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

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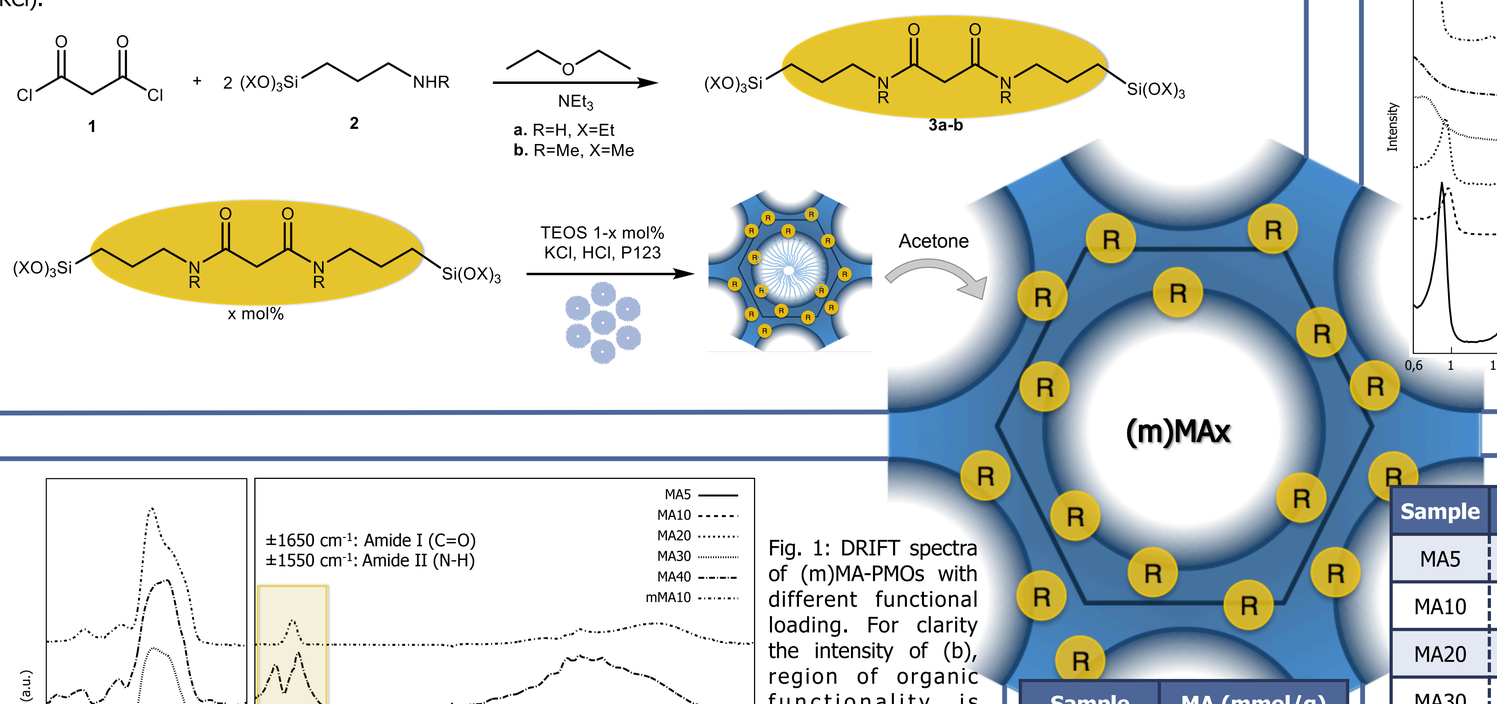
Introduction

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 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 H-bond donors and acceptors is developed and thoroughly characterised. 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).



