DEPOSITION OF SUBMICRON DRUG PARTICLES IN PREFORMED SOLID CARRIERS BY THE CONTROLLED PARTICLE DEPOSITION METHOD (CPD)

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Particle size reduction is widely used to enhance solubility and thus oral bioavailability of poorly water-soluble compounds. The production of small particles often encounters problems like thermal or mechanical strain on the product or the need for organic solvents. Supercritical fluid processes like the Rapid Expansion of Supercritical Solutions (RESS) present an alternative way of producing submicron particles without residual organic solvents, under mild operating conditions. The handling of the obtained submicro- or nanoscaled products, however, is difficult due to particle agglomeration and dust formation. To avoid these difficulties, the aim of this study was to develop a method for the controlled deposition of fine particles inside of preformed carriers using a precipitation process from supercritical solutions. Porous tablets with a diameter of 9 mm were made by gentle compression and drying of a mixture of microcrystalline cellulose pellets using an aqueous solution of hydroxyethylcellulose as binder. The porosity of these carriers was about 44 %, as calculated from the density determined by air comparison pycnometry and the dimensions of the tablets. As a model drug, ibuprofen was loaded into the tablets using supercritical carbon dioxide at a temperature of 313 K and a pressure of 25 MPa in a static pressure chamber, where both drug and carrier were present in separate compartments. The drug content in the carriers was 3.37±0.37 to 4.6±1.48 wt-%, depending on the experimental conditions. Dissolution of the drug at pH 7.4 from the carriers reached an extent of 82.17±3.85 % after 12 minutes, vs. only 53.0±6.70 % for the unprocessed starting material, establishing the CPD-method as suitable for the preparation of monolithic drug formulations, containing nanoscale particles, to be used for oral drug delivery.

INTRODUCTION

Today's drugs are often highly specific and potent, characteristics that are in most cases associated with a distinct lipophilicity. This, in turn, leads to poor solubility and/or low dissolution rate in physiological media. Because solubility as well as dissolution rate are major parameters affecting bioavailability, the design of novel concepts to improve dissolution characteristics is an increasingly important aspect of modern drug product development.

Particle size reduction offers a possibility to increase dissolution rate [1]. However, commonly used comminution techniques, e.g. milling, spray drying or recrystallization, have

disadvantages like mechanical or thermal strain on the processed substance, or the need for organic solvents.

Supercritical fluid processes like RESS offer possibilities for particle size reduction under mild operating conditions, without residual solvents [2]. Yet, collection, handling and further processing of the resulting submicron and nanoparticulate powders is difficult due to particle agglomeration and dust formation.

In this work, the Controlled Particle Deposition Method (CPD) [3], has been adapted to load preformed monolithic porous carriers with drug substance (ibuprofen), using supercritical carbon dioxide. The process yields a tablet containing fine drug particles. The product shows improved dissolution behaviour compared with the starting material, while handling and processing difficulties, caused by aforementioned RESS product disadvantages, can be avoided. Also, an evaluation of the obtained drug content, based on the calculation of an estimated drug content, is presented.

I – MATERIALS AND METHODS

1.1 Materials

Ibuprofen was generously supplied by Knoll Pharmaceuticals (UK). Cellets®, which were used for manufacturing porous tablets, were kindly provided by Pharmatrans Sanaq AG (Switzerland). Employed binders were hydroxyethylcellulose (HEC; Tylose H 20, Hoechst AG, Germany) and polyvinylpyrrolidone (PVP, Kollidon® 90 F, BASF AG, Germany). Sugar cubes (Würfelzucker, SÜDZUCKER AG, Germany) were also used as a porous carrier. Carbon dioxide (M = 44.01 g/mol, Air Liquide; Germany) was chosen as supercritical solvent since it is a non-flammable, inexpensive, and non-toxic solvent. N-hexane (fisher scientific, United Kingdom), acetonitrile (J.T. Baker, Netherlands) and water used in the HPLC assays were of gradient grade.

1.2 Manufacture of porous tablets

Carriers were prepared from microcrystalline cellulose pellets (Cellets®) with a binder solution (Tab. 1). A self-made apparatus was used to shape the mixtures into tablets with a diameter of 9 mm by gentle compression and subsequent drying at 40 °C.

