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Research paper

Porous hydroxyapatite tablets as carriers for low-dosed drugs

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Abstract

The present study evaluated an innovative technique for the manufacturing of low-dosed tablets. Tablets containing hydroxyapatite and a pore forming agent (50% (w/w) Avicel PH 200/20, 37.5% and 50% corn starch/37.5% sorbitol) were manufactured by direct compression followed by sintering. The influence of pore forming agent (type and concentration), sinter temperature and sinter time on tablet properties was investigated. Sintering (1250 °C) revealed tablets with an acceptable friability (<1%). Using 50% (w/w) Avicel PH 200 as pore forming agent resulted in tablets combining the highest porosity (50%) and the highest median pore diameter (5 μm). Aqueous drug solutions (metoprolol tartrate, riboflavin sodium phosphate) were spiked on the tablet surface. The maximum volume of drug solution absorbed was limited (2 × 100μl), revealing that these porous carriers were ideal for low dosed formulations. Drug release from the tablets was slow, independent of the drug. To accelerate drug release, tablets were manufactured using a modified gelcasting technique yielding tablets with a median pore size of 60 and 80 μm. Release from these tablets was drastically increased indicating that the permeability of the tablets was influenced by the pore size, shape and connectivity of the porous network. Changing and controlling these parameters made it possible to obtain drug delivery systems providing different drug delivery behaviour.
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Keywords: Hydroxyapatite; Low-dosed drugs; Sintering; Porous tablet; Modified gelcasting technique

1. Introduction

A major challenge during the manufacturing of tablets containing low-dosed drugs is to ensure drug content uniformity of all units. To achieve this, the formulator can resort to several strategies in case of tablet production via direct compression: optimisation of particle size and shape, selection of specific excipient grades, use of appropriate mixers, formation of ordered mixture [1]. When these are unsuccessful to obtain content uniformity, wet granulation of the powder mix can be used to agglomerate drug and excipients. However, these approaches cannot completely eliminate the risk of particle segregation [2]. The objective of this study was to evaluate an innovative technique for the manufacturing of low-dosed tablets. To this end porous calcium phosphate scaffolds were prepared and spiked with a drug solution (100–200 μl). After absorption of the solution in the porous structure of the tablet and evaporation of the solvent, a tablet-shaped dosage form is obtained having the drug incorporated in its inner pores. This approach would minimize the risk of drug inhomogeneity in the tablets as the drug dose per tablet only depends on the volume spiked on each tablet and small volumes of liquid can be dosed with very high accuracy.

Scaffolds based on calcium phosphate were selected as a carrier. These porous ceramics are already well established as bone implants and they have a proven track record as

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bio-safe and bio-compatible material [3]. The pores in these calcium phosphate implants are not only essential for the ingrowth of bone tissue, they also allow to incorporate a drug in the bone implants for local drug delivery [4,5].

In the research work, presented in this paper, the porous hydroxyapatite matrices were mainly manufactured by direct compression of hydroxyapatite (HA) and an organic material, followed by removal of the latter via heat treatment. To obtain a strong tablet, the resulting porous HA skeleton is consolidated at higher temperatures due to the densification of the HA particles by mass transport (sintering at 800–1250 °C) [6,7].

The pore forming agent, its concentration, sinter time and sinter temperature were varied to investigate their influence on the quality of the porous matrix. After selecting an appropriate matrix, its potential as drug carrier of low-dosed drugs was evaluated based on the drug loading capacity of the HA tablets and on the drug release profiles in different dissolution media (metoprolol tartarte and riboflavin sodium phosphate were used as model drugs).

2. Materials and methods

2.1. Materials

Hydroxyapatite (HA, Ca/P-ratio: 1.667) was obtained from Acros Organics (Geel, Belgium). Avicel PH 200 (microcrystalline cellulose) (FMC Biopolymer, Cork, Ireland), corn starch (Amylum, Koog a/d Zaan, the Netherlands) and sorbitol (Sorbidex P 16616) (Cerestar, Mechelen, Belgium) were used as pore forming agents. Magnesium stearate (Alpha Pharma, Zwevegem, Belgium) was added as lubricant. Riboflavin sodium phosphate (Certa, Braine-l'Alleud, Belgium) and metoprolol tartrate (Esteve Quimica, Barcelona, Spain) were selected as model drugs.

2.2. Manufacturing of porous tablets

Tablets (∅13.5 mm, flat edged, 550 mg) consisting of HA, a pore former and magnesium stearate (2%) were prepared via direct compression (14.5 kN) using an instrumented eccentric press (Korsch type EK0, Berlin, Germany). Avicel PH 200 (50%, w/w), corn starch (20%, 37.5% and 50%, w/w) and sorbitol (37.5%, w/w) were added as pore formers. Prior to compression powder blends were prepared via physical mixing (using a tumbling mixer) of the materials as received from the suppliers or after a preprocessing step. During preprocessing, agglomerates of HA and pore formers were removed to ensure a homogeneous distribution of the pore former inside the tablet. Therefore, 50 g HA was suspended in 150 ml acetone and this suspension was ground in a ball mill (containing 25 grinding balls, ∅10 mm) (Pulverisette 6, Fritsch, Idar-Oberstein, Germany) during 15 min (grinding speed 500 rpm). Afterwards the pore forming agent was added to the suspension and ground for 5 min at 250 rpm. After evaporation of the acetone fraction, 2% magnesium stearate was added to the HA/pore former-mixture.

