# Stable dispersion and prolonged dissolution of hydrophilic pharmaceutical achieved by room-temperature atmospheric pressure atomic layer deposition

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## SUPPLEMENTARY INFORMATION

#### 1. Experimental procedures

#### 1.1. Materials and chemicals

Diclofenac sodium (DCF –  $C_{14}H_{10}Cl_2NNaO_2$ ) was purchased from Auro Laboratories Ltd., India. Silicon tetrachloride (SiCl<sub>4</sub>, 99.8%, Merck, Germany) was used as the precursor and deionized water was used as the co-reactant for depositing SiO<sub>2</sub>. Both the precursor and the reactant (distilled water) were contained in stainless-steel bubblers.

### 1.2. Atomic layer deposition of SiO<sub>2</sub>

The deposition of SiO<sub>2</sub> was conducted in a home-built fluidized bed reactor ALD system (FBR-ALD), operating at atmospheric pressure as described in Fig. S1. This system is similar to the FBR-ALD system reported in other studies.<sup>1–3</sup> The reactor is a quartz column (30 mm/24 mm in outer/inner diameter and 500 mm in height) placed vertically on top of a vibration table, which can vibrate vertically with a frequency in the range of 7 – 50 Hz and an amplitude in the range of 1 – 3 mm (Fig. S1a). For each ALD experiment, 10 g of DCF powder were loaded into the reactor. The vibration was fixed at a frequency of 8 Hz and an amplitude of 3 mm. Throughout the deposition, a continuous flow of 1500 sccm (1.5 L·min<sup>-1</sup>) of compressed Argon (Ar, 99.999 vol.%) was introduced into the reactor using a separate gas line to fluidize the powder (Fig. S1b and Video S1).



**Fig. S1.** (a) A photograph of the quartz reactor placed on top of a vibration table; (b) a photograph of the reactor containing 10 g of the DCF powder fluidized under an Ar flow of 1500 sccm (1.5  $L\cdot min^{-1}$ ) with a vertical vibration at a frequency of 8 Hz and an amplitude of 3 mm.

A schematic drawing describing the operation of the FBR-ALD system is presented in Fig. S2. The reactor and the vibration table are indicated by the numbers (1) and (3), respectively. Number (2) indicates the thermocouple measuring the temperature inside the reactor. This thermocouple is inserted into the reactor through a port shown in Fig. S1b. The system consists of five gas inlets (i.e., five gas lines). For the deposition of SiO<sub>2</sub> on DCF, three gas lines are used. Gas line number (4) is only for introducing Ar with a constant flow rate of 1500 sccm throughout the coating process. Number (5) indicates the thermocouple and number (6) indicates the mass flow control (MFC) of this gas line. Numbers (7) – (11) indicate the SiCl<sub>4</sub> bubbler (7), the thermocouple measuring the temperature of the SiCl<sub>4</sub> bubbler (8), the SiCl<sub>4</sub> gas line (9), the thermocouple measuring the temperature of this gas line (10), and the MFC controlling the carrier gas through the SiCl<sub>4</sub> bubbler (11). Numbers (12) – (16) indicate the H<sub>2</sub>O gas line (14), the thermocouple measuring the temperature of the H<sub>2</sub>O gas line (15) and the MFC (16). Panel number (17) indicates

the gas control unit that controls the gas flow through the MFCs. Panel number (18) indicates the temperature control unit that controls the temperature of the bubblers, the gas lines, and the reactor. During the coating process, the operation of the system can be operated autonomously by WinCC programming.



Fig. S2. Schematic drawing describing the operation of the FBR-ALD system.

Each ALD cycle consisted of 4 steps:

- (1) Introducing the precursor (SiCl<sub>4</sub> vapour) with a flow of 50 sccm (0.05 L·min<sup>-1</sup>) for 15 s.
- (2) Purging the reactor with compressed Ar for 60 s with a flow of 1500 sccm (1.5 L·min<sup>-1</sup>).
- (3) Introducing the reactant ( $H_2O$  vapour) with a flow of 50 sccm for 60 s.
- (4) Purging the reactor with compressed Ar for 120 s with a flow of 1500 sccm.

