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Tablet preformulations of indomethacin-loaded mesoporous silicon microparticles

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ABSTRACT

In this study, indomethacin-loaded thermally oxidized mesoporous silicon microparticles (TOPSi-IMC) were formulated into tablets with excipients in order to improve the dissolution and permeability properties of the poorly soluble drug. Formulations of TOPSi-IMC particles and excipients were prepared at different TOPSi-IMC particle ratios (25, 30 and 35%). The formulations were compressed by direct compression technique with a single punch tablet machine. For comparison, a formulation containing the bulk IMC (indomethacin) and the same excipients without thermally oxidized mesoporous silicon microparticles particles (TOPSi) was prepared and compressed into tablets. The TOPSi-IMC tablets were characterised according to weight, thickness, crushing strength, disintegration time and dissolution rate. The results of this study show that TOPSi-IMC particles can be compressed to a conventional tablet. The release rate of the drug and its permeation across intestinal cells model (Caco-2) from TOPSi-IMC tablets was improved compared to the bulk IMC tablets. The dissolution rate and permeability of IMC from the tablets decreased with increasing ratio of the TOPSi-IMC particles in the formulation. The phenomenon is, presumably, a result of the loss of unique pore structure of the particles due to deformation of the particles under the compression load.

1. Introduction

The increasing number of poorly soluble drugs is a challenge for drug delivery applications. In oral drug delivery, the bioavailability of such drugs remains low due to the poor dissolution properties of the drug molecule (Kerns and Di, 2008). Mesoporous materials offer an interesting possibility to enhance the dissolution properties of poorly water-soluble drugs by fast releasing the drug entrapped in the nanopores (usually of 2–50 nm in diameter) of these materials (Horcajada et al., 2004; Vallet-Regi et al., 2001, 2007; Vallet-Regi, 2006; Kaukonen et al., 2007; Limnell et al., 2007; Prestidge et al., 2007; Salonen et al., 2005, 2008; Wang et al., 2010; Bimbo et al., 2011; Santos et al., 2011). It is assumed that the narrow pore size of the mesoporous materials prevents the formation of ordered structures of the loaded drug molecules, and thus, they remain in amorphous form after loaded into the particles with physicochemical properties different from the bulk crystalline form (Salonen et al., 2005), e.g. improved solubility and dissolution properties.

Mesoporous silicon (PSi) is a material with unique and easily adjustable properties that can be utilized to enhance the bioavailability of poorly soluble drugs in oral drug delivery (Kaukonen et al., 2007; Limnell et al., 2007; Salonen et al., 2005, 2008; Prestidge et al., 2007; Wang et al., 2010; Bimbo et al., 2011). The fabrication process using electrochemical anodization allows the adjustment of the pore size and volume of the particles (Prestidge et al., 2007; Salonen et al., 2008), and also enables easy particle surface modifications for suitable adsorption of different type of drug

Abbreviations: BET, Brunauer–Emmett–Teller theory; BJH_{des}, Barrett–Joyner–Halenda theory; Caco-2, differentiated human colon carcinoma cells; CMOS, complementary metal-oxide-semiconductor; DMEM, Dulbecco's modified Eagle's medium; DMSO, dimethyl sulfoxide; DSC, differential scanning calorimetry; EDTA, ethylenediamine tetraacetic acid; HBSS, Hanks' balanced salt solution; IMC, indomethacin; MCC, microcrystalline cellulose; MCM-41, mobil composition of matter no. 41; μCT, the computed X-ray microtomography; NaCMC, sodium carboxymethylcellulose; PSi, mesoporous silicon; PVP, polyvinylpyrrolidone; Q_{30}, the percent amount of IMC dissolved at 30 min; Q_{120}, the percent amount of IMC dissolved at 120 min; SEM, scanning electron microscope; TG, thermogravimetry; TEER, transepithelial electrical resistance; TOPSi, thermally oxidized mesoporous silicon microparticles; TOPSi-IMC, indomethacin-loaded thermally oxidized mesoporous silicon microparticles.

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molecules with high drug payloads. The fresh PSi surface is susceptible to oxidation in ambient air due to the existing of hydrogen-terminated atoms remaining on the surface after anodization, and thus, further modification of the surfaces is required after anodization for stabilization of the material's surface. For example, thermal oxidation and carbonization of the surfaces can be used to produce more stable PSi structures (Kaukonen et al., 2007; Limnell et al., 2007). The surface modification of PSi also determines the interactions of the particles with the surrounding environment (e.g. drug molecules, media, and solvents). The loading of the drug molecules into the pores is usually performed by immersing the PSi microparticles in highly concentrated drug loading solution (Vallet-Regi et al., 2001; Salonen et al., 2008; Wang et al., 2010). The loading parameters, such as the solvent, pH, drug concentration and temperature affect differently the efficiency of the loading process (Salonen et al., 2008). The important issue is that no crystalline drug should be formed on the external surface of the particles. The dissolution of the drugs from the pores of PSi is also enhanced due to better wetting properties of the particles and their higher surface area (Salonen et al., 2005).

