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Influence of parallel nozzle electroencapsulation parameters on microcapsule properties – A case study using the Taguchi robust design method

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ABSTRACT

The production of microcapsules by electrospraying two immiscible liquids from oppositely charged parallel nozzles and the subsequent microcapsule collection constitute an electroencapsulation process influenced by numerous parameters. The electroencapsulation parameters include the liquid properties, *e.g.* bulk liquid conductivity K, viscosity η, density ρ, and surface tension γ; the electric field, gravity field, and the electrospraying and collection geometries; and the atmospheric properties. In the present work, NaI-doped glycerol was used as core liquid, with an optional payload of dispersed thermally carbonized porous silicon nanoparticles (PSi). Chloroform with dissolved Eudragit E 100 cationic copolymer and dispersed talc particles as an anti-tacking agent was used as shell liquid. The influence of varying ten electrospraying parameters (liquid flow rates Q_i, electrospraying voltages $|U_i|$ and polarity, solid concentrations, and temperature T) within the cone-jet mode regime on the structure and yield of microcapsules produced by parallel nozzle electroencapsulation was investigated simultaneously using the Taguchi robust design method. Of the investigated parameters, the most important were found to be NaI concentration and T, both influencing the core liquid conductivity; and the liquid flow rates. The Taguchi experiment and additional results suggest that optimally, the parameters affecting liquid conductivities should be set for a coarse atomization current balance when using a maximal shell liquid flow rate. Then, the core liquid flow rate can be adjusted for best process efficiency.

1. Introduction

Electrostatic atomization (*electrospraying*) is the method of breaking up a liquid into a jet of charged droplets by electrical forces. A typical basic electrospraying setup consists of a conducting nozzle and a ground electrode with a controllable potential difference ΔU between the two, generating an electric field that powers the electrospraying process. A liquid (of a suitable conductivity and viscosity) to be electrosprayed is fed via the nozzle to the electric field. Electrospraying is often conducted in the stable *cone-jet mode*, which requires the applied electric field strength to lie within a specific range. While in the cone-jet mode, the liquid apex outside the nozzle assumes a stable cone shape (*i.e.* Taylor cone) due to a force balance at the liquid surface. At the tip of the Taylor cone, the electrical forces overcome the liquid surface tension and a steady jet emerges, breaking into droplets. The droplets produced in the cone-jet mode can be extremely small and monodisperse in size, and they repel one another due to each carrying a net electric charge of the same sign. Before droplet deposition or collection, excess solvent can be evaporated from the droplets, and they can be electrically neutralized. The electrospraying technique is used for the production and electrostatic deposition (ESD) of micro- and nanosized droplets, particles, and thin-films [1–4] in a diverse range of applications, including coating, painting, printing, insecticide spraying [5–8], as well as topical, oral and inhalation drug delivery [9,10].

It is not uncommon for promising drug molecule candidates to exhibit poor physicochemical properties that restrict their bioavailability in oral administration. Such traits include the slow dissolution rate, low water-solubility, poor gastrointestinal (GI) tract permeability, and high first-pass metabolism of the drug [11–14]. Electrospraying can be utilized in a number of ways to help improve the bioavailability of orally taken drugs. Firstly, the solid state (*i.e.* crystallinity and crystal form), particle size and porosity of electrosprayed drug particles can be controlled to some extent by adjusting the electrospraying parameters, and consequently, electrospraying can be used to produce very small amorphous drug particles of high specific surface area in order to improve the drug dissolution rate [15–17]. Furthermore, electrospraying pharmaceutical materials could potentially lead to the discovery of new drug crystal forms with unprecedentedly low lattice energies, and thus

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increased intrinsic dissolution rates, since a novel drug polymorph produced by electrospraying has already been reported [18]. Secondly, by using electrospraying, pharmaceutical materials can be encapsulated as molecular, amorphous or nanocrystalline solid dispersions in drug delivery micromatrix particles. The matrix consists of a biodegradable polymer or other solid which is soluble in the electrospraying solvent, and the physical confinement of the drug can retain the disordered state of the drug solid dispersion during greatly extended periods of time. The drug release conditions can be controlled by choice of the matrix material to minimize unnecessary exposure to the harsh conditions of the GI tract, and the dissolution rate of the released drug can be improved tremendously because of its disordered state [11,19–21]. Finally, drugs (or other payload materials) can be encapsulated in shell-core structured microcapsules, by electrospraying two immiscible liquids using a dual-capillary electrospraying system (co-axial or parallel capillaries) [2,22–24]. A shell-core type structure presents more versatile design possibilities for the loading and release of pharmaceutical materials or other types of payload [2,22,24,25], or assembly of multistage release composite carrier systems [23,26]. An encapsulation process involving electrospraying is called *electroencapsulation*, due to the employment of electrical forces [2,23].

In the present work, the parallel capillary electroencapsulation process was investigated using Eudragit E 100 cationic copolymer and glycerol as model shell and core base materials, respectively. The effects of ten electrospraying parameters (*control factors*) – liquid flow rates Q_i, electrospraying voltages $|U_i|$ and polarity, solid concentrations, and temperature T – were investigated on the properties of produced microcapsules and the process yield (by component). As compared to a full factorial analysis, the complex task was approached by performing a single low resolution experimental arrangement, the design of which utilized orthogonal arrays (OAs, a part of Taguchi methods) [27–29]. With preset control factor levels, three series of 12 electroencapsulation trials were conducted using control factor level combinations in accordance to the selected two-level L12 OA. The control factors determined the compositions, charge distributions and size distributions of the electrosprayed core and shell droplet jets, and subsequently the corresponding capsule properties. The production rate, size distribution and composition of the produced microcapsules were measured for each experiment, and the influence of the control factors on the process yield and capsule properties were assessed by response and signal-to-noise (S/N) ratio analysis. Based on the analysis and confirmation experiments, optimal control factors were obtained for improving the overall process efficiency and yield, and in particular for the core (payload) component. The optimal value of core liquid flow rate was refined in an additional experiment. Finally, based on the obtained results, initial optimization steps for any similar electroencapsulation setup were suggested.

