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RESEARCH ARTICLE

Porous pellets as drug delivery system

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Abstract

Background: Multiparticulate drug delivery systems, such as pellets, are frequently used as they offer therapeutic advantages over single-unit dosage forms. *Aim*: Development of porous pellets followed by evaluation of potential drug loading techniques. *Method*: Porous microcrystalline pellets were manufactured and evaluated as drug delivery system. Pellets consisting of Avicel PH 101 and NaCl (70%, w/w) were prepared by extrusion/spheronization. The NaCl fraction was extracted with water and after drying porous pellets were obtained (33.2% porosity). Immersion of the porous pellets in a 15% and 30% (w/v) metoprolol tartrate solution, ibuprofen impregnation via supercritical fluids and paracetamol layering via fluidized bed coating were evaluated as drug loading techniques. *Results*: Raman spectroscopy revealed that immersion of the pellets in a drug solution and supercritical fluid impregnation allowed the drug to penetrate into the porous structure of the pellets. The amount of drug incorporated depended on the solubility of the drug in the solvent (water or supercritical CO_2). Drug release from the porous pellets was immediate and primarily controlled by pure diffusion. *Conclusion*: The technique described in this research work is suitable for the production of porous pellets. Drug loading via immersion the pellets in a drug solution and supercritical fluid impregnation resulted in a drug deposition in the entire pellet in contrast to fluid bed layering where drugs were only deposed on the pellet surface.

Key words: *Fluidized bed coating; immediate release; porous pellets; supercritical fluid impregnation*

Introduction

Multiparticulate drug delivery systems, such as pellets, are used frequently because they offer therapeutic advantages over single unit dosage forms. The drug delivery systems disperse freely in the gastrointestinal tract, and this action contributes to maximum drug absorption, reduced peak plasma fluctuations, and less side effects. Furthermore, pellets also allow the formulator to modify the drug release by coating the pellets, and a mixture of pellets with different release characteristics can be used to obtain the desired release profile[1]. The objective of the study was to develop porous pellets that allow the incorporation of a large drug fraction (deposited inside the porous structure or layered on the surface of the pellets). To this end, pellets consisting of Avicel PH 101 and sodium chloride (NaCl) were manufactured and after the removal of the NaCl fraction via extraction porous pellets were obtained. Their potential as drug carriers was tested by loading the pellets with drugs. Three techniques were evaluated as loading techniques to incorporate drugs into the porous pellets: fluidized bed layering, immersing the pellets in a drug solution, and supercritical fluid impregnation. Fluidized bed layering is the most commonly used technique to load pellets with drugs. Pellets are fluidized in the fluidized bed system and a drug solution or suspension is sprayed on the pellets[2]. Soaking the pellets in a drug solution is the simplest method to incorporate drugs into the pellet. The drugs are dissolved in an appropriate solvent and pellets are soaked in the solution for a certain time period[3]. Recently, supercritical impregnation was explored for the

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formulation of drug delivery systems[4]. This technique offers a number of advantages as it avoids organic solvents and heat. Generally, for successful impregnation, drugs should have sufficient solubility in the supercritical carrier and the partition coefficient should be favorable to enable drug loading in the matrix[5–8].

Materials and methods

Avicel PH 101 (microcrystalline cellulose) was obtained from FMC Biopolymer (Cork, Ireland). NaCl obtained from Alpha Pharma (Zwevegem, Belgium) was used as a pore forming agent.

Metoprolol tartrate (Esteve Quimica, Barcelona, Spain) was used as a model drug using the immersion of the pellet in a drug solution as loading technique. Ibuprofen (BASF, Ludwigshafen, Germany) was used as a model drug using supercritical fluid impregnation as drug loading technique. Paracetamol (Alpha Pharma, Zwevegem, Belgium) and hydroxypropylmethylcellulose (HPMC; Methocel E3) (Colorcon, Kent, UK) were used as a model drug and binder, respectively, using fluidized bed layering as the drug loading technique.

