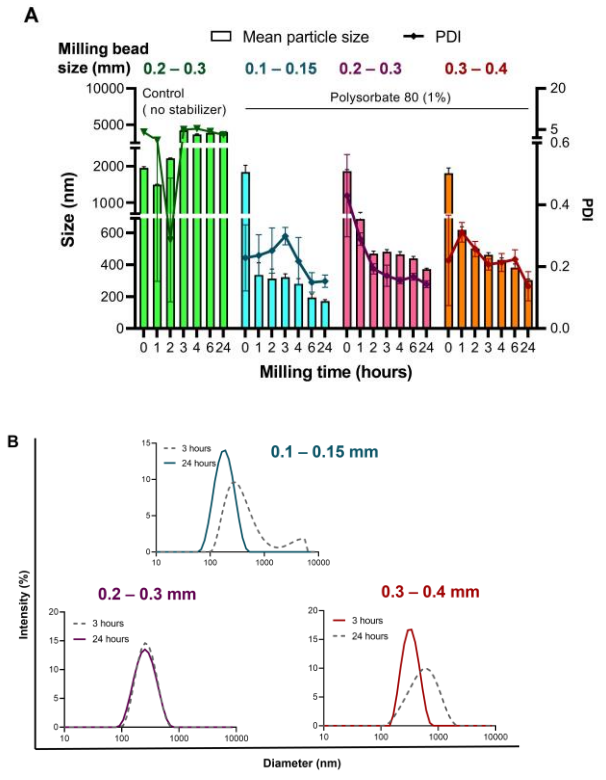

Fig. 1. *A: The effect of milling bead size 0.1 - 0.15, 0.2 – 0.3, and 0.3- 0.4 on budesonide particle size as a function of milling time. B: Particle size distribution after milling for 3 vs 24 hours. Mean ± SD, n = 2-3.*

Following this, the effects of stabilizer concentration on particle size was determined using bead size of 0.2 – 0.3 mm. This size was selected as there were no significant changes to both the particle size and distribution after 3 hours of milling (Figure 1B), and therefore provided the optimum condition. The result displayed in Figure 2 showed that increasing Polysorbate 80 concentration increased budesonide particle size. This could be a result of increased budesonide solubility with increasing surfactant concentration which could accelerate Ostwald ripening upon storage.

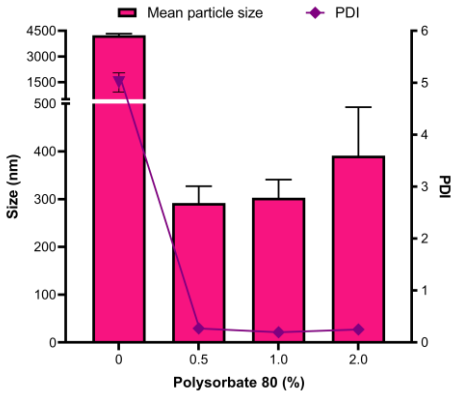

Fig. 2. *Effect of polysorbate 80 concentration on budesonide particles milled for 3 hours with bead size 0.2-0.3 mm. Mean ± SD, n = 2-3.*

CONCLUSIONS

The miniaturized approach to nanomilling was successful in producing budesonide particles in the nanometre range. This process can aid in the selection of optimal formulation parameters that can usually be time and resource intensive.

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REFERENCES

Knoch, M., Keller, M ., 2005. The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems. Expert Opin Drug Deliv, 2, 377-90.

Gregori, B.R., Cornelia, M., Rainer, H.M., 2016. Simple low -cost miniaturization approach for pharmaceutical nanocrystal production. ijpharm, 501, 236 -244