2. Materials and methods

2.1. Materials

Eudragit E 100, a cationic copolymer which is water-soluble below pH 5.0, was received from Evonik Industries (Germany). Analytical-grade glycerol (99.9% purity) was obtained from MP Biomedicals (Solon, OH). Analytical-grade chloroform (99.0% purity) and KI salt were obtained from Merck KGaA (Germany). Talc was received from Ciba Specialty Chemicals Oy (Finland), and ground into fine (< 53 μm) particles. Thermally carbonized porous silicon (TCPSi) nanoparticles with a hydrodynamic diameter (Z-average) of 147.0 nm and polydispersity index (PdI) of 0.109 were manufactured in our laboratory, using a method reported elsewhere [30–32]. The Si wafers used for the TCPSi nanoparticle fabrication were purchased from Siegert Wafer GmbH (Germany). Polystyrene Petri dishes of 140 mm diameter were purchased from VWR (USA).

2.2. Microcapsule production by dual-capillary electrospraying

In this work, chloroform (with surface tension $\gamma_s = 0.027$ N/m) was used as the shell liquid base solvent, and Eudragit E 100 polymer was dissolved to the shell liquid [33]. Talc was used as an anti-tacking agent in the shell liquid. Glycerol ($\gamma_c = 0.063$ N/m) was used as the core liquid base solvent, and a model payload of PSi nanoparticles was optionally dispersed to the core liquid [33]. Additionally, NaI was dissolved to the core liquid to enhance its conductivity K. The shell and core liquids were immiscible, and mutually wettable. The concentrations of Eudragit E 100 (C_{pol}), talc (C_{talc}), PSi (C_{PSi}) and NaI (C_{NaI}) used in this work are discussed in Chapter 2.8.1.

The electroencapsulation setup is shown schematically in Fig. 1. The shell and core liquids were electrosprayed simultaneously, using a pair of nozzles which were angled 20° relative to the vertical and held at oppositely signed high potentials U_s and U_c, respectively (Fig. 1a). The potentials were generated using two high-voltage DC-DC converters (Spellman MM-series, U.K.) which were regulated by a shared low-voltage (12 V) control circuit. The shell and core liquid flow rates Q_s and Q_c were controlled using a pair of syring pumps (New Era Pump Systems, Inc. NE-501 model, U.S.A.). For both electrosprays, to shape the electric field, the nozzle crossed the center of an equipotential circular surface from which a parallel ground ring with a thickness of $c = 2.0$ mm and a central hole of diameter $Ø = 12.0$ mm was suspended at a distance of $a = 10.0$ mm apart (Fig. 1a–c, suspension frame not shown). For both nozzles, the nozzle tip was positioned $h = 4.0$ mm above the surface level of the ground ring (Fig. 1b–c). As seen from the simulated electric field and equipotential lines (Fig. 1b, Comsol 4.3b software, $U_s = +3.25$ kV, $U_c = -3.77$ kV), a roughly homogenous electric field was generated in the area between the circular high potential surface and the ground ring surface. The electric field was much weaker below the grounded discs, so the Coulombic interactions between electrosprayed droplets were of comparatively much greater significance to the droplet paths in that area. The imbalance between the absolute potentials $|U_s|$ and $|U_c|$, necessary to electrospray the two different types of liquids in this work, did not affect the electric field significantly below the ground rings. The typical shape, mutual attraction and combination of the electrosprayed, oppositely charged jets is seen clearly in the photograph shown in Fig. 1a and b, taken for an electroencapsulation process with chloroform (Eudragit E 100 concentration $C_{pol} = 150.0$ mg/ml) as the shell liquid, and pure glycerol as the core liquid.

Precision stainless steel dispensing tips (EFD, U.S.A.) were used as electrospraying nozzles. A nozzle of outer and inner diameters $d_o = 0.64$ mm, $d_i = 0.33$ mm was used for the shell liquid; and a nozzle of $d_o = 0.30$ mm, $d_i = 0.15$ mm was used for the core liquid. In Fig. 1d, a close-up photograph is shown of the core liquid nozzle tip, with Taylor cone and droplet jet visible, as glycerol with a NaI concentration $C_{NaI} = 0.50$ mg/ml is electrosprayed at $U_c = -3.75$ kV and $Q_c = 0.50$ ml/h. The electrospraying devices were mounted in a polyoxymethylene (POM) lid on the top of a grounded cylindrical steel chamber with an inner diameter of 210 mm and inner height of 1000 mm. For ventilation, a pipe was installed to the top surface of the electrospraying chamber, and the open bottom was elevated by 23 mm. The chamber was depressurizable and heatable. Heating was applied by a heating cable (Horst, Germany), coiled around the chamber and operated by a temperature control unit (Meyer-Vastus, Finland). The electrospraying jets were monitored through an opposite pair of observation windows in the upper part of the chamber (Fig. 1a). Compared to a previously used, smaller chamber design, the chamber used in this work allowed for a longer shell solvent evaporation time, and less material was observed to accumulate to the chamber walls [23]. This resulted in reduced necessity for heating or depressurization to enhance evaporation, and a possibility to improve capsule collection efficiency *CE* (Chapter 2.8.2).

The encapsulation process is shown schematically in Fig. 1e. The