Manufacturing of porous pellets

NaCl was grinded in a ball mill (Pulverisette 6; Fritsch, Idar-Oberstein, Germany) for 10 minutes and the sieve fraction <125 μm was collected. Avicel PH 101 and NaCl were dry mixed (30/70, w/w) in a planetary mixer (Kenwood Major Classic). Subsequently, 42.5% (w/w) water was added to the mixture and the wet mass was granulated for 10 minutes. Extrusion was performed using a single screw extruder (Dome extruder lab model DG-L1; Fuji Paudal, Tokyo, Japan) at 50 rpm, equipped with a 1-mm perforated screen. The extrudates were spheronized on a spheronizer (Calvea model 15) with a cross-hatched friction plate, operating at 1000 rpm with a residence time of 5 minutes. The pellets were oven-dried at 40°C, followed by sieving whereby the 710–1400 μm pellet fraction was collected. The NaCl fraction was removed from the pellets by aqueous extraction: 30 g pellets were placed on to a 500 mL bottle top filter (0.22 μm) (Corning, New York, NY, USA), the filter was placed on a 2-L flask and connected to a vacuum pump. An aliquot of 2 L of water was poured on to the filter in steps of 250 mL to extract the NaCl fraction. Later, the pellets were oven-dried at 40°C.

Pellet evaluation

To determine the residual NaCl content after extraction, the amount of Na^+ ions in the porous pellets was quantified using atomic emission spectroscopy (AES) (Jenway PEP 7; Essex, England). An aliquot of 11 g of porous pellets were soaked in 100 mL demineralized water and after disintegration of the pellets (using magnetic stirrer) and centrifugation, the Na^+- concentration in the supernatant was determined (emission $\lambda = 589$ nm).

The friability was determined by placing 10 g pellets (F_s) in a abrasion wheel (together with 200 glass beads, diameter 4 mm) of a friabilator (PTFE, Hainburg, Germany). The pellets were subjected to falling shocks at a rotational speed of 25 rpm for 10 minutes. Later, the fine pellets were removed by sieving through a 250-μm sieve for 5 minutes (2 mm amplitude). The fraction above 250 μm (F_a) was used to calculate the friability using the following equation:

$$\text{Friability}(\%) = [(F_s - F_a)/F_s] \times 100 \quad (1)$$

The porosity and pore size distribution (0.003–360 μm) of the pellets were determined using mercury intrusion porosimetry (Autopore III, Norcross, GA, USA) and compared with conventional nonporous microcrystalline pellets (Pharmatrans Sanaq, Basel, Switzerland). Sample size (0.6–1.4 g) was adjusted to use 20%–80% of the stem volume. The sample was evacuated to 50 mm Hg, followed by low pressure mercury intrusion in a pressure range from 4.3 to 193 kPa, with a mercury filling pressure of 4.3 kPa, maximal intrusion volume of 100 mL/g, and an equilibration time of 10 s. Then, high pressure intrusion was performed in a pressure range from 207 to 41×10^4 kPa, with a mercury filling pressure of 4.3 kPa, maximal intrusion volume of 100 mL/g, and an equilibration time of 10 second.

Pellet size and shape were determined using an image analysis system. Photomicrographs were taken using a digital camera (Camedia C-3030 Zoom; Olympus Optical, Tokyo, Japan). Obtained images were processed by using image analysis software (AnalySIS®; Soft Imaging System, Münster, Germany) to characterize each individual pellet by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°), aspect ratio (AR) (ratio of the longest FD and its longest perpendicular diameter), and two-dimensional shape factor (e_R)[9]:

$$e_R = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \quad (2)$$

where r is the radius, P_m is the perimeter, l is the length (longest FD), and b is the width (longest perpendicular diameter to the longest FD) of the pellet.

The surface roughness of the pellets was evaluated using Autoprobe® CP atomic force microscopy (AFM; Park Scientific Instruments, Sunnyvale, CA, USA). Scanning was performed in contact mode by using a cantilever

(UL20 B) operating at a scan rate of 1 Hz. The maximum peak-to-valley distance (Rp-V), the average roughness ($R_{ave} = \sum_{n=1}^{N} \frac{|Z_n - \bar{Z}|}{N}$, i.e., the average deviation of all heights Z_n measured in the scanned region from the mean height), the median height, and the mean height (calculated from all heights measured in the scanned region) were determined.

Scanning electron microscopy (SEM) (JSM-5510; JEOL, Tokyo, Japan) was used to visualize the porous structure of the pellets. Pellets were coated with a gold layer using a sputter coater (Autofine Coater, JFC-1300; JEOL, Tokyo, Japan) to assure conductivity.

Drug loading

Three techniques were evaluated to incorporate drugs into the pellets: (a) immersing the pellets into a drug solution, (b) supercritical fluid impregnation, and (c) fluid bed layering.

Method (a): 1 g of porous pellets ($n = 3$) was added to 100 mL of a metoprolol tartrate solution (15% and 30%, w/v). After 5 minutes, 24 hours, and 48 hours, the pellets were separated using a sieve (250 μm) and then oven-dried at 40°C.

