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Analysis of cohesion forces between monodisperse microparticles with rough surfaces

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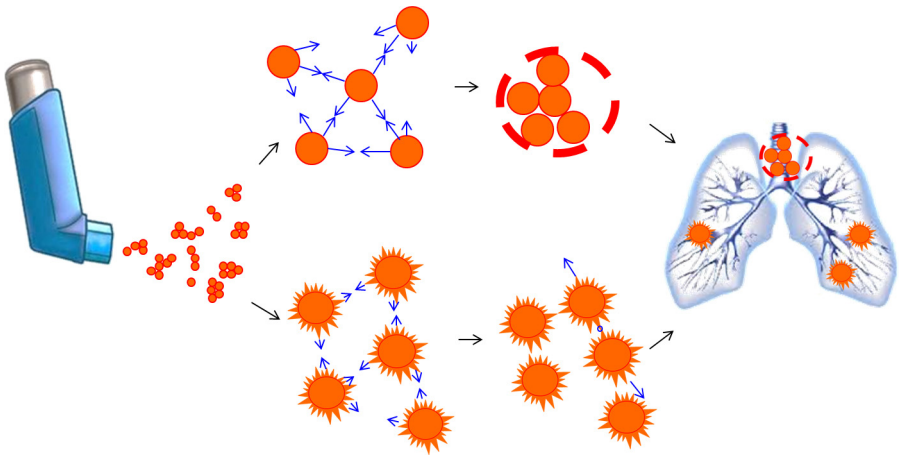
HIGHLIGHTS

- Monomorph microparticles facilitate colloidal probe microscopy for the determination of cohesion between microparticles.
- Roughness and crystal size are the main particle properties affecting cohesion.
- Cohesion can be reduced by controlling the process parameters which affect the particle formation process during drying.
- Cohesion models that incorporate surface roughness are best suited to predict cohesion between structured microparticles.

GRAPHICAL ABSTRACT



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ABSTRACT

This project investigated the impact of roughness, morphology and crystal size on the cohesion forces between microparticles of different size and shape. A chain of droplets with an initial diameter of about 70 μm was used for the production of monodisperse and monomorph microparticles in a diameter range of 0.7–17 μm. Droplets were composed of sodium nitrate and deionized water. Initial conditions of the process differed in temperature of the external environment, from 50 to 150 °C, and in solution concentration, from 5 to $5{\cdot}10^{-4}$ mg/ml. By varying these initial conditions, microparticles with different diameter and morphology were generated. Their root mean squared roughness was in a range from 2 to $6{\cdot}10^{-5}$ μm. Pull-off forces between particles of the same morphology and of different morphology were determined using colloidal probe microscopy. A wide range of cohesion forces was measured and was found to be affected primarily by the microparticle roughness. The utility of several theoretical cohesion models in predicting the experimental results was tested.

1. Introduction

Pulmonary drug delivery is an area of constant growth for research studies [1–5]. These studies focus on two main methods of delivery: inhalation and instillation. Drugs are most commonly

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Nomenclature

A	Hamaker constant [J]
α	Adhesiveness [N/m^2]
E	Young's modulus [Pa]
ε_i	Dielectric constant for solvent or solute
F	Cohesion force [N]
ν	Poisson's ratio
h	Planck's constant
H_o	Minimum distance between two microparticles [m]
γ	Surface tension [N/m]
γ_s	Surface tension of a solid smooth surface [N/m]
γ_l	Surface tension of a liquid [N/m]
k	Boltzmann's constant [m^{2}kg/s^{2}K]
L	Load normal force [N]
λ	Peak to peak distance [m]
μ	Dimensionless coefficient used to choose between DMT or JKR model
n_i	Refractive index of solute or solvent
θ_a	Advancing contact angle [°]
θ_r	Receding contact angle [°]
r	Radius of asperities [m]
R	Radius of microparticles [m]
R_q	Root mean square roughness [m]
$R_{q,i}$	Root mean square roughness for different scanning area i [m]
S	Contact area between two particles [m^2]
T	Temperature [K]
Δt_c	Crystallization window [s]
ω	Absorption frequency [rad/s]

delivered to the lungs through inhalation [6,7] due to its multiple advantages. The risks involved in inhalation are minimal compared to other techniques, such as liquid instillation [8]. In addition, inhalation is a non-invasive and often self-applied treatment [8,9]. The main disadvantage of drug inhalation, however, is inefficiency; a large portion of the drugs commonly does not reach the lungs [10,11]. This issue can be improved by using calculations and predictions to refine the delivery process. The predictions are based on the influence of the properties of drugs on their delivery location inside the respiratory tract.