In 2001 the silica-based mesoporous material, MCM-41 (Mobil Composition of Matter No. 41), was observed to act as a host for the anti-inflammatory agent ibuprofen, and the loading and release of the drug from the pores of the particles were demonstrated (Vallet-Regi et al., 2001). Since then, several studies have been carried out with different porous materials for drug delivery applications (for further details please see the following reviews and the references therein: Prestidge et al., 2007; Vallet-Regi et al., 2007; Manzano et al., 2009; Santos et al., 2011). Recently, both the size of the pores and the surface chemistry of the particles have been shown to significantly influence the release rate of the drugs from the pores, either by increasing or sustaining the drug dissolution rate (Horcajada et al., 2004; Vallet-Regi, 2006; Limnell et al., 2007). The most important properties for the mesoporous materials to be employed as drug carriers in oral drug delivery are to provide high drug payloads, enhanced or prolonged release of the drugs incorporated into the pores, and biocompatibility when in contact with the cells (Bimbo et al., 2010; Santos et al., 2010).

Recently, our group and others have shown that improvement of drug dissolution can be achieved by loading drug molecules into the pores of surface-modified PSi microparticles (Salonen et al., 2005; Kaukonen et al., 2007; Limnell et al., 2007; Wu et al., 2008; Gu et al., 2010; Wang et al., 2010). Wang et al. (2010) have reported the development of an aqueous suspension containing thermally oxidized mesoporous silicon microparticles (TOPSi) for the oral delivery of indomethacin (IMC). However, there are only a few studies of tablet formulations of porous-based materials for controlled drug release applications reported in the literature (Safwat et al., 1995; Sharma et al., 2005; Cosjins et al., 2007; Wu et al., 2007; Limnell et al., 2011; Vialpando et al., 2011), and studies of PSi tablet formulations are still lacking. The purpose of this study was to demonstrate that the drug-loaded PSi microparticles can be formulated as tablets and that the release rate of a poorly soluble drug, IMC, from the tablets is improved compared to the release rate of bulk IMC. In addition, the release profiles of the formulated tablet were also compared to the release profiles of the uncompressed drug-loaded PSi microparticles.

2. Materials and methods

2.1. Materials

IMC was purchased from Hawkins Pharmaceuticals (Minneapolis, USA) and used as received. Lactose monohydrate (lactose; 200 M, DMV International, The Netherlands), microcrystalline cellulose (MCC; Avicel PH102, FMC BioPolymer, Ireland), polyvinylpyrrolidone (PVP; Kollidon30, BASF Corporation, Germany), croscarmellose sodium (NaCMC; AcDiSol, FMC BioPolymer, Ireland), magnesium stearate (Yliopiston Apteekki, Finland) and Aerosil 200 (Degussa AG, Germany) were used as tablet excipients. Water in use was purified (Millipore®, Milli-Ro 12 Plus, Millipore S.A., France). For HPLC analysis acetonitrile (HPLC quality; VWR, BDH, Prolabo®; EC) and ortho-phosphoric acid (85%; p.a.-plus; Riedel-de Haën; Germany) were used. Dimethylsulfoxide (DMSO; puriss. p.a.) was purchased from Sigma–Aldrich (France). Dissolution medium (pH 5.5) was prepared from monobasic potassium phthalate (puriss. p.a.; Sigma-Aldrich; Japan) and sodium hydroxide (98%; Fluka; Switzerland).

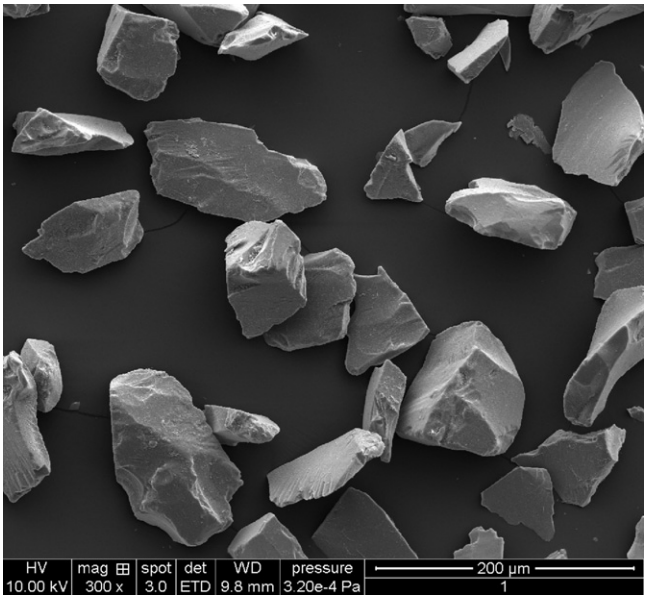

Fig. 1. SEM image of TOPSi-IMC microparticles used in the tabletting experiments.