Table 1: Composition of tablet mixtures

R1		R2	
Cellets®	2 parts	Cellets®	4 parts
HEC sol. 8 %	1 part	PVP sol. 5 %	1 part

1.3 Determination of tablet porosity

Porosity ε (Eq. 1), was determined for the manufactured tablets and the purchased sugar cubes, respectively. In Eq. (1) ε is the porosity, ρ_s the apparent density, calculated from tablet dimensions and corresponding weight and ρ_w is the true density, determined by air comparison pycnometry.

$$\varepsilon\,[\%] = \left(1 - \left(\frac{\rho_s}{\rho_w}\right)\right) \cdot 100 \qquad (1)$$

1.4 Preparation of ibuprofen-loaded tablets with the CPD method

The CPD experiments were carried out in a static pressure vessel (Fig.1) at a temperature of 40 °C and a pressure of 25 MPa. Ibuprofen and the carrier tablets were placed into their individual chambers inside the pressure vessel. The amount of ibuprofen used in the

experiments (16 g) results from the saturation solubility of ibuprofen in supercritical CO_2 at the chosen experimental conditions. The required amount of liquid carbon dioxide was condensed into the vessel and the system was heated to 40 °C. A piezo-resistive pressure gauge was used to determine the system pressure. After a period of 15.5 h, during which temperature and pressure were kept at the desired level, the system was depressurized to ambient pressure within 4 minutes.

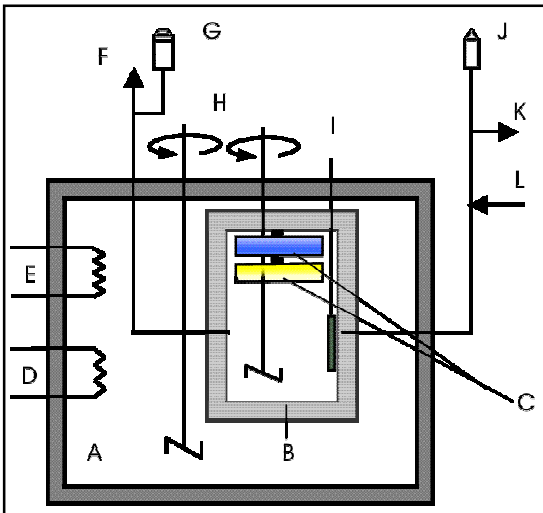


Figure 1: CPD apparatus. A) liquid thermostat, B) pressure vessel, C) carrier and drug container, D) heating, E) cooling, F) pressure-relief valve, G) pressure gauge, H) stirrer, I) temperature sensor, J) gas discharge safety valve, K) vacuum exhaust, L) inlet

1.5 Determination of drug content

Drug content of the carriers was determined by HPLC-UV. The HPLC system consisted of a Shimadzu LC-6A pump, a Shimadzu SPD-6A UV detector, a Shimadzu C-R6A integrator (Shimadzu Europe, Germany) and a Merk/Hitachi AS-200A autosampler (Merk/Hitachi, Germany). The chromatographic determinations were carried out on a Nucleosil 100-5 C18 (125 x 4) column (Macherey-Nagel, Germany), using acetonitrile-phosphate buffer (pH 4; 20 mM; 50:50, v/v) as an eluent at a flow rate of 1,5 ml/min. Injection volume was 20 µl and the effluent was monitored at 230 nm.

1.6 Sample preparation

Each CPD-loaded tablet was assayed individually. A powdered sample was suspended in n-hexane to separate the ibuprofen from the carrier material. The supernatant was filtered through a 0.45 µm cellulose filter (Sartorius, Germany), and an aliquot was evaporated under reduced pressure. The residue was then dissolved in the mobile phase and injected onto the column.