Method (b): Supercritical fluid ($scCO_2$) was used to impregnate porous pellets with ibuprofen using Separex® equipment (Champigneulles, France). At a pressure between 80 and 220 bar and a temperature from 35°C to 45°C, the solubility of ibuprofen in $scCO_2$ was found to be in the range from 10^{-5} to 10^{-3} mole fraction[10]. During the impregnation experiment, $scCO_2$ (in which ibuprofen is dissolved) enters the pores of the pellets under pressure. Following a depressurization step, the drug is deposed in the internal pore structure of the pellet. The impregnation vessel (volume: 17 mL) was filled with 500 mg porous pellets. Ibuprofen was placed on top of the pellets and for 45 minutes the vessel was pressurized at a constant operating temperature. To optimize the impregnation process, the influence of the experimental parameters (temperature, pressure, and the amount of ibuprofen relative to the amount of pellets used) was studied by using an experimental design. Preliminary experiments were carried out to establish appropriate ranges for the processing variables. The amount of ibuprofen varied from 50% to 150% relative to the amount of pellets used, the pressure varied between 150 and 250 bar while the temperature varied from 35°C to 45°C. The upper limit of the amount of ibuprofen was limited to avoid overfilling of the impregnation vessel. In addition, the upper and lower limits of temperature and pressure were selected to ensure the solubility of ibuprofen in $scCO_2$. Because interaction between the variables were expected, the following quadratic model was proposed:

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{3} \sum_{j=i+1}^{3} \beta_{ij} X_i X_i + \sum_{i=1}^{3} \beta_{ii} X_{i^2} \qquad (3)$$

where Y is the response; X_j and X_j are the set points of the process variables 'i' and 'j,' respectively; and β_0, β_i, β_{ij}, and β_{ii} are the coefficients.

The design points were chosen by using the software (Design-Expert version 6.0.10; Stat-Ease Inc., Minneapolis, MN, USA). Eighteen experiments were carried out using a face-centered central composite statistical design for the study of the three variables, each at three levels. The amount of ibuprofen impregnated in the pellets was the response variable. Repeated observations ($n = 4$) at the center point (temperature: 40°C; pressure: 200 bar; ibuprofen concentration: 100%, w/w) were used to estimate the experimental error. Manual regression was performed. The highest order significant polynomial (significance threshold: 0.05) was selected, where only significant model terms were included without destroying the model hierarchy. Outlier-t limit was set at 3.5. The probability plot of the residuals was performed to evaluate the model and to detect outliers. The model provided several comparative measures for model selection: (a) R^2 statistics, which give a correlation between the experimental response and the predicted response, should be high for a particular model to be significant; (b) adjusted R^2, which gives a similar correlation after ignoring the insignificant model terms, should have a good agreement with predicted R^2 for the model to be fit[11]; (c) predicted and adjusted R^2 should be within 0.20 of each other. Contour plots for the response were drawn.

Method (c): Aqueous coating solutions containing 1% (w/v) paracetamol and 0%, 0.5%, 1%, or 1.5% (relative to the amount of pellets used) HPMC (Methocel E3) were prepared. An aliquot of 4 L of each coating solution was sprayed on the pellets (batch size: 300 g) in a fluid bed (GPCG 1; Glatt, Binzen, Germany) using a Wurster setup. The operating conditions while coating were set at 20 g/min spray rate, 1.5 bar atomization pressure, 38°C outlet temperature, and 4 hours process time. The same procedure was performed using nonporous microcrystalline cellulose pellets (Pharmatrans Sanaq, Basel, Switzerland). On the basis of the theoretical amount of paracetamol layered on the pellets, the coating efficiency was calculated.

Characterization of the drug-loaded pellets

The distribution of the drug throughout the pellets was evaluated by Raman spectroscopic mapping. A pellet was cut into two halves and the inner surface of the pellet was scanned in point-by-point mapping mode with a step

size of 50 μm in both the *x* and *y* directions using a long working distance objective lens (spot size laser = 50 μm). The detection system used in this study was a RamanRxn 1 Microprobe (Kaiser Optical Systems, Ann Arbor, MI, USA), equipped with an air-cooled CCD detector (back-illuminated deep depletion design). The laser wavelength during the experiments was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded at a resolution of 4 cm^{-1} using a laser power of 400 mW and a laser light exposure time of 15 second per collected spectrum. Before data analysis, spectra were baseline corrected. Data collection and data analysis were performed by using the HoloGRAMS™ data collection software package, the HoloMAP™ data analysis software package, and the Matlab® software package (version 6.5).

