

Development of Novel Intravesical Inserts via 3D-Printing

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Introduction

Pressure-assisted microsyringe (PAM) printing is a novel technology that has evolved from the area of 3D-printing technologies and allows the use of semisolid formulations. In this study we investigated the potential of PAM as a tool to print flexible inserts that can be placed into the urinary bladder via a catheter. Two different approaches were explored utilizing eroding and non-eroding polymers. They offer the advantages of preventing the explantation of the insert as well as creating an insert that may be used for a long-term presence within the urinary bladder.

The innovative approach aims at enabling a local application of active pharmaceutical ingredients (API) for various bladder diseases such as e.g. overactive bladder in order to overcome systemic side-effects of orally applied drugs [1].

Materials and Methods

In preliminary experiments various plasticizers were assessed for manufacturing flexible films. They were produced via film casting of formulations containing the plasticizer, the biodegradable polymer polycaprolactone (PCL) or the non-eroding polymer ethylene vinyl acetate copolymer (EVA) and tetrahydrofuran (THF) as solvent. Dibutyl sebacate (DBS) was selected as most suitable plasticizer by performing a puncture test (Texture Analyzer TA.XT plus, Stable Micro Systems, UK) on the casted films and used for further formulation development. The composition of the most promising printable formulations can be seen in Table 1.

Formulation [% w/w]	EVA	PCL	THF	DBS	LC-HCl	Printing speed [mm/s]	Printing pressure [bar]
A	35	-	41	7	17	25	2
B	-	24	36	24	16	15	0.4
C	43	-	41	8	8	20	2
D	-	36	36	19	9	20	1.5

Table 1. Composition of the semisolid printing formulations (LC-HCl = lidocaine hydrochloride).

The formulations were mixed on a stirring plate overnight and subsequently heated for 20 min at 100 °C. After cooling to room temperature LC-HCl was added and manually mixed for 5 min. The resulting formulation was then transferred into a 30 ml syringe and inserted into the print head of the PAM-operated 3D-Biplotter (EnvisionTec, Germany).

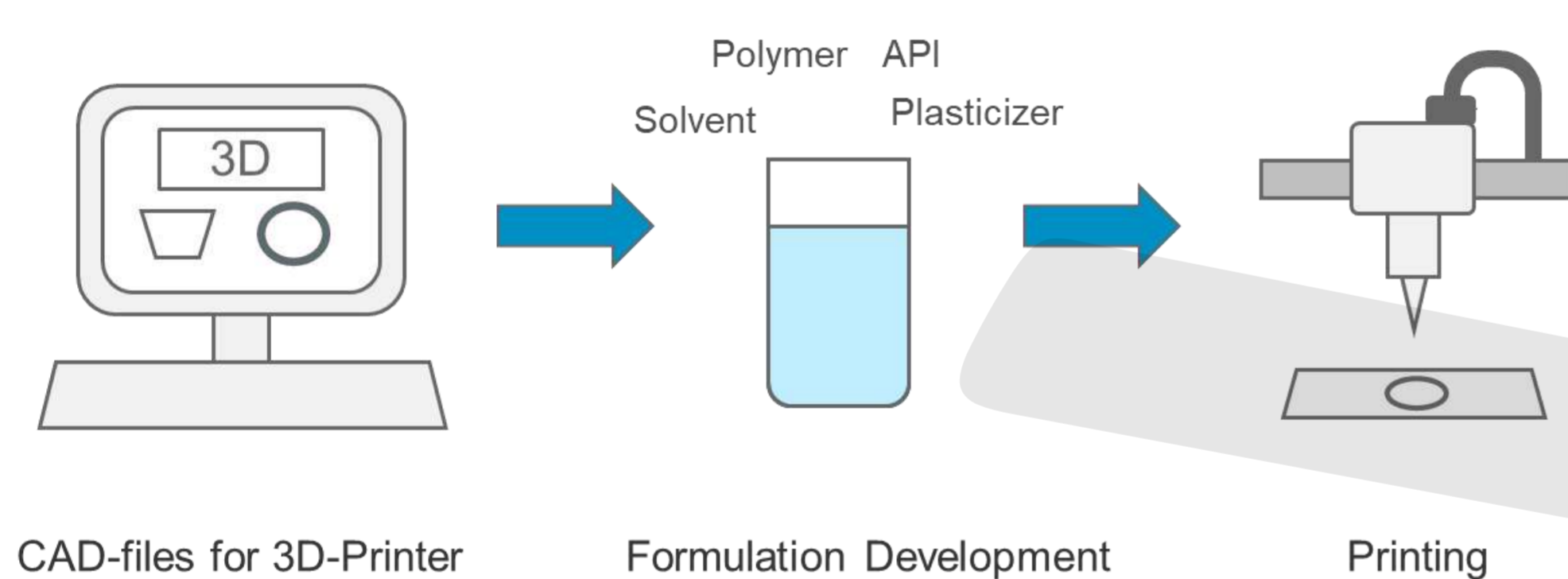


Figure 1. Schematic overview of printing process.