2.2. Fabrication and characterisation of TOPSi microparticles

Free standing PSi films were fabricated by anodizing Si(1 0 0) wafers electrochemically in HF (38%)–ethanol (99.6%) solution (1:1, v/v) with a constant current density of 50 mA/cm^2. The silicon wafers were boron doped, p$^+$-type with a resistivity of 0.01–0.02 Ωcm. Free-standing films were obtained by sharply increasing the current density after the etching process to the electropolishing region. After the anodization the free-standing PSi films were milled and sieved repeatedly until the selected size fraction of 53–75 μm was obtained. After the dry-sieving, the particles were rinsed with ethanol on the mesh to remove small agglomerates and dried at 65 °C under reduced pressure for 1 hour. The PSi microparticles were stabilized by thermal oxidation in ambient air at 300 °C for 2 h. The surface treatment provides TOPSi microparticles with a relatively stable, hydrophilic surface chemistry. Nitrogen sorption isotherms were determined with TriStar 3000 (Micromeritics; USA) instrument at −196 °C. The specific surface area was calculated using the Brunauer–Emmett–Teller theory (BET) (Brunauer et al., 1938). Pore volume and average pore diameter of the PSi particles were calculated using the Barrett–Joyner–Halenda (BJH) theory from the nitrogen isotherm (Barrett et al., 1951). The surface morphology of the IMC-loaded TOPSi was studied by scanning electron microscope (SEM; FEI Quanta 250 FEG; The Netherlands). The samples were sputter coated with platinum before the imaging (Fig. 1).

Table 1
Composition of the studied IMC-loaded TOPSi particles and excipients used in the tablet formulations (wt%).

TOPSi-IMC particles	Kollidon 30; PVP (binder)	AcDiSol; NaCMC (disintegrant)	Magnesium-stearate (lubricant)	Aerosil 200 (glidant)	Avicel PH 102; MCC (filler)	Lactose 200M (filler)
25	4.5	1.5	0.2	0.1	27.8	40.9
30	4.5	1.5	0.2	0.1	25.8	37.9
35	4.5	1.5	0.2	0.1	23.6	34.9

2.3. Loading of IMC in TOPSi microparticles

Loading of IMC into the TOPSi microparticles was done by immersing the particles into highly concentrated solution of IMC (500 mg/mL) pre-dissolved in DMSO solution for 1 h at room temperature under gentle magnetic stirring. After the loading, the microparticles were vacuum filtered from the solution and dried at 105 °C under reduced pressure for 24 h.

The total amount of loaded IMC into the particles was 23 wt% and was determined using thermogravimetry (TG; TGA 7; PerkinElmer; USA) by heating the samples from room temperature to 700 °C under N_2 flush. The possible crystallinity of the drug loaded into the TOPSi samples was characterised using differential scanning calorimetry (DSC; Diamond DSC; PerkinElmer; USA) (Lehto et al., 2005). DSC analyses were performed at a heating rate of 10 °C/min under N_2 gas purge of 40 mL/min, in 30 μL aluminium sample pans with holes.

2.4. Compression of the tablets

Mixtures of TOPSi-IMC microparticles and excipients were prepared at different particle ratios (25, 30 and 35 wt%). In the composition, the amounts of magnesium stearate, Aerosil, PVP and NaCMC were kept constant in all particle ratios. In order to compensate for the decrease of the amount of TOPSi-IMC particles in the mixtures, the amounts of MCC and lactose were adjusted while keeping the ratio of these excipients the same for all mixtures (MCC:lactose, ~40:60). Table 1 shows the compositions of the tablets used in this study. The TOPSi-IMC and the other excipients, except magnesium stearate, were mixed in Turbula mixer (WAB; Switzerland) for 2 min at 96 rpm. The final mixing was made after adding magnesium stearate for 1 min at 96 rpm.

The mixtures of TOPSi-IMC and the excipients were compressed by direct compression technique (automatic compression) with a single punch tablet machine (Korsch EK-0; Erweka-Apparatenbau GmbH; Germany) using flat punches with a diameter of 5 mm. The aim for crushing strength of the tablets was 40–50 N and for the tablet weight was 30 mg. The small weight of the tablets was pursued to have sink conditions in the dissolution experiments. The upper and lower compression forces monitored during the compaction are shown in Table 2.

In order to evaluate the effect of the compression pressure on the process of dissolution of the drug from the tablets, a series of tablets was prepared at different compression forces. A formulation containing 35% of TOPSi-IMC particles (Table 1) was compacted using Lloyd LRX testing machine (Lloyd Instruments Ltd; UK) equipped with flat punches with a diameter of 4 mm. The compression forces used were 1.0, 1.5 and 2.0 kN and the rate of compression was 4 mm/min.