After compression the tablets were sintered in a chamber furnace (Thermoconcept, Bremen, Germany) at 800, 1000 and 1250 °C during 1, 3 and 5 h. After cooling down (2 °C/min) to room temperature the properties of the porous tablet were evaluated.

2.3. Tablet evaluation

The tablet strength was measured using a tensile strength bench (Type L1000R, Lloyd Instruments, Segenworth, Fareham, United Kingdom) operating at a crosshead speed of 8 mm/min. The tablet crushing strength was determined based on the force (N) required to break the tablet diametrically.

The tablet friability was determined in a Pharmatest-friabilator (PTFE, Hainburg, Germany) using the method described in the European Pharmacopoeia 5 (rotating 20 tablets inside a drum for 4 min at 25 rpm).

The tablet porosity was calculated based on the skeletal volume (V_s) and the apparent volume (V_a) of the tablets Eq. (I). The skeletal volume was measured using helium pycnometry (Accupyc 1330, Norcross, GA, USA), while the apparent volume was calculated from the height and radius of the tablet.

$$[(V_a - V_s)/V_a] \times 100 = \text{porosity } (\%) \quad \text{(I)}$$

The pore size distribution (0.003–360 μm) of the sintered tablets was determined using mercury intrusion porosimetry (Autopore III, Norcross, GA, USA).

Scanning electron microscopy (SEM) was used to visualize the porous structure of the tablets. Tablets were coated with a gold layer using a sputter coater (Autofine Coater, JFC-1300, JEOL, Tokyo, Japan) to assure conductivity. The SEM micrographs were obtained using a scanning electron microscope (JSM-5510, JEOL, Tokyo, Japan).

For the determination of the three-dimensional internal structure of the samples, the nano-CT scanner of the UGCT facility (www.ugct.ugent.be) was used. This scanner combines a transmission X-ray tube (Feinfocus) with a focal spot size of 900 nm and as X-ray detector, a 4008×2667 pixel CCD camera (Photonic Science). The commercially available reconstruction software "Octopus" was used for the conversion of the raw images into the reconstructed cross-section. Data about the 3D structure were obtained by using the 3D analysis software "μCTanalySIS [8], providing parameters like total porosity, number of pores, volume of each pore together with its maximum inscribed and equivalent diameter. The maximum inscribed diameter is defined as the diameter of the largest sphere that can be enclosed in the volume and the equivalent diameter is the diameter of a spherical pore with the same volume as the pore (non-spherical) being examined. Combining the data of the maximum inscribed diameter (d_{max}) and the equiva-

lent diameter (d_e) provides information about the structure of the pores.

To determine the thermostability of hydroxyapatite at high temperatures, the X-ray pattern of tablets sintered at 1250 °C was compared with the X-ray pattern of pure unsintered hydroxyapatite powder. The X-ray patterns were obtained using a D5000 Cu Kα Diffractor ($\lambda = 1.54$ A) (Siemens, Karlsruhe, Germany) with a voltage of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

2.4. Drug loading

Riboflavine sodium phosphate and metoprolol tartrate were incorporated in the tablets as highly water soluble model drugs. Therefore, an aqueous drug solution (100, 150 and 200 μl) of riboflavine sodium phosphate (3.7%, w/v) or metoprolol tartrate (1.5%, 4%, 15% and 40%, w/v) was spiked on one side of the tablet. After absorption of the liquid into the porous inner structure of the tablet, they were oven-dried for 8 h at 40 °C. Afterwards, the same procedure was done at the other side of the tablet.

The surface tension of the drug solutions was determined by a dynamic 'Wilhemy Plate' method whereby a strip of cellulose chromatography paper (Whatman Chr 1, smooth surface, 0.18 mm tick with a lineair flow rate for water of 130 mm/30 min) is lowered into the solution. The plate was brought in the solution during 10 s for stabilization and then slowly pulled out of the solution. The surface tension of the solution is determined from the downward force directed on the strip.

The content uniformity of the drug-loaded tablets was determined by soaking a tablet ($n = 10$) in 50 ml water during 24 h followed by stirring during 15 min. The drug concentration was measured using UV spectrofotometry.

2.5. Drug release

Drug release from the porous tablets was determined using the USP II method (VanKel VK 8000, VanKel Industries, New Jersey, USA) with a paddle speed of 50 rpm and at a temperature of 37 ± 0.5 °C. Demineralised water, phosphate buffer, pH 6.8, and 0.1 N hydrochloric acid were used as dissolution media. Samples were collected at different time points and analysed using a UV/Vis double beam spectrophotometer (Perkin–Elmer, Zaventem, Belgium) at 222 and 266 nm for metoprolol tartrate and riboflavine sodium phosphate, respectively.

The effect of the surface tension of the drug solution on drug uptake and release was evaluated by adding polysorbate 80 (Tween®) (0.1% and 1%, w/v) (Alpha Pharma, Zwevegem, Belgium) as tensioactive agent to the aqueous drug solution.

Fick's second law of diffusion, considering axial as well as radial mass transfer in a cylinder was used to quantitatively describe the experimentally measured drug release profiles:

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r}\left(r \cdot D \cdot \frac{\partial c}{\partial r} \right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r} \cdot \frac{\partial c}{\partial \theta} \right) + \frac{\partial}{\partial z}\left(r \cdot D \cdot \frac{\partial c}{\partial z} \right) \right\} \quad (1)$$

where c is the drug concentration, t represents time; r, z denote the radial and axial coordinates and θ the angle perpendicular to the r–z-plane; D represents the apparent diffusion coefficient of the drug within the porous tablet.