Prior to printing, computer aided design (CAD)-files were created with the software Inventor (Autodesk, USA) and subsequently imported into the slicing software Perfactory 3.0 (EnvisionTec, Germany).

A net-shaped circular model insert with a layer thickness of 0.64 mm and a diameter of 5 cm was designed. The printing process was carried out at 27 °C for formulations A and B and at 35 °C for formulations C and D.

Dissolution Studies

Dissolution studies were performed in purified water (900 ml) at 37 ± 0.5 °C. The drug release was determined via UV-spectrometry at 230 nm. The dissolution apparatus DT 700 (Erweka, Germany) was operated at 100 rpm, using the basket method (USP type 1).

Scanning Electron Microscopy (SEM)

The surface morphology of the printed inserts was investigated via SEM (Phenom G2 pro, Thermo Fisher Scientific, USA) after applying gold sputter coating.

Results and Discussion

Manufacturing of Inserts

It was feasible to print net-shaped inserts (see Fig. 2) with the 3D-Biplotter. Challenges regarding flexibility of the structures as well as printability of the semisolid formulations could be overcome by carefully adjusting the critical printing parameters and the ratios of the components. By choosing a net-shaped design, a clogging of the urethra after insertion may be prevented, while ensuring a high drug load and enlarged surface area.

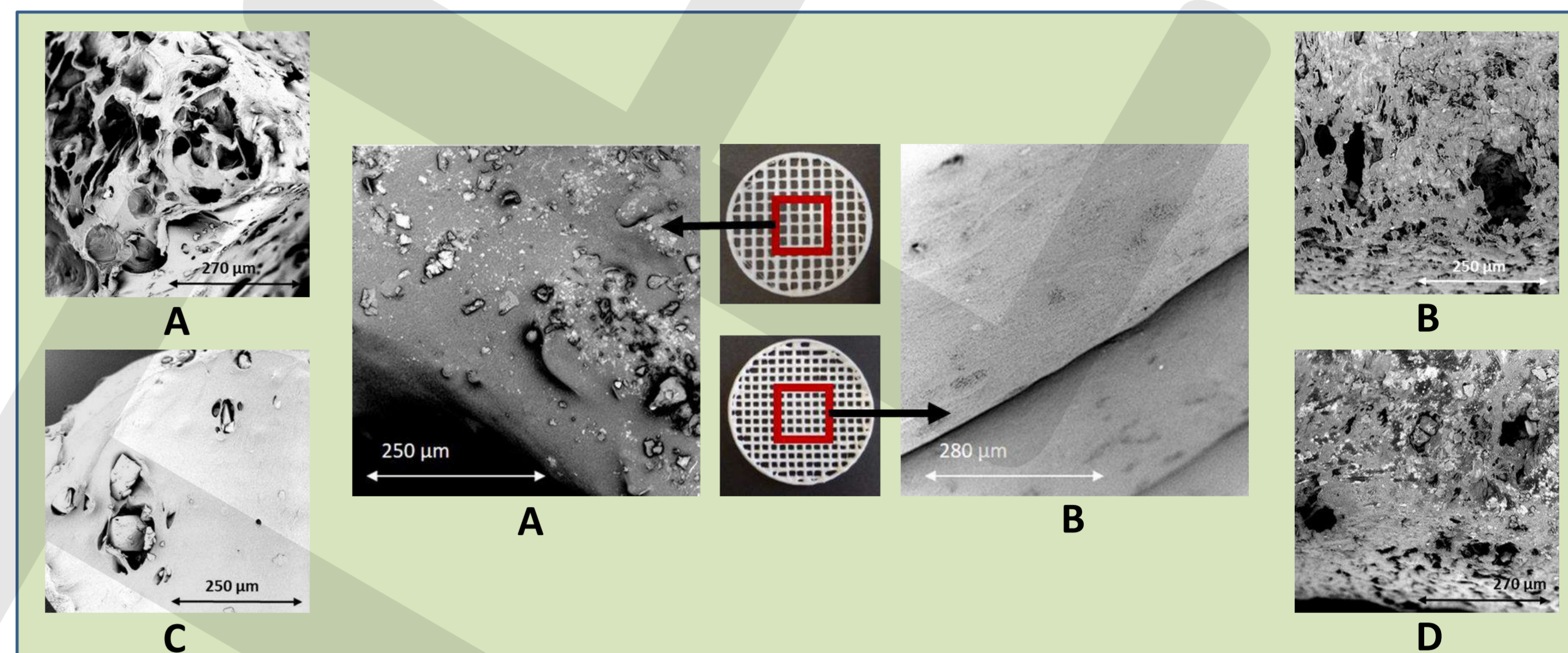


Figure 2. SEM images of drug-loaded EVA (formulations A and C, left) and PCL (formulations B and D, right) inserts. Top view displayed in the center and cross sections on the sides.

The SEM images of the drug-loaded inserts in Figure 2 show crystallization of LC-HCl on the surface of the EVA insert (A). This effect is less apparent for the PCL insert (B). The cross section of the inserts show a highly porous structure caused by evaporated solvent and could be significantly reduced for the EVA insert by reducing the solvent to polymer ratio as seen in Figure 2 (A and C).