Raman spectroscopy was also used to characterize the solid state of ibuprofen on the pellet surface as well as inside the pellet. X-ray diffraction was carried out to confirm the results obtained using Raman spectroscopy.

For the determination of the loading yield (mg drug/g pellets), the pellets were crushed, placed in a solvent (water for metoprolol tartrate and paracetamol, and phosphate buffer, pH 7.2, for ibuprofen), and stirred for 30 minutes, followed by centrifugation. The amount of drug in the supernatant was determined using UV spectroscopy.

Drug release

Drug release from the porous pellets was determined using the USP II method (VanKel VK 8000; VanKel Industries, Chatham, NJ, USA) with a paddle speed of 50 rpm and at a temperature of 37 ± 0.5°C. Phosphate buffer (pH 7.2) was used as a dissolution medium for ibuprofen pellets and water for metoprolol tartrate and paracetamol pellets. Samples were collected at different time points and analyzed using a UV/VIS double beam spectrophotometer (Perkin-Elmer, Zaventem, Belgium) at 265, 222, and 243 nm for ibuprofen, metoprolol tartrate, and paracetamol, respectively.

The following analytical solution of Fick's second law of diffusion was used to describe metoprolol tartrate and ibuprofen release from the porous pellets[12]. This model considers that drug release is purely diffusion-controlled, that the drug is molecularly dispersed within the pellets at $t = 0$, and that perfect sink conditions are maintained throughout the experiments:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left(-\frac{\mathrm{n}^2 \cdot \pi^2}{\mathrm{R}^2} \cdot \mathrm{D} \cdot t \right)$$

where M_∞ and M_t denote the absolute cumulative amounts of drug (mg) released at infinite time and time *t*, respectively; *R* represents the radius of the pellets; and *D* the apparent diffusion coefficient of the drug within the system.

Results and discussion

Characterization of porous pellets

Preliminary experiments were carried out to determine the maximum concentration of pore forming agent (NaCl), which could be incorporated into the pellet formulation. The results showed that the concentration was limited to 70% (w/w) as at a higher NaCl fraction the mass could not be extruded.

Image analysis revealed an AR ($n = 303 \pm$ SD) of 1.15 ± 0.08, an e_R of 0.94 ± 0.03, and FD of 946 ± 142 μm, indicating that spherical pellets were obtained, and 89.1% of the pellets was found in the 710–1400 μm size range.

Most of the NaCl fraction was removed during aqueous extraction as analysis of the porous pellets using AES determined the residual NaCl content at 4%.

The porosity and median pore diameter of the porous microcrystalline cellulose pellets were 33.2 ± 0.8% and 0.7 ± 0.2 μm, respectively, whereas the corresponding values of conventional nonporous MCC pellets were 15.1 ± 1.2% and 0.02 ± 0.01 μm. Although almost 70% NaCl was removed from the porous pellets by extraction, their porosity was only 33.2% due to the shrinkage of the pellets during drying. Despite their high porosity, the porous pellets were sufficiently strong to withstand the friction forces during handling as the friability was below 0.1%. AFM showed that the surface of the porous pellets was more irregular and rough compared with nonporous pellets: all AFM parameters (Rp-V, average roughness, mean height, and median height) were higher in the case of porous MCC pellets (Table 1). The difference in porosity between the conventional nonporous and porous pellets was visualized using SEM (Figure 1).

Table 1. Analysis of surface structure via atomic force microscopy of conventional nonporous pellets and porous pellets (manufactured by means of NaCl extraction).

	Rp-V (μm)	R_{ave} (μm)	Mean height (μm)	Median height (μm)
Nonporous pellet	1.33	0.12	0.55	0.28
Porous pellet	3.47	0.47	1.86	1.77

Rp-V: maximum peak-to-valley distance;

$R_{ave}: \sum_{n=1}^{N} \frac{|Z_n - \bar{Z}|}{N}$, the average deviation of all heights z_n measured in the scanned region from the mean height.

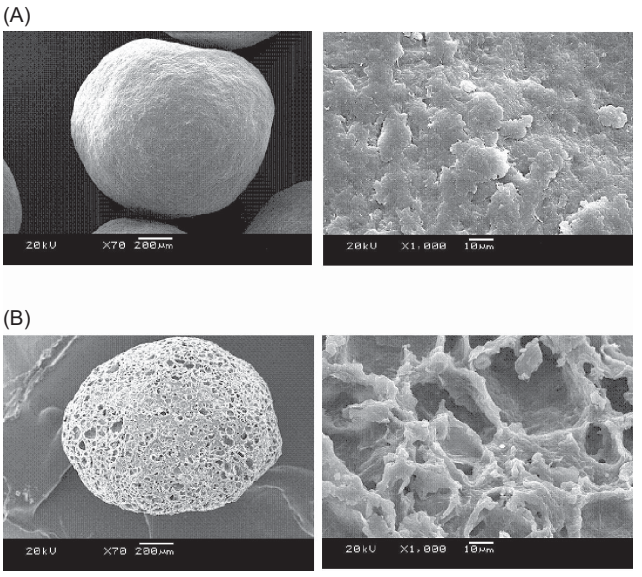

Figure 1. SEM micrographs of the surface of (A) conventional non-porous pellets and (B) porous pellets.

