A novel Malonamide Periodic Mesoporous Organosilica (PMO) for controlled Ibuprofen release

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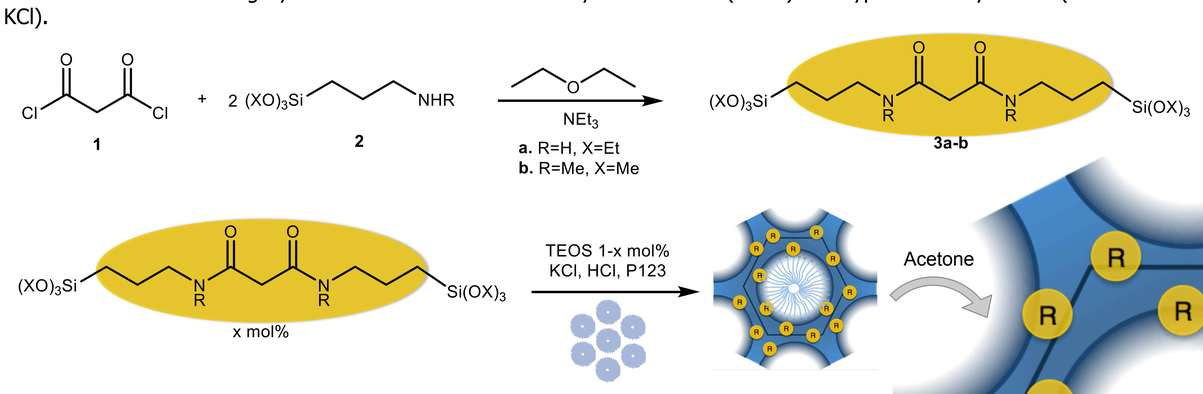
Introduction

Controlled drug release gained a sharply increasing interest over recent years. Multiple materials have been screened as possible drug carriers, ranging from biodegradable polymers to hydroxyapatite[1]. Periodic Mesoporous Organosilicas are valuable alternatives as they possess a high chemical and thermal stability combined with a biocompatible nature[2]. Furthermore, their large internal surface area permits a high drug loading. Careful selection of the organic 'bridged' functionality allows a controlled release with respect to external stimuli, such as pH or temperature, of the drugs which are adsorbed via weak and reversible interactions, e.g. H-bonding, ionic and hydrophobic-phobic interaction[3]. In this contribution a novel malonamide (MA-PMO) and a methyl-malonamide PMO (mMA-PMO) bearing a high amount of functionalities, capable of multiple intramolecular interactions, are developed and thoroughly characterized[4]. Subsequently, these hybrid materials are evaluated in the controlled drug release of Ibuprofen.

Synthesis and analysis of (methyl)malonamide-PMOs

Scheme 1: Schotten-Baumann reaction of (3-aminopropyltriethoxy)silane **2a** and (N-methyl 3-aminopropyltrimethoxy)silane **2b** with malonylchloride **1.** Next, the novel silsesquioxane PMO precursors are used to obtain an extensive range of 2D hexagonal PMOs with different functional loading by co-condensation with tetraethyl orthosilicate (TEOS) in a typical PMO synthesis (acidic medium, P123, KCl).



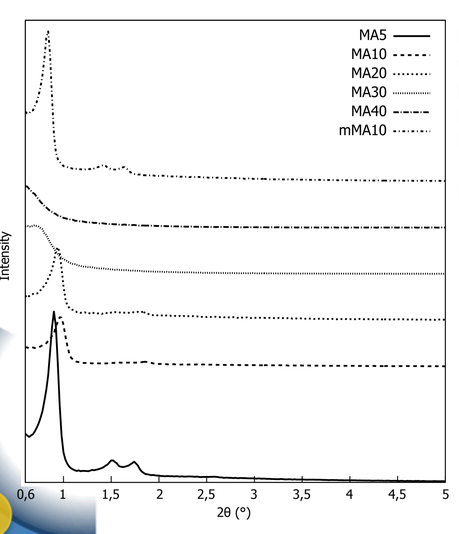


Fig. 2: XRD patterns showing P6mm 2D hexagonal ordering for MA5, MA10, MA20 and mMA10. This ordering is lost for MA30 and MA40.