The chemical reactions between SiCl<sub>4</sub> and H<sub>2</sub>O to form SiO<sub>2</sub> films in ALD are described in other studies.<sup>4,5</sup> The thickness of the coating layer is controlled by repeating the ALD cycle to a certain number. We note that the growth rate of SiO<sub>2</sub> was found to be around 0.08 nm/cycle,<sup>6</sup> which is close to the growth rate of 0.1 nm/cycle of the SiO<sub>2</sub> deposited at 40 °C reported by La Zara *et al.*<sup>7</sup> Therefore, with the number of ALD cycles of 50, the thickness of the SiO<sub>2</sub> is expected to be in the range of 4 - 5 nm.

Throughout the coating process, the temperature of the  $SiCl_4$  bubbler was maintained at 30 °C, while the H<sub>2</sub>O bubbler was heated to 45 °C to assist the vaporization of water. The gas lines from

the bubblers to the reactor were heated to 50 °C to prevent any condensation of vapours before entering the reactor. No heating was applied to the reactor.

## 1.3. Materials characterization and analysis

The surface morphology of the DCF powders was investigated by using a field-emission scanning electronic microscope (FE-SEM, HITACHI S4800). Energy dispersive X-ray spectroscopy (EDX) was used to investigate the elemental composition and mapping using the same system equipped with a HORIBA 7593-H detector.

The composition and chemical bonding state of the elements were investigated by X-ray photoelectron spectroscopy (XPS) using a Themo Fisher Scientific spectrometer equipped with a monochromated Al K $\alpha$  X-ray source (1486.7 eV). Survey scans were acquired in the spectral range of 0 – 1350 eV, with steps of 1 eV and pass energy of 200 eV. High-resolution scans of core-level spectra were acquired with steps of 0.1 eV and pass energy of 40 eV. To take into account the peak shift due to the charging effect, the C 1s peak of carbon at 284.8 eV was used to calibrate the peak position.

X-ray powder diffraction (XRD) was employed to investigate the crystalline structure of original material, and whether the SiO<sub>2</sub> coating was accompanied by any change in the sample. The XRD diffractograms were acquired using an PANalytical X'pert Pro diffractometer, equipped with Cu-K $\alpha$  anode ( $\lambda$  = 1.54184 Å). The scanning angle 20 was recorded from 10° to 50°.

To investigate the impact of  $SiO_2$  coating on the molecular structure of DCF, Fourier transform infrared spectroscopy (FTIR) was employed. The measurements were conducted using a Spectrum TwoTM spectrometer (PerkinElmer). For each measurement, approximately 2 mg of powder was spread onto a glass substrate, which was then pressed by a clamping arm of the device. FTIR spectra were recorded in the wavenumber range of  $500 - 2000 \text{ cm}^{-1}$ , with steps of  $1 \text{ cm}^{-1}$ .

## 1.4. Dissolution tests

Drug release was observed in an *in vitro* environment using phosphate buffer solution at pH of 6.8. This pH value simulates the condition in the duodenum, which is identified as the major absorption site of diclofenac sodium in the gastrointestinal tract.<sup>8</sup> In each experiment, 1.0 g of the powder was dispersed into 500 ml of *in vitro* environment, maintained at 37 °C and stirred at a constant speed of 50 rpm. 5 ml of media containing each sample was collected after 10, 20, 30, 45, 60, 90, 120, 180, and 240 minutes. Subsequently, each obtained sample was diluted in water by a certain ratio to be available for UV-VIS absorption mesurements using a Shimadzu 2600 UV-VIS spectrophotometer.

The absorption spectra were recorded in the spectral range of 220 - 340 nm. The intensity of the characteristic peak of DCF at 276 nm was used to determine the concentration of the dissolved DCF following the Lambert – Beer law.<sup>9</sup> The dissolution tests were conducted at least three times for each sample.