2.5. Tablet characterisation and dissolution experiments

The TOPSi-IMC tablets were characterised according to weight and thickness (Sony Digital Indicator; Sony Magnescale Inc.; Japan), crushing strength (Schleuniger-2E; Dr. K. Schleuniger & Co.; Switzerland), disintegration time (Sotax DT3; Sotax AG; Switzerland), and dissolution (Sotax AT7; Switzerland). The disintegration time was measured at 37 ± 0.5 °C in purified water (Millipore®, Milli-Ro 12 Plus; Millipore S.A.; France; Ph.Eur.).

The dissolution tests were carried out according to the USP Basket Method at 37 ± 0.5 °C in neutralized phthalate buffer (pH 5.5) using a stirring speed of 100 rpm. In order to maintain sink conditions, the dissolution tests were performed in buffer solutions of 1050 mL. The choice of the volume of dissolution medium was made on the basis the solubility of bulk IMC (57 ± 6 μg/mL; $n = 3$) determined by us in the neutralized phthalate buffer (pH 5.5) at 37 ± 0.5 °C. Samples of 5 mL were taken from the dissolution medium at time points ranging from 20 s to 120 min. For the series of the tablets compacted at the different compression forces the sampling times were from 1 up to 120 min. The sample volume removed was replaced with fresh pre-warmed buffer of the same volume. Samples were then centrifuged during 2 min at 12 000 rpm prior HPLC analysis. The HPLC (Agilent 1100; Agilent Technologies; Germany) system consisted of a micro vacuum degasser (G1379A), a binary pump (G1312A), a Gemini-NX column (C18, 100 mm × 4.6 mm, 3 μm) thermostated at 30 °C, an auto sampler (G1367A) and an UV detector (G1365B) set at wavelength of 320 nm. The mobile phase used was a mixture of acetonitrile and 0.2 vol.% of phosphoric acid (pH 2.0) in a ratio of 65:35. For comparison, the dissolution profiles of IMC from uncompressed TOPSi-IMC particles and tablets containing 6.9 wt% of crystalline IMC and the same excipients (Table 2, IMC-tablets) were studied using the same methodology and conditions described above.

2.6. X-ray microtomography analyses

The computed X-ray microtomography (μCT) measurements were carried out using a custom-made μCT device nanotom®

Table 2
Properties of the formulated TOPSi-IMC and IMC tablets: weight ($n > 13$), thickness ($n > 13$), crushing strength ($n = 6$), disintegration time ($n = 6$), upper ($n > 13$) and lower ($n > 13$) compression force, and the amount of IMC dissolved in 30 min ($n = 6$).

Characteristic	IMC-tablets (6.9 wt% of crystalline IMC)	25 wt% TOPSi-IMC tablets	30 wt% TOPSi-IMC tablets	35 wt% TOPSi-IMC tablets
Weight (mg)	29.9 ± 0.4	30.1 ± 0.2	30.1 ± 0.2	29.9 ± 0.4
Thickness (mm)	1.16 ± 0.08	1.12 ± 0.01	1.13 ± 0.01	1.12 ± ± 0.02
Crushing strength (N)	45 ± 2	47± 1	44 ± 3	47 ± 2
Disintegration time	<1 min 10 s	<1 min 40 s	<2 min 30 s	<2 min 15 s
Upper compression force (kN)	6.1 ± 0.3	13.2 ± 0.3	12.5 ± 0.2	12.8 ± 0.4
Lower compression force (kN)	5.0 ± 0.3	12.2 ± 0.3	11.1 ± 0.2	12.2 ± 0.4
Amount of IMC dissolved at 30 min (Q_{30}, %)	31 ± 4	79 ± 6	73 ± 6	68 ± 6

supplied by Phoenix|Xray Systems + Services GmbH (Wunstorf, Germany). The main hardware components of the device were a high-power nanofocus transmission-type X-ray tube with tungsten anode, a high resolution computer-controlled translation/rotation stage for the sample and a complementary metal–oxide–semiconductor (CMOS) flat panel detector with 2304 × 2284 pixels of 50 μm size (Hamamatsu Photonics, Japan).

For the μCT measurements, the tablets containing TOPSi-IMC particles were mounted on top of a steel pin using beeswax. The samples were measured using 80 kV and 180 μA power. The measurement consisted of 900 X-ray transmission images taken at 0.4° intervals around a full circle of rotation. The exposure time was 750 ms for each image, and the final projection images were formed at an average of 6 exposures. The images were taken with 20x geometric magnification factor, resulting in an effective pixel size of 2.5 μm.

3D reconstructions were made using datos|x rec -software supplied with the μCT device. Reconstruction of the detail of the sample was made at full resolution, and the entire sample was reconstructed with half magnification by down-sampling the projection images with a factor of 2. Visualization of the reconstructed volumes was carried out using the program VGStudio MAX 1.2.1 (Volume Graphics GmbH, Germany). For visualization, random noise in the 3D reconstructions was suppressed using a Gaussian convolution filter with 5 × 5 × 5 voxel kernel.