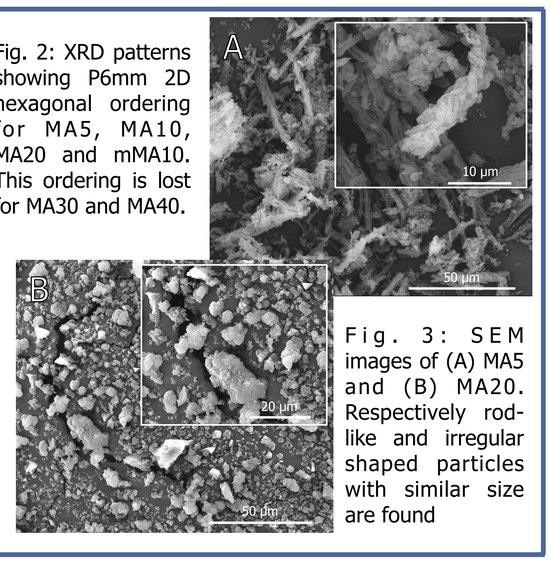


Fig. 3: SEM images of (A) MA5 and (B) MA20. Respectively rod-like and irregular shaped particles with similar size are found

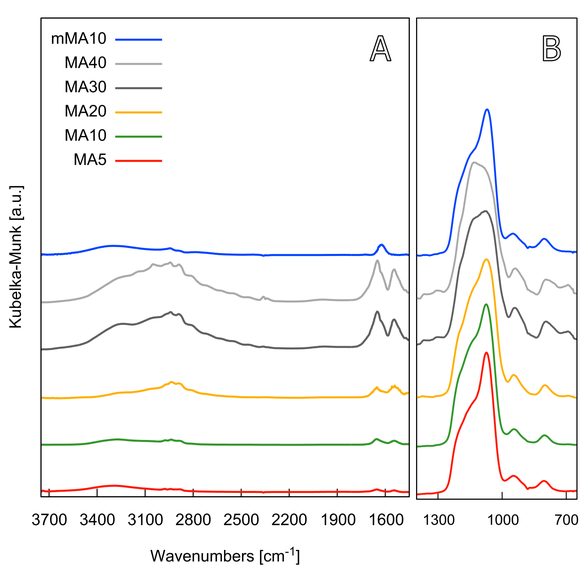


Fig. 1: DRIFT spectra of (m)MA-PMOs with different functional loading. For clarity the intensity of (A), region of organic functionality, is enhanced compared to (B), region of Si-O stretch. Amide vibrations (highlighted) and C-H stretch (v ~ 2950 cm^{-1}) confirm the presence of (m)MA moieties in the PMO-materials.

Sample	MA (mmol/g)
MA5	0,45
MA10	0,93
MA20	1,34
MA30	1,86
MA40	2,28
mMA10	0,92

Table 1: CHNS determined (m)MA functional loading

Sample	S_{BET} (m^2/g)	V_p (mL/g)	d_p (nm)
MA5	545	0,82	6,8
MA10	341	0,53	5,2
MA20	276	0,41	5,0
MA30	176	0,26	/
MA40	102	0,22	/
mMA10	621	0,91	6,8

Table 2: Surface area (S_{BET}), total pore volume (V_p) and pore size (d_p) of (m)MA-PMOs. d_p for MA30 and MA40 is indeterminable due to lack of ordering.

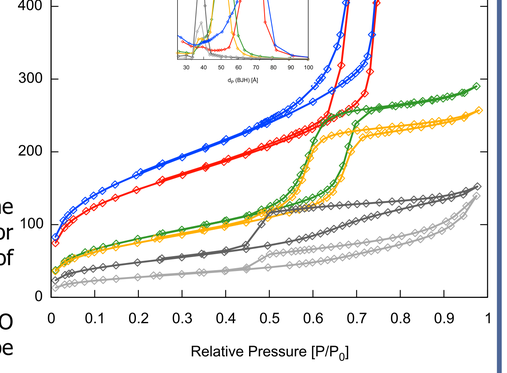


Fig. 4: N_2 sorption isotherm of a typical MA-PMO (MA10) with pore size distribution (inset). H1 type IV hysteresis is clearly distinguished.

Sample	q_e (mg_{IBU}/g)	q_e (mg_{IBU}/m^2)
SBA-15	103,06	0,159
MA5	109,75	0,201
MA10	81,28	0,238
MA20	83,95	0,303
mMA10	150,11	0,241

Table 3: Ibuprofen loading at adsorption equilibrium (q_e) in mg_{IBU}/g of MA-PMO and corrected for the surface area (S_{BET}) in mg_{IBU}/m^2.