#### 2. Results

Fig. S3 shows SEM images of the initial DCF powder (a - b), and the DCF coated with SiO<sub>2</sub> for 25 cycles (c - d) and 50 cycles (e - f). The results show that the coating does not cause any considerable change in the morphological appearance of the drug.



**Fig. S3.** SEM images acquired with different maginifcations of the initial DCF powder (a - b), and the DCF coated with SiO<sub>2</sub> for 25 cycles (c - d) and 50 cycles (e - f).

Fig. S4 shows the XPS spectra of the uncoated DCF and the DCF coated with  $SiO_2$  for 50 ALD cycles. In the survey spectrum (Fig. S4a) of the uncoated DCF indicates the presence of the elements of DCF ( $C_{14}H_{10}Cl_2NNaO_2$ ), represented by the peaks of Na 2s, Na 1s, Cl 2p, Cl 2s, C 1s, N 1s, and O 1s. Several Auger peaks are also observed, as denoted in the figure (NaKL1, OKL2, OKL2, CKL2, and ClLM1).

After coating with SiO<sub>2</sub>, all the peaks of DCF are preserved, and two new peaks of the Si 2p and Si 2s appear. The high-resolution spectra of the O 1s and Si 2p core levels are shown in Fig. S4b and S4c, respectively. The O 1s spectrum of the uncoated DCF is best deconvoluted into three components with the peaks at binding energies of 531.7 eV, 532.8 eV and 535.7 eV. These peaks correspond to the chemical bonds between O and Na,<sup>10</sup> C,<sup>10</sup> and the oxygen in adsorbed H<sub>2</sub>O.<sup>11</sup> For the SiO<sub>2</sub> coated DCF, the peak of the O 1s spectrum considerably shifts to the higher binding energy side. The deconvolution of this spectrum results in also three components, which include the peaks represents the bond between O and Na, and the peak of the adsorbed H<sub>2</sub>O. The third peak at 533.2 eV is attributed to the chemical bond between O and Si.<sup>12</sup> This peak in conjunction with with the peak at 104.0 eV of the Si 2p spectrum (Fig. S4c) represent the SiO<sub>2</sub> state of the coating deposited film.



**Fig. S4.** XPS specra of the uncoated DCF and the DCF coated with  $SiO_2$  for 50 ALD cycles: Survey scan (a), O 1s (b) and Si 2p (c) core levels.



**Fig. S5.** EDX spectrum (a) of the uncoated DCF measured on the area shown by the SEM image (b); EDX elemental mapping of C (c), Na (d), Cl (e), N (f), O (g), and Si (h). Hydrogen was not detectable by our EDX measurements due to its light mass, whereas nitrogen was not detectable due to its low concentration. This element commonly require a minimum of ~2% to be detectable by EDX. Hence, the mapping in (f) presents the noise of the measurement. Similarly, no Si is detected in the EDX spectrum in (a), the mapping in (h) therefore also shows the noise level. This can be concluded based on the distribution which does not follow the morphology as observed for the mappings of other elements as well as the SEM image in (b).



**Fig. S6.** EDX spectrum (a) of the  $SiO_2$ -coated DCF for 25 ALD cycles measured on the area shown by the SEM image (b); EDX elemental mapping of C (c), Na (d), Cl (e), N (f), O (g), and Si (h). In this case, N was also not detectable, however, the presence of Si is clearly indicated in the EDX spectrum (a) as well as the EDX mapping in (h), which indicates a good uniformity of the distribution of the coating accross the measured area.

