Slot-die coating as a versatile technique for microfabrication of buccal patches and oral drug delivery systems

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Clean-room based fabrication techniques are predominantly used for the manufacturing of microfabricated oral drug delivery systems. However, most of these fabrication approaches lack the possibility for scale-up with high reproducibility, thus causing a severe bottleneck for *in vivo* studies during the phase of research and development. Slot-die coating (SDC), a thin film deposition technique, could potentially be considered to bridge this gap by enabling the manufacture of microfabricated oral drug delivery systems. SDC is primarily used for preparation of continuous, highly uniform films in the 10^{-3} to 10^{-8} m thickness range [1] for various applications such as solar panels, capacitors, window coatings, battery applications among others. In the current study, we for the first time demonstrate the suitability of SDC for microfabrication of buccal patches and oral drug delivery systems, thus promoting a roadmap for scalable continuous manufacturing.

Oral drug delivery (ODD) is the most popular method for drug administration due to its ease of use, non-invasiveness, low cost and a high degree of patient compliance [2]. However, ODD faces serious challenges in the gastrointestinal (GI) tract, such as harsh acidic conditions in the stomach, poor penetration of active pharmaceutical ingredient (API) across the GI tract and the subsequent clearance of drugs, which may happen before drug absorption at the intestinal mucosa.

Here, the first strategy considered to overcome the challenges of conventional ODD is drug delivery through the buccal cavity. The buccal delivery route enables a straightforward absorption of drugs into the systemic circulation by completely avoiding the first-pass metabolism [3]. In our study, buccal patches with Atenolol as API were fabricated by a simple one-step process using SDC. The buccal patch formulation was prepared using mucoadhesive polymers HPMC and chitosan with 55 % drug load, followed by feeding the formulation into the slot-die head with a syringe at room temperature (Fig. 1a). The coating was performed using a 50 mm wide slot-die head at 60º C substrate-bed temperature. The target wet thickness of 500 µm was verified using a thickness comb immediately after coating, yielding an approx. 23 µm thick dry film (Fig. 1c) after evaporation of the solvent. To assess the thickness and drug distribution uniformity of the fabricated buccal patch, random sampling of ⌀10 mm punches of the slot-die coated film was performed by Xurography (Fig. 1b). The random sampling was followed by weight measurement (Table 1) and atenolol release studies using UV-vis spectroscopy (Fig. 1d), showing high reproducibility for the randomly punched samples.

As a second strategy addressing common issues in ODD, we developed oral drug delivery systems using micro-and nanoscale technologies with the aim to transport the drug to the target sites safely. Microparticles were fabricated in a two-step process combining SDC and hot punching. Firstly, a dry film of polycaprolactone (PCL) with a thickness of about 80 µm was prepared using SDC. To obtain microparticles of desired particle geometry, a Si master template was fabricated by photolithography and deep reactive ion etching (DRIE) (Fig. 2a) and the structures were subsequently replicated in a cyclo olefin polymer (COP) stamp (Fig 2b). A stack was prepared placing a PTFE sheet and the SDC coated PCL film over the COP stamp in a nanoimprinting tool. A pressure of 7 bars and a temperature of 85º C were applied for about 30 min, allowing the COP stamp to penetrate the PCL film. This resulted in hot punching of individual microparticles with the shape corresponding to the stamp geometry (Fig. 2c).

The fabrication method for drug microparticle fabrication proved to be simple and repeatable, thus establishing a road map for scalable continuous production that is not restricted to batch processing limitations. Loading of

PCL polymer matrix with Furosemide as a model drug is currently being studied along with water soluble PVA substrates for harvesting microparticles.

