A polyhedral oligomeric silsesquioxane/molecular sieve codoped molecularly imprinted polymer for gastroretentive drug-controlled release in vivo

Xu Wang, Fang-Fang Yang, Li-Ping Zhang, Yan-Ping Huang* and Zhao-Sheng Liu*

A novel molecularly imprinted polymer co-doped by polyhedral oligomeric silsesquioxane and molecular sieve for gastroretentive drug-controlled release.

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A polyhedral oligomeric silsesquioxane/molecular sieve codoped molecularly imprinted polymer for gastroretentive drug-controlled release in vivo†

Xu Wang, Fang-Fang Yang, Li-Ping Zhang, Yan-Ping Huang* and Zhao-Sheng Liu*

Flotation drug delivery system (FDDS) is recognized as an efficient means to improve the therapeutic efficiency and enhance the drug bioavailability. Herein, we have developed a molecularly imprinted polymer (MIP) against capcitabine (CAP) to fabricate a FDDS by exploiting polyhedral oligomeric silsesquioxane (POSS) and Mobil composition of matter no. 41 (MCM-41) as the codopant. The synergistic effect of POSS and MCM-41 endows MIPs with enhanced imprinting effect and improved mass transfer efficiency. The impacts of the type of dopant, the type of functional monomer, the template/functional monomer ratio and the functional monomer/cross-linker ratio on imprinting effect have been investigated in detail. The POSS/MCM-41 codoped MIPs present favourable sustained release property in vitro and in vivo, displaying a high relative bioavailability of 173.4%. The proposed MIPs with high selectivity and superior physical and chemical stability exhibit potential as an alternative drug carrier applied in FDDS.

Introduction

Oral administration as a facile and non-invasive treatment strategy has been widely applied in clinics, facilitating movement of drugs to different parts of the body via the bloodstream to have a systemic effect. However, the rapid clearance and low bioavailability severely limit the therapeutic efficacy of drugs, particularly acid-sensitive drugs or drugs with a narrow absorption window in the gastrointestinal tract. Great efforts have been devoted to develop gastric-retentive drug delivery systems (GRDDS) to bypass the gastric emptying process. Flotation drug delivery system (FDDS), firstly introduced by Davis in 1968, is recognized as an efficient means to improve the therapeutic efficiency. A series of systems have been proposed to promote the intragastric buoyancy of drugs such as dry solid systems with low-density (<1.004 g cm−3) or non-effervescent and effervescent systems via swelling or CO2 generation to decrease their densities in gastric fluids. However, tedious preparation procedures and high costs still hinder the wide application of current flotation drug delivery systems.

Molecularly imprinted polymers (MIPs) are tailored affinity materials with predetermined specificity to template molecules. An excess of monomers are assembled onto template molecules via covalent or noncovalent interactions, followed by polymerization in presence of cross-linker to obtain well-defined receptor sites. Removal of the template from the MIPs exposes specific binding sites or empty cavities complementary to template molecules in size, shape and ligand. By mimicking the interactions between natural receptors and target molecules, MIPs are capable of retaining desired drugs based on their reciprocal interaction, enhancing the loading capacity and enabling sustained drug release. Moreover, their molecular memory of MIPs can be retained under high temperature, high mechanical stress, strong basic or acidic conditions and even exposure to organic solvents. Until now, several drug delivery systems that exploit MIPs as carriers have been successfully fabricated, such as therapeutic contact lenses, enantiomers transdermal delivery system, or metal-based drug delivery system. Although there are some favourable properties of MIPs. For e.g., there is unavoidable embedding of imprinted sites due to the high crosslinking that retains the memory of template molecules. This results in limited loading capacity of drugs and restricts their applications in MIP-based drug delivery systems.