2.7. Cell culture

Differentiated human colon carcinoma (Caco-2) cells (ATTC; Rockville, MD, USA) were cultured in 75 cm^2 culture flasks (Corning Inc. Life Sciences, USA) using Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 1% non-essential amino acids, 1% L-glutamine, penicillin (100 IU/mL), and streptomycin (100 mg/mL) (all from Euroclone; Italy). The culture was maintained at 37 °C (BB 16 gas incubator; Heraeus Instruments GmbH; Germany) in an atmosphere of 5% CO_2 and 95% relative humidity. The growth medium was changed every other day until the time of use. Caco-2 cells from passage numbers 31–40 were used in the experiments. Prior to each test, the cells were harvested using trypsin (Euroclone, Italy) – ethylenediamine tetraacetic acid (EDTA; Sigma; USA) – phosphate-buffered saline (PBS; Euroclone; Italy) solution (0.25% trypsin-0.05 mM EDTA).

2.8. Permeability experiments

The transport experiments of IMC across Caco-2 cell monolayers were performed in the apical-to-basolateral direction. The cells were seeded at 2.8 × 10^5 cells/cm^2 onto polycarbonate filter membranes (pore size 0.4 μm, growth area 4.67 cm^2) in 6-Transwell cell culture inserts (Corning Costar Corp.; Cambridge, MA, USA). The medium was replaced every other day and the cells were used in the permeation experiments 21–26 days after the seeding. Transepithelial electrical resistance (TEER) was measured using a Millicell ERS Voltohmmeter (Millipore Corp.; Bedford, MA, USA) and monolayers with TEER values below 250 Ωcm^2 were discarded (Kaukonen et al., 2007). TEER values of 350–500 Ωcm^2 were used across all the monolayers. The transport experiments were performed in 10 mM Hanks' Balanced Salt Solution (HBSS) (Gibco, Invitrogen, USA) at 37 °C, pH 5.5 (apical compartment; 2 mL) and 7.4 (basolateral compartment; 3 mL) using an orbital shaker (25 rpm). Tablets of IMC-loaded TOPSi microparticles or pure IMC and uncompressed TOPSi-IMC particles were placed in the apical side of the inserts. Aliquots of 100 μL samples were taken from the basolateral side (pH 7.4) of the inserts at different time points, and 100 μL of fresh pre-warmed HBSS buffer was added to replace the withdrawn volume. Sample concentrations were quantified by HPLC and the amount of IMC permeated was calculated. The monolayer integrity was determined after each experiment using TEER. Results with TEER values lower than 250 Ωcm^2 were discarded. In all the permeation experiments performed the amounts of drug in the basolateral compartment during individual sampling intervals did not exceed 10–15% of the amounts of drug in the apical compartment (Koljonen et al., 2006; Kaukonen et al., 2007; Bimbo et al., 2011).

2.9. Statistical analyses

Results from the several tests are expressed as mean ± SD from of at least three independent experiments. The analysis was performing using Microsoft Office Excel program and the statistical ANOVA test.

3. Results and discussion

The aim of this study was to formulate mesoporous IMC-loaded TOPSi microparticles as tablets with improved solubility and dissolution properties of the poorly soluble drug. The mesoporous microparticles increase the solubility and dissolution rate of the drug based on the fact that the crystallization of the drug is restricted by the confined space of the pores, and thus, retains its amorphous form (Salonen et al., 2005, 2008; Riikonen et al., 2009). In the amorphous form the drug molecule exhibits higher dissolution rate than its crystalline counterpart. The dissolution rate of the less soluble bulk drug is also improved when loaded into the porous materials due to their high surface area and better wetting properties (Salonen et al., 2005). It is well-known that the compression of the particles into tablets is a complex process, which can be influenced dramatically by the physical state of the drug (amorphous/crystalline), drug-substance itself, pore structure and surface area of the carrier-material (Yoshioka et al., 1994; Morris et al., 2001; Alderborn, 2002; Vyazovkin and Dranca, 2005; Koivisto et al., 2006; Bhugra et al., 2008; Vialpando et al., 2011). Hence, the excipients of a drug formulation have to prevent such a deformation of the particles, which affects the dissolution rate of the drug from the tablet. At the same time, the excipients have to provide certain mechanical properties for the tablet. In other words, the ideal formulation should protect the TOPSi-IMC particles, support essential hardness and provide rapid disintegration of the tablet.