Dissolution Studies

The dissolution profiles of the inserts show an initial quick drug release that is more pronounced for the PCL insert (see Fig 3, left graph). Drug release reaches a plateau after approx. 15 h. For the EVA insert however, LC-HCl has not been fully released after 38 h, which indicates the potential for sustained release applications over a longer time period. The crystallization of the drug on the surface of the EVA insert might explain the initial high drug release. For the PCL insert this phenomenon could be caused by good water permeation into the insert and subsequent dissolving of the drug crystals within the PCL matrix. It may also have occurred due to increased chain mobility of the polymer after adding the plasticizer [2].

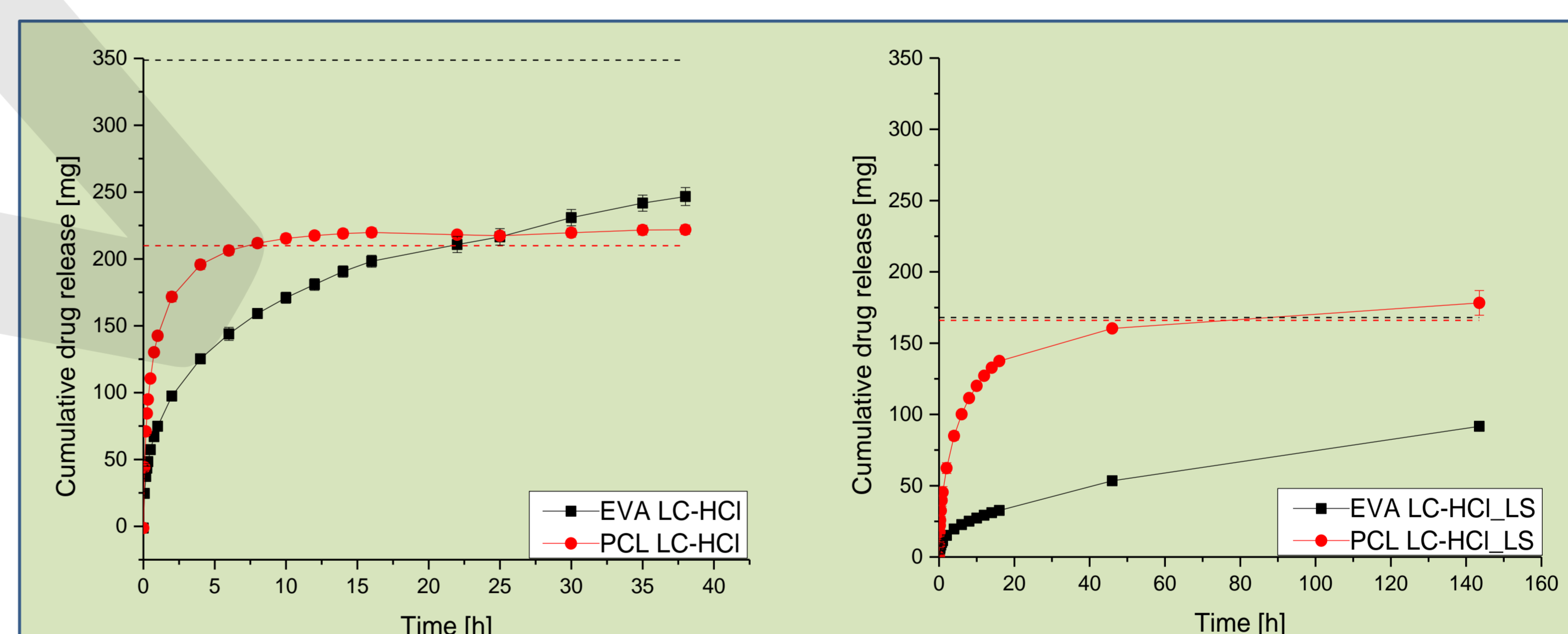


Figure 3. Dissolution profiles of printed inserts. Formulations A and B displayed left; formulations C and D containing less solvent (LS) right, mean ± s, n=3. Dashed lines: theoretical drug content.

The porous internal structures seen in the SEM images further explain the initial rapid drug release. Reducing the solvent to polymer ratio in formulations C and D resulted in smaller inner surface areas and the drug release could be significantly sustained. For the EVA insert (formulation C, right graph) after 6 d 54% of the API was released, whereas for the PCL insert (formulation D, right graph) the plateau was reached already.

CONCLUSION

It was feasible to use a PAM-operated 3D-Biplotter to manufacture drug-loaded flexible inserts for a potential long-term presence within the urinary bladder. The investigated polymers show differences regarding the drug release profiles. While PCL inserts release the complete drug within 15 h, EVA inserts might promise a long term release (> 38 h). After improving the formulation by reducing the solvent to polymer ratio and therefore reducing the inner surface area of the inserts, the drug release could be further sustained up to 144 h for the PCL insert and has not yet been completed after six days for the EVA insert.

Further studies should investigate different polymer blends with PCL as well as incorporation of less water soluble drugs to meet the requirements of the degradation rate and sustained release properties of an insert for a long-term application within the urinary bladder.

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