Polyhedral oligomeric silsesquioxane (POSS), an inorganic silica-like core (Si8O12) that is approximately 1.5 nm in dia-
molecule, has attracted wide attention as building blocks to construct multifunctional materials. Recent results have suggested that the incorporation of POSS into polymer can retard the chain motion of polymer. It has been observed that the incorporation of POSS unit into polymer leads to dramatic changes in the copolymer’s properties, including the enhanced thermal stability and permeability. In the field of molecular imprinting, it is found that the use of POSS monomer can increase effective sites for rebinding template molecules by suppressing nonselective binding sites.

For further elevating the loading capacity of drug on FDDS, nanoparticle/MIPs hybrids have huge potential for the improvement of MIP-based FDDS by using nanoparticles as an ideal scaffold. Particularly, molecular sieves with benign biocompatibility and large specific surface area exhibit fascinating features in encapsulation of drugs. Integration of encapsulation and imprinted effect into the molecular sieves doped-MIPs provides high loading capacity of drugs and enhanced imprinted effect. However, to our knowledge, no POSS/molecular sieve co-doped hybrid MIPs applied for drug delivery have been reported so far.

Herein, we have developed alternative hybrid MIPs for oral drug delivery by exploiting POSS/molecular sieve as codopant (Scheme 1). Mobil composition of matter no. 41 (MCM-41), a typical molecular sieve with large specific surface area (300–1000 m² g⁻¹) and adjustable structure of pores, was codoped with POSS in MIPs to increase transfer efficiency and to enhance the selectivity. Acrylamide (AAm) and 2-acrylamido-2-methylpropanesulfonic acid (AMPS) were obtained from J&K CHEMICA Co., Ltd (Beijing, China). Ethylene glycol dimethacrylate (EDMA, 98%) was purchased from Sigma-Aldrich Co., Ltd (St Louis, MO, USA). Azobisisobutyronitrile (AIBN, AR grade) was purchased from J&K CHEMICA Co., Ltd (Beijing, China). Acetonitrile (ACN, HPLC grade) was purchased from Thermo Fisher Co., Ltd (NJ, USA). Unless otherwise indicated, all other chemicals were purchased from Tianjin Chemical Reagent Co., Ltd (Tianjin, China).

**Characterization**

The morphology and microstructure of the hybrid MIPs were characterized by a FEI Nova NanoSEM 450 high-resolution field emission scanning electron microscopy (FE-SEM) (Eindhoven, Netherlands). The pore characters of the hybrid MIPs were measured by nitrogen adsorption–desorption at 77 K using a VSorb 2800TP pore size distribution analyser purchased from Gold APP Instruments Corporation China (Beijing, China). The simultaneous thermal analyser (Netzsch, Germany) was used for thermal degradation studies by heating powdered samples to 600 °C at a heating rate of 10 °C min⁻¹ under nitrogen atmosphere with a flow of 20 mL min⁻¹.

**Silanization of MCM-41**

As indicated in Scheme S1, in general, 5 mg mL⁻¹ of pristine MCM-41 toluene solution (50 mL) was mixed with 10 mL of γ-MPS. After ultrasonication for 10 min, the obtained homogeneous solution was degassed with N₂ for 5 min and sealed, followed by stirring at 60 °C for 24 h. The crude product was washed repetitively by methanol and toluene to remove excessive molecular sieves and reagents and dried in vacuum to obtain the white powder (MCM-41-MPS).

**Preparation of CAP-imprinted monolithic columns**

CAP-imprinted monolithic columns were synthesized by in situ polymerization. As shown in Table 1, a certain amount of CAP and AIBN (20 mg) were dispersed in the binary porogens of [BMIM]BF₄ and DMSO. POSS dissolved in the cross-linker of EDMA was added into the mixture, followed by ultrasound for 20 min. Then, the binary monomers of AAm and AMPS, and
MCM-41 were subsequently added into the mixture treated by ultrasound for 15 min. A stainless steel column was fed into the prepolymerization solution with its ends sealed and then maintained at 60 °C for 3 h. To remove template molecules and unreacted reagents, the monolithic column was washed with 100 mL of acetonitrile and 150 mL of methanol/acetic acid (9 : 1, v/v), respectively. The non-imprinted polymer (NIP) was synthesized and washed under the same conditions except for the absence of CAP.

