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COMMENTARY

Building Membrane Emulsification into Pulmonary Drug Delivery and Targeting

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Inhalation therapy is desirable for both local and systemic drug delivery due to the large lung surface area for absorption, abundance of capillaries, elevated blood flow and low local metabolic activity [1,2]. For inhalation administration, the active agent(s) have to be presented as an aerosol via appropriate devices including nebulizers, metered-dose inhalers (MDI) and dry powder inhalers (DPI). The particle size and size distribution play an extremely important role in their airway deposition and hence affect the therapeutic outcome. It is generally accepted that inhalation aerosols with a size (aerodynamic diameter) ranging from 0.5 to 5 μm show efficient delivery to the lung, aerosols with a size ca. 2 μm are capable of targeting to the deep lung, i.e. alveolar region [3]. Therefore, particle engineering has been pivotal in pulmonary drug delivery and targeting. The properties of particles, such as size, size distribution and shape, are critical for achieving optimum particle performance and efficient drug delivery. Currently, the main pharmaceutical particle engineering techniques for inhalation consist of milling, spray-drying, spray freeze-drying, supercritical fluid processing, controlled crystallisation, particle coating and particle formation from liquid dispersions, e.g. emulsions [1]. Despite their own merits, the above methods show limited capability to control the size, size distribution and shape of particles together, whilst a technique called 'membrane emulsification' or 'microchanel emulsification' (ME) could manipulate these particle properties.

Initially, ME emerged as an emulsion manufacturing technique over two decades ago [4]. It utilizes an appropriate pressure to drive the dispersed phase through a membrane with uniform pore size distribution into the continuous phase forming a water-in-oil (w/o) or oil-in-water (o/w) single emulsion in the presence of suitable emulsifier(s). When employing a single emulsion (w/o or o/w) as the dispersed phase, water-in-oil-in-water (w/o/w) or oil-in-water-in-oil (o/w/o) multiple emulsions can be generated. Previous work has employed a plethora of membranes, including ceramic, silicon, polytetrafluoroethylene and shirasu porous glass (SPG), among which SPG is the most extensively investigated and commercially available with the average pore diameter ranging from 0.1 to 20 μm [4,5]. In contrast to conventional emulsion generation methods, such as homogenisation, the size of emulsion droplets is mainly governed by the membrane pore size other than the break-up of droplets by abundant energy input. Depending on the process parameters (membrane type, average pore size and porosity, crossflow velocity, trans-membrane pressure and temperature) and formulation parameters (physicochemical properties and amount of emulsifier, dispersed and continuous phases), the mean size of emulsion droplets is usually

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proportional (ca. 1–12 times) to the membrane pore diameter [4]. As the size distribution of these membrane pores is engineered to be very narrow, emulsions with uniform (monodispersed) droplets are obtained. Using the uniform emulsions produced via ME, uniform particles that are spherical in shape can be created following the evaporation of volatile organic solvent. For example, once a polymer solution in an organic solvent with low boiling point such as dichloromethane is dispersed into aqueous continuous phase, an o/w emulsion is generated and the evaporation of solvent leads to the formation of polymer particles. Similarly, particles made of hydrophilic excipients, e.g. chitosan, can be made using a w/o emulsion template followed by the solidification of particles via the use of suitable crosslinking agents [6]. Employing a w/o/w multiple emulsion leads to the construction of hollow particles, i.e. capsules [5].

ME presents several advantages in terms of engineering pharmaceutical particles: (a) the particle size is primarily determined by the membrane pore diameter and thus can be easily controlled via the selection of appropriate membrane in designing a rational particulate delivery system [4]; (b) the particle size distribution is very narrow, i.e. the coefficient of variation of size is usually less than 0.2 and can even be limited to lower than 0.1 depending on the process and formulation factors [5,6], which contributes to the uniform membrane pore size, resulting in a physically stable uniform emulsion with minimised Ostwald ripening during the formation of particles; (c) because the particles are derived from emulsions, they often exhibit a spherical shape, and solid, hollow and porous particles can be produced [4]; (d) a large collection of carrier excipients is suitable for use, including naturally existing polymers (e.g. gelatin, albumin, alginate and chitosan), synthetic polymers (e.g. polyesters, polyanhydrides, and polyacrylates) and various types of cellulose [4,5]; (e) they are capable of loading hydrophilic and lipophilic small active agents together with therapeutic peptides and proteins [5,7,8]; (f) in contrast to the mechanical milling process with high energy input, ME as a benign process is less likely to affect the crystallinity of the material and thus the long-term drug chemical stability can be maintained [1,4].

