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Preparation of sustained-release coated particles by novel microencapsulation method using three-fluid nozzle spray drying technique

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ABSTRACT

We prepared sustained-release microcapsules using a three-fluid nozzle (3N) spray drying technique. The 3N has a unique, three-layered concentric structure composed of inner and outer liquid nozzles, and an outermost gas nozzle. Composite particles were prepared by spraying a drug suspension and an ethylcellulose solution via the inner and outer nozzles, respectively, and mixed at the nozzle tip (3N-PostMix). 3N-PostMix particles exhibited a corrugated surface and similar contact angles as ethylcellulose bulk, thus suggesting encapsulation with ethylcellulose, resulting in the achievement of sustained release. To investigate the microencapsulation process via this approach and its usability, methods through which the suspension and solution were sprayed separately via two of the four-fluid nozzle (4N) (4N-PostMix) and a mixture of the suspension and solution was sprayed via 3N (3N-PreMix) were used as references. It was found that 3N can obtain smaller particles than 4N. The results for contact angle and drug release corresponded, thus suggesting that 3N-PostMix particles are more effectively coated by ethylcellulose, and can achieve higher-level controlled release than 4N-PostMix particles, while 3N-PreMix particles are not encapsulated with pure ethylcellulose, leading to rapid release. This study demonstrated that the 3N spray drying technique is useful as a novel microencapsulation method.

1. Introduction

Controlled-release particles with smaller particle sizes have recently become more desirable, as small particles are more likely to distribute homogeneously in the gastrointestinal tract than large particles (Davis et al., 1986; Meyer et al., 1988; Clarke et al., 1993), thus reducing the variation in bioavailability and the risk of toxicity caused by local high drug concentrations. In addition, the application of controlled-release fine particles to the manufacture of high-performance orally disintegrating tablets (ODT) or tablets that have both rapidly disintegrating and modified-release properties is expected. Because ODT must disintegrate in the oral cavity, a pleasant feeling in the mouth after disintegration is an important criterion. Thus, controlled-release particles applied to ODT should be smaller than 200 μm in order to decrease particle roughness in the mouth (Mizumoto et al., 2008; Maeda et al., 2011). Furthermore, it is desirable to design controlled-release particles to be as small as possible, since fine particles are less subject to damage by compression and exhibit higher compactability than course particles, and this can reduce the problems in preparing ODT containing functional particles as described previously (Kondo et al., 2011). However, there are few reports on fine-particle coating techniques for the manufacture of controlled-release particles smaller than several tens of microns (Ichikawa et al., 1997; Watano et al., 2004). We have therefore focused on microencapsulation technology through spray drying, which can yield functional particles of the range from several microns to several tens of microns.

Microencapsulation by spray drying involves a common solvent in which two different materials are dissolved or suspended being sprayed and dried to produce composite particles composed of a core of one material and a shell of another, and is used in the pharmaceutical (Vehring, 2008; Sollohub and Cal, 2010), food (Gharsallaoui et al., 2007) and inorganic fields (Nandiyanto and Okuyama, 2011). In the pharmaceutical industry, microencapsulation technology is utilized to mask the taste (Yajima et al., 1996; Mizumoto et al., 2008) or modify the release (Año et al., 2011; Rattes and Oliveria, 2007) of pharmaceutical drugs, to stabilize protein conformation (Adler et al., 2000; Elversson and Millqvist-Fureby, 2006) and to improve the dispersibility of inhalational powders (Rabbani and Seville, 2005; Lechuga-Ballesteros et al., 2008). However, microencapsulation by spray drying is limited by the solubility and diffusional coefficient of the materials, the formulation of spray fluid and drying conditions, because coating agents in droplets move to the interface between the droplets and air, and

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are rapidly precipitated by solvent evaporation to form a shell, resulting in the encapsulation of other materials (e.g. drug) with the coating agent (Iskandar et al., 2003; Vehring, 2008). In addition, conventional spray nozzles (two-fluid and rotational nozzles, etc.) can spray only one solvent, in which both coating agent and drug are dissolved or suspended. This suggests that microencapsulation by conventional spray drying methods is unsuitable for preparing microcapsules that can distinguish completely between the shell and core, and would therefore require large amounts of coating agents to gain the desired function.

The three-fluid nozzle (3N) has a unique, three-layered concentric structure that consists of inner and outer liquid passages and an outermost gas passage, and can therefore spray two different solvents separately, overcoming the problems described above. Furthermore, the inner and outer liquid passages are individually connected with the center and peripheral nozzles, which may allow a solvent sprayed via the outer peripheral nozzle to coat another solvent sprayed via the inner center nozzle during a very brief atomizing process. Thus, the 3N spray drying method is expected to be a novel microencapsulation technique. On the other hand, the four-fluid nozzle (4N), which has two liquid and two gas passages, has been utilized to prepare microparticles containing submicron-size polymers by anti-solvent effects (Ozeki et al., 2006; Mizoe et al., 2007), to improve drug solubility (Chen et al., 2004, 2007) and to design the matrix microparticles that modified the release profile (Chen et al., 2006a,b). This nozzle, which can spray two different solvents separately, was used as a reference for the 3N.

