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Supercritical impregnation of polymer matrices spatially confined in microcontainers for oral drug delivery: Effect of temperature, pressure, and time

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The present study is aimed to enhance the oral bioavailability of ketoprofen by inserting it into the matrix of poly(vinylpyrrolidone) (PVP) K10 spatially confined into microcontainers, by means of supercritical CO2-aided impregnation. Microcontainers are cylindrical reservoirs, with typical sizes in the micrometer range, with a cavity open on one side, where the drug formulation is loaded. Differently to traditional tablets, microcontainers have a higher surface area per unit volume, and release the drug only in one direction. This design is meant to enhance the absorption of problematic drugs, like those with poor solubility in water. In a previous study we introduced a novel technique for drug loading of microcontainers, based on inkjet printing and supercritical impregnation (SCI). We showed that SCI produces accurate and reproducible drug loading for large arrays of microcontainers. In the attempt of enhancing the throughput of the loading methods, we propose the replacement of polymer inkjet printing with an easier manual compression of the PVP powder into the microcontainers. As the second step, the polymer powder filled-microcontainers were submitted to SCI. The separate role of different impregnation parameters (temperature, pressure, time, drug concentration in the supercritical phase) was elucidated with respect to the loading capacity. The microcontainer filling was observed by means of optical macroimaging, X-ray microtomography and scanning electron microscopy. The physical state of the drug was investigated by means of Raman spectroscopy and compared with selected representative PVP-ketoprofen physical mixtures. Finally, the drug loading was estimated by means of in vitro dissolution tests.

The characterization study shows that the present loading method is a valuable alternative to the one previously described. The drug loading can be controlled with high accuracy and reproducibility and the impregnated drug is in amorphous state. These results demonstrate that SCI can be used as a high throughput loading technique for microfabricated devices for oral drug delivery.

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1. Introduction

Among the different drug delivery routes oral administration is still the most preferred one for its simplicity, minimal invasiveness, and high patient compliance. Nevertheless, the human digestive system presents a sequence of physiological barriers which drastically reduce the bioavailability of many active pharmaceutical ingredients (API): enzymatic degradation, hydrolysis in the gastric acidic environment, thick mucus layer covering the intestinal mucosa, selective transport action of peptide receptors in the epithelial cells [1]. In particular, oral delivery of APIs that exhibit either low solubility in water or low permeability through biological membranes or both is challenging. The solid state properties of drugs have a strong influence on their solubility. Whilst amorphous drug candidates exhibit an enhanced solubility and dissolution rate compared to their crystalline counterparts, amorphous forms often suffer from rather short thermodynamic stability and they spontaneously tend to crystallize [2]. As a result, stabilization of amorphous forms is necessary in order to preserve the above-mentioned advantages [3]. Physical stabilization of the
amorphous form can be achieved by the addition of a polymeric carrier wherein the drug is confined in supramolecular domains or even molecularly dispersed [4]. Together with the solid state properties, the solubility and dissolution rate can be improved by reducing the particle size of the formulation [5]. Among the several formulation approaches [6] supercritical fluid based technology is a promising technique to produce micro- and nanoparticulate systems with high drug dispersion and enhanced stability and dissolution properties [7].

Besides the properties of the drug formulation, an important role in the therapeutic performance is often played by the design of the administration form. Conventional oral dosage forms like tablets provide an omni-directional drug release through their limited interfacial area when exposed to the physiological fluids. Furthermore, drug release from tablets is often slow compared to the peristaltic flow in the small intestine, where the most permeable tissue for drug absorption is located. As a result, a large amount of API is not delivered, and patients need to ingest multiple drug doses to receive the desired therapeutic benefit. This increases the occurrence of potentially harmful side effects in patients [8].