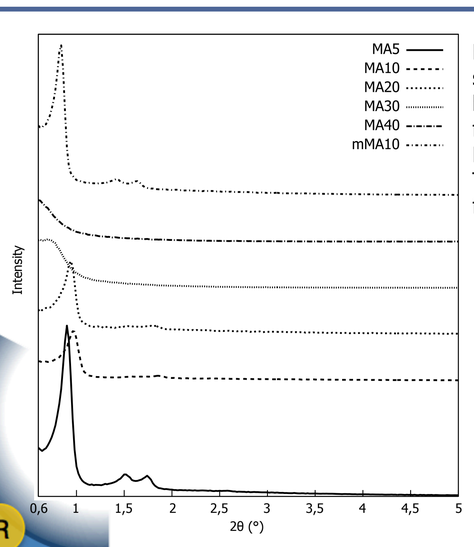


Fig. 2: XRD patterns showing P6mm 2D hexagonal ordering for MA5, MA10, MA20 and mMA10. This ordering is lost for MA30 and MA40.

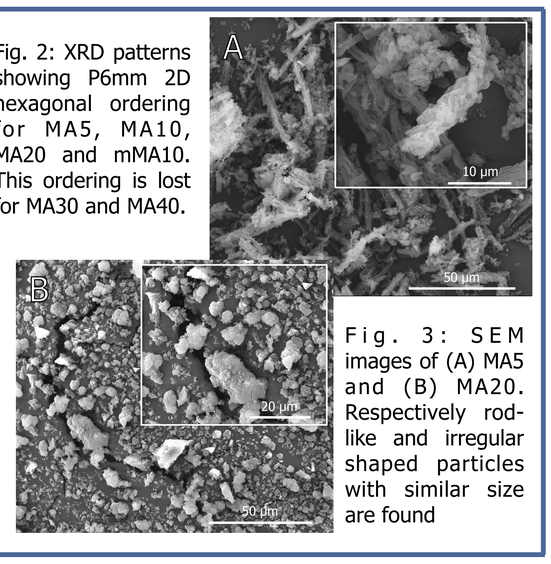


Fig. 3: SEM images of (A) MA5 and (B) MA20. Respectively rod-like and irregular shaped particles with similar size are found

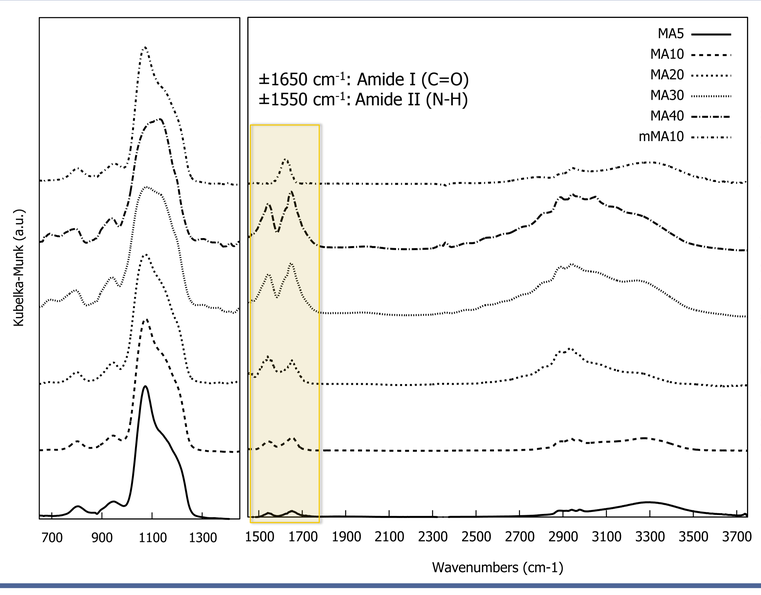


Fig. 1: DRIFT spectra of (m)MA-PMOs with different functional loading. For clarity the intensity of (b), region of organic functionality, is enhanced compared to (a), region of Si-O stretch. Amide vibrations (highlighted) and C-H stretch (ν~2950 cm^{-1}) confirm the presence of (m)MA moieties in the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

