BUILD-IT2023 Workshop
19-20 October, Rome, Italy

ENHANCED METHODOLOGY FOR DEVELOPING A SOFT SENSOR TO ESTIMATE SURFACE AREA AND ZETA POTENTIAL IN ADVANCED MANUFACTURING SYSTEMS

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Porous silica, with its unique structural and surface properties, has gained significant attention in the drug delivery field as a carrier material or a matrix for controlled and targeted drug release. Porous silica-based drug delivery systems offer high drug loading capacity, and protection of drugs. Silica-based excipients are commonly utilized to improve product performance due to the ease of modifying the silica surface through chemical reactions. The surface area and zeta potential of silica are critical factors in assessing the effectiveness of excipients. However, these critical quality attributes (CQAs) have to be measured using time-consuming offline methods. In this work, we have developed a quick method for estimating surface area and zeta potential of porous silica particles. We propose for the first time the use of dye adsorption and quick conductivity measurements combined with machine learning (ML) based soft sensor for estimating surface area and zeta potential. In order to adequately train the ML-based soft sensor, we have developed a phenomenological model and results obtained from it to complement available experimental data. The models, approach, and developed soft sensor presented will be useful in in-line CQAs estimation and will facilitate the development of decentralised 'Factory-in-a-Box' manufacturing of porous silica particles.

Keywords: *ML-based soft sensor, silica, excipient, surface area, zeta potential*

1. Introduction

Porous silica can be used to encapsulate drugs within its porous structure. The high surface area and large pore volume of silica allow for the efficient loading of drug molecules. The drug can be loaded into the pores through physical adsorption or by chemical conjugation [1]. Porous silica offers the advantage of controlled drug release. The porous structure allows for the diffusion of drugs out of the silica matrix in a sustained and controlled manner. By adjusting the pore size, pore volume, and surface properties of the silica, the release rate of the drug can be tailored to meet specific therapeutic needs [2, 3]. The surface area of silica particles in drug delivery systems significantly influences drug loading capacity, surface functionalization, drug release kinetics, interactions with biological systems, and stability. Understanding and optimizing the surface area is crucial for designing effective drug delivery platforms that can enhance therapeutic outcomes [1, 4]. A lower surface area may result in a slower release rate, which can be beneficial for sustained or controlled drug delivery. A larger surface area enhances the particle's ability to interact with target cells, improving bioavailability of drugs and internalization. The surface area of nanocarriers can be tuned based on synthesis methods for different drugs and targeting molecules [5]. The zeta potential of silica surface is another important surface property with a crucial role in drug delivery systems, especially those that utilize nanoparticles. Zeta potential refers to the electric potential difference between the surface of a particle and the surrounding fluid medium. It is a measure of the net electrical charge on the particle's surface. This potential arises from the adsorption of ions or charged molecules onto the particle surface, as well as the ionization of functional groups present on the particle's surface [6, 7]. surface area can indirectly influence zeta potential through factors like surface charge density or surface modification. For example, increasing the surface area of silica particles allows for more functional groups or surface modifications, which can alter the charge distribution on the surface and influence the resulting zeta potential [8, 9]. BET (Brunauer-Emmett-Teller) analysis, which is commonly used for determining specific surface area through gas adsorption, can be time-consuming due to the multiple steps involved in the measurement process [10]. Therefore, the use of soft sensor can be an excellent solution to solve this issue in the advanced manufacturing system. They are virtual sensors that estimate process variables or properties using mathematical models and available process data, eliminating the need for direct measurements. They can be employed to estimate CQAs such as surface area or other relevant parameters in real-time during manufacturing processes, providing timely information for process control and optimization [11, 12]. Overall, soft sensors based on machine learning (ML) tools play a crucial role in enabling real-time monitoring, control, adaptability, and estimations of CQAs to enhance operational efficiency within both digital twin and factory-in-a-box concepts. In this work, a methodology for developing a ML-based soft sensor for estimation of surface area and zeta potential is discussed with the aim of being used in advanced manufacturing.

2. Methodology

A stock solution of excipient was prepared using deionized water (DI) and a magnetic stirrer. The initial conductivity of the solution was measured. Various silica suspensions were prepared and sonicated. Through the addition of silica slurry to the excipient solution by syringe pump, the excipient within the solution underwent adsorption onto the porous silica particles, with the extent of adsorption being dependent on factors such as the surface area, zeta potential, and interactions between silica and excipient. The reduction in excipient concentration within the solution can be determined by measuring the conductivity of the solution. The achieved conductivity profiles were applied to develop the adsorption model and optimization of model parameters. By modeling excipient

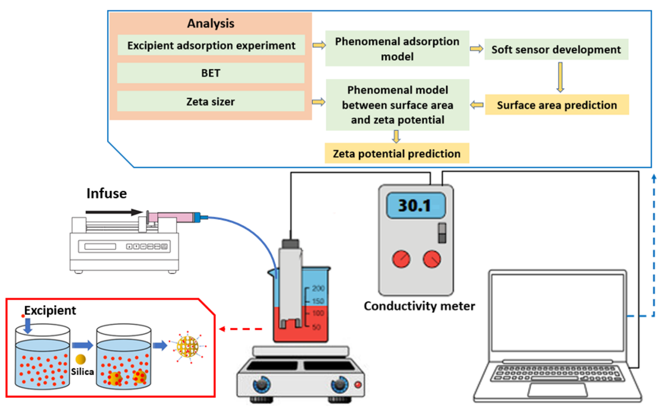

Figure 1: Concept of excipient adsorption experiment.

adsorption, a relationship between the concentration of dye and the surface area of silica can be established. This correlation enables us to predict various silica surface areas by considering the concentration of excipient. Since this relationship is grounded in physical principles, the data generated can be used to develop a soft sensor model, to provide highly accurate predictions. The initial differential equation governing the solute flux from the bulk to the liquid phase on the surface of the particle is directly proportional to the concentration difference between the bulk and the solute at the particle's surface in the liquid phase:

$$\frac{d(VC_D)}{dt}d = -Vk_{SL}\bar{a}(C_D - C_{Ds}). \tag{1}$$

Whereas V, k_{SL}, C_D, C_{Ds} and $\bar{a}$ are volume of solution, mass transfer coefficient, the concentration of dye in liquid, equilibrium concentration of excipient in liquid and surface of silica particles per volume of solution, respectively. The final adsorption model was achieved based on Eq. 1 and Langmuir isotherm model. The model-based profiles were applied for soft sensor training and development to estimate surface area. The predicted surface areas were adjacent to the real surface area and were used to estimate zeta potential with a proposed phenomenal model (a model based on surface charge density, surface area and zeta potential) between these two attributes. The soft sensor will be used for online estimation in bioinspired silica production process to control the CQAs.

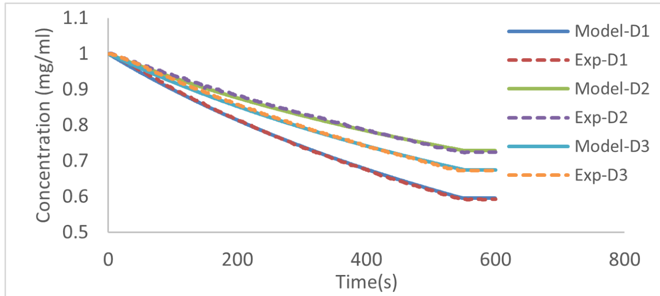

Figure 2: Comparison between adsorption experiment and model

3. Results

Outcome of this work will be practically useful for manufacturing process development and specially for characterizing any porous silica particles and developing a table top manufacturing of tailored silica for personalized medicine.

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