Studies of pulmonary drug delivery have recently focused on the control of the main properties of drugs to improve the quality and the efficiency of their delivery [12]. Pulmonary drugs are commonly delivered to the lungs using microparticles [13]. The diameter of the microparticles is important for their deposition in the lungs; a range of 0.1–5 μm is suggested to allow the microparticles to reach the lungs [14]. While smaller particles easily reach the lungs and their alveoli [15], they may be exhaled again to some extent. Large particles may also reach the lungs and alveoli, if they have a suitable morphology [16].

Morphology is, thus, a property of the microparticles that can influence their delivery. Several studies improved knowledge of the relationship between morphology and delivery efficiency [17–19]. Morphology describes the shape and structure of the particle interface and interior; it includes parameters such as crystal size for particles composed of smaller crystals, and measures of surface roughness. The crystal size of composite microparticles is directly connected to their roughness; smaller crystal size tends to generate greater roughness [20]. This relationship depends on the material of which the microparticles are composed. The roughness can affect the delivery of the microparticles to the lung primarily by reducing the strength of cohesion between microparticles [5,16], thereby causing improved powder dispersibility and better aerosol properties [21,22].

The determination of cohesion forces between two microparticles is quite complicated. Firstly, interlocking of rough microparticles can occur randomly between any possible points of contact on the interface [23], increasing measurement variability. Secondly, it is more practically difficult to measure cohesion forces between two microparticles than between a microparticle and a flat surface [24,25].

Studies addressing the relationship between the properties of microparticles and their cohesion forces can be seen as a subdiscipline of particle engineering [26]. The main goal of particle engineering is to improve the properties of the microparticles. To achieve this, the process of producing the microparticles is studied. The microparticles used for pulmonary drug delivery are commonly produced via spray drying [27], a process that has the following advantages among others: low manufacturing cost, low loss of activity of chemicals, broad choice of solutions or suspensions, and control over fundamental properties of the final particles [28].

The process by which pulmonary drug microparticles are generated from solution or suspension droplets is called particle formation [29,30]. Two possible outcomes may result from the particle formation process: homogenous or core shell particles. In systems with crystalizing excipients or drugs the time at which the solute reaches saturation on the surface of the evaporating droplet is one of the critical time variables for the prediction of the particle formation process. A late time to reach saturation may produce solid particles [26,29], because insufficient time is left in the evaporation process for nucleation and crystallization. Another similar variable is the time for crystallization. This time variable indicates, for solutes with a tendency to crystallize, the moment at which sufficient supersaturation is reached such that one or more crystal nuclei may start to grow. The knowledge of this time variable facilitates the prediction of the morphology of final dried microparticles; if the time for crystallization occurs late in the evaporation process, particles smooth, amorphous and with a small crystal size may result.

The basis for the theoretical description of particle formation was provided by Vehring et al. [26] using an approach based on liquid phase diffusion in droplets evaporating with a constant evaporation rate. Different types of formation mechanisms were considered, depending on the nature of the solutes or suspended materials in the droplets. Boraey and Vehring [31] included new variables into the analysis, for example shell thickness or the void volume of the dried particles. The particle formation process for solutes undergoing crystallization is a topic of current investigations [32].

In order to describe the particle formation process, the evaporation sub-process [33] has to be studied. The evaporation of the solvent is the main part of the particle formation process [34]. Several experimental methods are available for understanding the evaporation process. Recent studies have focused on the monodisperse droplet chain method [35,36] because it overcomes many disadvantages of other commonly used methods. The monodisperse droplet chain is not affected by heat conduction through the support wire encountered in the method of suspending droplets on filaments. In addition, the monodisperse droplet chain is less affected by time constraints, encountered in the method involving a single levitated droplet evaporating in a quiescent environment or in a gas flow [37]. The piezoceramic dispenser is the most suitable choice for the production of microparticles with high homogeneity in their properties. In response to an input voltage pulse, the piezoceramic dispenser expands and then contracts to its normal size. Thus, acoustic waves are produced in the solution contained in the piezoceramic dispenser and droplets are generated with consistent ejection velocity and diameter [38].