

Preliminary evaluation of molecular imprinting of 5-fluorouracil within hydrogels for use as drug delivery systems

Baljit Singh*, Nirmala Chauhan

Department of Chemistry, Himachal Pradesh University, Shimla 171 005, India

Received 5 November 2007; received in revised form 2 March 2008; accepted 28 March 2008

Available online 8 April 2008

Abstract

Molecular imprinting is a new and rapidly evolving technique used to create synthetic receptors and it possesses great potential in a number of applications in the life sciences. Keeping in mind the therapeutic importance of 5-fluorouracil (5-FU) and the technological significance of molecular imprinting polymers, the present study is an attempt to synthesize 2-hydroxyethylmetacrylate- and acrylic acid-based 5-FU imprinted hydrogels. For the synthesis of these hydrogels, *N,N'*-methylenebisacrylamide was used as a crosslinker, ammonium persulfate as an initiator and *N,N,N',N'*-tetramethylethylenediamine as an accelerator. Both molecular imprinted polymers (MIPs) and non-imprinted polymers were synthesized at the optimum crosslinker concentration obtained from swelling studies and used to study their recognition affinity, their swelling and the *in vitro* release dynamics of the drug. It was observed from this study that the recognition affinity of MIPs is increased when these are synthesized in a high concentration template solution.

© 2008 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.

Keywords: Drug delivery devices; Hydrogels; Molecular imprinted polymers; Release dynamics

1. Introduction

Molecular imprinting is a rapidly developing technique for the preparation of polymeric materials that are capable of molecular recognition for selective separation and chemical identification. To prepare molecularly imprinted polymers (MIPs), a functional monomer and a crosslinker are polymerized in the presence of a template molecule. The template is then extracted, leaving sites which are complementary in both shape and chemical functionality to those of the template. This polymer is capable of selectively absorbing the template species. Because of the stability, predesigned selectivity and easy preparation of MIPs, they were applied in a wide range of technologies for a wide range of purposes, such as catalysis [1], separation and purification [2,3], detection [4] and drug delivery [5].

Recently, there has been rapid growth in the area of drug discovery, facilitated by novel technologies, which

has resulted in a more urgent focus on developing novel techniques to deliver these drugs more effectively and efficiently. This can be achieved by the use of polymeric matrix as a delivery system. Hydrogels have been used in the controlled delivery of drugs. Hydrogels are three-dimensional polymeric networks that swell quickly by imbibing a large amount of water or shrink in response to changes in their external environment. These changes can be induced by changing the surrounding pH, temperature, ionic strength and electrostimulus [6,7]. There is ongoing interest in identifying additional tools to modify the release profile of a drug from a polymer matrix, and molecular imprinting has been suggested as one of those tools [8]. Molecular imprinting technology has an enormous potential for creating satisfactory drug dosage forms. Although its application in this field is just at the incipient stage, the use of MIPs in the design of new drug delivery systems and devices useful in closely related fields, such as diagnostic sensors, is receiving increasing attention [9]. Examples of MIP-based drug delivery systems were found for the three main approaches developed to control the moment at

* Corresponding author. Tel.: +91 1772830944; fax: +91 1772633014.
E-mail address: baljitsinghphu@yahoo.com (B. Singh).

which delivery should begin and/or the drug release rate and activation-modulated or feedback-regulated drug delivery. These systems were used for administering drugs by different routes, such as oral, ocular or transdermal [10–12]. The uses of MIPs in different drug delivery systems have been reported in the literature. Alvarez-Lorenzo and co-workers have developed norfloxacin delivery systems by imprinting it into soft contact lenses prepared from poly(hydroxyethylmethacrylate)-based hydrogels [5,13]. Hiratani et al. [14–16] have made ocular release of timolol possible from molecularly imprinted soft contact lenses. Affinity sites for an antibacterial drug, ampicillin, were created by Sreenivasan [12] on the surface of polyurethane using the technique of non-covalent molecular imprinting to study the interactions with two bacterial species, *Escherichia coli* and *Staphylococcus aureus*. The macromolecular recognition of biologically significant molecules, such as drugs, amino acids, steroids, nucleotide bases and carbohydrates, has also been carried out via molecular imprinting methods to observe the receptor–ligand association and dissociation constant [17]. Due to the high biocompatibility of MIPs and their ability to recognize the template, MIPs were considered as good means of delivering proteins as part of an implantable drug delivery system [18,19].