However, current experimental data employing ME for inhalation delivery is very limited and all exclusively focused on generating rifampicin-loaded PLGA microparticles to improve tuberculosis treatment [9–13]. Although the idea of incorporating rifampicin into uniform repairable biodegradable carriers for deep lung targeting is excellent, such carriers (PLGA) are considered inappropriate for inhalation therapy, especially in cases of frequent dosing as a consequence of their relatively slow degradation rate and potential immunogenicity [14]. In addition, the degradation of PLGA produces lactic and glycolic acid, which can irritate the lungs [2]. That is why PLGA-based inhalation systems, despite being investigated intensively previously [1,3,15], have not been commercialised yet. Because only very few pharmaceutical excipients, e.g. lactose and mannitol, are approved by the regulatory agencies for inhalation therapy [1], recent investigations start to engineer inhalable pure drug (i.e. carrier-free) particles in the form of nanoparticle agglomerates [16,17] or relatively large porous drug particles (>5 μm) [18,19]. Further benefits of such an approach include the improved aeroionisation efficiency, rapid dissolution rate due to the increased particle surface area, avoidance of macrophage update due to the large particle size, and, hence, potential sustained drug release. Nevertheless, all these studies heavily relied on spray-drying that is hard to manipulate particle size and distribution.

On the contrary, ME holds promise in generating the above tailor-made uniform drug particles. For drug nanoparticle agglomerates, ME can employ membranes with low pore size (e.g. <1 μm) to control the particle size within nano- or submicron-range. For example, Wei *et al.* successfully prepared uniform poly(lactide) submicron particles (300–700 nm) using SPG membrane [20]. Yanagishita *et al.* generated polymer nanoparticles (80 nm), and submicron particles (200–750 nm) utilised ordered a series of highly ordered anodic porous alumina membranes [21]. Subsequent agglomeration of nanoparticles can be achieved via the addition of flocculating agents, and finally these agglomerates are collected after spray-drying or freeze-drying. To date, a range of active agents has been formulated as agglomerates, including budesonide [17], nifedipine [22], paclitaxel [23], ciprofloxacin [24], diatrizoic acid [25], insulin [16] and bovine serum ablumin [26], and very encouraging results, e.g. enhanced dissolution and improved aerosolisation, have been shown in these investigations. Engineering inhalable large porous drug particles (>5 μm) originated from the pioneer work of Edwards *et al.* in 1997 [3] in which both insulin and testosterone-loaded porous polymer particles showed significant boost of drug systemic bioavailability compared to the nonporous control particles. After this, a plethora of work has been done in this topic, among which some still employed carriers such as PLGA [27–29], whist others used carrier-free large porous microparticles [18,19]. ME is also capable of producing such porous drug particles. For instance, a pore-forming agent, e.g. ammonium carbonate, is dissolved in the internal aqueous phase, which emulsified with the drug-containing volatile organic phase forming a w/o emulsion. Then, driving the above emulsion through a suitable membrane leads to the generation of a w/o/w emulsion. With the removal of organic solvent and the pore-forming agent, porous drug microparticles can be made. Although such work has not been seen in the literature previously, it would be highly advantageous in pulmonary delivery as the particle

size and size distribution of drug particles can be precisely controlled to achieve optimum aerosolisation performance, which is hard to manipulate in conventional particle engineering methods such as spray-drying.

In spite of the above benefits of ME in engineering inhalable particles, there are still some limitations for this method. First, when generating drug nanoparticles via ME, membranes with very small pore size have to be employed. Due to this, the trans-membrane flux (i.e. the amount of drugs across the membrane within unit time and area) is quite low, and the particle production process is time-consuming. This might present a barrier for scale-up production. Second, the ME-engineered particle generation involves the use of volatile organic solvents to form either an o/w or w/o/w emulsion. The use of organic solvent is not environmentally friendly; the solvent residue is also hazardous to the lung and has to be removed thoroughly. Finally, ME-based particle generation method is only suitable for hydrophobic active agents because the drug has to be dissolved in the organic phase forming an emulsion with an aqueous phase. It shows poor capability to manufacture particles of hydrophilic drugs and therapeutic peptides and proteins without using any carrier excipients.

To sum up, it is anticipated that uniform large porous drug microparticle or nanoparticle aggregation generated by ME would be an efficient inhalation delivery system due to the superior aerosolisation and targeting capability despite the lack of experiment data currently. Future work on particulate inhalation delivery should pay more attention to these tailor-made pure drug particles. Particularly, the production of pure anti-tuberculosis drug particles with an aerodynamic size of ca. 2 μm would be a great advance for improving tuberculosis treatment by reduced dose and systemic side-effects.

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