References

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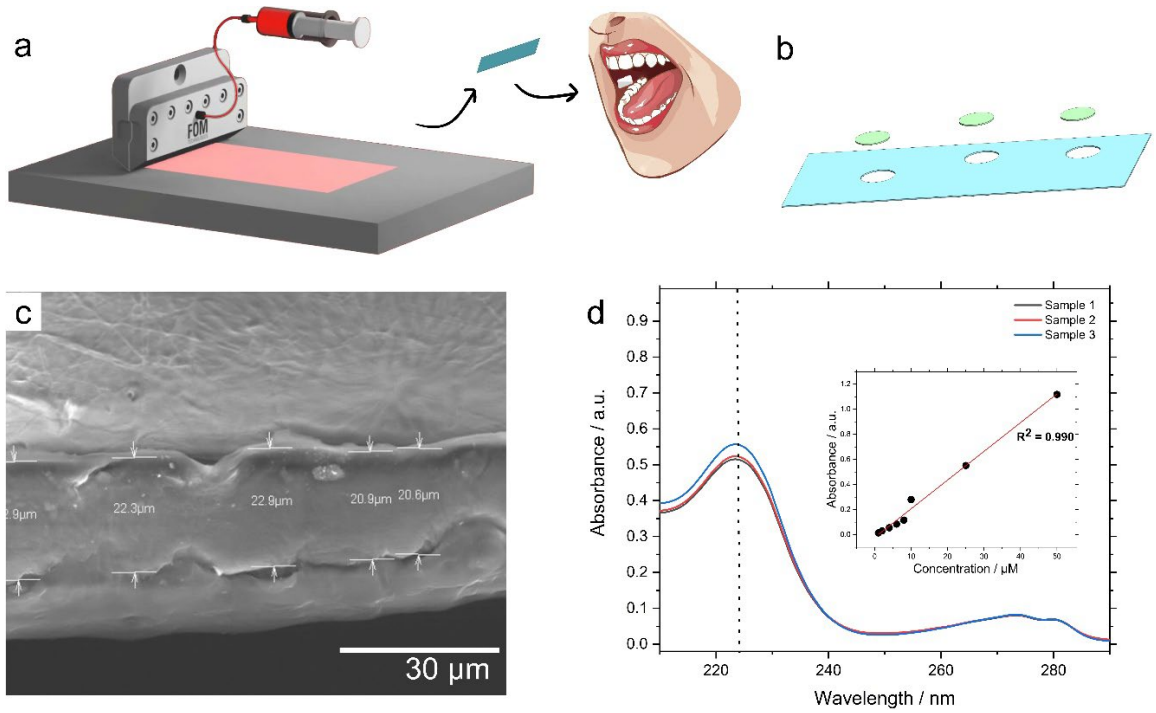

Figure 1. a) Illustration of lab-scale slot-die coating. The buccal patch formulation is supplied via a syringe which is controlled using a pump built within the slot-die coater. Buccal patch is obtained after drying and is ready for application into the buccal cavity © FOM Technologies A/S, Denmark; **b)** Random sampling of ⌀10 mm of buccal patch by Xurography, for weight and drug distribution analysis; **c)** SEM micrograph of a cross section of buccal patch. The average thickness is 23 µm; **d)** UV-vis absorption spectra of Atenolol released from the buccal patch and calibration curve for Atenolol (inset).

Table 1. Table showing weight of the sampled punches in the buccal patch and corresponding drug concentration using UV-vis spectroscopy.

	Sample 1	Sample 2	Sample 3	Average	SD	CV%
Weight (mg)	06.24	06.34	06.73	06.44	0.20	3.28
Concentration (µM)	23.44	23.79	25.25	24.16	0.78	3.24

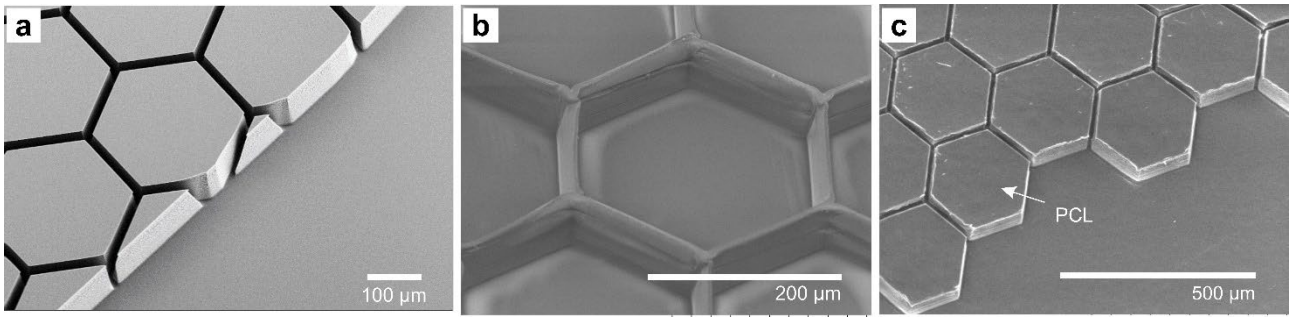

Figure 2. SEM micrographs of 75 µm x 600 µm hexagonal shaped particles **a)** Si master template fabricated by photolithography and DRIE, **b)** hexagonal wells imprinted in a COP foil by hot embossing, **c)** PCL microparticles (white arrow) fabricated by hot-punching of slot-die coated PCL films using the COP stamp.