



Short Review Paper

Role of molecularly imprinted polymers for selective determination of antiepileptic drug-carbamazepine: a short review

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Abstract

Epilepsy is a neurological condition marked by frequent and unprovoked seizures. Antiepileptic drugs (AEDs) play a prominent role for treatment of epilepsy by achieving good control with medications. But, in past few decades, lot of studies shows that with the continuous release of these drugs into the environment, equally contributes them in a category of persistent organic pollutants (POP). Carbamazepine (CBZ), an antiepileptic drug is over a great extent used to treat epilepsy and bipolar disorder. This is also included in the POP category because of its profound use and possible ecotoxicology. Analytical methods should have the sensitivity for contamination detection and quantification, but in case of complex matrices or real matrices the direct application of the analytical methods can be rarely achieved. Thus, sensitive and selective analytical methods are required. The increasing use of molecular imprinted polymers during recent years in pharmaceutical analysis in complex matrices is because these materials seem to be particularly desirable for applications where analyte sensitivity and selectivity is essential. They show preferred affinity to a particular template molecule as compared to other molecules present in complex matrices, and this property of selectivity is the main driving force for such diverse application of this techniques. Such techniques have been more and more employed in a wide range of applications such as sample pretreatment, chromatography, catalysts, drug delivery, sensors, purification, bio-analytical areas etc.

Keywords: Molecular imprinted polymers, Carbamazepine, Molecular imprinted solid phase extraction, Antiepileptic drugs.

Introduction

Pharmaceuticals are considered as a significant contributors of water pollutants due to their extensive use and residues in aquatic environment¹⁻⁵. Epilepsy affects more or less 1 % of general population. Antiepileptic drugs (AEDs) are the primary supporter for the epilepsy treatment. The past decennary has witnessed the outgrowth of multiple AEDs⁶ and some of them are listed in Table-1. Carbamazepine (CBZ) whose chemical structure is given in Figure-1, is a well-established antiepileptic drug employed for the treatment of epilepsy. Usually CBZ is metabolized mostly in the body but some of it is eliminated unchanged via urine. In the aquatic biota it was not anticipated to produce acute toxicity, but chronic and synergistic effects with other pollutants could not be omitted⁷. In its clinical use it shows some side effects, most probably when the serum concentration is quite high and the side effects like dizziness, nausea, diplopia, headache and fatigue may occur. Research efforts for their remotion are the need of the hour so as to avoid such untoward health effects on both humans as well as on environment. Hence, substantial concern has been focused for analyzing this compound in biological samples as well as in environmental samples at low concentrations by formulating effective analytical methods. For the determination of different pharmaceuticals various analytical techniques have been proposed, but a sample preparation step is very essential with

the intention of their detection at trace levels. Liquid liquid extraction (LLE) and solid phase extraction (SPE) have been often applied to clean up and preconcentrate from composite matrices. But they both suffer major disadvantages in case of complex matrices. Of the many different solutions proposed to overcome such disadvantages, molecularly imprinted approach has been successful. Molecularly imprinted polymers (MIPs) shows a diverse applicability to a variety of compounds which are present in many different complex matrices. This powerful technique is used to synthesize preconcentrated materials with extremely binding cavities or recognition sites for a particular molecule or its structurally associated compounds⁸⁻¹¹. However, in the recent years their use as a sorbent in solid phase extraction, also called molecularly imprinted solid phase extraction (MISPE), is by far the most innovative technical application of MIPs.

Molecularly imprinted solid phase extraction (MISPE)

There are various distinct approaches for the preparation of imprinted polymers, which includes precipitation polymerization^{12,13}, suspension polymerization^{14,15}, swelling polymerization¹⁶ and grafting procedures¹⁷. Molecular imprinted polymer (MIP) is prepared with a reaction mixture composed of a template, a functional monomer, cross-linking monomer,

polymerization initiator in a porogen solvent. A prepolymerization complex is formed between the template and the functional monomer during initial phase of polymerization, and this complex is confined on all sides by the extra cross-linking monomers, yielding a three-dimensional polymer mesh where the template molecules are entrapped after completion of polymerization. With in-depth washing, the template molecules are eliminated to provide cavities complementary to the template in shape, size, and molecular interactions.

Table-1: Showing antiepileptic drugs belonging to different generations.