Using infinite series of exponential functions this partial differential equation can be solved considering the respective initial and boundary conditions [homogeneous drug distribution before exposure to the release medium ($t = 0$), high drug solubility and perfect sink conditions], as well as symmetries (e.g., there is no concentration gradient with respect to θ), leading to [9]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D \cdot t \right) \cdot \sum_{p=0}^{\infty} \times \frac{1}{(2 \cdot p + 1)^2} \cdot \exp\left(-\frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H^2} \cdot D \cdot t \right) \quad (2)$$

where M_t and M_∞ represent the absolute cumulative amounts of drug released at time t and infinite time, respectively; q_n are the roots of the Bessel function of the first kind of zero order [$J_0(q_n) = 0$], and R and H denote the radius and height of the cylinder.

In case drug release leveled off below 100%, the experimentally determined plateau value (amount of mobile drug) was considered as 100% reference value for drug diffusion.

To investigate the influence of the pore size on the drug release, tablets with larger pores were manufactured by a modified gelcasting technique. Originally developed to manufacture dense ceramic components [10], the gelcasting procedure can be modified for the production of highly porous ceramic foams as a result of the aeration of the ceramic suspension containing gelling and foaming agents. Conventionally, the gelling of foamed suspensions results from the in situ polymerisation of water-soluble (mostly acrylamide-based) monomers [11]. Due to the main drawback of this process, being the toxicity of the monomers, alternative gelling agents have been introduced, e.g., gelatine, pectines, carrageenan and agar [12–14]. In this project pure hydroxyapatite powder was suspended (concentration range 40–60%, w/v) using a dispersing agent (Targon®). An agar solution was added to the ceramic suspension as gelling agent and the mixture was stirred during 5–10 min at 70 °C. The foamed slurry was poured in a mould and the mould was cooled down to 25 °C to transform from the liquid state to a gelled state. After demoulding, the foam was dried at room temperature and calcinated at 500 °C, followed by sintering at 1350 °C during 3 h. After cooling down the sintered block was cut into tablets (∅13 mm, height 3 mm).

3. Results and discussion

3.1. Manufacturing and characterization of porous tablets

Preliminary experiments showed that the amount of pore forming agent in the tablets was limited to 50%. Using higher concentrations, the amount of hydroxyapatite in the formulation was too low to obtain a solid structure when the organic pore former was removed during heat treatment.

Physical mixing of HA and the pore former (using a tumbling mixer) resulted in a poor blending uniformity. Consequently the removal of agglomerates of pore former during heat treatment yielded a potholed surface texture of the tablets. To deagglomerate these lumps and to obtain a homogeneous distribution of the pore forming agent, a suspension of HA and the pore former in acetone was ground in a ball mill. After evaporation of the organic solvent and production of porous tablets via direct compression and sintering, this procedure resulted in tablets with a smooth surface.

Porosity of the sintered tablets depended on the amount of pore former and on the sinter temperature (Table 1). Increasing the amount of pore forming agent resulted in a higher porosity as the inorganic phase was removed during the heat treatment. Increasing the sinter temperature decreased the porosity. The lowest porosity values were recorded for tablets processed at 1250 °C. During the initial phase of the heat treatment (<1000 °C) the HA particles only coalesced (without densification), whereas at sinter temperatures above 1000 °C densification of the material occurred [15,16]. This densification correlated with the shrinking of the tablets: after 3 h sintering at 1250 °C the tablet diameter and height had decreased by 24.6% and 28.0%, respectively.

For tablets sintered at 1250 °C, the type of pore forming agent and a variable sinter time (range: 1–5 h) had no effect on tablet porosity.

Table 1
Porosity and friability of porous calcium hydroxyapatite tablets containing different ratios of pore forming agent (Avicel PH 200, corn starch or sorbitol), sintered at 800, 1000 and 1250 °C during 3 h

Pore forming agent (%, w/w)	Sinter temperature (°C)		
	800	1000	1250
Porosity (%)			
Avicel PH 200 50%	79.3 ± 0.5	73.7 ± 0.4	52.5 ± 0.6
Corn starch 20%	64.5 ± 0.3	60.1 ± 0.9	26.0 ± 2.2
Corn starch 37.5%	74.6 ± 0.9	70.5 ± 0.6	43.0 ± 1.1
Corn starch 50%	79.2 ± 0.2	76.5 ± 1.0	48.6 ± 0.9
Sorbitol 37.5%	71.6 ± 0.3	65.2 ± 0.7	52.7 ± 0.9
Friability (%)			
Avicel PH 200 50%	5.5	3.9	1.2
Corn starch 20%	–[a]	0.7	0.2
Corn starch 37.5%	3.8	3.2	0.7
Corn starch 50%	–[a]	–[a]	0.5
Sorbitol 37.5%	1.1	0.7	0.4

[a] Tablets disintegrated during friability testing.

