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# Macromolecular crowding of molecular imprinting: A facile pathway to produce drug delivery devices for zero-order sustained release

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ABSTRACT

This paper reported the facile fabrication of drug delivery devices for zero-order sustained release by molecular crowding strategy of molecularly imprinting technology. Crowding-assisted molecularly imprinting polymers (MIPs) matrices were prepared by free-radical precipitation polymerization using aminoglutethimide (AG) as a model drug. The crowding effect was achieved by adding polystyrene as a macromolecular co-solute in pre-polymerization mixture. The MIP prepared under the non-MMC condition and the two corresponding non-imprinted particles were tested as controlled vehicles. The release profiles presented zero-order behaviors from two crowding-assisted polymers, the duration of approximately 18 h for the crowding-assisted MIP and 10 h for the crowding-assisted NIP, respectively while AG were all very rapid released from the other two controlled particles (85% occurring in the first hour). The BET surface area and pore volume of the crowding-assisted MIP were about ten times than those of the controlled MIP. The value of imprinting factor is 6.02 for the crowding-assisted MIP and 1.19 for the controlled MIP evaluated by the equilibrium adsorption experiment. Furthermore, the values of effective diffusivity ($D_{eff}$) obtained from crowding-assisted MIP ($10^{-17}$ $cm^2/s$) was about two orders of magnitude smaller than those from the controlled MIP, although the values of free drug diffusivity ($D$) were all found in the order of $10^{-13}$ $cm^2/s$. Compared with the commercial AG tablet, the MMC-assisted MIP gave a markedly high relative bioavailability of 266.3%, whereas the MMC-assisted NIP gave only 57.7%. The results indicated that the MMC condition can modulate the polymer networks approaciate to zero-order release of the drug and maintain the molecular memory pockets, even if under the poor polymerization conditions of MIPs preparation.



## 1. Introduction

Zero-order release systems have been developed and still under development because of their advantages over other conventional dosage forms to maintain the drug concentration within the body at an optimum level. However, according to Fick's law of diffusion, the release of a drug from matrix is inherently non-linear (Chidambaram et al., 1998). A strategy to solve the problem is to design a device through which drug is released via more than one mechanism, such as simultaneous swelling and diffusion through hydrogels, mass transfer through multiple resistances in series, and diffusion with desorption (Varelas et al., 1995). Molecularly imprinted polymers (MIPs), a relatively new class of materials, are expected to be exploited as the third device (Vijayakumari et al., 2008; Rostamizadeha et al., 2012). Because of designed artificial recognitive domains exhibited by MIPs, the imprinted drug molecule permeates the network partition preferentially adsorbed to the memory pockets within polymer matrices, which can be served as reservoirs. On exposure to drug-free surroundings, the drug exits the MIP by diffusion through the bulk phase and is then restored to the bulk from the reservoirs by binding-desorption. If these two fluxes are comparable, then the concentration of drug in the bulk phase will reach a pseudo-steady state, providing a near constant driving force for diffusion to the surroundings, hence zero-order release. Therefore, as a powerful technique for creating artificial macromolecular networks with a highly specific recognition to the interested drug, molecular imprinting has been used to develop the advanced drug delivery systems (DDS) (Kirby et al., 2005; Van Nostrum, 2005; Hilta and Byrne, 2004; Alvarez-Lorenzo and Concheiro, 2004; Schirhagl, 2014).

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Molecular imprinting technology (MIT) normally forms 3D polymer networks through an assembly of functional monomers around the target drug that serves as a template molecule. The complex is then immobilized into a polymer matrix by copolymerization of cross-linking monomers. Subsequent removal of the drug leaves specific binding sites or empty cavities complementary to the drug in size, shape and molecular interactions. The unique property of MIPs, which introduce specific binding sites into polymer matrices, endows MIPs with the ability to sustain the release of a therapeutic agent and enhance the loading capacity of the polymers (Puoci et al., 2011; Luliński, 2013; Kupai et al., 2015; Ganjali et al., 2014). Moreover, the imprinted materials can maintain their molecular memory under conditions of mechanical stress, high temperature, and exposure to organic solvents and strong basic or acidic pH. Up to now, MIP-based drug delivery vehicles have successfully applied in several interesting systems such as therapeutic contact lenses for sustained in vivo release (Tieppo et al., 2012), a transdermal enantioselective-controlled delivery (Suedee et al., 2008, 2010), and metal-chelate imprinting polymer for a metal-based drug (Vijayakumari et al., 2008). However, zero-order release systems based on MIPs are rarely obtained since the control of morphology and affinity of MIPs by varying polymerization parameters are far from clear.

