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Continuous and sustainable granulation of nanopharmaceuticals by spray coagulation encapsulation in alginate

Kunn Hadinoto *, Yue Yang

School of Chemical and Biomedical Engineering, Nanyang Technological University, 637459, Singapore

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ABSTRACT

Nanopharmaceuticals (NPs) have emerged as an attractive formulation strategy for bioavailability enhancement of poorly soluble drugs. Their oral solid dosage form preparation requires them to undergo granulation before they can be processed into tablets. Existing NP granulation methods (e.g., spray drying, spray granulation), however, are lacking in sustainability due to their high energy expense and low mass efficiency. Herein we developed a one-step continuous NP granulation process via encapsulation by spray coagulation (ESC) in alginate, which transforms the NP immediately upon their preparation, thus removing the need for NP recovery prior to granulation, resulting in a highly sustainable process. Moreover, unlike spray-dried NP granules, the ESC-prepared granules are readily compacted into tablets owed to their larger size, thus further enhancing the overall sustainability of the solid dosage form preparation. Crystalline fenofibrate nanoparticles prepared by confined impinging jet crystallization were used as the model NP. Granules containing 25% NPs by mass with size $\approx 300 \pm 100$ μm were successfully prepared at >80% yield. The NPs maintain their fast dissolution (relative to native microcrystalline fenofibrate) after granulation. The tableted NP granules, having uniform dosage, exhibit similar drug release profiles as the free granules indicating complete granule disassociation from the tablets.

1. Introduction

Nanopharmaceuticals (NPs), defined as drug particles prepared in the nanoscale, have recently emerged as a highly promising formulation platform for bioavailability enhancement of poorly water-soluble drugs, which represent a vast majority (>60%) of newly discovered drugs due to the increasingly complex chemistry of these drugs (Serajuddin, 2007). The bioavailability enhancement capability of NPs is attributed to their high surface area to volume ratio that leads to their higher dissolution velocity in comparison to that of conventional drug microparticles (Keck and Muller, 2006). NPs have also found wide-ranging applications in targeted drug delivery attributed to their ability to overcome various biological barriers (Alonso, 2004).

In order to deliver NPs orally, which represents the most common route of drug delivery, the NPs must undergo a granulation process in which they are transformed into microscale nanocomposite granules ($\sim 10^2$ μm), before they can be processed into the traditional oral solid dosage form (i.e., tablets). Upon their administration into the body, the NPs must be effectively liberated from their granulated structures for full realization of their therapeutic potential. Granulation of NPs, however, represents a highly challenging task due to their small size that makes their physical handling in the dry powder state extremely difficult. As a result, conventional granulation methods applicable for drug microparticles, such as low shear wet granulation and fluid bed granulation, are not suitable for NPs due to the expectedly low mass and energy efficiencies (i.e., poor sustainability) (van Ommen et al., 2012).

Spray drying represents the most straightforward granulation method for NPs as it enables direct transformation of the aqueous NP suspension to dry granules, hence evading the issue of difficult physical handling of dry powder NPs (Ho and Lee 2012; Wang et al., 2012). However, spray drying is limited in the size of granules that it can produce ($\sim 10^1$ μm) (Vehring, 2008), thereby the spray dried granules must be further granulated, typically by fluid bed granulation, to produce granules sufficiently large for tableting

Abbreviation: AV, acceptance value; CIJC, confined impinging jet crystallization; DLS, dynamic light scattering; DSC, differential scanning calorimetry; ESC, encapsulation by spray coagulation; NP, nanopharmaceutical; PXRD, powder X-ray diffraction; SDS, sodium dodecyl sulfate; SEM, scanning electron microscope; USP, United States Pharmacopeia.

* Corresponding author. Tel.: +65 6514 8381; fax: +65 6794 7553.
E-mail address: kunnong@ntu.edu.sg (Y. Yang).

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(Li et al., 2011). The two-step granulation process thus makes spray drying unattractive from the energy sustainability perspective. Furthermore, the high temperature operation of spray drying rules out its application for thermally labile drugs.

Another granulation method that evades physical handling of dry powder NPs is spray granulation. In this method, the NP suspension is sprayed onto fluidized microparticles acting as a granulation substrate to produce granules in which the NPs are physically adsorbed onto the microparticle substrate, facilitated by the use of binder materials (Bose et al., 2012; Lv et al., 2014). The drawback of spray granulation is in its intricacy, where the characteristics of the granules produced are influenced by numerous parameters (both of the process and material's), rendering the process difficult to control, resulting in high batch-to-batch variations, hence a low mass efficiency (Poutiainen et al., 2012).

A less intricate alternative to the spray granulation is to carry out the physical adsorption of the NPs in the aqueous state using electrostatics as the driving force (Yang and Hadinoto, 2013), followed by a drying step. This method, however, faces the risks that the NPs undergo transformation during the wet adsorption step, resulting again in a low mass efficiency. Furthermore, it requires a sufficiently large electrostatic driving force between the NPs and the granulation substrate to be effective, which may not be feasible for all NPs. Thus, it is clear that existing granulation methods for NPs are lacking in either their sustainability (i.e., mass and energy), or wide-ranging applications.