First-Generation AEDs	Second-Generation AEDs	Third-Generation AEDs
Carbamazepine (CBZ)	Felbamate (FBM)	Clobazam (CLB)
Ethosuximide (ETX)	Gabapentin (GBP)	Lacosamide (LCM)
Phenobarbital (PHB)	Lamotrigine (LTG)	Perampnenel (PER)
Phenytoin (PHT)	Levetiracetam (LEV)	Rufinamide (RUF)
Valproic Acid (VPA)	Oxcarbazepine (OXC)	Vigabatrin (VGB)
	Topiramate (TPM)	
	Zonisamide (ZNS)	

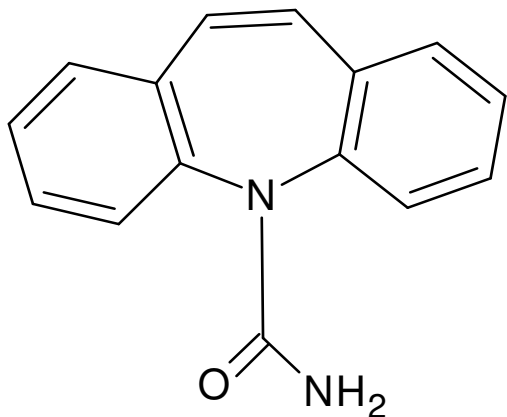


Figure-1: Showing chemical structure of Carbamazepine.

MIPs show their main novelty with the ability of binding a compound of particular interest, or sometimes to bind class of structurally-related compounds¹⁸, present in a complex mixture. This characteristic property is directly related to selectivity and analysis or separation purposes. So with the help of this feature a desirable selective protocol can be developed for the determination of an individual compound from very complex matrices. Hence, making imprinting polymers appealing as molecularly selective sorbents in solid-phase extraction (SPE) in the form of a technique molecularly imprinted solid-phase extraction (MISPE)¹⁹. MISPE has allowed separation and

quantification of many pharmaceutical samples in environmental as well as in bio-samples²⁰. Regeneration of MIPs is an much anticipated property in which an imprinted polymer can be reprocessed multiple times without substantial losses in its performance.

Applications to determination of carbamazepine

A general synthesis by bulk polymerization for molecular imprinted polymer of CBZ (MIP-CBZ) is discussed here with template (CBZ), functional monomer (MAA), cross-linking monomer (EGDMA) and polymerization initiator (AIBN) in a solvent. During initial stage of polymerization, there is a complex formation between the CBZ and the MAA in a porogens solvent (ACN) which is known as prepolymerization complex and the complex is surrounded by the EGDMA, yielding a three-dimensional polymer mesh where the CBZ molecules are entrapped after completion of polymerization. By repeated washing with methanol and acetic acid (MeOH:AcOH; 9:1 v/v), the template molecules are eliminated to impart cavities complementary to the template in shape, size, and molecular interactions. The schematic representation of MIP for CBZ is given in Figure-2.

There has been indefinite number of research articles regarding imprinting polymers of CBZ. General research articles on MIP-CBZ will be discussed here. SPE is a practicable sample pretreatment/enrichment method. MIPs have been incorporated in SPE, and some reviews on their linking have appeared in the literature and they are discussed here briefly.

Beltran A *et al.*²¹ synthesized an imprinted polymer of CBZ by a non-covalent imprinting approach. They were able to bind CBZ in waste water treatment plants (WWTP) and urine samples. To check the selectivity of synthesized MIP they percolated CBZ solution with a mixture of drugs such as benzaifibrate (BZF) and ibufuran (IBP) through MISPE. Recoveries of CBZ up to 65% and 80% were obtained in case of spiked urine samples and WWTPs samples respectively. Beltran A *et al.*²² describes one pot synthesis for CBZ and Oxcarbazepine (OXC) with high recoveries of analytes in MISPE protocol with >80% in urine samples. These high recoveries were due to the modified imprinted polymers in the form of porous molecularly imprinted polymers. They can be packed efficiently into columns and cartridges as they achieve beaded morphology and hence distribute all the molecular beads in a uniform pattern.

Esfandyari-Manesh M *et al.*²³ attempts to ensure the size and morphological of carbamazepine-imprinted polymers under various synthetic conditions like varying amounts of monomers, porogens, cross linkers, initiator and time of polymerization. The obtained results suggests new perceptions into particle size, which can pave the path for development of the different controlled size ranges. Esfandyari-Manesh M *et al.*²⁴ synthesised uniformly sized nanospheres and microspheres imprinted polymers of CBZ by varying the ratio of methacrylic acid

(MAA) and methyl methacrylate (MMA). The efficient imprinting, specific binding and high selectivity was shown by MIPs prepared by 1 : 2 and 2 : 1 mole ratios of MAA to MMA respectively. The controlled release of CBZ was obtained by using imprinted polymers containing different mole ratios of MMA and MAA. Dai CM *et al.*²⁵ confirmed the applicability of imprinted polymer of CBZ for its removal in water samples with recovery >80%.

The one-stage nanoparticle preparation of imprinted polymers of CBZ by miniemulsion polymerization was studied by Esfandiyari-Manesh M *et al.*²⁶ For the preparation of nanoparticles a specific mole ratio of 2:8 template to functional monomer was highly effective. The imprinting technique, by miniemulsion polymerization, is anticipated to be a best method for preparation of watercompatible imprinted nanoparticles meant for use in micro-SPE and sustained-release drug delivery systems. Dai CM *et al.*²⁷ for the first time develop double templates for effective recognition of CBZ and clofibrac acid (CA) from water samples. The adsorption studies shows comparatively very good results as equated to commercial adsorbents (like PAC and C18) for CBZ and CA. The dispersive solid phase extraction method by Khalilian F *et al.*²⁸ with the help of SiO₂- coated graphene oxide surface for the imprinting

promises to be reliable technique for the low level analysis of CBZ in biological samples.

