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Review

Molecularly imprinted polymers based drug delivery devices: a way to application in modern pharmacotherapy. A review

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ABSTRACT

This review presents the current status of molecularly imprinted polymers (MIPs) for drug delivery, in particular the studies that focus on biocompatibility, cytotoxicity, and *in vitro* or *in vivo* behavior of MIPs. It also shows the limitations that hamper the introduction of MIPs to pharmacotherapy and prevent this class of polymers from commercialization. MIPs are promising materials in the construction of drug delivery devices because they can provide improved delivery profiles or longer release times and deliver the drugs in the feedback regulated way, which is extremely important in modern pharmacotherapy. Here, a brief overview of the imprinting process and a concise description of drug release mechanisms from the imprinted materials will be presented followed by the discussion of potential MIP drug delivery devices for ocular, dermal, intravenous and oral routes of administration. Finally, future prospects for imprinted drug delivery forms will be outlined.

Contents

1. Introduction

The common model of therapy known as 'one-size-fits-all' has resulted in moderate success for the predominant group of patients. Despite the fact that an appropriate drug is taken at an appropriate dose and in an appropriate manner, numerous side effects are often reported [1]. A vast amount of adverse drug reactions is due to overdosing because individual variability does not comply with the manufacturer's recommended dosages [2]. A modern therapy allowing one to apply for a single patient the best suited drug which needs to be delivered in the right place and at the right time could be a solution to reduce adverse effects, accelerate patient recovery, and finally ensure positive therapeutic effects [3].

The traditional pharmaceutical formulations commonly did not fulfill the demands of modern pharmacotherapy. Thus, extensive studies were carried out to develop new drug delivery devices suitable for such a purpose [4–6]. The above efforts were facilitated by great progress in technology and material science, for instance novel nanobiomaterials such as polymeric nanofibres for drug delivery or liposomes for gene delivery. These materials offer improved transport properties, provide optimized pharmacokinetic profiles, control the drug release rate and maintain the drug

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concentration within its therapeutic window as well as enhance delivery efficacy by increasing diffusivity and biodistribution. However, the commercial application of novel drug delivery materials still poses a great challenge for modern pharmacotherapy. The optimum drug delivery carrier should be synchronized with the physiological status of the patient and should provide a drug in response to the changing intracorporeal environment [7]. Here, the molecularly imprinted polymers (MIPs) could be a group of materials that have great potential in the drug delivery for modern pharmacotherapy.

Molecularly imprinted polymers are promising materials in the construction of drug delivery devices because they can provide improved delivery profiles and longer release time as well as extended residency of the drug [8,9]. This class of polymers could also release the drugs in the feedback regulated way, which could be extremely important in a modern model of pharmacotherapy oriented towards the delivery of the best suited drug to a single patient in the right place and at the right time. Finally, MIPs are highly selective materials capable of maximizing the delivery of a given eutomer, the isomer of interest, and of reducing or even eliminating the delivery of the distomer, the undesirable isomer [10,11].

In spite of its great potential, the application of MIPs in drug delivery is still at the developing stage. In recent years we could observe significant progress in the synthesis of MIPs for drug delivery with novel sophisticated formats of polymers. However, this progress does not correspond to the implementation of MIPs in modern pharmacotherapy. Thus, a question arises why such promising materials cannot find a widespread applicative role in the field of drug delivery?

In this review, different barriers that prevent the implementation of MIPs into pharmacotherapy will be outlined in order to formulate the answer to the above questions. First a brief overview of the imprinting process together with a concise description of drug release mechanisms from the imprinted materials will be presented. Then the present status of MIPs as potential drug delivery devices for ocular, transdermal, intravenous and oral routes of administration will be discussed with emphasis on biocompatibility, cytotoxicity, and *in vitro* or *in vivo* behavior of MIPs. Current barriers that prevent implementation of MIPs into pharmacotherapy will be identified. Finally, future prospects for imprinted drug delivery forms will be outlined.