1.7 Dissolution studies

Dissolution studies were carried out using a dissolution model according to Stricker (Fig. 2) (Sartorius, Germany). Tablets were placed in a thermostated (37 °C) dissolution vessel containing 100 ml of dissolution medium (isotonic phosphate buffer, pH 7.4). Every 3 minutes, samples were withdrawn automatically and replaced with an equal amount of fresh dissolution medium. The samples were filtered through a membrane filter (Sartorius, Germany) and assayed photometrically at 264 nm.

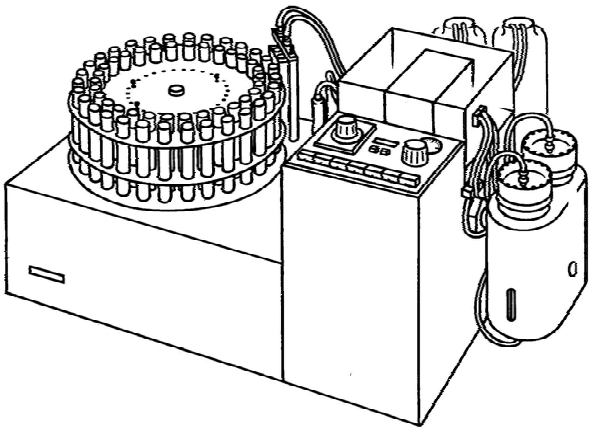


Figure 2: Stricker dissolution model

II – RESULTS AND DISCUSSION

2.1 Carrier porosity

The porosity ε of the carriers was 37.2 ± 0.5 % (mean ± S.D.; n = 3) for sugar cubes, 49.0 ± 2.2 % (n = 23) for carriers consisting of Cellets® and HEC (R1), and 49.5 ± 5.5 % (n = 31) for carriers made up of Cellets® and PVP (R2).

2.2 Drug content

For composition R1, a mean ibuprofen content of 3.9 ± 1.2 % (m/m) was obtained (Fig. 3a). Reducing the amount of ibuprofen in the loading chamber to 5.7 g resulted in a significant reduction of the ibuprofen content (Fig. 3a, rightmost column). For composition R2, a mean ibuprofen concentration of 4.5 ± 0.7 % (m/m) was obtained.