In this study, we attempted to prepare sustained-release coated particles by microencapsulation technique using 3N spray drying. A drug-phase fluid containing the model drug and a polymer-phase fluid containing ethylcellulose from a water-insoluble polymer were used. The drug-phase and polymer-phase fluids were sprayed via the inner center nozzle and outer peripheral nozzle, respectively, to produce composite particles. The obtained particles were characterized by evaluation from physicochemical and pharmaceutical perspectives. Furthermore, to investigate the microencapsulation process by this approach and its usability, composite particles of the same formulation were prepared using three spray drying methods based on different mixing patterns for the drug-phase and polymer-phase fluids. The first method used the above-mentioned system, in which the two-phase fluids are separately sprayed via the concentric two-layer liquid nozzles of the 3N, and are mixed at the nozzle tip. In the second method, the two-phase fluids are separately sprayed via the two face-to-face liquid nozzles of the 4N, and are then mixed at the nozzle tip. In the third method, a one-phase fluid homogeneously mixed with the two-phase fluids is sprayed via the 3N. The characteristics of composite particles obtained by these methods were compared.

2. Experimental

2.1. Materials

Ethenzamide (ETZ) (API Corporation Ltd., Osaka, Japan) was used as the model drug. Hypromellose 2910 (HPMC) (TC-5 S, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) was used as a suspending agent. Ethylcellulose (EC) (Ethylcellulose 10, Wako Pure Chemical Industries Ltd., Osaka, Japan) was used as a sustained-release coating agent. All other chemicals and solvents were of analytical reagent grade.

2.2. Preparation of composite particles

Composite particles were prepared using a spray drier (Micro Mist Dryer MDL-050B, Fujisaki Electric Ltd., Tokushima, Japan) equipped with the 3N or 4N. Schematic diagrams of these nozzles are shown in Fig. 1. The 3N has a unique, three-layered concentric structure that consists of a center nozzle (inner liquid passage), a peripheral nozzle (outer liquid passage), and an air nozzle (outermost gas passage). Two spray fluids are individually provided via the center and peripheral nozzles. The spray fluid provided via the peripheral nozzle is accelerated on the outside of the center nozzle by compressed air supplied from the air nozzle. The accelerated spray fluid and the other spray fluid provided via the center nozzle collide and are mixed at the tip of the center nozzle, and are then atomized by compressed air. Meanwhile, the 4N, which consists of two liquid passages and two gas passages, has been reported in previous studies as being able to separately spray two spray fluids similarly to the 3N. Two spray fluids provided via the two liquid nozzles are withdrawn on the acceleration zone of nozzle edge by compressed air supplied through the two gas passages. The two accelerated spray fluids collide and are mixed at

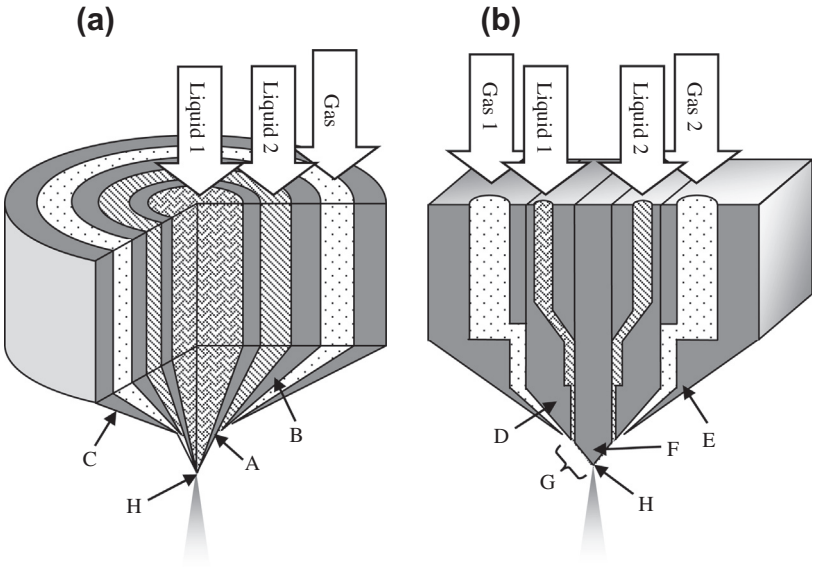

Fig. 1. Schematic diagrams of (a) three-fluid nozzle and (b) four-fluid nozzle. (A) Center nozzle, (B) peripheral nozzle, (C) air nozzle (3N), (D) liquid nozzle, (E) air nozzle (4N), (F) nozzle edge, (G) acceleration zone, (H) collision point.