The SEM micrographs of the tablet surface and the three-dimensional images of the internal structure of the porous tablet (via nano CT-scan) are shown in Fig. 1. The analysis of the CT-scan images is given in Table 2. Within the fraction of the tablet evaluated via nano CT-scan one pore system was detected for all tablets. For each formulation the equivalent diameter was larger compared to the maximum inscribed diameter, indicating that the internal pore structure is branched. The larger pore size detected for tablets formulated with 50% Avicel PH 200 is correlated with the larger size of the microcrystalline cellulose fibres (200 μm vs. 25 μm and 165 μm for corn starch and sorbitol, respectively). The pore system detected in tablets formulated with 50% Avicel PH 200 or corn starch represented more than 90% of the porosity volume, indicating that an interconnecting network of pores is formed. In contrast, the pore system in tablets using sorbitol as pore forming agent accounted for only 63.9% of the total porosity. As no other pore classes were detected which contributed to more than 2% of the total pore volume, the rest of the porosity is attributed to individual pores.

In contrast to the pore size detected via nano CT-scan the pore size distribution determined via mercury porosimetry was much smaller, the majority of the pores being smaller than 10 μm (Fig. 2). However, comparison between both techniques is difficult since their approach is different. Nano CT-scan analysis provides only the maximum inscribed diameter which represents the largest pore volume, whereas the entire pore size distribution is detected via mercury porosimetry. In addition, mercury porosimetry could underestimate the actual pore size due to the ink bottle effect.

Despite the porous structure of the tablets, their mechanical strength after sintering was high (diametrical crushing strength ranging between 250 and 450 N). However, only sintering at 1250 °C resulted in tablets having a friability below 1%.

Stoichiometric (Ca/P-ratio: 1.667) hydroxyapatite (used as the main component in the tablets) is thermostable at high temperatures [17,18]. The X-ray pattern of HA after sintering at 1250 °C (Fig. 3) showed only diffraction peaks corresponding to HA, indicating that no decomposition products and additional phases like α- and β-TCP, tetracalciumphosphate and CaO were formed during sintering and that no fraction of the pore forming agent remained after sintering. The diffraction peaks of the sintered material were sharper and higher, indicating a higher crystallinity and the presence of larger crystals, respectively.

3.2. Porous tablets as drug carriers

Tablets formulated with the highest concentration of each pore forming agent (50% Avicel PH 200, 50% corn starch, 37.5% sorbitol) were selected as drug carriers as these tablets sintered at 1250 °C combined a high porosity with a low friability.

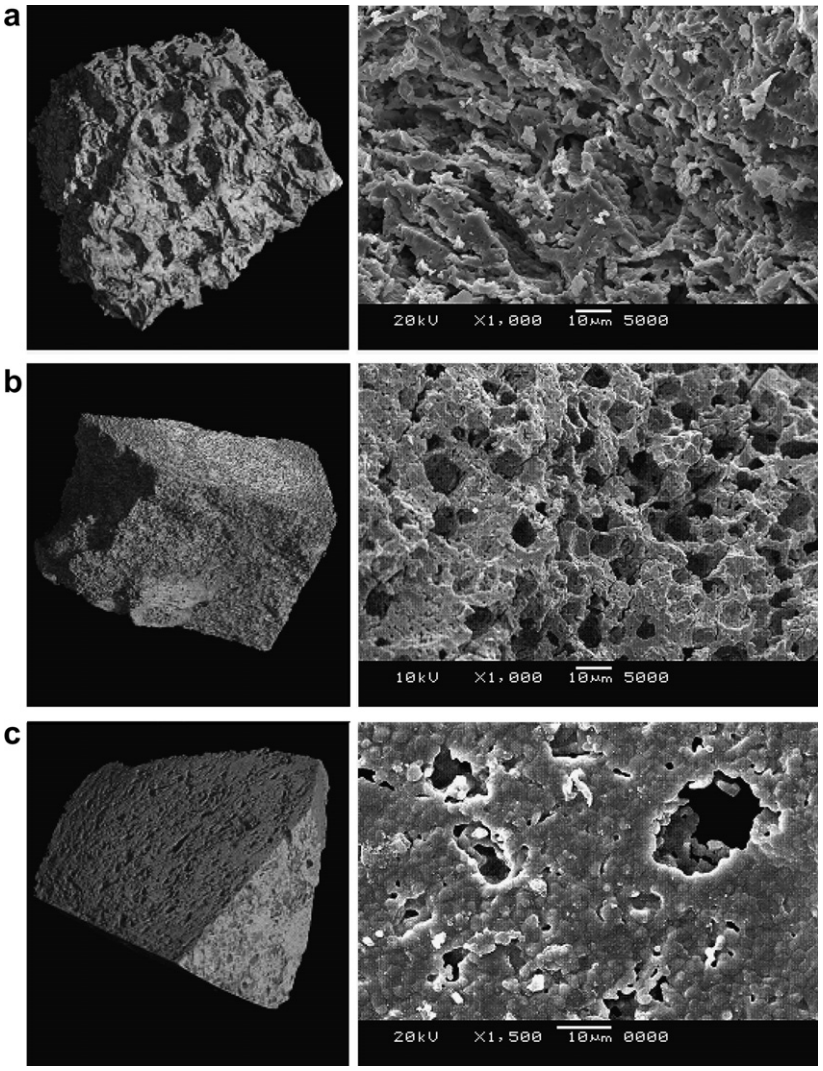

Fig. 1. SEM micrographs of the porous surface and three-dimensional images of the internal structure of sintered tablets (3 h, 1250 °C) whereby (a) 50% (w/w) Avicel PH 200, (b) 50% (w/w) corn starch or (c) 37.5% (w/w) sorbitol was used as pore forming agent.