Herein we aim to develop a new granulation method of NPs by encapsulating them in alginate microparticles prepared by spray coagulation, followed by a drying step. While spray coagulation of alginate has been commonly used to prepare alginate microparticles encapsulating therapeutic compounds (Tapia et al., 2008; Tu et al., 2005), to the best of the authors' knowledge, the said method has never been utilized to encapsulate NPs intended for their granulation. Alginate is used as the encapsulating materials because it has been widely used as binders and disintegrants in tablet preparation (Liew et al., 2006). Nanoparticles of a BCS Class II anti-cholesterol drug, fenofibrate, known for its poor aqueous solubility that limits its oral absorption is used as the model NP.

Similar to the existing NP granulation methods, the method of encapsulation by spray coagulation, or ESC in short, does not require physical handling of the dry powder NPs. However, unlike spray drying, the ESC method enables a one-step granulation process, whose products are ready for tableting, resulting in better energy sustainability. In contrast to spray granulation, the ESC method is not at all intricate, thus a better mass efficiency is anticipated. Lastly, unlike the wet electrostatic adsorption method, the ESC method is applicable to most NPs owed to its simpler operating principles.

Another sustainability feature of the ESC method is the continuous mode of the granulation process, whereby the NPs are immediately granulated upon their preparation, therefore eliminating the mass and energy expenses required to recover and purify the NPs prior to the granulation step. To facilitate the continuous operation mode, the NPs are prepared by a bottom-up approach via confined impinging jet antisolvent crystallization (Panagiotou et al., 2009), instead of the conventional top-down approach by wet milling, as the latter requires separate recovery and purification of the NPs (Knieke et al., 2013). Furthermore, besides enabling the continuous operation mode, the confined impinging jet crystallization also results in a high mass efficiency of the NP preparation as demonstrated later.

In addition to the ESC method development, another objective of the present work is to examine, in comparison to the raw NPs, the *in vitro* drug release profiles from the NP granules in their free and tableted powder forms. These results will serve as indicators for how effective the NPs are liberated from their granulated and compacted forms. Furthermore, physical characteristics of the granules important for tableting (i.e., size, powder flowability, tap density), NP loading, dosage content uniformity, and production yield as the indicator for mass efficiency are examined. The results are compared with NP granules prepared by spray drying and wet electrostatic adsorption.

2. Materials

The model NP (i.e., fenofibrate, FB), the NP's surfactant stabilizer (i.e., sodium dodecyl sulfate, SDS), and the capsule materials (i.e., alginic acid sodium salt) were obtained from Wako Pure Chemical (Japan), Sigma–Aldrich (USA), and Alfa Aesar (USA), respectively. The coagulating agent (i.e., calcium chloride, $CaCl_2$) and the solvent (i.e., ethanol) were obtained from Merck Millipore (USA). The materials used to prepare the granulation substrate in the wet electrostatic adsorption method, i.e., high molecular weight chitosan (310–375 kDa, 75–85% deacetylation) and glacial acetic acid, were purchased from Sigma–Aldrich (USA), while the crosslinking agent (i.e., sodium tripolyphosphate (TPP)) was obtained from Alfa Aesar (USA). Phosphate buffer saline (PBS, pH = 7.4) and Tween 80 for the *in vitro* release study were purchased from Sigma–Aldrich (USA).

3. Methods

3.1. Preparation and characterization of fenofibrate nanoparticles

The FB nanoparticles were prepared in a confined impinging jet crystallization (CIJC) reactor built following the setup of Siddiqui et al. (2009). The reactor was made of stainless steel with internal

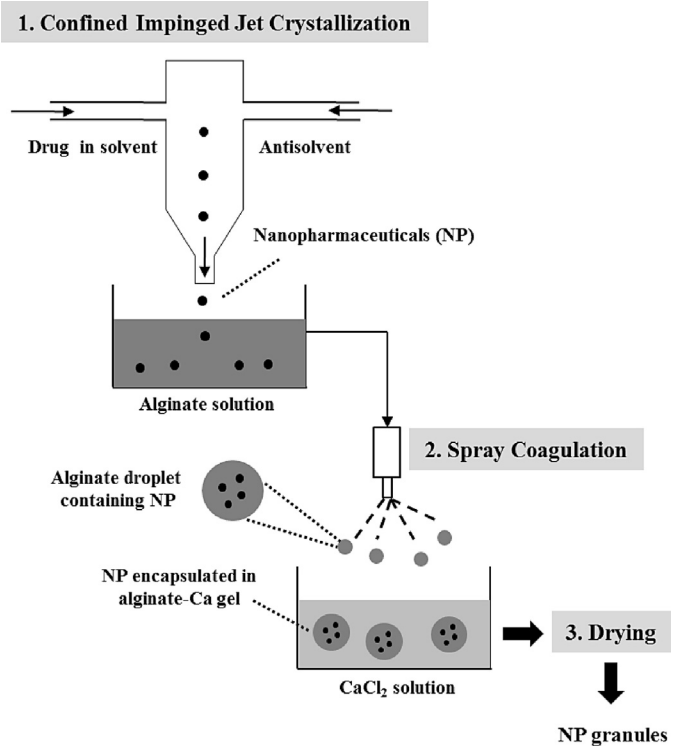

Fig. 1. Schematic of the continuous granulation process of nanopharmaceuticals (NPs), where the NPs upon their production in the CIJC reactor are immediately encapsulated in alginate microparticles by spray coagulation in $CaCl_2$, followed by drying to produce dry powder NP granules.