Macromolecular crowding (MMC) is one key distinguishing feature between biochemical reactions and fabrication of artificial materials (Ellis, 2001a). The principle of MMC is derived from the notion that biological macromolecules evolve and function within highly crowded/dense intracellular or extracellular environments and therefore it can profoundly influence the kinetics and equilibrium of reactions by volume exclusion effects that reduce diffusion rates and enhance binding rates of macromolecules (Miyoshi and Sugimoto, 2008). By bridging a key gap between artificial and living cells, the application of crowding theory can increase thermodynamic activities and biological processes by several orders of magnitude. Therefore, the addition of crowding agents should become as routine as controlling pH in in vitro experiments (Ellis, 2001b). Up to now, macromolecular crowding has been applied in multiple displacement amplification (Ballantyne et al., 2006), regenerative medicine (Satyam et al., 2014), gene expression (Tan et al., 2013) and tissue engineering (Saeidi et al., 2012). In the case of molecular imprinting, Matsui et al. (2007) have demonstrated that the crowding strategy can be applied in organic solvents to synthesize MIPs based on non-covalent interactions. The crowding agent is capable of promoting hydrogen bond formation between the template and the monomer at the pre-polymerization stage, and thus the resultant polymers possess superior retention properties and excellent selectivity for the template. Although several crowding-assisted MIPs have been successfully prepared and evaluated in our research group, such as molecularly imprinted monoliths (MIM) (Li et al., 2012a), MIM by atom transfer radical polymerization (Ban et al., 2013), low cross-linked MIM (Mu et al., 2011) imprinted microparticles (Shi et al., 2011) and MIP-based drug delivery system (DDS) (Li et al., 2012b), the effects of molecular crowding on synthesis of MIPs are still under investigation.

This paper reported on the facile fabrication of zero-order release MIP devices by the crowding strategy using aminoglutethimide (AG) as a model drug. AG, an oral aromatase inhibitor, has been introduced for breast cancer treatment more than 40 years (Geisler et al., 1996) even though it is associated with a high incidence of idiosyncratic drug reactions (IDRs) caused by its primary aromatic amine functional group (Ng et al., 2015). In addition to the cheapness of AG as a racemic mixture, it was reported that while pharmacokinetics of S- and R-enantiomers of AG following oral administration of racemic drug is large potency difference between the R- and S- forms (R > S), the statistically significant differences are relatively small. The pharmacokinetic differences between R-AG and S-AG appear to contribute only marginally to the activity of this drug as an aromatase inhibitor (Alshowaier et al., 1999). Therefore, *rac*-AG was used as a model template to fabricate a new controlled anticancer drug release devices for oral chemotherapy in present work. The crowding effect was achieved by adding polystyrene (PS) as a macromolecular co-solute in pre-polymerization mixture. The influence of various polymerization parameters under crowding condition on the behaviors of AG release was studied in detail. Furthermore, the optimum concentration of drug soaking solution was investigated. Two kinds of diffusion coefficients, the free drug diffusivity ($D$) and the effective diffusivity ($D_{eff}$), were measured to account for the kinetics of drug release from polymeric matrices where both diffusion and desorption mechanisms control the overall release rate.

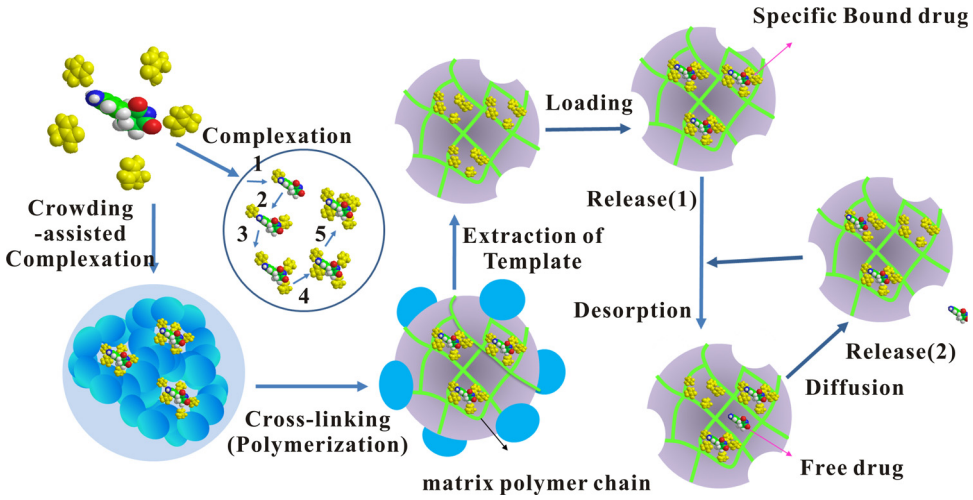


**Fig. 1.** The schematic representation of procedures of synthesising crowding-assisted MIPs, loading and release: (1) formation of a pre-polymerisable complex with template (AG) and functional monomers in the presence of porogen and crowding agents by interactions (primary hydrogen-bond interaction) that occur between complementary functionalities in the template molecule and functional monomer units. (2) Polymerization with excess initiating and crosslinking agents (namely initiator and crosslinker, respectively) to produce the MIPs. (3) Extraction of AG, which leaves specific recognition sites that are complementary to the templates in terms of size, shape and chemical functionality orientations, thus enabling subsequent recognition of the template or other substitutes during the rebinding process. (4) Loading AG in the specific imprinted sites of crowding-assisted MIP. (5) Release (1): AG desorbed from the sites of intraparticles and became unbound; release (2): free AG diffused from the intraparticles network.