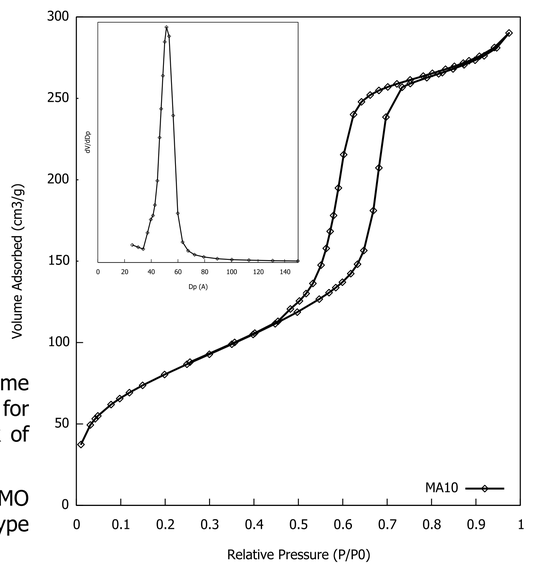
Sample	MA (mmol/g)
MA5	0,45
MA10	0,93
MA20	1,34
MA30	1,86
MA40	2,28
mMA10	0,92

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.



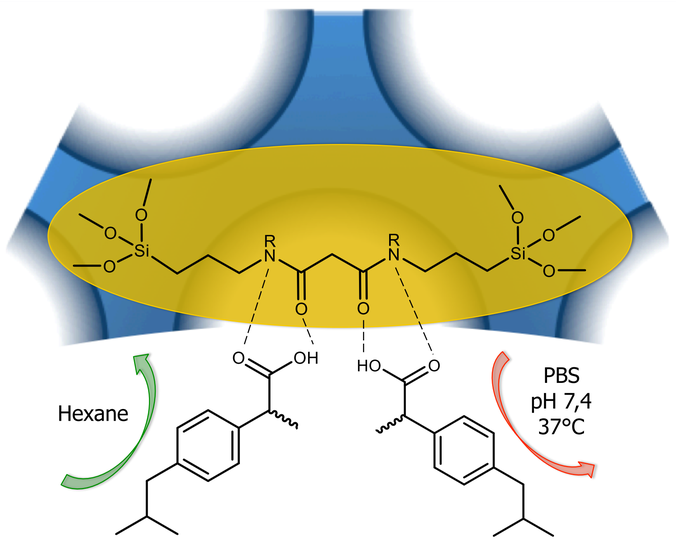
Ibuprofen controlled-release

Adsorption experiment

(m)MA-x —IBU/hexane, 24h, 25°C→ IBU-(m)MA-x

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

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. Intrinsically more IBU is adsorbed as the functional malonamide loading increases.



Scheme 2: Overview of Ibuprofen adsorption on malonamide functionalized PMO materials and controlled release in a phosphate buffer solution (PBS) at pH 7,4, mediated by H-bonding interactions (dashed) and/or hydrophobic-phobic interactions

Release experiment

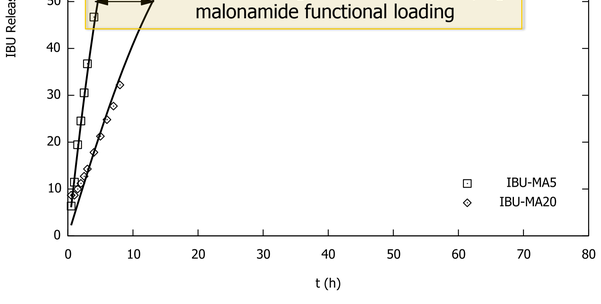


Fig. 5: Ibuprofen release profiles of IBU-MA5 and IBU-MA20. Controlled drug release was found during a long period (10-12h), with high amounts of IBU released. A lower drug release rate is observed for higher MA-functional loading, which implies a tunable release rate. The longer retention of IBU in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

Summary

Two new well-ordered 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 via H-bonding and hydrophobic interactions. 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. The influence of H-bonding interactions, which possibly give rise to a longer retention of Ibuprofen, can be investigated further by experiments with methyl-malonamide PMOs (mMA-PMOs). Also, these new drug carriers may be employed 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 [4].

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