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Nanoparticle agglomerates of indomethacin: The role of poloxamers and matrix former on their dissolution and aerosolisation efficiency

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ABSTRACT

Nanoparticles (NPs) were prepared and assembled to microsized agglomerates with and without matrix formers (mannitol and L-leucine) by coupling wet milling and spray drying to harmonise the advantages of NPs with handling and aerodynamics of microparticles without induction of amorphisation. Indomethacin was selected as poorly water-soluble drug and poloxamers with different ratios of hydrophilic to hydrophobic domains were evaluated as stabilisers comparatively to D-α-Tocopherol polyethylene-glycol succinate (TPGS). Particle size of nanosuspensions and morphology, size, crystal form, drug loading, redispersibility, in vitro dissolution, and in vitro aerosolisation of NP-agglomerates were determined. Molecular weight of stabilisers affected the rate but not the limit of NP size reduction and the length of hydrophilic segment in poloxamers was found important for the nanosuspension stabilisation. SEM revealed the structure of agglomerates consisting of nanocrystal assemblies. XRPD with DSC proved that NP agglomerates retained their crystallinity. NP-agglomerates exhibited enhanced dissolution compared to physical mixtures of drug and stabilisers while incorporation of matrix formers enabled redispersibility upon hydration and further increased the drug dissolution. Also, matrix formers resulted in significantly improved aerosolisation with higher fine particle fractions (49–62%) and smaller mass median aerodynamic diameters (<3.5 μm), compared to cases without matrix formers (34–43% and <4.5 μm).

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1. Introduction

Several of the drugs used for the treatment of respiratory diseases exhibit poor aqueous solubility (antifungals, corticosteroids, oligopeptides and opioids) affecting their availability and retention in the lung tissue and subsequently their therapeutic efficacy, safety and dosing (Tolman and Williams, 2010). Reduction of drug particle size to the nano-range is considered one of the most prevalent methods to overcome the obstacle of poor water solubility (Brough and Williams, 2013). The large surface of nanoparticles (NPs) results in increased saturation solubility and accelerated dissolution while their small size enables them to escape from the lung phagocytic clearance mechanisms (Rogueda and Traini, 2007; Zhang et al., 2011).

However, delivery of individual NPs to the lungs (with the exception of particles below 50 nm in size) appears to be problematic, as due to their small size (<1 μm) they have increased probability of exhalation before deposition (Byron, 1986; Rogueda and Traini, 2007). Moreover, the high interparticulate forces dominate resulting in uncontrolled aggregation and preventing deaggregation upon aerosolisation under the normal air flow rates in passive dry powder inhalers (DPIs) (Watts and Williams III, 2011). Therefore, in order to overcome these limitations, the controlled agglomeration of NPs to micro-sized clusters has been recently proposed as "*an approach to harmonize the features of nanoparticles with the aerodynamics of small microparticles so as to achieve an improved bioavailability and aerosolisation behaviour of the drug*" (El-Gendy et al., 2009).

The formation of NP-agglomerates involves two processing steps: (a) the preparation of a nanosuspension (submicron colloidal dispersion of nanosized drug stabilised by surfactants, polymers or a combination of both) (Chingunpituk, 2007) and (b) the removal of liquid (water) from the nanosuspension with simultaneous controlled NP assembling (agglomeration).

Considering the various nanosizing techniques, wet bead milling has been characterised as a reproducible, cost-effective and scalable way producing nanosuspension with a typical size ranging from 200 to 500 nm (Möschwitzer, 2013). Especially for poorly water soluble drugs, wet milling can take place in water

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avoiding the use of organic solvents and producing crystalline nanosuspensions due to the plasticizing effect of water on the potentially generated amorphous material, triggering recrystallisation (Kayaert and Van den Mooter, 2012).

For the water removal from nanosuspensions and controlled nanoparticle agglomeration, processes as freeze drying and spray drying have been evaluated. The high energy consumption, long processing times and reduced flowability of freeze dried products limit the use of freeze drying for the preparation of respirable NP-agglomerates (Zhang et al., 2014). On the other hand, spray drying is a manufacturing technique of particular interest for respiratory drug delivery as particle characteristics (size, flowability, redispersibility, moisture content) can be controlled by formulation and process parameters (Van Oort and Sacchetti, 1996).

Prior to spray drying, addition of matrix formers and surface active agents was found to enhance the dissolution rate and the aerosolisation behaviour of the particles, respectively. More specifically, incorporation of mannitol as matrix former in NP-agglomerates was found to improve their dissolution rate by preventing the irreversible aggregation of NPs during drying (Chaubal and Popescu, 2008; Van Eerdenbrugh et al., 2008a; Yamasaki et al., 2011; Cerdeira et al., 2013). The amino acid L-leucine was found to act as an aerosolisation enhancer forming a coat (shell) on the dry particle surface preventing any particle fusion and therefore preserving the individual NP-agglomerates as collected from the dryer (Seville et al., 2007; Sou et al., 2011).