The theoretical amount of excipients needed to fill the voids between densely packed spherical particles is about 36% of volume fraction (Onoda and Liniger, 1990; Berryman, 1983) and, although the TOPSi particles have an irregular non-spherical shape (Fig. 1), the experiments were preceded by preliminary tests of formulations containing non-loaded TOPSi particles and a diluent (mass ratio of 70:30, particles:diluent). As a result, silicified microcrystalline cellulose (Prosolv 50) was chosen as the diluent for the formulations. PVP (4.5 wt%) and NaCMC (0.5 wt%) were used as binder and disintegrant, respectively, for the formulations with non-loaded TOPSi particles and diluents at mass ratios of 70:30, 60:40 and 50:50 (particles:diluents). Tablets were compressed from these formulations at a range of weights from 30 to 50 mg and showed substandard crushing strengths and disintegration times. On the bases of the preliminary tests it was decided to continue the experiments with formulations containing 25, 30, and 35 wt% of the IMC-loaded TOPSi particles.

PVP, NaCMC, magnesium stearate, Aerosil, MCC and lactose were chosen as excipients for the formulations at amounts shown in Table 1. MCC and lactose were used as fillers due to their good compaction properties and high porosity (van den and Vromans, 2002). Porous fillers can absorb higher compression forces and protect the particles against fragmentation (Bodmeier, 1997). Combinations of

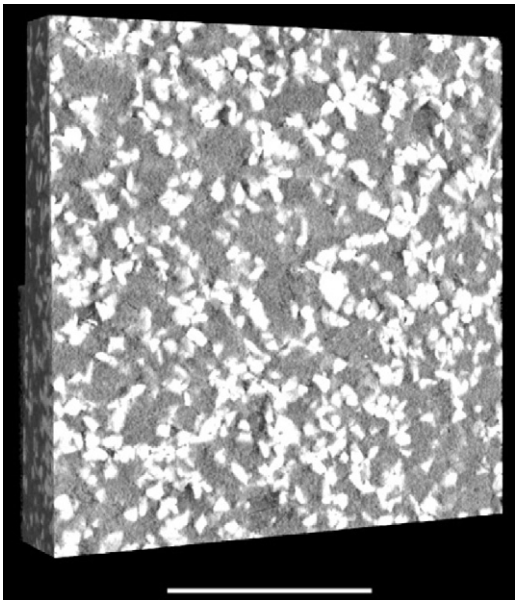

Fig. 2. X-ray tomography image of a tablet containing IMC-loaded TOPSi microparticles. Scale bar 1 mm, voxel size 2.5 μm.

MCC and lactose are often used in formulations. The fillers have a strong synergistic effect on disintegration time and an increase of the crushing strength of the tablet (Lerk et al., 1974; van Kamp et al., 1988). To avoid the anti-adherent treatment of the tablet machine punches, magnesium stearate was added to the formulation. Since our goal was to formulate quickly disintegrated tablets, NaCMC was also added to the formulations (van Kamp et al., 1986). The addition of 0.1 wt% of Aerosil was aimed to improve the flow properties of the formulation and aid the particle rearrangement within the die during the early stages of compression. According to Augsburger and Shangraw, formulations that flow evenly into the die during the tableting operation result in uniformity in tablet weight and drug content (Augsburger and Shangraw, 1966). Furthermore, it has been shown that the improved wettability of the tablets due to the hydrophilic properties of the amorphous silicon dioxide assists in the disintegration of tablets and dissolution of a drug in the dissolution media (Cabot Corporation, 2004). Because of the good solubility in water and, hence, low influence on the disintegration time of tablets, PVP was added in the formulation as a binder (Bühler, 2005).

The prepared tablets were imaged with X-ray tomography to verify whether the particle distribution inside the tablets was homogenous. As can be seen in Fig. 2, the TOPSi-IMC particles were homogenously dispersed inside the tablets, without any apparent aggregation. This shows that the tableting was successful.

Fig. 3 shows the dissolution profiles of IMC from uncompressed TOPSi-IMC particles and also from tablets contained 25, 30, and 35 wt% of TOPSi-IMC particles or crystalline IMC. The percent amount of IMC dissolved at 30 min (Q_{30} value) from TOPSi-IMC tablets was decreased as the relative amount of the particles was increased (Table 2). For uncompressed TOPSi-IMC particles the Q_{30} value was equal to 82 ± 6%, while for the IMC-tablets the Q_{30} did not exceed 31 ± 4%. The difference in the values of Q_{30} for the uncompressed particles and tablets containing 25 wt% of the TOPSi-IMC particles is not statistically significant ($P = 0.57$; $\alpha = 0.05$). However, with increasing amount of the particles in the formulation the difference becomes significant. For the tablets containing 30 and 35 wt% of the particles the Q_{30} value decreased by 9% ($P = 0.02$; $\alpha = 0.05$) and 16% ($P = 0.002$; $\alpha = 0.05$), respectively, compared to the Q_{30} for the uncompressed particles. Since the disintegration times