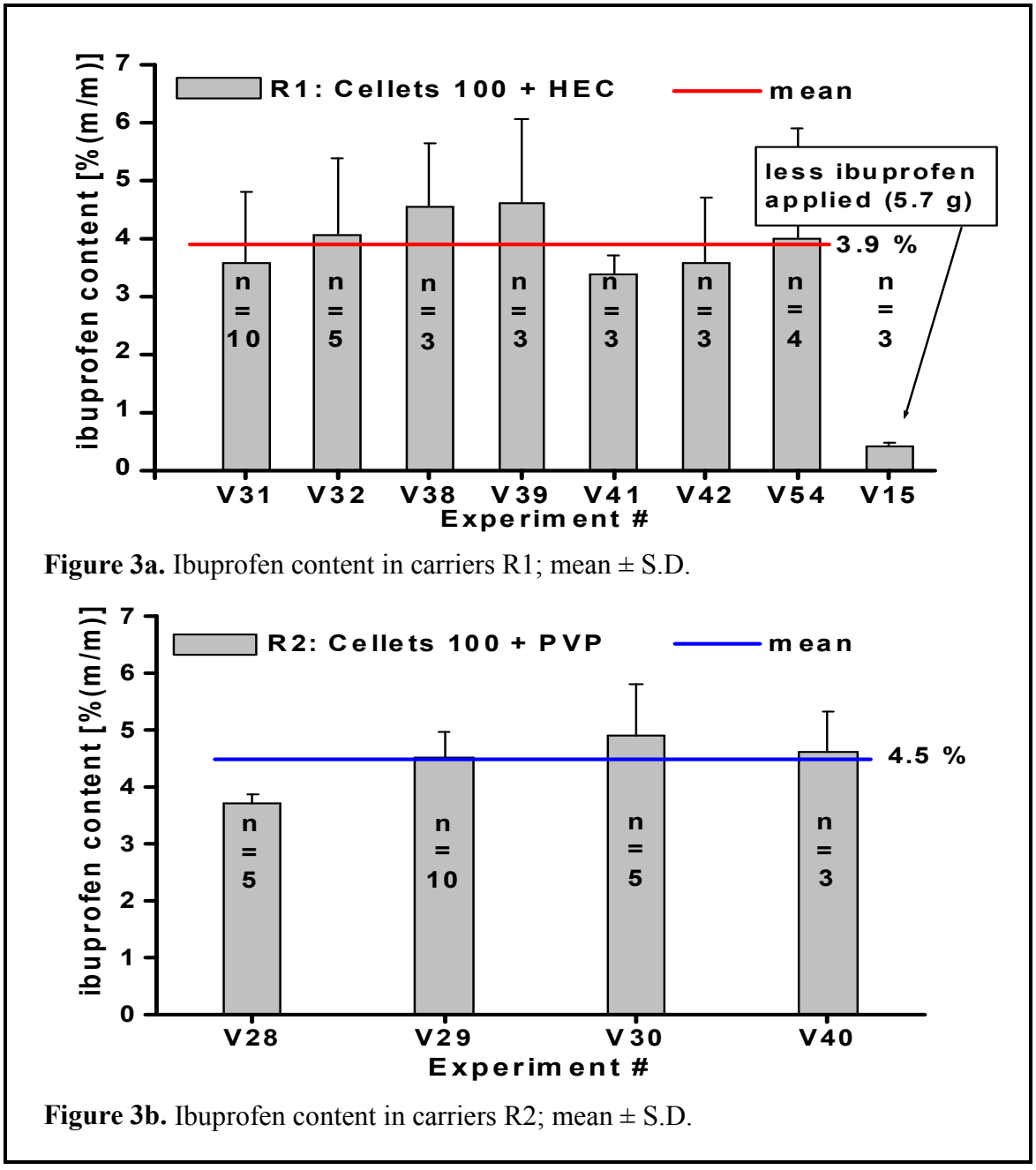


Figure 3a. Ibuprofen content in carriers R1; mean ± S.D.

Figure 3b. Ibuprofen content in carriers R2; mean ± S.D.

2.3 Evaluation of the drug content

An evaluation of the measured drug content was carried out to assess the efficiency of the loading process and the possibility to retrace loading results mathematically. For this purpose, the estimated drug content was determined and compared with the measured drug content. To obtain estimated ibuprofen concentrations, the following calculations were made:

The apparent volume of the carrier tablet V_{app} (Tab.2, Eq. 2) is calculated from carrier dimensions. The void volume V_{void} inside the carrier, which is penetrated by the supercritical solution, is calculated from porosity ε and V_{app} (Tab. 2, Eq. 3). The concentration of ibuprofen in the supercritical fluid $c_{ibuscCO2}$ is the quotient of the amount of ibuprofen used (m_{ibu}) and the volume of supercritical CO_2 in the pressure vessel V_{scCO2} (Tab. 2, Eq. 4) [4]. Finally, the estimated concentration of ibuprofen inside the carrier tablet c_{ibuest} is calculated from $c_{ibuscCO2}$, V_{void}, and the weight of the carrier tablet $m_{carrier}$ (Tab. 2, Eq. 5).

Table 2: Estimated drug content in carriers

Equations	Numerical example
$V_{app} = \pi \cdot r^2 \cdot h \ \left(m^3\right)$ (2)	$V_{app} = 8.41 \cdot 10^{-7} \ (m^3)$
$V_{void} = \varepsilon \cdot V_{app} \ \left(m^3\right)$ (3)	$V_{void} = 0.493 \cdot 8.41 \cdot 10^{-7} = 4.15 \cdot 10^{-7} \ (m^3)$
$c_{ibu\,scCO_2} = \frac{m_{ibu}}{V_{scCO_2}} \left(kg \cdot m^{-3}\right)$ (4)	$c_{ibuscCO_2} = \frac{0.016}{4.91 \cdot 10^{-4}} = 32.58 \ (kg \cdot m^{-3})$
$c_{ibu\,est} = \frac{c_{ibu\,scCO_2} \cdot V_{void}}{m_{carrier}} \cdot 100 \ \left(\%(m/m)\right)$ (5)	$c_{ibuest} = \frac{32.58 \cdot 4.15 \cdot 10^{-7}}{6.86 \cdot 10^{-4}} \cdot 100 = 1.93 \ (\%(m/m))$

Measured and estimated concentration are in acceptable agreement, showing good efficiency of the process, for higher and lower drug loading, respectively (Tab. 3).With constant porosity of the carriers, the ibuprofen loading concentration is controlled by the amount of drug present in the pressure vessel.