Table 2
Nano CT-scan analysis of the three-dimensional internal structure of the porous tablets

Pore forming agent	Maximum inscribed diameter (μm)	Equivalent diameter (μm)	Total porosity represented by pore system (%)
Avicel PH 200 50%	102	322	93
Corn starch 50%	27	188	98
Sorbitol 37.5%	36	300	64
Gelcasted tablets	156	306	23
	178	359	70

After spiking only 100 μl of drug solution on the surface of the porous tablets, the solution was not completely absorbed by any of the tablets. Adding a surfactant to the spiked solution did not improve absorption of the liquid phase. Increasing the tablet size (18 mm diameter before sintering) was required to improve the liquid uptake by the porous tablets. The pore size distribution of these tablets (determined via mercury intrusion) showed a similar intrusion curve as for the smaller tablets, indicating that the improved liquid absorption of the tablets is due to the larger pore volume available for drug uptake. These carriers formulated with Avicel PH 200 and corn starch were able to completely absorb a volume of 100 μl spiked on the surface of the tablet as the interconnected pore network allowed the drug solution to penetrate and distribute in the tablet. In contrast, the carrier formulated with sorbitol failed to completely adsorb 100 μl drug solution. The results of the nano CT-scan showed that not all the pores were part of the pore network what decreased their ability to completely adsorb the drug solution. The fastest adsorp-

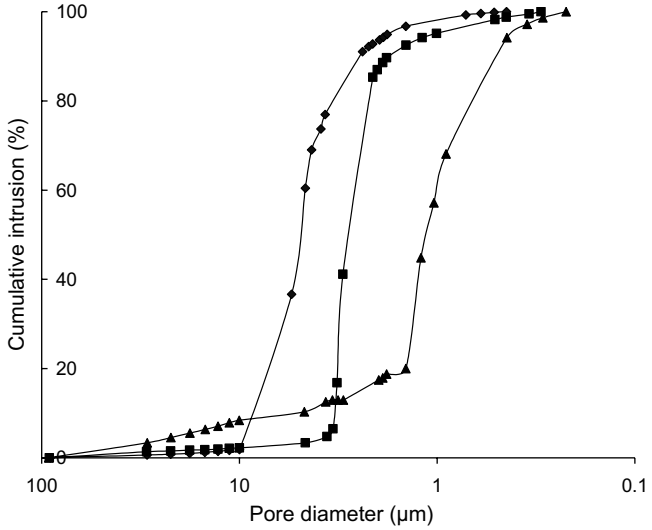

Fig. 2. Pore size distribution, obtained by mercury intrusion, of porous tablets with an initial diameter of 13.5 mm after sintering during 3 h at 1250 °C whereby 50% (w/w) Avicel PH 200 (♦), 50% (w/w) corn starch (■) or 37.5% (w/w) sorbitol (▲) was used as pore forming agent.

tion was observed for the carrier formulated with Avicel PH 200 as these tablets had the largest pores.

Spiking the tablets with 150 μl drug solution to increase the drug load was unsuccessful since the porous matrix became oversaturated and liquid leaked through the tablet. This effectively limits the application of these carriers to the formulation of low dosed dosage forms. Although it was possible to increase the drug load by spiking both sides of the tablet (with an intermediate drying step), a drug load in this application was limited to 30 mg metoprolol tartrate and 7.5 mg riboflavin sodium phosphate in a 550 mg porous tablet. The content uniformity test showed an average drug concentration of 100.7% (RSD 2.7%) and 99.7% (RSD 1.8%) of the theoretical concentration for metoprolol tartrate and riboflavine sodium phosphate loaded tablets, respectively. In addition to the volume spiked on the porous carriers

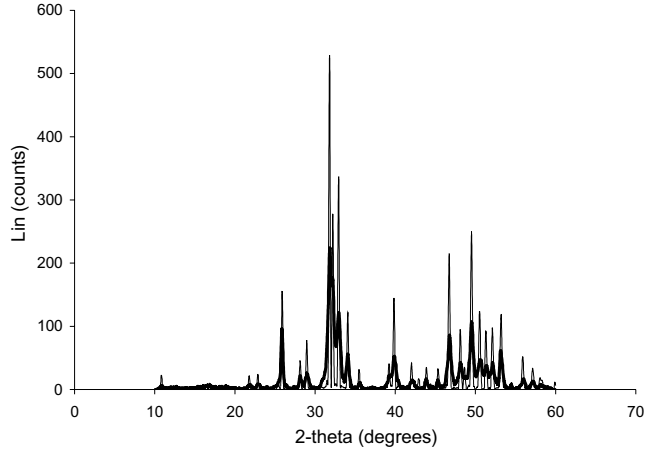

Fig. 3. X-ray diffraction pattern of calcium hydroxyapatite before sintering (——) and after sintering at 1250 °C (——).

the drug load will also be determined by the drug concentration in the solution. Consequently, tablets were loaded with differently concentrated metoprolol tartrate solutions (1.5%, 4%, 15%, 40%). As tablets were spiked with 100μl of the 1.5% and 4% solution (applied on each side of the tablet), an immediate and complete solution absorption was observed, whereas for the 15% and 40% solution the drug uptake was complete but slower. The surface energy of all solutions was lower compared with pure water, the highest drug concentration having the lowest surface tension, meaning that the drug molecules have some tensioactive properties. Based on this observation an improved liquid penetration into the tablets would be expected at higher drug concentration. However, the uptake of the solution is, besides the surface tension (air-liquid), also determined by the phase tension between the solid phase (tablet surface) and the liquid phase (drug solution). Due to the hydrophilic tablet surface (hydroxyl groups in hydroxyapatite) there will be competition between the tablet surface and the aqueous phase (water) to interact with the hydrophilic part of the drug molecules; a factor which increases the phase tension between liquid and solid phase. Since this competition will increase at higher drug concentrations in the solution, the increasing phase tension in function of drug concentration accounts for the slower absorption of these drug solutions [19].