**HPLC evaluation**

The interactions of hybrid MIPs and analytes were evaluated at 25 °C by an Agilent 1100 HPLC equipped with G131513 DAD detector, G1311A pump, HPCORE workstation, G1322A degasser and Rheodyne 7225 injector (Cotati, CA). Acetonitrile/acetate buffer (99 : 1, v/v) (50 mmol L⁻¹, pH 3.6) was selected as the mobile phase. To measure the void volume of the MIP monolith, 20 μL of acetone (0.1%) was injected into the HPLC system for analysis. The retention factor \(k\) was calculated according to the equation \(k = \frac{t_r - t_0}{t_0}\), where \(t_r\) and \(t_0\) are the retention time of the void marker (acetone) and the eluted substance, respectively.

The equation of IF = \(k_{\text{MIP}}/k_{\text{NIP}}\) was used to calculate the imprinting factor (IF) to evaluate the imprinting efficiency of the prepared monolith columns, where \(k_{\text{MIP}}\) or \(k_{\text{NIP}}\) is the retention factor of CAP on the imprinted monolithic column or on the non-imprinted monolithic column, respectively.

**Frontal analysis**

The affinity of MIPs to the template molecules of CAP was investigated by frontal analysis using various concentrations of CAP solutions in acetonitrile/acetate buffer solution (99 : 1, v/v) (pH 3.6, 50 mmol L⁻¹), which were detected at 254 nm.

The binding behaviours of MIPs were evaluated by the Langmuir-Freundlich (LF) isotherm model according to eqn (1)

\[
B = \frac{N_a a^m F}{1 + a^m F}
\]

where \(B\) or \(F\) represents the equilibrium concentration of binding or free template molecules. \(N_a\) (mmol g⁻¹) represents the amount of affinity sites. \(a\) indicates the binding affinity \((K_0, \text{ L mmol}^{-1})\) which can be calculated according to \(K_0 = a^{1/m}\), \(m\) varies from 0 to 1, representing the heterogeneity index. When there is a heterogeneous material, \(m\) is less than 1, whereas when there is a homogeneous material, \(m\) is equal to 1.

**Equilibrium adsorption experiment**

Equilibrium adsorption experiments were used to investigate the drug loading capacity of CAP on hybrid MIPs. A series of CAP solutions (300, 500, and 750 μg mL⁻¹, 4.0 mL) were added into the hybrid MIPs (40 mg) ethanol solution followed by shaking for 5 h. After centrifugation at 8000 rpm for 10 min, the supernatant was collected to measure the concentration of CAP by a UV spectrophotometer. The equilibrium adsorption amount of CAP \(Q_e\) (mmol g⁻¹) was calculated according to eqn (2)

\[
Q_e = \frac{(C_0 - C_e) \times V}{m}
\]

where \(C_e\) or \(C_0\) is the equilibrium or initial concentration of CAP (mmol L⁻¹), \(m\) (g) represents the weight of the hybrid MIPs, and \(V\) (L) represents the volume of the solution.

**Drug release behavior in vitro**

The buoyancy of POSS/MCM-41 codoped MIPs and MIPs without any dopant was investigated in HCl buffer (pH 1.0), in PBS buffer (pH 7.4) or in ethanol. To investigate the drug release behaviours of the prepared hybrid MIPs, MIPs (30 mg) dispersed in 2 mL of ethanol were transferred to the dialysis bags respectively, which were soaked in 100 mL of ethanol under stirring. The cumulative release rate of CAP at appropriate time interval was determined with a UV spectrophotometer at 227 nm.

**Pharmacokinetic study in vivo**

Wistar rats (180–200 g, male, 8–10 weeks old) were provided by Experimental Animal Center of Academy of Military Sciences PLA China (Tianjin, China). All rats were housed and food manufactured by the Department of Laboratory Animal Science of Tianjin Medical University (laboratory animal certificate: syxk2014-0004). All experiments were performed according to the Regulations of Tianjin Municipality on Laboratory Animal Management and the Animal Management Rules of the Ministry of Health of the People’s Republic of China, and were approved by Tianjin Medical University institutional ethical committee.