Drug loading experiments

Several drug loading techniques were tested to maximize drug deposition in the porous structure of the pellets. For each technique, a model drug was used that had a good solubility in the solvent used.

After soaking the porous pellets for 5 minutes in a 15% and 30% (w/v) metoprolol tartrate solution (n = 3), the drug load was 208 ± 7 and 489 ± 2 mg/g pellets, respectively. A longer soaking time resulted in a higher drug load: 273 ± 13 mg/g pellets after 24 hours in a 15% (w/v) metoprolol tartrate solution (n = 3). However, after 48 hours soaking the drug load did not increase further. Immersion of the pellets in a 30% metoprolol tartrate solution resulted in a dramatic increase in the amount of metoprolol tartrate absorbed (616 ± 21 mg/g pellets). Raman spectroscopy revealed that this technique allowed to deposit drug in the inner pore structure because the solution can easily penetrate inside the porous network and after drying the drug is deposited in the pores. Figure 2 exemplarily shows that the Raman signal of metoprolol tartrate (encircled peaks in the spectrum, spectral range 627–652 and 806–867 cm^{-1}) was detected at the surface of the pellets as well as inside the pellets, indicating that the drugs was distributed homogeneously after 24 hours immersion of the pellets in a 15% metoprolol tartrate solution. All drug-loaded pellets had a friability below 1%.

Supercritical fluid impregnation using CO_2 was evaluated as a second drug loading technique. Analysis of variance of the response factor (Table 2) indicated that

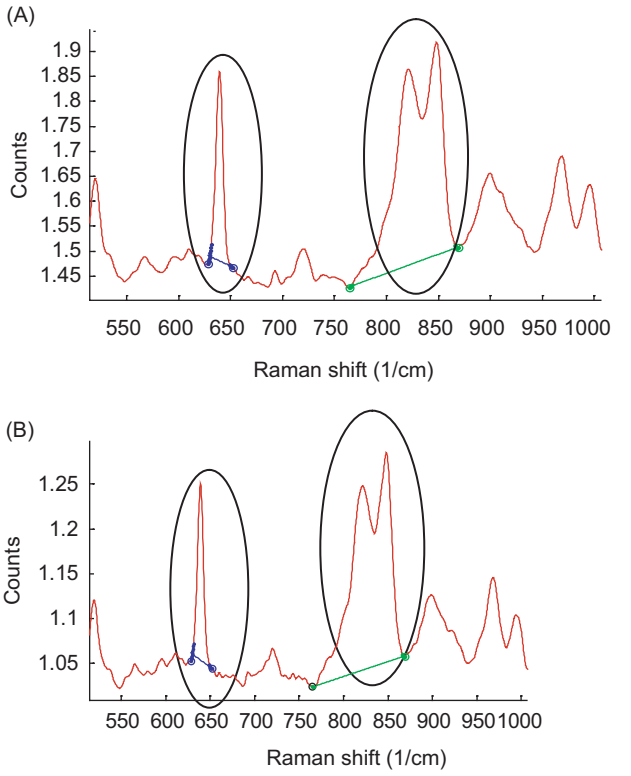

Figure 2. Raman spectra of porous pellets loaded via immersion in a 15% (w/v) metoprolol tartrate solution. Spectra recorded at (A) surface of the pellet and (B) inside the pellet.

Table 2. ANOVA results of face-centered control composite statistical design for drug loading of porous pellets via supercritical fluid impregnation.