Based on the yellow colour of riboflavin sodium phosphate it was visually observed that the drug was homogeneously distributed throughout the entire tablet.

3.3. Drug release from the porous tablets

Due to the fast and complete absorption of the aqueous drug solution in porous tablets formulated with 50% (w/w) Avicel PH 200 as pore forming agent, these tablets were evaluated as drug carriers during dissolution experiments.

Fig. 4 shows the dissolution profiles of metoprolol tartrate in water, phosphate buffer, pH 6.8, and 0.1 N HCl. Based on the highly porous nature of these tablets an immediate drug release was anticipated. However, the burst release from these tablets was very limited in all media. Metoprolol release in 0.1 N HCl was the fastest (79% within 60 min) as the HAP tablets partly dissolved in acid medium. In contrast, HAP tablets remained intact in water and phosphate buffer pH 6.8, reducing drug release after 60 min to 70.5% and 73.1%, respectively. Although the tablet dissolved in 0.1 N HCl the release of riboflavin sodium phosphate in this medium was slower compared to the release of metoprolol tartrate (Fig. 5), as the solubility of riboflavin sodium phosphate in acid medium was lower (0.2 g/100 ml vs. 81.8 g/100 ml for metoprolol tartrate). Adding a surfactant to drug solution used to spike the tablets did not improve the drug release rate.

The slower drug release from the tablets was strictly related to the porous structure of the matrices (the release rate depending on pore size, shape and connectivity) since

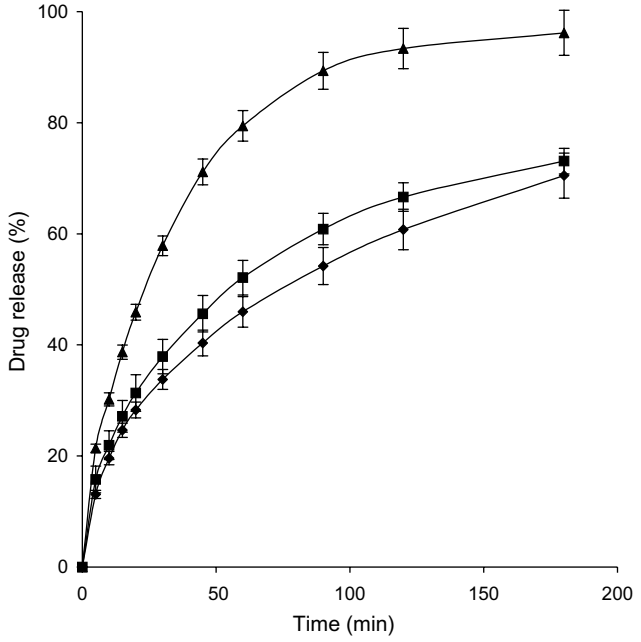

Fig. 4. Drug release from sintered porous tablets containing 30 mg metoprolol tartrate (1250 °C, 3 h) whereby 50% (w/w) Avicel PH 200 was used as pore forming agent in 0.1 N HCl (▲), water (♦) and phosphate buffer pH 6.8 (■).

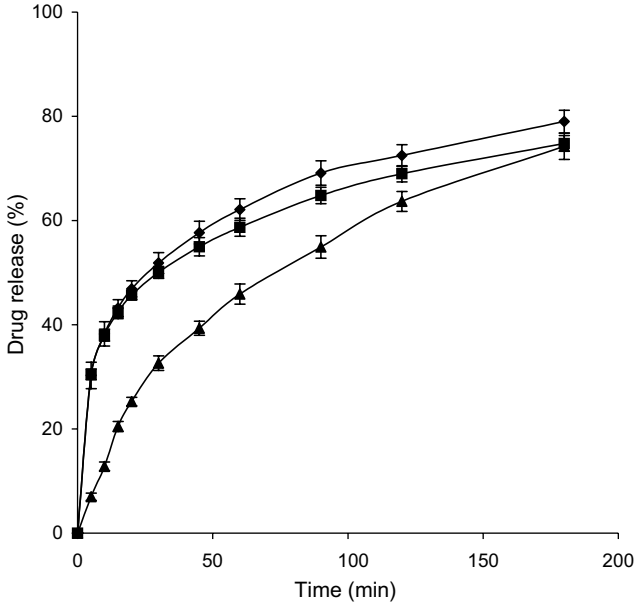

Fig. 5. Drug release from sintered porous tablets containing 7.5 mg riboflavin sodium phosphate (1250 °C, 3 h) whereby 50% (w/w) Avicel PH 200 was used as pore forming agent in 0.1 N HCl (▲), water (♦) and phosphate buffer pH 6.8 (■).

drug dissolution of crushed samples was immediate (showing that there was no interaction between HAP and the drugs) [20,21].