Imprinted magnetic polymers of CBZ based on chitosan-Fe₃O₄ particles were prepared for selective extraction of CBZ from environmental water bodies by Zhang YL *et al.*²⁹. This study involved adsorption as well as magnetic separation, and the incurred magnetic-MIP demonstrated much higher selectivity and specific recognition to CBZ in the presence of other interfering agent. Schweiger B *et al.*³⁰ synthesised MIP of CBZ by bulk polymerization for the selective extraction of carbamazepine from aqueous solutions.

Conclusion

MIPs have proven to be practicable as a tool in selective determination of CBZ in environmental and biosamples even at lower concentrations. But the use of MIPs still faces some challenges (like template leakage, low binding capacity *etc*), so, there is a room in this area of research by developing strategies' such as porous molecular imprinting, hollow molecular imprinting *etc* to overcome such disadvantages.

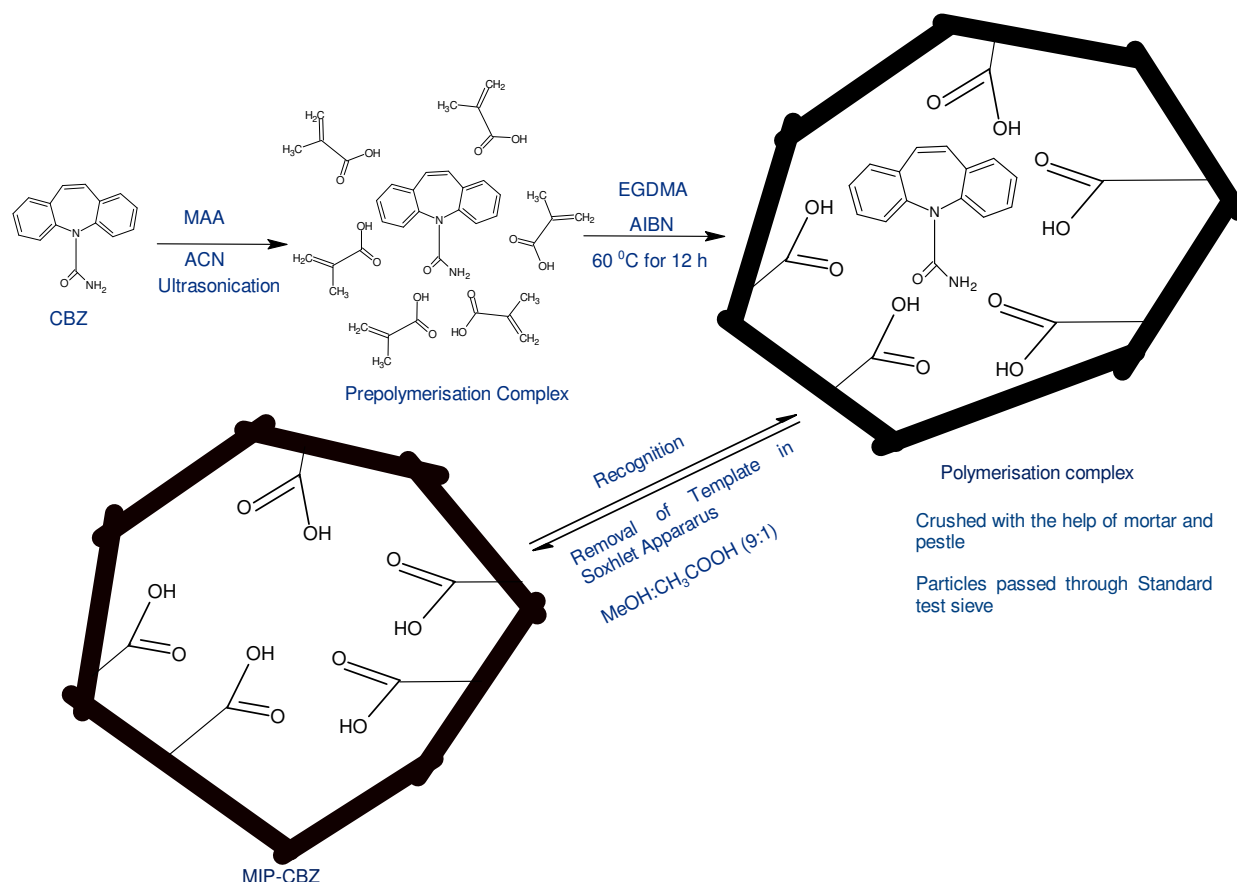


Figure-2: Schematic diagram of the synthetic strategy of MIP-CBZ.

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