In the last 10 years advances in field of micro- and nanofabrication have allowed the development of alternative drug delivery systems [9]. In particular there has been an increasing interest in microfabricated devices based on the concept of microcontainers [10]. A microcontainer is a reservoir with the typical dimensions falling in the micrometer range, composed of a non-permeable and inert shell and a cavity for the drug formulation open on one side from which the drug is released unidirectionally. The size of these microcontainers is chosen to allow an enhanced intimate contact with the irregular surface of the mucosa with respect to other macroscopic drug delivery systems and to avoid typical issues of smaller micro- and nano-sized systems like clustering, physical stability and unspecific endocytosis. Several groups developed microcontainers in different shapes, materials and designs, where fabrication is typically performed on flat silicon substrates. By virtue of its asymmetric shape and by applying appropriate bioadhesive coatings on microcontainers Ainslie et al. [11] showed an increased intestinal retention time for these microdevices and an enhanced bioavailability for a model poorly water soluble drug. One of the largest challenges in the fabrication of microcontainers concerns the drug loading step. In a previous work [12], we showed the fabrication of cylindrical microcontainers, fabricated with the epoxy resin SU-8. The microwells were filled with poly(vinylpyrrolidone) (PVP) by inkjet printing. This method showed high accuracy and a minimal waste of materials. In a more recent work [13] we proposed the combination of inkjet printing and supercritical technology to impregnate the polymer-filled microcontainers with ketoprofen, a poorly water soluble drug. We demonstrated that the supercritical impregnation technique allows a highly accurate and reproducible drug loading of large arrays of microcontainers. In an attempt to enhance the throughput of this loading method, we propose a simplified variant of our previous work. Here the polymer printing was replaced by an easier filling method, consisting of a manual compression of the polymer powder into the microcontainer. Later, the powder filled-containers were submitted to supercritical impregnation (SCI) as previously described [13]. This process modification enabled a significant reduction in the sample preparation time and made it possible to investigate the effect of temperature, pressure and impregnation times on different aspects concerning the drug loading in more detail.

The loading procedure was characterized with different techniques. X-ray microtomography was used to measure the level of filling and the morphology of the polymer powder in the microreservoir cavities before and after the SCI. In addition, microcontainers were visualized by scanning electron microscopy (SEM) to observe the effect of the impregnation parameters on the polymer morphology. Raman spectroscopy was used to investigate the drug solid state in the impregnated matrices and drug-polymer interactions. Finally, in vitro dissolution tests were carried out and the total drug loading was estimated. The results showed that the replacement of inkjet printing with the powder filling method enhances the throughput of the microcontainer loading technique without compromising the accuracy or the reproducibility of the whole loading process.

2. Materials and methods

2.1. Fabrication of SU-8 microcontainers

2.1.1. Materials and fabrication of microcontainers

Silicon wafers (4-in. b100N n-type) were supplied by Okmetic (Vantaa, Finland). SU-8 2075 and SU-8 developer were purchased from Microresist Technology GmbH (Berlin, Germany).

Cylindrical microcontainers were fabricated with a similar procedure as previously described [12]. The microwells were fabricated with the epoxy-based photoresist SU-8 on silicon wafers. A microcontainer has a cavity of approximately 300 μm in diameter and 250 μm in depth and an approximated volume of 18 nL. After the fabrication the wafer was cut into square chips containing 625 microcontainers (DISCO DAD 321, Automatic Dicing Saw).

2.2. Drug loading of microcontainers

2.2.1. Materials

Ketoprofen (98%, racemate) and poly(vinylpyrrolidone) (PVP K10, Mw 10,000) were supplied by Sigma Aldrich. In Fig. 1 the molecular structures of the compounds are shown. Carbon dioxide was supplied by SIAD (99% purity). Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antiinflammatory properties. In several pharmacopeias ketoprofen is considered as practically insoluble in water [14,15]. The solubility of the crystalline form of ketoprofen in pure water at room temperature (22–24 °C) was reported to be 0.010 mg/ml [15]. Thus, ketoprofen is classified as class II active principle in the biopharmaceutical classification system (BCS): It exhibits low aqueous solubility and a high intestinal permeability.

2.2.2. Filling with poly(vinylpyrrolidone) PVP powder

Microcontainers were filled with PVP powder with the following procedure: The powder was deposited and compacted with a spatula onto the microwells and the residual amount, placed in between containers, was blown away by means of pressurized air. The chip was weighed before and after filling and the average PVP weight per chip was 1.93 ± 0.08 mg (calculated from 35 samples). The level of microcontainer filling was measured by X-ray microtomography at different positions on the chip.