Fitting an appropriate analytical solution of Fick's second law of diffusion, considering axial as well as radial mass transport in cylinders, Eq. (2), to the experimentally

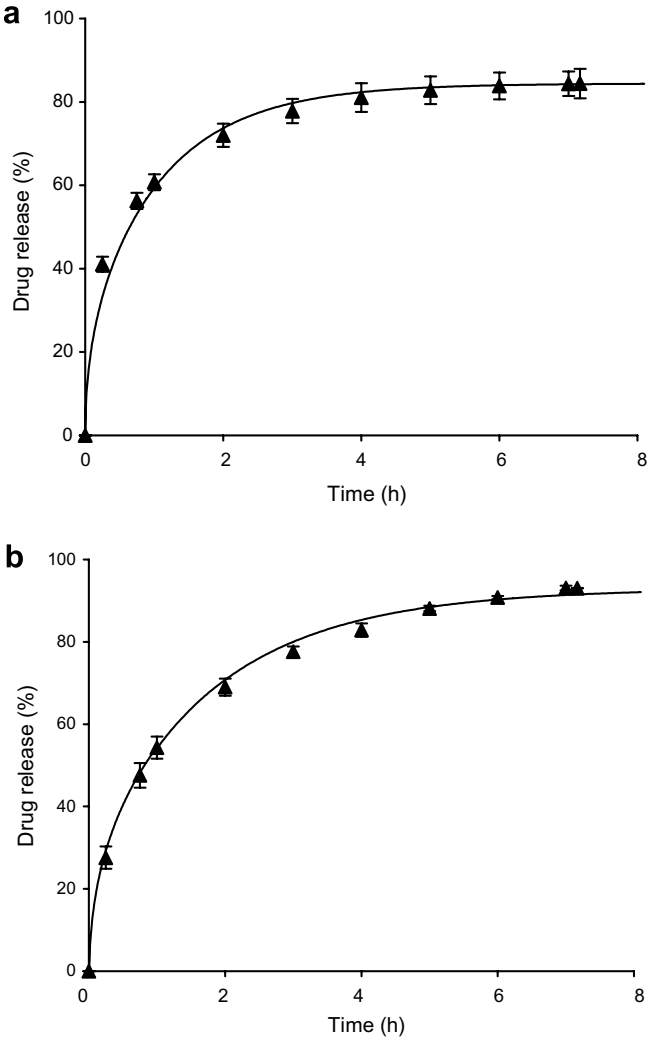

Fig. 6. Theory (curves, Eq. (2)) and experiment (▲): Riboflavin sodium phosphate (a) and metoprolol tartrate (b) release from sintered porous tablets (1250 °C, 3 h) [pore forming agent = Avicel PH 200 (50% (w/w)] in water.

measured riboflavin sodium phosphate and metoprolol tartrate release profiles obtained in water resulted in good agreement between theory and experiment (Fig. 6, curves and symbols). This indicates that drug release from these systems is primarily diffusion-controlled, irrespective of the type of drug. Based on these calculations, the apparent diffusion coefficients of riboflavin sodium phosphate and metoprolol tartrate in the porous tablets upon exposure to water could be determined $D = 1.9 \times 10^{-6}$ cm^2/s and $D = 1.2 \times 10^{-6}$ cm^2/s, respectively. As the tablets partly dissolved in 0.1 N HCl, also the disintegration of the porous HA networks contributes to the overall control of drug release in this release medium.

Fig. 7 shows the importance of the initial drug content (3, 8, 30 and 80 mg) on the release of metoprolol tartrate from porous tablets prepared with 50% (w/w) Avicel PH 200. Clearly, the relative release rate decreased with increasing drug loading. Interestingly, the presented analytical solution of Fick's second law of diffusion Eq. (2) can be

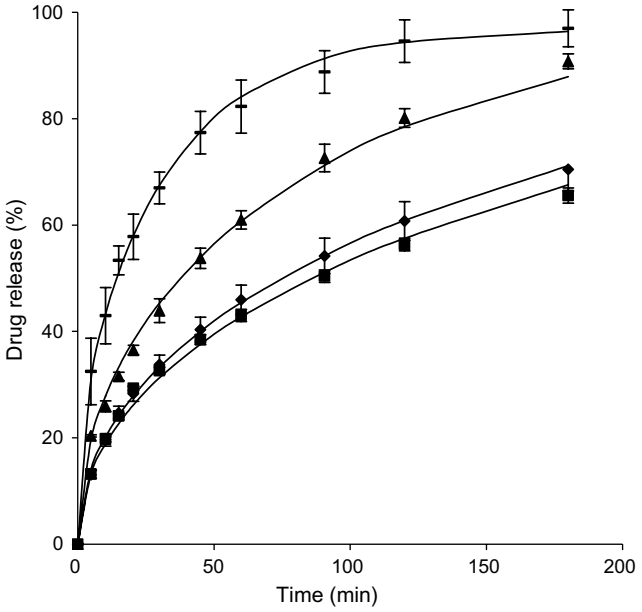

Fig. 7. Effects of initial drug content 3 mg (▬), 8 mg (▲), 30 mg (♦) and 80 mg (■) on release of metoprolol tartrate from sintered porous tablets (1250 °C, 3 h) [pore forming agent = Avicel PH 200, 50% (w/w)] in water: Theory (curves, Eq. (2)) and experiment (symbols).

used to quantitatively describe the experimentally measured drug release kinetics in all case (curves and symbols in Fig. 7). Based on these calculations, the following apparent diffusion coefficients of metoprolol tartrate in the porous tablets exposed to water could be determined: $D = 3.5 \times 10^{-6}\,\mathrm{cm^2/s}$, $D = 1.2 \times 10^{-6}\,\mathrm{cm^2/s}$, $D = 6.2 \times 10^{-7}\,\mathrm{cm^2/s}$ and $D = 5.4 \times 10^{-7}\,\mathrm{cm^2/s}$, respectively. The decrease in drug mobility with increasing initial drug content might be attributable to a concentration-dependent metoprolol tartrate diffusion coefficient in water-filled pores of the tablets and/or to limited solubility effects [22,23].