The drug-loaded MIPs (40 mg) dissolved in 2.0 mL of normal saline solution were administrated intragastrically by fixing the dose of CAP as 1 mg kg⁻¹. The same dose of commercial tablet CAP was set as the control. At different time intervals, the blood samples (100 μL) were drawn from anaesthetized rats via the vein of the eye socket and put immediately into the heparinized tubes. The plasma was collected by centrifugation at 4000 rpm for 5 min. Then, 150 μL of acetonitrile

### Table 1: Preparation of capecitabine-imprinted monolith

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*a* Initiating agent, AIBN (20 mg); porogen, [BMIM][BF₄] (1250 μL) and DMSO (990 μL).
was mixed with 50 μL of plasma for 30 s, followed by centrifugation at 13,000 rpm for 5 min to collect the upper organic layer. After drying the obtained organic layer, the residue was re-dispersed in mobile phase for further analysis in HPLC at 227 nm. Methanol : water : acetonitrile (23 : 41 : 36, v/v/v) was selected as the mobile phase with a flow-rate of 1.0 mL min⁻¹.

The distribution of CAP in vivo was evaluated by the pharmacokinetic parameters. The linear trapezoidal method was exploited to calculate the area under CAP concentration-time curve (AUC). $T_{\text{max}}$ indicated the time point of the maximum concentration of CAP in plasma. The relative bioavailability ($F$) was calculated according to eqn (3)

$$F = \frac{\text{AUC}_T}{\text{AUC}_R}$$

### Results and discussion

MIPs with predetermined specificity to template molecules exhibit the high potential as an alternative carrier for fabricating flotation drug delivery systems. For suppressing non-specific binding and improving mass transfer efficiency, POSS and MCM-41 were exploited as codopants to incubate with the functional monomers of AAm and AMPS to prepare the CAP-imprinted MIPs in the presence of initiating agent (Scheme 1). The prepared POSS/MCM-41 codoped MIPs with high rigidity and abundant binding sites exhibit high selectivity to template molecules.

### Optimization of the type of dopant

To clarify the effect of POSS or MCM-41 as the dopant on imprinting effect, MIPs with different dopants were prepared (Fig. 1A). In the absence of any dopant, the obtained MIPs (M4 indicated in Table 1) showed a low imprinted factor (1.946). After doping POSS into MIPs (M2), the imprinted factor was elevated to 3.348. There was no big difference in imprinted factor with MCM-41 as the dopant instead of POSS (3.023) (M3). An obvious enhancement in imprinted factor could be observed when MCM-41 and POSS were codoped in MIPs (6.124) (M1), leading to the elevated selectivity of MIPs to template molecules. Thus, POSS and MCM-41 were codoped in MIPs in the further experiments.

### Optimization of the type of functional monomer

The type of functional monomer with the greatest impact on the imprinting effect was also determined (Fig. 1B). The fabricated MIPs exploiting AAm as the sole-monomer presented a limited imprinted factor of 1.838 (M5). After replacing AAm with AMPS (M6), no obvious improvement could be observed in the imprinting effect (1.176). In contrast, the imprinted factor of MIPs prepared by dual-monomer (AAm/AMPS) (M1) was 6 times higher than that of the MIPs prepared by the sole-monomer. The dual-monomer with higher polarity, in contrast with sole-monomer, due to the coexistence of the amino group in AAm and the acylamino group in AMPS, facilitates the formation of hydrogen bonds between CAP and dual-monomer, thus enhancing the imprinting effect of MIPs. Thus, binary monomers of AAm and AMPS were exploited in further experiments.