2.2.3. Supercritical impregnation of polymer filled-microcontainers

After the powder deposition the drug was loaded into the polymer-filled microdevices by means of supercritical carbon
dioxide impregnation. Fig. 2 depicts a schematic of the high pressure setup used in the impregnation experiments. The operation was performed in a 100 mL reactor (KM 20-05 autoclave NWA, Germany) equipped with a magnetic stirrer drive (Mrk MINI 100) assembled in a sealed housing directly threading into the reactor head. During the impregnation experiments the reactor was fed with liquid CO₂ through an on/off valve (V1) by a high pressure pump (PM-10INWA, NWA, Germany). At the end of the experiments the reactor was slowly emptied through an on/off purge valve followed by a lamination valve (V2) and the outlet stream was connected to a deflux flask were the gaseous CO₂ was bubbled through an ethanol solution (95%). Finally, the drug free-CO₂ stream was connected to a flowmeter (SIM Brunt, Italy).

The impregnation experiments were carried out in batch conditions with defined steady-state values of CO₂ pressure, temperature and stirring velocity. In each experiment, weighted amounts of crystalline ketoprofen powder and one chip were placed in separate compartments of a sample carrier placed at the bottom of the reactor. In order to avoid damage to the microcontainers during the chamber filling with the supercritical fluid, the back of the chips were glued onto the sample carrier with a carbon tape pad. The reactor was then sealed and heated to the defined temperature. When the set point temperature was achieved, the inlet valve was gradually opened and the chamber was slowly filled with CO₂, in order to maintain isothermal conditions and avoid turbulence within the reactor, which could result in detachment of the chip and damaging of the microcontainers. When the desired pressure was achieved, the inlet valve was closed and the stirrer was switched on. During the experiment the supercritical CO₂ phase dissolved the solid drug powder and swelled the polymer within the microcontainers. The drug was therefore physically conveyed and loaded in the polymer matrices. The impregnations were carried out at a fluid pressure of 100 and 200 bar, temperatures of 40, 50 and 60 °C and durations of 1 and 4 h with a stirring velocity of 20 rpm.

In the experiments run at 100 bar the amount of drug placed in the chamber was selected to initially achieve complete dissolution in supercritical CO₂ and saturation conditions according to the solubility values of ketoprofen reported by Macnaughton et al. [16] at the chosen temperature. In this group of experiments the temperature and time were modified from batch to batch. Because of the batch conditions, the drug concentration could not be kept at saturation value over time. In contrast, in the tests performed at 200 bar a fixed amount of ketoprofen was weighted and dissolved, based on the amount to reach saturation concentration for the compound at 200 bar and 40 °C. As a consequence, at 200 bar and 50 °C and 60 °C operation will be below saturation conditions, as the solubility values are higher at these temperatures. In the experiment performed at 200 bar, the exclusive effect of temperature and time on the microcontainer impregnation was studied. At the end of the experiment the reactor was depressurized at a controlled rate for approximately 2 and 3 h when the operating pressures were 100 and 200 bar respectively. After the experiments the chips were stored in a desiccator until further analysis were performed. In Table 1 the operating conditions of the experiments are shown.

### 2.3. Characterization methods

#### 2.3.1. X-ray microtomography (µCT)

For the µCT measurements a Skyscan 1172/F instrument (Skyscan, Kontich, Belgium, control software v1.5.13) was used. A source voltage of 60 kV and current of 165 μA were used together with a 0.5 mm thick Al filter to attenuate the high energy X-rays. For each sample 780 shadow images were acquired over 180° of rotation. The resulting data acquisition time was 4h for each sample. Reconstruction of the cross-section images was performed using the program NRecon + GPUReconServer (Skyscan, beta v1.6.5) on a single PC using GPU accelerated reconstruction (Windows 7 64-bit workstation, 2 Intel Xeon X5647 with 4 cores each, 48 GB RAM, NVIDIA quadro 4000 with 256 cores). Image reconstruction using the Feldkamp algorithm [17] for cone beam geometry took about 30 min per sample and resulted in, depending on sample size, about 1450 slices of 2864 × 2876 pixels each (5.2 μm isotropic voxel size). Using the DataViewer (Skyscan, v1.4.4) the tablet was rotated to align the microwells parallel to the x-axis.

#### 2.3.2. Scanning electron microscopy (SEM)

The morphology of the impregnated microcontainers was examined using SEM. The investigations were carried out using a Nova600 NanoSEM from FEI (Eindhoven, the Netherlands). Imaging was performed in low-vacuum-mode at a pressure of 0.6 mbar and an operation voltage of 5 kV. Prior to examination, the samples were mounted onto metal stubs and were tilted by approx. 30°.