Source	Sum of squares	Mean square	*F*-value	Prob > *F*
Model	7.37	0.92	664.48	<0.0001
A: Temp	5.15	5.15	3716.10	<0.0001
B: Pressure	0.053	0.053	38.57	0.0004
C: IBU (%)	0.82	0.82	590.29	<0.0001
A^2	1.57	1.57	1131.00	<0.0001
B^2	0.053	0.053	37.96	0.0005
C^2	0.043	0.043	30.95	0.0008
AB	0.084	0.084	60.43	0.0001
AC	0.099	0.099	71.32	<0.0001
Residual	9.700E-003	1.386E-003		
Lack of fit	3.458E-003	8.646E-004	0.42	0.7922
Pure error	6.241E-003	2.080E-003		

the response surface model developed for drug loading was significant, without a significant lack of fit. The model summary statistics for the selected significant model showed that R^2 (0.9987), predicted R^2 (0.9905), and adjusted R^2 (0.9972) are in good agreement, resulting in a reliable model. The drug loading of run 9 and 14 was classified as an outlier. The fitted response

surface model in terms of coded factors for the drug loading was

$$\begin{aligned}\text{Ln(drug loading)} = {} & 2.89 + 0.94^{*}\text{A} - 0.084^{*}\text{B} + 0.33^{*}\text{C} \\ & - 0.98^{*}\text{A}^2 + 0.15^{*}\text{B}^2 + 0.14^{*}\text{C}^2 \\ & - 0.12^{*}\text{A}^{*}\text{B} - 0.13^{*}\text{A}^{*}\text{C}\end{aligned} \quad (4)$$

where *A* is the temperature, *B* is the pressure, and *C* is the amount of ibuprofen relative to the amount of pellets used. On the basis of Equation (4), contour plots of the response value in function of the variables are presented in Figure 3.

The highest ibuprofen concentration (342 mg/g pellets) within the set of parameters tested was achieved when the temperature and pressure were set at 45°C and 150 bar and when 150% (w/w) ibuprofen (relative to the amount of pellets used) was used (Table 1). The loading experiment at the center point was carried out four times, yielding a mean drug load of 180 ± 8.5 mg ibuprofen/g pellets, indicating that this procedure was reproducible. At constant drug amount dissolved in $scCO_2$ (Figure 3A) or at constant pressure (Figure 3B), the amount of ibuprofen deposited in the porous pellets was mainly determined by temperature: a higher temperature resulted in more drug deposition due to the higher solubility of ibuprofen in $scCO_2$. Combining a high temperature with a high pressure reduced the amount of drug deposited despite the higher solubility of ibuprofen under these conditions (Figure 3A). This could be an indication that at these conditions the interaction between ibuprofen and the supercritical fluid is stronger compared with the interaction between drug and pellets because a stronger interaction between the solute and CO_2 is detrimental for the bonding forces between solute and matrix[8,13]. After drug loading, the friability of the pellets was below 0.1%.

Raman spectroscopy of the pellets with the highest drug load (342 mg ibuprofen/g pellets) revealed that the drug was deposited on the surface as well as inside the porous pellet, as for all the mapped areas the specific spectrum of ibuprofen (spectral range: 624–645, 731–762, and 808–843 cm^{-1}) was detected. Raman spectroscopy also showed that ibuprofen was deposited on the surface and inside the pellet as a crystalline material, and this was confirmed using X-ray diffraction (data not shown).

Layering of the pellets with a drug solution using fluidized bed coating was also examined for drug loading because this technique is commonly used for loading inert spheres with drugs. The coating efficiency after 4 hour layering with a 1% (w/v) paracetamol solution and increasing amounts of binder (Methocel E3) are presented in Figure 4. The difference in coating efficiency between the nonporous (16.5%) and the porous pellets (61.7%) is most pronounced without binder, resulting in a drug load of 97.6 mg paracetamol/g porous pellets. The