### Optimization of template molecule/dual-monomer ratio

Pre-polymers formed by template molecules and functional monomers via non-covalent binding determine the selectivity of MIPs. The preparation of the hybrid MIPs was optimized by changing the feeding molar ratio of template molecule to dual-monomer from 1 : 6 to 1 : 2 while fixing the amounts of other reagents. As shown in Fig. 1C, while the ratio of CAP to AAm/AMPS was changed from 1 : 6 to 1 : 5, an increase in imprinted factor could be obtained from 1.36 to 6.12 on the basis of the complete reaction between template molecules and monomers, thus forming abundant binding sites to enhance the affinity. Further increasing the ratio of CAP to AAm/AMPS led to a declined imprinted factor due to the presence of excessive CAPs without abundant monomers to form the pre-polymers. Thus, the optimal ratio of template molecule to dual-monomer was selected as 1 : 5.

### Optimization of dual-monomer/cross-linker ratio

To ensure the integrity of imprinted cavities in MIPs, an optimal ratio of dual-monomer to cross-linker has been investigated with a fixed amount of CAP and codopant (Fig. 1D). The imprinted factor showed a sustained increase along with the elevation of the ratio of dual-monomer to cross-linker from 1 : 8 to 1 : 6, indicating increased number of binding sites due to the improved cross-linking degree. The maximum imprinted factor was obtained as 6.12 while the ratio of dual-monomer to cross-linker was 1 : 6. Further increase in the ratio resulted in the decrease of imprinting effect probably due to the excessive cross-linker inhibiting the access of template
molecules to binding sites. Thus, the optimal ratio of dual-monomer to cross-linker was selected as 1:6.

**Characterization of POSS/MCM-41 codoped hybrid MIPs**

Under the optimal conditions, the morphology of the POSS/MCM-41 codoped hybrid MIPs was revealed by SEM. As shown in Fig. 2, the prepared POSS/MCM-41 codoped hybrid MIPs (M1) were comb-like with a rough surface. There was no big difference in morphology between M1 and MIPs without any dopant (M4), indicating little impact of a low content of POSS or MCM-41 doped in MIPs on the size and morphology (Fig. 2A and B). Other MIPs such as POSS doped MIPs (M2), MCM-41 doped MIPs (M3), AAm-based MIPs (M5), and AMPS-based MIPs (M6), presented similar morphology as well (Fig. S1†). To further clarify the determinant on the morphology of MIPs, POSS/MCM-41 codoped MIPs were prepared by exploiting S-naproxen (S-NAP) as the template molecule and 4-vinylpyridine (4-VP) as the functional monomer (Fig. S2†). The S-NAP imprinted MIPs prepared by the same dopants, porogens and cross-linker were spherical particles with a smooth surface, revealing that the interactions between monomers and template molecules were the key to controlling the size and morphology of MIPs.

To reveal the relations between morphology and imprinting effect of MIPs, nitrogen adsorption measurements were carried out at 77 K (Fig. 2C and E). Typical type IV isotherms were observed in all MIPs, verifying the porous structures of the prepared MIPs. The profiles of hysteresis loops revealed the narrow slit-like pores in hybrid MIPs. A remarkable inflection point on desorption curve of POSS/MCM-41 codoped MIPs or POSS/MCM-41 codoped NIPs was presented at around 0.40/Po, indicating the ending of the monolayer adsorption stage and the beginning of the multilayer coverage stage.

Further evidence of the absorption capacity of the proposed MIPs was given by multipoint Brunauer–Emmett–Teller (BET) measurements. The BET surface area of POSS/MCM-41 codoped hybrid MIPs was calculated as 214.82 m² g⁻¹, demonstrating a favourable saturated adsorption capacity. In contrast, the POSS doped MIPs or MCM-41 doped MIPs presented a declined BET surface area (Table S1†). Moreover, the BET surface area of POSS/MCM-41 codoped hybrid MIPs (214.82 m² g⁻¹) was approximately 10 times higher than that of the MIPs without any dopant (22.63 m² g⁻¹). The BET surface areas of the AMPS-based MIP and AAm-based MIP were investigated as well. The former (167.37 m² g⁻¹) was approximately 6 times higher than that of the latter (27.73 m² g⁻¹), indicating AMPS had a notable impact on the absorption capacity.