#### 2.3.3. Raman spectroscopy

As described in a previous study [13], Raman spectroscopy can be used to elucidate the presence of chemical interactions amongst drug molecules and between drug and polymer. The spectra from the impregnated microcontainers were collected using a Thermo Scientific Raman DXR microscope equipped with a frequency-stabilized single mode diode laser. The Raman signal collection time was 5 s and the signal was averaged three times, using a 25 μm slit and a 1.0 μm diameter laser post. The Raman DXR microscope was coupled to a single grating spectrometer with a 5 cm⁻¹ FWHM (full width half maximum) spectral resolution and a ±2 cm⁻¹ wavenumber accuracy. All Raman spectra were recorded at a laser power of 10 mW, using a 10× objective lens and a laser excitation wavelength of 780 nm. In each sample 5 containers, located at different

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**Table 1**

Weighted mass of ketoprofen [mg] dissolved at different experimental conditions.

<table>
<thead>
<tr>
<th>Pressure [bar]</th>
<th>Temperature [°C]</th>
</tr>
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<tbody>
<tr>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>100</td>
<td>4.83</td>
</tr>
<tr>
<td>200</td>
<td>14.1</td>
</tr>
</tbody>
</table>

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![Fig. 2](image-url) Schematic of the high pressure plant. F₁ and V₁ indicate 0.5 μm filters and on/off valves.
positions on the chip, were selected and analyzed. The intrinsic fluorescence background was fitted to a polynomial function and subtracted from the collected signal.

2.3.4. In vitro drug dissolution studies

The loading of ketoprofen was determined by in vitro dissolution tests of impregnated microcontainers in 10 mL DI water at 37 °C using a UV spectrophotometer μDISS profiler (Pion, USA). Individual chips were glued with carbon pads on teflon-coated magnets which stirred at 100 rpm. For the detection of ketoprofen, the wavelength was set to 259 nm. After dissolution, the microcontainers were observed with an optical microscope (Zeiss, Germany, 10x magnitude) to confirm complete emptying. The amount of drug loaded per chip was estimated by the final concentration measured in the dissolution test at 16 h. Solubility of ketoprofen at 37 °C in aqueous solutions changes significantly with pH between 1 and 7 [14]. However, even in the test with the highest drug loading, the pH of the dissolution medium drop below 5.5 as ketoprofen is a weak acid (pKₐ 4.5). Therefore, according to solubility data reported in the literature [14], the dissolution tests were performed in conditions below saturation that is without drug precipitation, which was also confirmed by the non-decreasing monotonic trend of the drug dissolution profiles (data not shown).

3. Results and discussion

3.1. Polymer filling of microcontainers and X-ray microtomography

A picture of arrays of microcontainers filled with PVP powder is shown in Fig. 3. The powder filling required few seconds to be performed and resulted in an accurate deposition inside the cylindrical cavities of the microwells, with minimal residues in between, as representatively illustrated by the high color contrast between the dark silicon surface and the brilliant white of PVP powder. In Fig. 4 a scanning electron microscopy image of microcontainers filled with PVP powder is reported. The polymer granules are compacted inside the microwells and this confinement prevents them from being removed by the air flow which is used to remove the loose powder in between containers after the filling step. Fig. 5 shows the cross-sections that were reconstructed from the microtomography data of the XμCT measurements. Using this technique it is possible to measure the internal microstructure of the PVP powder within the containers and to visualize the effect of the impregnation on the particle morphology. The images clearly show that the microcontainers are filled with discrete PVP particles which subsequently coalesce in bigger clusters following supercritical impregnation with ketoprofen at 200 bar, 40 °C and 1 h for the example in Fig. 5.