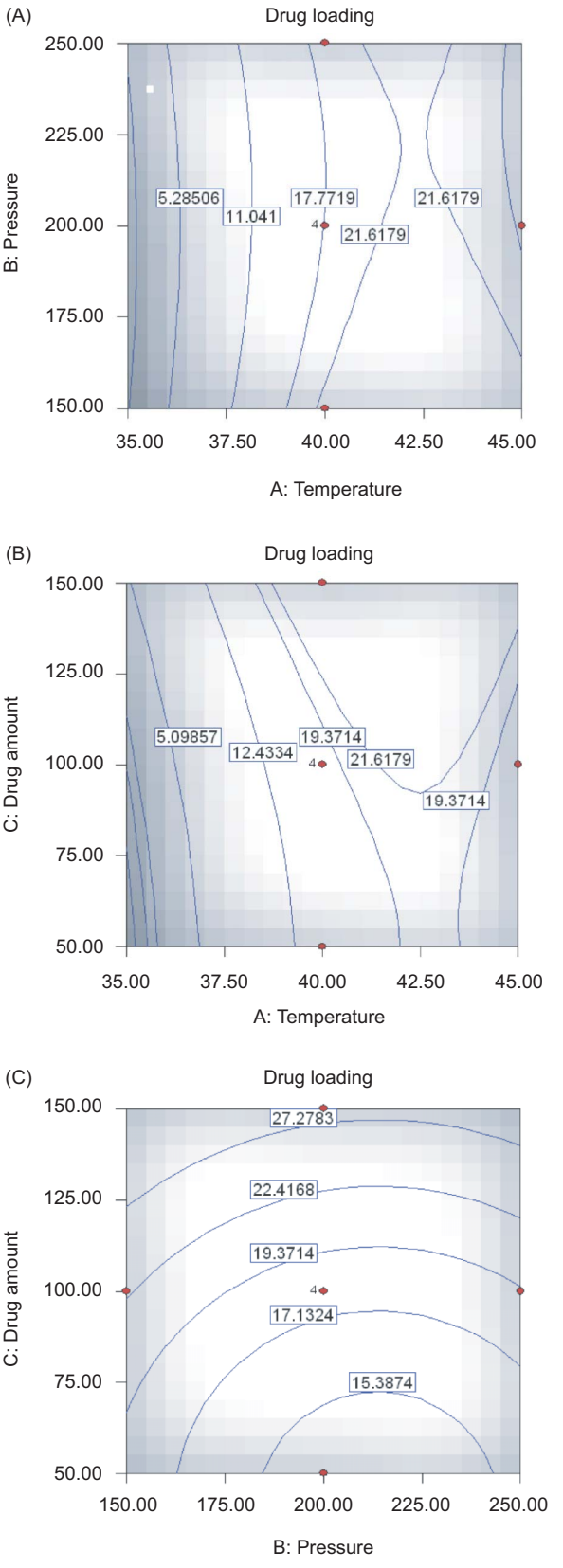

Figure 3. Contour plots for drug loading of porous pellets at (A) constant ibuprofen amount: 100% (relative to the amount of pellets used); (B) constant pressure: 200 bar; and (C) constant temperature: 40°C.

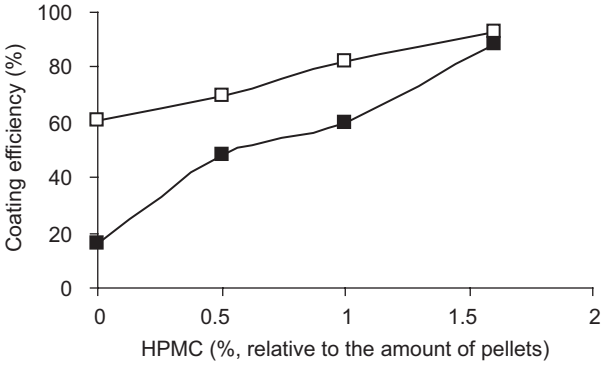

Figure 4. Coating efficiency (%) of paracetamol on nonporous (closed squares) and porous pellets (open squares) in the function of Methocel E3 concentration in the coating solution.

irregular surface of the porous pellets compared to the nonporous pellets (Figure 1) contributed to the difference in drug loading when no binder was used. The irregular surface of the porous pellets facilitated the sticking of the drug particles to the surface compared with the smoother surface of conventional nonporous pellets. When a binder is added to the coating solution, the drug particles are attached to the pellet surface independently of the morphology of their surfaces. The friability of the porous pellets after drug loading was in all cases <0.1%, whereas for the nonporous pellets the friability was higher (0.9%). Owing to the irregular surface of the porous pellets, the drug particles are better protected against friction during friability testing. A layering experiment was performed whereby the spray rate was gradually increased until agglomeration of the pellets occurred, in order to investigate the maximum spray rate that could be obtained. For porous pellets, a maximum spray rate of 35 g/min was obtained. In contrast, for nonporous pellets agglomeration already occurred at a spray rate of 20 g/min. The irregular surface of the porous pellets facilitated the evaporation of the coating liquid and its porous structure was able to improve the drainage of water from its surface. Raman spectroscopy (Figure 5) of the pellets coated with a 1% (w/v) paracetamol/1% (relative to the amount of pellets used) Methocel E3 solution identified that paracetamol (spectral range: 1587–1673 cm^{-1}) was only present at the surface of the pellet. The absence of drug inside the pellets was probably due to limited penetration of the drug solution within the pellets as most of the water evaporated once the droplet was distributed on the pellet surface.