5-Fluorouracil (5-FU) is an anticancer agent that is widely used in the clinical treatment of several solid cancers, such as breast, colorectal, liver and brain cancer. Because of its high rate of metabolism in the body, the maintenance of a high serum concentration improves its therapeutic activity, but this requires its continuous administration. However, concentration above a certain limit produces a severe toxic effect, and this must be avoided [20,21]. It has been reported in the literature that polypeptide- and polysaccharide-based drug delivery devices have improved the performance of 5-FU [22]. Keeping in mind the therapeutic importance of 5-FU and the technological significance of molecular imprinting polymers, the present study is an attempt to synthesize 2-hydroxyethylmethacrylate (HEMA) and acrylic acid (AAc) based 5-FU imprinted hydrogels. For the synthesis of these hydrogels, *N,N'*-methylenebisacrylamide (*N,N'*-MBAAm) was used as a crosslinker, ammonium persulfate (APS) as an initiator and *N,N,N',N'*-tetramethylethylenediamine (TEMED) as an accelerator. Both MIPs and non-imprinted polymers (NIPs) were synthesized at the optimum crosslinker concentration obtained from swelling studies and used to study their recognition affinity, their swelling and in vitro release dynamics of the drug.

2. Experimental

2.1. Materials and methods

HEMA and AAc were obtained from Merck-Schuchardt, Germany; APS and *N,N'*-MBAAm were obtained from S.D. Fine, Mumbai, India and were used as received. TEMED was obtained from the Sisco Research

Lab. Pvt. Ltd. 5-FU was obtained from the Dabar India Ltd., India.

2.2. Synthesis of molecular imprinted hydrogels (poly(HEMA-*cl*-AAc))

The hydrogels were synthesized by chemically induced polymerization through the free radical mechanism. To determine the optimum crosslinker concentration required for the synthesis of MIPs, hydrogels were synthesized in triplicate with three different crosslinker concentrations (i.e. 1.297×10^{-2} , 3.89×10^{-2} and $6.487 \times 10^{-2} \text{ mol l}^{-1}$ *N,N'*-MBAAm), along with $4.38 \times 10^{-2} \text{ mol l}^{-1}$ APS, $7.68 \times 10^{-1} \text{ mol l}^{-1}$ HEMA, $13.88 \times 10^{-1} \text{ mol l}^{-1}$ AAc and $1.72 \times 10^{-1} \text{ mol l}^{-1}$ TEMED in an aqueous solution without drug at 37 °C for 30 min. The hydrogels thus formed were washed with distilled water and dried at 37 °C in an oven. These were named poly(HEMA-*cl*-AAc) hydrogels. The optimum concentration of crosslinker obtained, on the basis of swelling of the hydrogels and structural integrity maintained by the gel after swelling, was $3.89 \times 10^{-2} \text{ mol l}^{-1}$. At this crosslinker concentration the MIPs of two different drug concentrations (i.e. 50 and $25 \mu\text{g ml}^{-1}$ 5-FU) were prepared and named MIPs-50 and MIPs-25, respectively; polymers without drug were called non-imprinted polymers (NIPs), as mentioned above.

Synthesis of molecular imprinted hydrogels was carried out with $4.38 \times 10^{-2} \text{ mol l}^{-1}$ APS, $7.68 \times 10^{-1} \text{ mol l}^{-1}$ HEMA, $13.88 \times 10^{-1} \text{ mol l}^{-1}$ AAc, $3.89 \times 10^{-2} \text{ mol l}^{-1}$ *N,N'*-MBAAm and $1.72 \times 10^{-1} \text{ mol l}^{-1}$ TEMED in the aqueous solution of a definite concentration of drug (5-FU) at 37 °C temperature for 30 min. Synthesis of non-imprinted hydrogels was carried without drug under similar conditions. Both MIPs and NIPs were synthesized in triplicate and were subjected to swelling and drug release studies. The MIPs were synthesized with two different concentrations of the drug to observe the effect of the number of recognition sites in the imprinted polymers on the entrapment of drug and on the release pattern of the drug. After removal of the template (drug) from the MIPs, these were dried at 37 °C in an oven and reloaded again in $200 \mu\text{g ml}^{-1}$ 5-FU. Loading of NIPs was also carried out in a solution of the same concentration of the drug. The MIPs and NIPs obtained after this loading were again subjected to swelling and drug release studies.

2.3. Characterization

Polymers were characterized by FTIR spectroscopy and swelling studies. FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO. Swelling of the polymers was carried out in distilled water by gravimetric method. A known weight of the polymers was taken and immersed in an excess of solvent for fixed time intervals at 37 °C and then the polymers were removed after 30 min, wiped with tissue paper to remove excess of solvent, and weighed immediately for 300 min. The gain in

Download English Version:

<https://daneshyari.com/en/article/1556>

Download Persian Version:

<https://daneshyari.com/article/1556>

[Daneshyari.com](https://daneshyari.com)