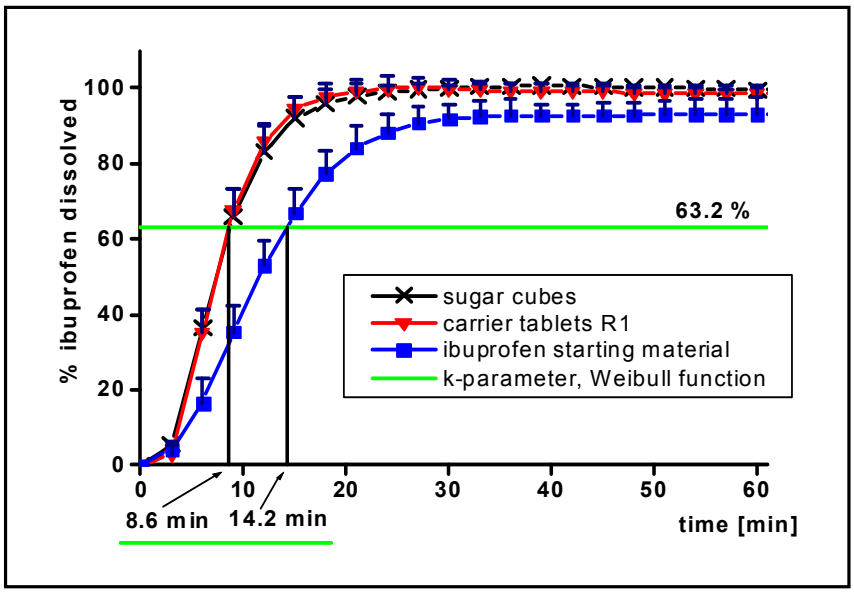
Table 3. Comparison of measured and estimated ibuprofen concentration in loaded carriers

carrier composition	measured conc. [%(m/m] (mean ± S.D.)	n	estimated conc. [%(m/m] (mean ± S.D.)	n
R1	3.9 ± 1.2	31	1.7 ± 0.3	31
R2	4.5 ± 0.7	23	2.2 ± 0.2	23
R1 (5.7 g ibuprofen)	0.41 ± 0.07	3	0.33 ± 0.06	3

2.4 Dissolution results

The dissolution profiles of two loaded carrier species, sugar cubes and carrier tablets R1 were recorded with the Stricker apparatus at pH 7.4. For comparison, the dissolution profile of the starting material was determined as well (ibuprofen, x_{50} = 50 µm). Both carrier species exhibited the same dissolution rate, which was increased in comparison to the starting material (Fig. 4). CPD-loaded carriers showed complete dissolution after 24 minutes, while

the starting material was not completely dissolved within 60 minutes. For further comparison, the k-parameter according to the Weibull function was used, indicating the time needed for 63.2 % of the drug to be dissolved [5]. Both loaded carrier materials reached this criterion faster by a factor of 1.65, with k = 8.6 min for loaded carriers and k = 14.2 min for the starting material.



III – CONCLUSION

The Controlled Particle Deposition method (CPD), a solvent-free supercritical process, was successfully applied to load tablets with fine particles of a model drug, ibuprofen. The loading results could be retraced mathematically by estimating an ibuprofen concentration inside the tablets. The calculations were based on parameters like carrier porosity, amount of ibuprofen used, and volume of supercritical carbon dioxide. Reasonable agreement of the results indicated good efficiency of the process. Loaded carriers showed, irrespective of the used carrier material, faster dissolution than the starting material. Thus, the CPD method is, indeed, a suitable and innovative technique for the preparation of tablets containing submicron particles with enhanced dissolution properties.

ACKNOLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (TU 93/6-1; WA 742/4-1).

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