The X-ray diffractogram of the uncoated sample (Fig. S7a) indicates the crystalline nature of DCF, represented by peaks at the 2 $\theta$  values of 11.2°, 15.2°, 17.2°, 27.1°, and 27.9°, consistent with a previous report.<sup>13</sup> No significant changes in the diffraction peaks are observed for the coated samples, indicating that the ALD process did not alter the crystalline structure of the original material. The FTIR spectra (Fig. S7b) also exhibit the characteristic peaks of DCF, such as the C=O stretching at 1575 cm<sup>-1</sup>, C=C ring stretching at 1554 cm<sup>-1</sup>, C–Cl stretching at 746 cm<sup>-1</sup>, and the scissoring vibration of the CH<sub>2</sub> group adjacent to the carbonyl, with bands between 1453 cm<sup>-1</sup> and 1393 cm<sup>-1</sup>.<sup>13</sup> For the DCF coated with SiO<sub>2</sub> after 25 and 50 ALD cycles, all characteristic peaks of DCF are preserved, confirming that the coating process does not affect its molecular structure. However, a new peak arises at 1693 cm<sup>-1</sup>, which is commonly attributed to the C=O stretching vibration.<sup>14</sup> This could arise from the interaction between a carbon atom in the original material and an oxygen atom in newly coated SiO<sub>2</sub> layer.



**Fig. S7.** XRD diffractograms (a) and FTIR spectra (b) of the uncoated and  $SiO_2$ -coated DCF for 25 and 50 cycles.



**Fig. S8.** Photographs showing the dispersion of the DCF (uncoated and coated with  $SiO_2$  for 25 and 50 cycles) in water at different stages of the experiment: After the powder is transferred into water without shaking (a), approximately 3 minutes after the transfer withou shaking (b), after a tender shaking by hand (c) and 10 minutes after the shaking. It can be seen that upon transfering (pouring) into water, the uncoated powder immediately sinks to the bottom, while the  $SiO_2$  coated DCF can automatically disperse in water even without shaking. No observable change in the turbidity of the dispersion of the coated powder 10 minutes after the shaking, indicating a highly stable state of the dispersion.



**Fig. S9.** Photographs of (a) the initial DCF powder (uncoated), (b) and (c) the DCF powder coated with  $SiO_2$  by ALD after 25 and 50 cycles, respectively. The images clearly demonstrate that  $SiO_2$  ALD coating significantly reduces adhesion and agglomeration of DCF powder. This improvement can be due to surface modification that alters surface energy and electrostatic interactions, leading to enhanced flowability and reduced particle aggregation.

Fig. S10 shows the UV-VIS absorption spectra measured after different time intervals during the dissolution tests of the DCF powders. The intensity of the absorption peak at the wavelength of 276 nm is used determine to concentration of the dissolved DCF following the Lambert – Beer law,<sup>9,15</sup> in which the concentration C of the dissolved DCF at the time t is proportional to the absorbance A according to the formula:

$$A = \varepsilon b \mathcal{C} \tag{1}$$

in which arepsilon is the absorptivity of the molecule (DCF), b is the length of the light path.

It can be seen that, in all cases, the absorbance of the peak at 276 nm reach the maximum absorbance  $A_0 = 0.57$ , indicating that the coated DCF dissolved completely after the test. Hence, the maximum concentration of the dissolved DCF is related to  $A_0$  by the formula:

$$A_0 = \varepsilon b C_0 \tag{2}$$

From (1) and (2), we have:

$$\frac{C}{C_0} = \frac{A}{A_0} \tag{3}$$

Therefore, the plots of the ratio  $C_0$  as a function of the time t presents the dissolution behavior of the drug. This is presented in Fig. 3a of the manuscript.

The dissolution rate k can be determined from the first-order kinetic model, described by the equation:<sup>16</sup>

$$\ln (C_0 - C) - \ln (C_0) = -kt_{, \text{ or }} \ln \left(1 - \frac{C}{C_0}\right) = -kt$$
(5)

Therefore, by plotting the  $\ln\left(1-\frac{C}{C_0}\right)$  as a function of the time t, the slope of the linear regression (linear fitting) represents the dissolution rate k of the drug. This is presented in Fig. 3b of the manuscript.



**Fig. S10.** UV-Vis absorption spectra at different sampling time intervals of the uncoated DCF and the DCF coated with  $SiO_2$  for 25 ALD cycles (b) and 50 ALD cycles (c).

In the current work, the dissolution tests were conducted three times for each sample synthesized by three different experiments. The data plotted in Fig. 3 present the average values for three experiments, and the error bars represent the standard deviations of the data.

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