Ibuprofen controlled-release

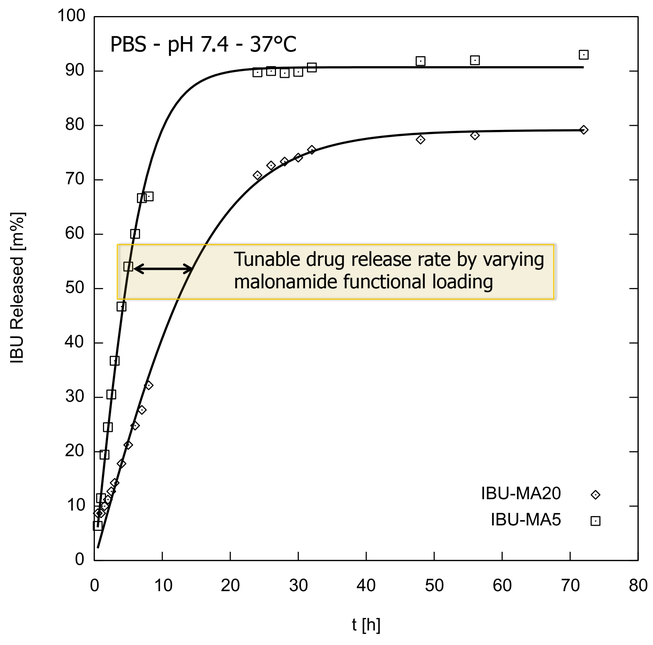
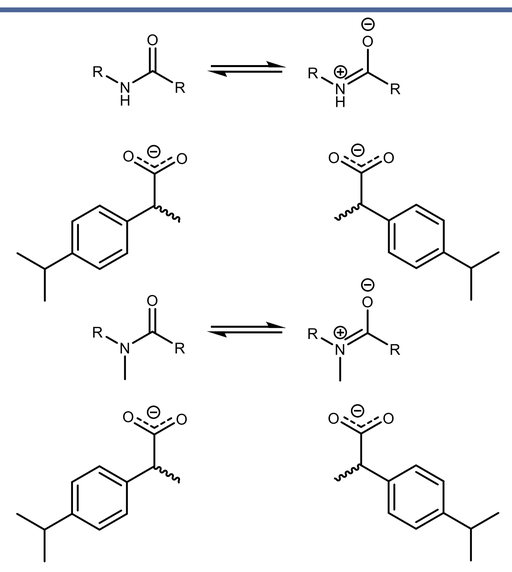
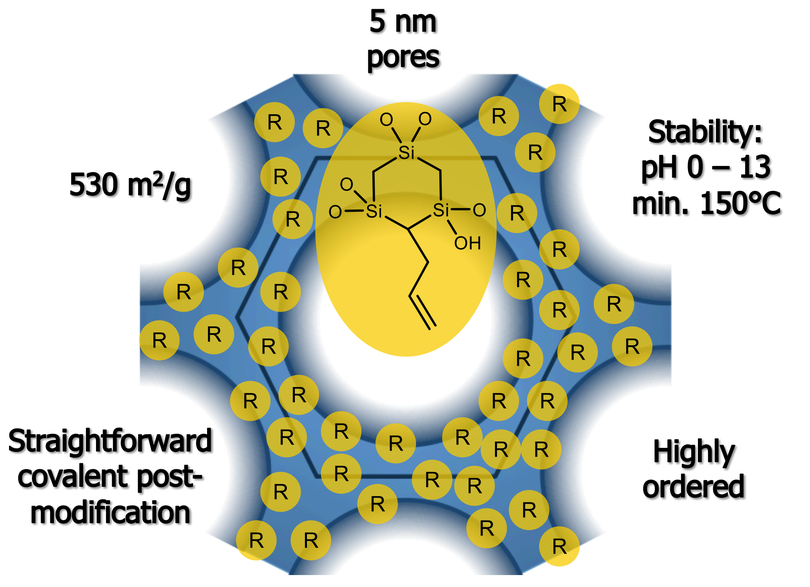


Fig. 5: Ibuprofen release profiles of IBU-MA5 and IBU-MA20. Controlled drug release was found during a long period (10-12h), with high amounts of IBU released. A lower drug release rate is observed for higher MA-functional loading, which implies a tunable release rate. The longer retention of IBU in the MA20-PMO can be ascribed to more interactions between IBU and the PMO drug carrier. A 10% mMA shows the same release profile as MA5.



Scheme 2: Interaction of Ibuprofen with malonamide PMOs (top) and methylated malonamide (bottom): Above hydrophobic-phobic interactions, conjugation gives rise to ionic interactions, a H-bonding interaction is lacking for mMA materials.

Recent work: 100% allylic PMO



Summary

New, well-ordered (methyl-) malonamide-type PMOs are developed, showing high porosity and large pore sizes. A malonamide PMO (MA-PMO) is shown promising for controlled drug release as the high functional loading leads to large Ibuprofen adsorption. As the functional loading of the drug carrying PMO is increased, intrinsically more Ibuprofen is adsorbed. Furthermore, high amounts of drug are released in a controlled, linear fashion over a long timespan in a phosphate buffer solution (pH 7.4) at body temperature. Most interestingly, the rate of drug release is tunable by varying the malonamide functional loading. Intramolecular ionic interactions, through conjugation of the amide moieties and deprotonation of Ibuprofen at pH 7.4, are believed to be the major contribution of this delayed release. H-bonding in MA-PMOs gives rise to a longer retention of Ibuprofen compared to methyl-malonamide PMOs (mMA-PMOs). The combination of these possible interactions makes these new drug carriers widely applicable, e.g. in the controlled release of 5-fluorouracil (5-FU), an anti-cancer agent, or they can even be used as a combined pH-triggered release system of both IBU and 5-FU [5].

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