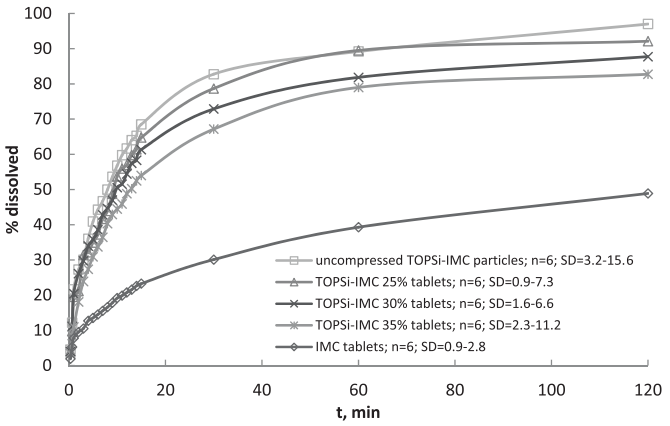

Fig. 3. Dissolution curves of the uncompressed IMC-loaded TOPSi microparticles and tablets containing TOPSi-IMC microparticles or bulk IMC. All the dissolution tests were performed at 37 °C and pH 5.5. Values represent mean ± SD.

observed and the compression forces used were almost equal for all tablets, the decrease in the Q_{30} value with increasing amount of the particles in the formulation can be attributed to the limited ability of the excipients of the formulation, in particular lactose and cellulose, to protect the porous structure of the particles from deformation during tableting.

In order to evaluate the effect of the compression pressure on the process of dissolution of the IMC from the tablets, a series of tablets from the formulation containing 35 wt% of the TOPSI-IMC particles was prepared using different compression forces. In addition, for the same formulation a specific surface area, pore volume and average pore diameter were calculated from the nitrogen isotherm before and after tableting. For this, the formulation and tablets were disintegrated in hot water, rinsed with ethanol and dried at 40 °C. The amount of TOPSi in the washed sample was estimated with TG through pyrolysis of the remaining formulation components under nitrogen flush. The results from the nitrogen sorption isotherms were then normalized with the estimated mass fraction of TOPSi particles in the washed mixtures. The dependence of the Q_{120} parameter (the percent amount of IMC dissolved at 120 min) on the compression pressure for the formulation containing 35 wt% of IMC-loaded TOPSi microparticles is shown in Fig. 4. We observed that the disintegration of the tablets during the dissolution tests occurred within 3 min regardless of the compression pressure used in the compaction of the tablets, and thus, the decrease in the dissolution rate cannot be associated with a change in the disintegration times. Apparently, the release of IMC from the compressed particles is dependent on the compression pressure applied during compaction. On the other hand, according to the results shown in Table 3, the specific surface area remained

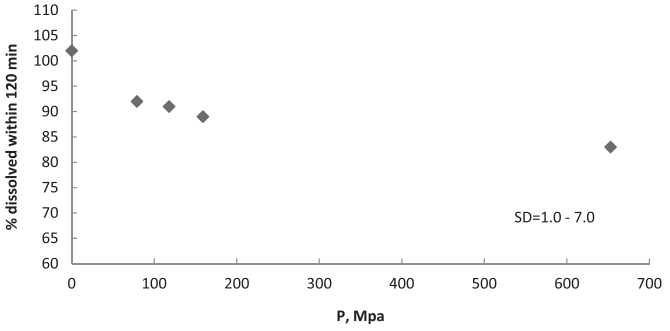

Fig. 4. Dependence of Q_{120} parameter on the compression pressure for the formulation containing 35 wt% of IMC-loaded TOPSi microparticles. Values represent mean ± SD.

Table 3
The specific surface area, pore volume and average pore diameter of the pure TOPSi-particles, TOPSi-IMC particles in formulation and tablets after disintegration. Q_{120} is the percent amount of IMC dissolved at 120 min taken from Fig. 3.

Sample	Q_{120} (%)	Specific surface area (m^2/g)	Pore volume (cm^3/g)	Pore diameter (nm)
		BET	BJH_{des}	BJH_{des}
TOPSi	–	234	0.89	11.1
TOPSi-IMC, 35 wt%, uncompressed formulation	102 ± 2	223	0.79	11.2
TOPSi-IMC, 35 wt% tablets	83 ± 7	232	0.71	8.7

practically unchanged, while the pore volume and average pore diameter decreased after the tableting. These changes in the structure of the particles corresponded to the decrease in the rate of the dissolution of IMC. The absence of clear signs of particle fragmentation indicates that the mechanism responsible for the decrease in the rate of the dissolution of IMC can be a deformation of the pore structure of the particles caused by the compression forces during tableting. Similar results have been reported by Vialpando et al. (2011) in a study related to itraconazole-loaded mesoporous silica particles. Based on the above results, the choice of the components added to a formulation should be directed to the excipients with a high plasticity in order to provide protection against deformation of the particles during compression. In our case, at the level of compression forces used (12–13 kN), the content of the particles in the formulation has to be lower than 25 wt% to avoid the particle deformation and to maintain the improved dissolution rate of IMC. It also must be noted that the excipients added to TOPSi-IMC particles did not affect the dissolution rate of IMC from the particles. For the uncompressed formulations containing 35 and 25 wt% of the TOPSi-IMC particles and the uncompressed TOPSi-IMC particles without any excipients, the parameter Q_{120} reached 102 ± 2, 102 ± 2 and 101 ± 1%, respectively, which indicates a complete IMC release from the TOPSi microparticles within the experimental time studied. To design acceptable tablets, the dissolution rate of the drug, strength, thickness, weight and disintegration time of the tablets are all very important factors. As shown in Table 2, the measured crushing strengths for all the tablets with different particle ratios were of 41–49 N, which allowed fast disintegration times in accordance with the limits of Ph. Eur. and are acceptable for immediate release tablets.