The effects of pore sizes on absorption capacity were further revealed by single point adsorption analyses (Fig. 2D and F). The MIPs without any dopant showed the maximum single point adsorption of total pore volume (Vp = 0.40 m² g⁻¹) and total adsorption average pore width (Dmean = 68.32 nm), which were consistent with its low surface area and limited adsorption capacity (Table S1†). The doping of POSS and MCM-41 led to the decrease of total pore volume and total adsorption average pore width, resulting in the improved absorption capacity. TGA experiments showed the thermal stability of the POSS/MCM-41 codoped hybrid MIPs (Fig. S3†). An obvious weight loss appeared between 240 °C and 440 °C, demonstrating good thermal stability of the prepared hybrid MIPs.

The binding characteristics between CAP and hybrid MIPs were evaluated by frontal chromatography. Langmuir–Freundlich model was applied in fitting the adsorption isotherms (Fig. S4†). As can be seen in Table S2,† the correlation coefficients (R²) were approximately 0.999 for all MIPs, indicating that this model fitted well with the adsorption isotherms. The MIPs made without any dopant gave a low absorption capacity as 25.72 mg g⁻¹. No obvious change could be observed after doping MCM-41 or POSS into MIPs. In contrast, a significant improvement in absorption capacity was observed in the POSS/MCM-41 codoped MIPs (158.98 mg g⁻¹), indicating the increased binding sites and the elevated recognition ability of MIPs induced by the codoping of POSS and MCM-41 into MIPs. Particularly, the POSS/MCM-41 codoped MIPs showed the maximum heterogeneous distribution in cavity sizes, verifying the successful doping of POSS and MCM-41. To further investigate the impact of the monomer type, the absorption capacity of AAm-based MIP or AMPS-based MIP were determined individually. The absorption capacity of dual-monomer-based MIPs was around 4-fold high as compared to those of sole-monomer-based MIPs, revealing the synergistic effect of AAm and AMPS on imprinting effect of MIPs.

Fig. 2 (A, B) SEM images of MIPs: POSS/MCM-41 codoped MIP (A) and MIPs without any dopant (B). (C, D) Nitrogen adsorption/desorption curves and pore size distributions of POSS/MCM-41 codoped MIP, POSS/MCM-41 codoped NIPs and MIPs without any dopant. (E, F) Nitrogen adsorption/desorption curves and pore size distributions of POSS doped MIP, MCM-41 doped MIP, AAm-based MIP and AMPS-based MIP.
Drug release behaviour in vitro

To optimize the drug loading capacity on MIPs, the POSS/MCM-41 codoped MIPs were soaked in a series of CAP solutions. After centrifugation, the CAPs in supernate were measured by a UV spectrophotometer to determine the loading capacity of CAP on MIPs. The loading capacity of MIPs increased from 6.9 mg g\(^{-1}\) to 10.9 mg g\(^{-1}\) while the feeding concentration of CAP ranging from 300 µg mL\(^{-1}\) to 750 µg mL\(^{-1}\). A similar increase of the drug loading capacity in POSS/MCM-41 codoped NIPs was also observed, but it always presented a lower loading capacity in comparison to that of MIPs in the entire concentration range investigated.