To increase the drug release rate from porous HA tablets, carriers having larger pores were manufactured using a modified gelcasting technique resulting in tablets with a median pore size of 60 and 80 μm (determined via mercury porosimetry). Nano CT-scan for visualisation of the porous structure (Fig. 8) detected two pore systems with a branched structure (equivalent diameter > maximum inscribed diameter) (Table 2). These pore systems represented 92.5% of the total porosity volume, indicating that nearly all pores are incorporated in an interconnected network. These large and interconnecting pores resulted in a faster drug absorption when the tablets were spiked with a metoprolol tartrate drug solution and in faster drug release during dissolution testing (Fig. 9, symbols). The enhanced release rate is due to the larger pore size (which promotes water penetration and drug diffusion) and to the regular shape of the pore channels (which decreases the tortuosity of the matrix). As it can be seen in Fig. 9, good agreement between theory (curves, Eq. (2)) and experiment (symbols) was obtained in all cases, indicating that drug diffusion is the rate-limiting

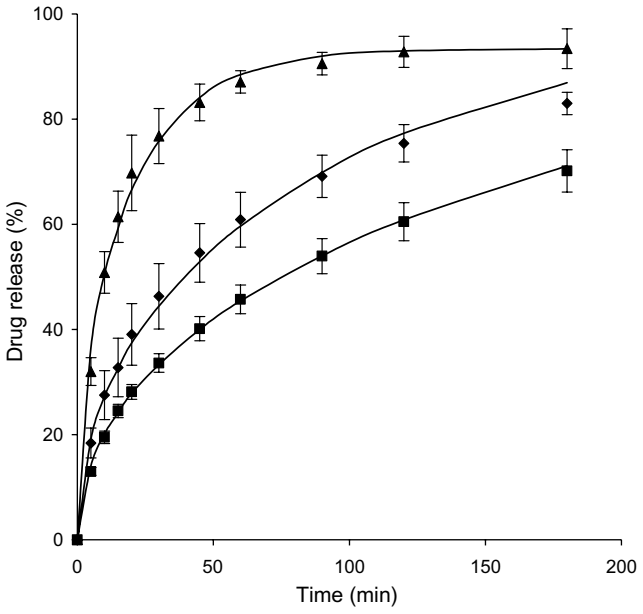

Fig. 9. Drug release from sintered porous tablets containing 30 mg metoprolol tartrate whereby 50% Avicel PH 200 was used as pore forming agent (■) and obtained via a modified gelcasting technique with a pore size of 20 (♦) and 80 μm (▲): Theory (curves, Eq. (2)) and experiments (symbols).

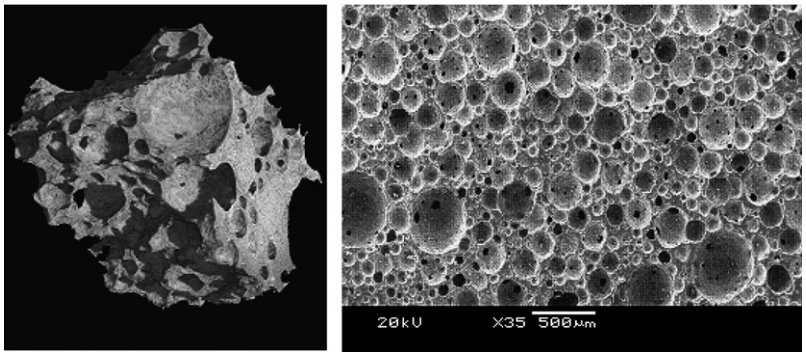

Fig. 8. Three-dimensional images of the internal structure and SEM micrograph of the porous surface of a tablet manufactured by a modified gelcasting technique.

step. The apparent diffusion coefficients of metoprolol tartrate within the porous tablets increased with increasing pore size: $D = 6.2 \times 10^{-7}$ cm^2/s, $D = 1.2 \times 10^{-6}$ cm^2/s and $D = 5.5 \times 10^{-6}$ cm^2/s for porous tablets prepared with 50% (w/w) Avicel PH 200 as pore forming agent and tablets prepared by the modified gelcasting technique with a pore size of 20 and 80 μm, respectively.

4. Conclusion

Porous tablets obtained by burning out a pore forming agent followed by sintering or by a modified gelcasting technique can be used as an alternative carrier for low-dosed drugs.

The drug is incorporated into the pore network via spiking of the drug solution on each side of the tablet, whereby the drug uptake depends on the pore volume, the presence of interconnecting pores and the drug concentration.

In most cases, drug release from the porous carrier is primarily diffusion controlled, the apparent drug diffusivity is depending on the pore size and tortuosity of the porous network. Transfer of this novel concept for low-dosed tablets to industrial scale production is straightforward since the porous carriers can be easily produced via direct compression and sintering, and fully automated systems are available for dosing small amounts of liquids on the tablets.

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