The aim of this work is to apply wet bead milling followed by spray drying as an industrially feasible formulation- based approach for the preparation of NP-agglomerates that can be used primarily as pulmonary drug delivery formulations and potentially as components of solid oral dosage forms (Bosch et al., 1999). This study will primarily focus in the use of NP-agglomerates for the delivery of NPs of poorly water soluble drugs to the lungs, as design and production of inhalable particles is considered one of the most challenging areas of particle engineering (Chow et al., 2007).

Indomethacin was selected as a model of poorly water-soluble drug and three poloxamers as amphiphilic non-ionic copolymers differing in their molecular domains were used for the production of nanosuspensions. In this way the effect of stabiliser characteristics (total molecular weight and molecular weight of the hydrophilic polyoxyethylene, EO, moiety) on the nanosuspension formation will be elucidated. Besides poloxamers, D-α-tocopherol polyethylene glycol succinate (TPGS) was selected as a stabiliser for comparative purposes, since it has been reported as efficient for drugs with different functional groups and for different pharmaceutical applications (Duret et al., 2012; Van Eerdenbrugh et al., 2008b). Moreover, the effect of mannitol and L-leucine addition during the spray drying of nanosuspensions on the solid state, dissolution rate, redispersibility (reformation of NPs after rehydration) and aerosolisation efficiency of the NP-agglomerates will be investigated. Indomethacin was selected as a model poorly water-soluble drug, prone to polymorphic transformations and amorphisation during milling and spray drying (Karmwar et al., 2012; Legendre and Feutelais, 2004; Martena et al., 2012).

2. Materials and methods

2.1. Materials

γ-Indomethacin (IND), 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (diameter, $D_{4,3}$: 54.10 ± 8.12 μm, LKT Laboratories, USA), was used as model drug. Poloxamers: 407, 188 and 184 (Pluronics®: F127, F68, and L64 respectively) from BASF Co. (Ludwigshafen, Germany) and D-α- Tocopherol polyethylene glycol 1000 succinate (TPGS, Sigma Aldrich Co., St. Louis, USA) were used as stabilisers (Fig. 1). The physicochemical properties of the stabilisers used in this study are given in Table 1. Mannitol (Pearlitol 160C, Roquette Freres, Lestrem, France) and L-leucine (Sigma) were used as matrix formers of the NP-agglomerates. Water for injection quality (HyPure™) obtained with a Hyclone® I (Thermo Scientific, UK) was used for the preparation of

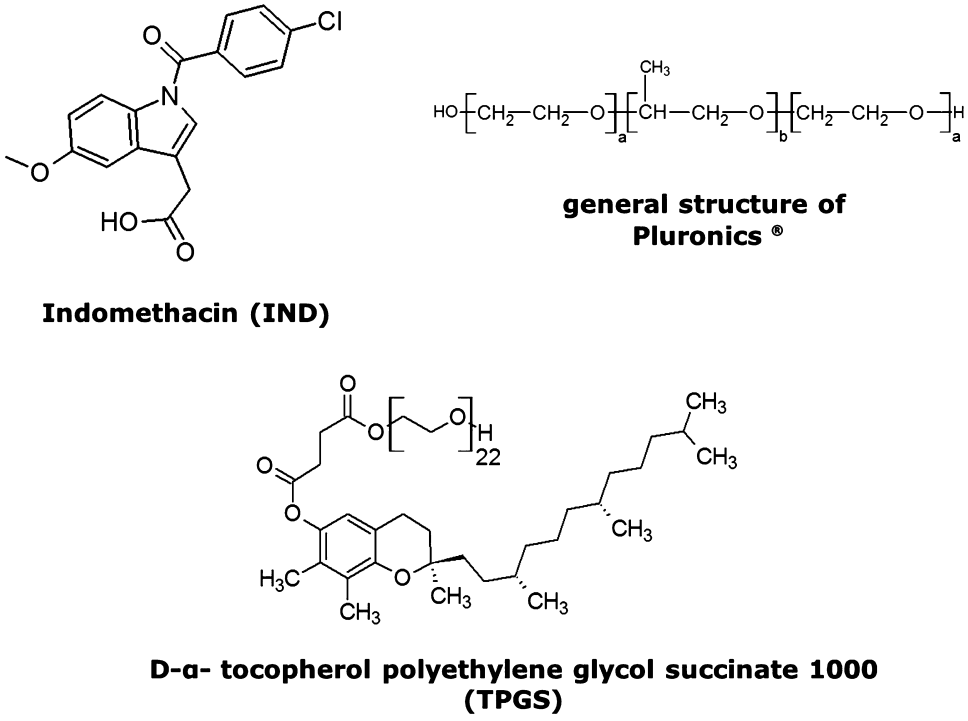

Fig. 1. Chemical structures of indomethacin and stabilisers used.

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