![Fig. 3. Optical macro images of microcontainers filled with PVP powder by manual compaction: (a) detail of the chip corner, (b) arrays in the middle of the chip.](image)

![Fig. 4. SEM images of microcontainers filled with poly(vinylpyrrolidone) before treatment with supercritical CO₂. The scalebar indicates 300 μm.](image)

3.2. Scanning electron microscopy of impregnated microcontainers

After the supercritical treatment, the microcontainers were analyzed by scanning electron microscopy to observe the effects of the impregnation on the polymer morphology. As shown previously [13], the SEM micrographs (see Fig. 6) confirm that scCO₂ does not visible effects on the epoxy resin SU-8 used to fabricate the microcontainers, which maintain their size, the cylindrical shape and the adhesion to the silicon substrate. The supercritical fluid has instead a much more pronounced effect on PVP. At all the tested conditions, the morphology of PVP radically changes as the polymer particles undergo swelling and subsequent coalescence as confirmed by the XμCT images (Fig. 5b). By comparing the SEM micrographs of microcontainers treated at different pressures it is clear that the volume of the polymer visibly increases with increasing CO₂ pressure. This might be also due to the presence of higher drug amounts loaded in the polymer matrix. This can be explained by an increase of CO₂ uptake in PVP with pressure, in accordance with what was previously reported by Kikic and co-workers [18]. At high pressures, CO₂ has a well-known plasticizing effect on certain polymers [19,20]. The plasticization leads to a drop of the Tg from 120 to 128 °C for PVP [21] to a temperature close to the operating temperature during impregnation. As a result, the polymer gets close to the glass-rubber transition. The increase of impregnation time in general leads to a higher extent of swelling of the matrix and to the appearance of holes. At 40 °C and 50 °C these holes got larger when the pressure was set at 200 bar, and this fact can be attributed to the release of CO₂ from the highly swollen matrices upon depressurization. At 200 bar and 50 °C small spots appear on
the polymer surface. At 200 bar and 60 °C these particles clustered in larger aggregates (see Fig. 6k and l) on a small number of containers on the chip. As scCO₂ acts as a plasticizer for polymers the viscosity of the CO₂ saturated matrix decreases during impregnation in some cases causing spillages from the containers. This aspect is more pronounced during longer experiments.

3.3. Loading of ketoprofen into polymer filled-microcontainers

The solubility of ketoprofen in scCO₂ monotonically increases with the fluid density, and therefore with the fluid pressure at isothermal conditions [16]. Furthermore, for many active compounds under isobaric conditions the temperature influences the solubility according to the operating pressure and with respect to the crossover pressures. At the crossover points solubility isotherms overturn their trend [16]. The upper crossover pressure of ketoprofen in carbon dioxide was measured between 160 and 180 bar [18,22]. Below this pressure, such as at 100 bar, the drug solubility decreases with temperature. At higher pressures, such as at 200 bar, the effect of temperature is the opposite. The impregnation pressures were chosen at a value below and above the upper crossover point in order to explore the influence/effect of the supercritical phase on the drug loading. In Fig. 7 the resulting weight fraction of ketoprofen (ωketo) respect to drug + polymer mass, loaded in a chip containing 625 PVP filled-microcontainers is compared for the different impregnation conditions. In Table 2 the overall drug loading results are shown.

Despite the simplicity of the method the overall accuracy of the loading is similar to the one previously reported where the polymer was deposited by inkjet printing [12].

In the tests carried out at 100 bar (Fig. 7a) the drug was dissolved in saturation conditions. Here the loading is strongly dependent on the drug concentration in the supercritical phase, which was higher at 40 °C and lower at 60 °C. There is an increase in drug loading over time for any tested temperature meaning that after 1 h the equilibrium is not yet attained. After 4 h the drug weight fraction is approximately doubled at all temperatures. To investigate the partition equilibrium of the drug between the CO₂ and the polymer phases an impregnation experiment was carried out at 100 bar and 40 °C for 24 h. The attained drug fraction was 0.27, which is very

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Fig. 5. Cross-sections non-destructively acquired by XpCT through the microcontainers filled with poly(vinylpyrrolidone) before (a) and after impregnation with ketoprofen by supercritical CO₂ (200 bar, 40 °C, 1 h)/(b). The original gray scale images are shown together with a binary threshold image to highlight the change in polymer morphology.

Fig. 6. Scanning electron microscopy images of polymer filled microcontainers impregnated with ketoprofen by supercritical CO₂ at different pressure, temperature and time. The scalebars indicate 300 μm.
enhanced mobility of the polymer chains, which is suggested by the visible swelling observed in Fig. 6d, h and l. In contrast to the results at 100 bar, at 200 bar more limited loading gains were achieved with increased impregnation time. This might be due to the proximity of the drug concentration in the polymer to saturation, which can slow down the impregnation process.