Besides the dissolution tests, we also performed permeability experiments of IMC across Caco-2 monolayers using for comparison uncompressed TOPSi-IMC microparticles and tablets contained 25 and 35 wt% of TOPSi-IMC microparticles or bulk IMC. The idea was to evaluate whether or not the permeability properties of IMC was affected by formulating TOPSi-IMC particles into tablets. To mimic the microclimate of the small intestine, a pH-gradient was set in which the pH on the apical and basolateral sides were kept at 5.5 and 7.4, respectively. The results in Fig. 5 show that both uncompressed TOPSi-IMC particles and 25 wt%-containing TOPSi-IMC tablets increased the permeated drug amount about 8-fold after 120 min across Caco-2 monolayers compared to the bulk IMC. The permeation of IMC from the 35 wt% containing TOPSi-IMC tablets was slightly slower that from 25 wt% containing TOPSi-IMC tablets, yielding an increase in the permeated amount of IMC of about 6-fold after 120 min compared to the bulk IMC. This is probably related with the slightly difference in the dissolution properties between the two TOPSi-IMC tablet forms (see Fig. 3). The enhanced permeation is further explained by the possibility of TOPSi microparticles to increase the high local drug concentrations, and even drug supersaturation, which can increase the net drug absorption and respective permeation (Kaukonen et al., 2007; Brouwers et al., 2009; Bimbo et al., 2011). Overall, these results clearly indicate that when IMC is loaded into TOPSi particles and formulated into tablets at certain wt%, both the release/dissolution and the permeation properties across Caco-2 monolayers are kept unchangeable and give similar results as the uncompressed TOPSi-IMC particles.

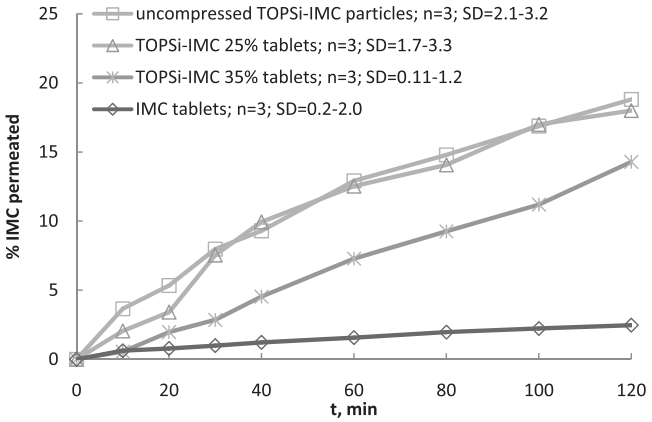

Fig. 5. Permeability of the uncompressed IMC-loaded TOPSi microparticles, tablets containing TOPSi-IMC microparticles or IMC across differentiated Caco-2 cell monolayers at 37 °C and pH of 5.5 and 7.4, apical and basolateral compartments, respectively. Values represent mean ± SD.

4. Conclusions

We have shown that IMC-loaded TOPSi microparticles can be compacted into conventional tablets with acceptable crushing strengths and disintegration times. For a formulation containing 75 wt% of fillers (lactose:cellulose, 60:40) and 25 wt% of TOPSi-IMC particles, the difference in the dissolution rates of IMC in the tablets and in the uncompressed TOPSi-IMC particles was not statistically significant. When reducing the total content of the fillers in the formulation, the dissolution rate of IMC from the tablets decreased compared to the dissolution rate of IMC from the uncompressed TOPSi-IMC particles. Increasing the compression pressure on the TOPSi-IMC particles led to a decrease in both the dissolution rate and permeability of IMC from the compressed TOPSi-IMC particles. The reduction in the dissolution rate and permeability of IMC from the compressed TOPSi-IMC particles is, presumably, a result of the loss of unique pore structure of the particles due to deformation of the particles under the compression load. Nevertheless, the dissolution and permeation of the drug across the Caco-2 monolayers was still greatly enhanced when compared to the bulk IMC. This indicates that even when compressed into tablets, the drug loaded into TOPSi can contribute to an enhanced dissolution/solubility and permeation of IMC across Caco-2 monolayers. Finally, we have also demonstrated that the choice of components for formulations containing TOPSi-IMC particles should be directed to excipients of high plasticity in order to provide the best protection against deformation of the particles during compression.

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