2. Insight into imprinting process

The molecularly imprinted polymers are characterized by a high level of selectivity due to the presence of specific recognition sites formed in the polymer network by the template-tailored synthesis. The synthesis of imprinted materials consists of the following steps: the formation of the prepolymerization structure, the polymerization reaction and the template removal (Fig. 1). The formation of the prepolymerization structure could be obtained by covalent or non-covalent strategies. The covalent approach assumes that there is a chemical reaction between the template molecule and the functional monomer that is necessary in order to form a functionalized compound prior to the polymerization. The non-covalent approach utilizes a range of weak intermolecular interactions such as ionic forces, hydrogen bonds, or π-π interactions that can exist between the template molecule and the functional monomer. The various aspects of the imprinting process were accurately described in numerous reviews and book chapters [12,13].

The main parameter describing the efficacy of the imprinting process is called the imprinting factor. In simple terms, the imprinting factor is defined as a ratio of the binding capacity of the template on the imprinted polymer to the binding capacity of the template on the non-imprinted reference polymer. Hence, the synthesis of the non-imprinted polymer has to be carried out in the same conditions omitting the addition of the template molecule.

The specificity of imprinted polymers could be affected by formats of material. Depending on the synthetic strategy various formats of MIPs can be obtained. Let me mention here some of the formats that were recently designed and investigated as potential drug delivery devices: molecularly imprinted soft contact lenses and bioinspired metal ion coordinated hydrogels [14,15], imprinted transdermal patches [16], imprinted like biopolymeric micelles [17], imprinted magnetic nanoparticles [18–20], composite hydrogel delivery systems [21], molecularly imprinted layer-coated hollow polysaccharide microcapsules [22], biodegradable imprinted drug delivery nanostructures [23,24] and others [25,26]. Those formats of MIPs were evaluated for the following routes of drug administration: ocular, dermal, intravenous and oral with extended support of *in vitro* and *in vivo* analyses of drug release as well as cytotoxicity tests. The above examples will be discussed in the next sections of this paper to outline the current barriers as well as to present the ways to overcome the problems in both

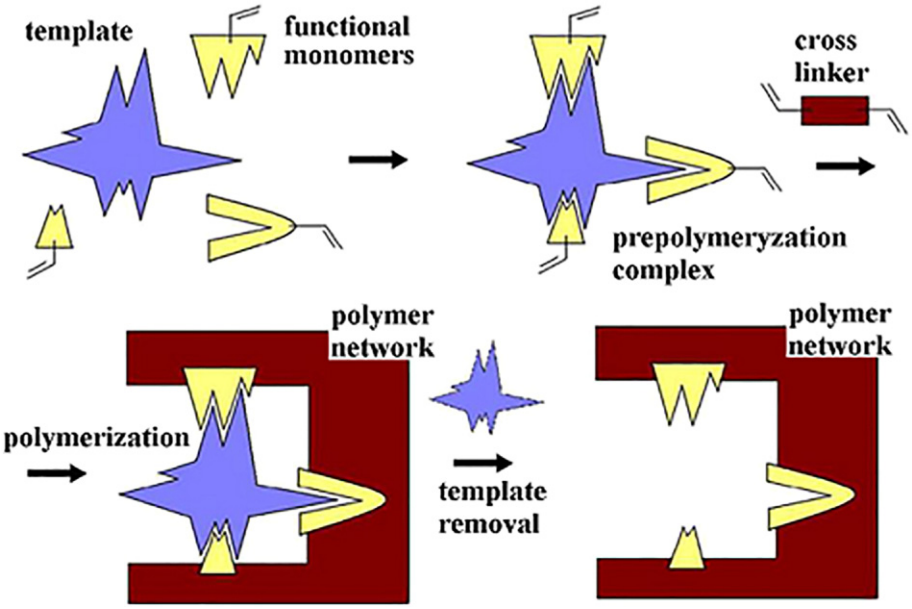

Fig. 1. A schematic presentation of the imprinting process.