3.4. Raman spectroscopy

Another important aspect for a drug delivery device are the API solid state properties and the stabilization of the amorphous phase in a polymer matrix. For this purpose, Raman scattering spectroscopy was utilized to detect the presence of amorphous ketoprofen and the molecular interactions with the polymer. The supercritical impregnation of PVP films with poorly soluble drugs was previously investigated by vibrational spectroscopy [23–25]. In order to elucidate the presence of drug-polymer interactions, additional Raman spectra were collected from microcontainers filled with physical mixtures (PMs) of the polymer and drug. Physical mixtures were obtained by gentle mixing PVP and ketoprofen powders and subsequent filling in microcontainers as previously described [13]. Raman scattering spectra of both fresh ketoprofen: PVP PMs and mixtures prepared by supercritical CO2 are shown in Fig. 9. In the ketoprofen: PVP PM case, the Raman scattering spectra from both compounds are added together and retain all characteristics of isolated ketoprofen and PVP, see Fig. 9a. To illustrate this, the inter-ring ketoprofen carbonyl [C=O] stretching mode found at 1657 cm\(^{-1}\) is examined for different drug/PVP ratios [26]. A previously reported by Carvalho et al. [27], a frequency shift for this signal can be associated to the formation of H-bonds involving the C=O group between ketoprofen and PVP. In all cases the Raman intensity of the ketoprofen C=O stretching mode compared to the 1602 cm\(^{-1}\) C–C stretching mode is \(I_{1657}/I_{1602} > 1\). The
Raman vibration can be fitted to two Lorentzian functions outlining modes that belong to both ketoprofen and PVP. The FWHM of the C=O stretching mode is similar to the one recorded for pure ketoprofen shown in the bottom part of Fig. 9a. The PM result indicates no observable intermolecular interaction between the two compounds [13]. The 1657 cm\(^{-1}\) Raman mode for supercritical CO\(_2\) impregnated ketoprofen:PVP mixtures behaves differently, i.e. the vibrational mode intensity is reduced and the FWHM is significantly increased, see Fig. 9b. In this case, the two Lorentzian fits yield essentially a single Raman peak without a clear contribution from PVP and \(I_{1657}/I_{1002}\) ≤ 1 almost for all drug/PVP ratios. Since there is no observable frequency shift, the result suggests that this carbonyl group is not involved in the formation of hydrogen bonds with PVP molecules. The recorded change rather indicates rearrangement of ketoprofen molecules into a less organized amorphous solid state, and a similar effect was previously observed for aged ketoprofen:PVP PM mixtures [13]. The presence of amorphous ketoprofen was previously confirmed by X-ray diffraction [13]. It is also expected that the CO\(_2\) assisted impregnation of PVP with ketoprofen breaks or reduces the interaction between adjacent ketoprofen molecules and induces the formation of the hydrogen bonds between hydroxyl groups of ketoprofen molecules and carbonyl groups of PVP [24].

4. Conclusions

The present study investigates the use of CO\(_2\)-aided impregnation to load ketoprofen into microcontainers filled with PVP by tuning temperature, pressure, time, and drug concentration in the fluid phase. The characterization study shows that drug loading can be controlled with high accuracy and reproducibility and the impregnated drug is in the amorphous state. At any tested pressure there is an increase of drug loading over time for any tested temperature meaning that after 1 hour the equilibrium between the polymer and the CO\(_2\) phases is not yet attained. From the tests at 100 bar it was observed that the loading is strongly dependent on the drug concentration in the impregnating medium. Unexpectedly, in the tests at 200 bar the loading increased with the temperature despite the increasing drug solubility in the scCO\(_2\). This was attributed to the predominant effect of drug diffusivity in the polymer matrix. In contrast, at 200 bar more limited loading gains for increasing impregnation time were obtained probably due to drug saturation in the polymer. The Raman scattering spectra of the impregnated matrices indicate a rearrangement of ketoprofen molecules into a less organized state. However, no observable frequency shift in was noticed for the spectral modes typically ascribed to drug-polymer interactions, which suggests that the drug molecule is unlikely to be involved in the formation of hydrogen bonds with PVP molecules.

Our results demonstrate that the combination of powder loading and SCI can be used as a high throughput loading technique for microfabricated devices for oral drug delivery.

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