Drug release from porous pellets

Figure 6 exemplarily shows the in vitro release profile of ibuprofen from the porous pellets loaded by supercritical fluid impregnation. Clearly, most of the drug is released within less than 10 minutes. Even higher release rates

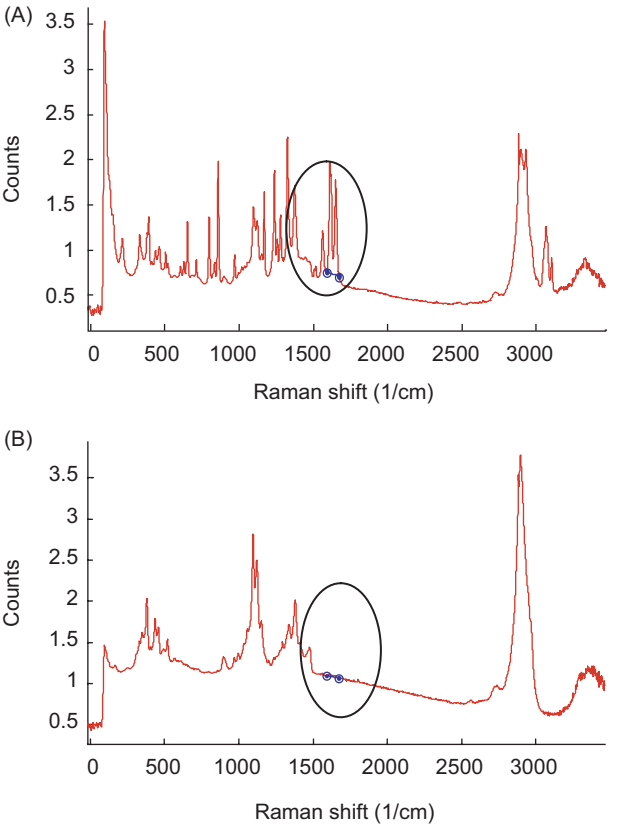

Figure 5. Raman spectra of porous pellets loaded with paracetamol via fluid bed coating. Spectra recorded at (A) surface of the pellet and (B) inside the pellet.

were observed with metoprolol tartrate-loaded pellets, irrespective of the concentration of the soaking solution (data not shown). Fitting of an appropriate analytical solution of Fick's second law of diffusion (considering the given initial and boundary conditions, Equation 1) to the experimentally determined drug release kinetics showed a good agreement between theory and experiment. As an example, Figure 6 shows the theoretical release profile of ibuprofen from the porous pellets (curve) and the experimentally measured values (symbols). Diffusion is the governing mass transport mechanism in these systems, irrespective of the type of drug and concentration. On the basis of these calculations, the apparent diffusion coefficients of the drugs within the porous pellets could be determined: $D = 4.8 \pm 0.2 \times 10^{-8}$ cm^2/s for ibuprofen and $1.5 \pm 0.1 \times 10^{-6}$ cm^2/s for metoprolol tartrate, respectively.

The paracetamol release from layered porous pellets was immediate (data not shown).

Conclusion

Porous pellets manufactured by the extraction of NaCl from Avicel PH 101-NaCl pellets can be used as drug

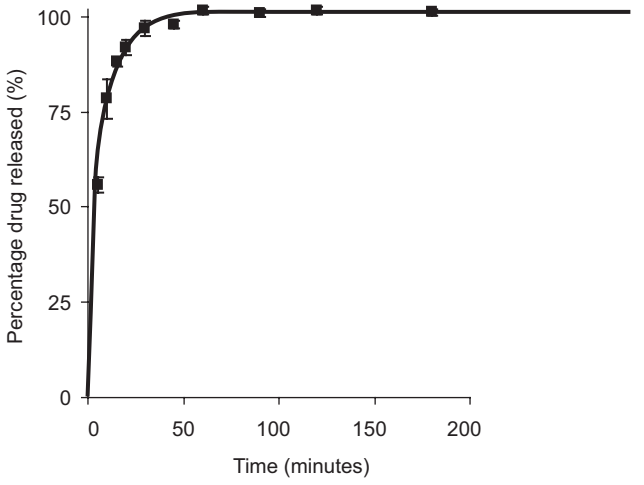

Figure 6. In vitro drug release from ibuprofen-loaded, porous pellets: experimental (symbols, $n = 3$, ± SD) versus theoretical (curve, Equation 1) profiles.

carriers. The drug loading studies have shown that immersing the pellets in a drug solution and supercritical fluid impregnation are able to deposit drugs inside the porous pellets. By using fluidized bed coating on the other hand, no drug was found inside the porous pellets.

Drug release from the porous pellets is immediate and primarily controlled by diffusion.

Declaration of interest: The authors report no conflicts of interest.

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