However, either non-specific absorption or specific absorption is capable of leading to a sustained increase of loading capacity along with the increase of feeding concentration of drug. To clarify the interaction mechanism between template molecules and MIPs, the drug release behaviour of the obtained MIPs has been investigated. A prerequisite to fabricate the flotation drug delivery system is the buoyancy of MIPs. POSS/MCM-41 codoped MIPs exhibited remarkably enhanced floating properties in HCl (pH 1.0) or PBS buffer (pH 7.4) compared to MIPs without any dopant, indicating its potential to be an alternative carrier in gastroretentive drug delivery systems (Fig. S5†). In contrast, it dispersed fast in ethanol within 10 min along with the sustained drug release. Thus, ethanol was selected as the release medium (Fig. 3). The release equilibrium of MIPs or NIPs was achieved simultaneously after incubation in release medium for 5 h where the feeding concentration of CAP was fixed as 300 µg mL\(^{-1}\). Further increasing the feeding concentration of CAP to 500 µg mL\(^{-1}\) resulted in a prolonged release equilibrium time of MIPs (11 h), indicating improved slow-release effect. A zero-order release phenomenon was presented with prolonged time, facilitating an optimum level of drug concentration maintained in vivo.

However, when the feeding concentration of CAP was increased to 750 µg mL\(^{-1}\), the release equilibrium time of MIPs went down (6.25 h) as well as the cumulative release percentage went up, probably due to the enhanced non-specific absorption of template molecules. To reduce non-specific absorption, the optimal feeding concentration of CAP was selected as 500 µg mL\(^{-1}\).

To reveal the effect of dopant type on drug release, the drug release behaviour of POSS doped-, MCM-41 doped-, POSS/MCM-41 codoped-MIPs and those without any dopant were investigated (Fig. 4). The drug release equilibrium was achieved within 6 h where MIPs in the control groups were used as the drug carriers. In contrast, the release time of POSS/MCM-41 codoped MIPs was nearly 2 fold higher than those of other MIPs, exhibiting a favourable slow release effect. Moreover, the POSS/MCM-41 codoped MIPs showed a significantly prolonged release time (11 h) in comparison to that of POSS/MCM-41 codoped NIPs (3 h). The high affinity of imprinted sites to template molecules in MIPs resulted in the superior sustained release effect. The types of monomers have a remarkable effect on release time as well. MIPs synthesized by a sole-monomer released the drug within 8.5 h, whereas MIPs prepared by dual-monomers, AAm and AMPS, showed a prolonged release time (11 h), confirming the results obtained in imprinted factor measurements and frontal chromatography (Fig. S6†).

Pharmacokinetic study in vivo

To investigate the feasibility of POSS/MCM-41 MIP-based flotation drug delivery systems in vivo, the drug concentration in plasma versus time was plotted to investigate the pharmacokinetics in rats (Fig. 5). The POSS/MCM-41 codoped MIPs showed the maximum \(T_{\text{max}}\) of 4 h with a high plasma concentration of 113.5 ng mL\(^{-1}\) and gave the optimum bioavailability of 173.4% by comparing the value of AUC\(_{0-8}\) with that of the commercial tablet (Table 2). In contrast, the MIPs made without any dopant gave the minimum \(T_{\text{max}}\) of 1 h with a low
bioavailability of 72.5%, indicating the short circulation time without doping POSS and MCM-41. A slight increase in bioavailability was obtained after doping MCM-41 (96.8%) or POSS (93.6%), revealing that the porous structure of POSS or MCM-41 facilitated the extension of release time but still lacked abundant binding sites to trap the template molecules. The low $T_{\text{max}}$ gave further evidence of inferior sustained release properties of MCM-41 doped MIPs (2 h) and POSS-doped MIPs (0.5 h). The MIPs prepared solely by AMPS or AAm showed a low bioavailability as 99.4% or 83.0% respectively, verifying the key role of the synergistic effect of dual-monomer.

Conclusions

CAP-imprinted MIPs exploiting POSS and MCM-41 as c o dopant have been developed to fabricate flotation drug delivery systems. The synergistic effect of MCM-41 and POSS endows MIPs with higher imprinting effect and adsorption capacity. The POSS/MCM-41 doped MIPs with favourable buoyancy in an aqueous medium present sustained drug release property and high bioavailability in vivo. The proposed MIPs with high affinity to template molecules, good mechanical strength as well as superior physical and chemical stability have provided an alternative for the next generation of flotation drug carriers.

Conflicts of interest

The authors declare no competing financial interest.

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Notes and references

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