In recent years, a significant progress has been attained in the field of drug delivery devices. Development of novel technologies in the material science has created an opportunity towards new drug-carriers with the ability to directly respond to the patient’s individual needs (1, 2). Moreover, it could be seen that some new drug delivery systems have been introduced to the well-known therapeutic agents. Recently, many laboratories have carried out quite extensive investigations to develop some new drug delivery forms capable to maximize the drug efficacy, to reduce the frequency of application, to minimize the toxicity or to modify the drug release profile (3). Those advantages are obvious for many patients, because they improve their quality of life and the safety of treatment. It is important to highlight that the beneficiary is also the healthcare system. However, the introduction of new drug delivery devices required some vast investments, but overall spendings are decreasing because of the effectiveness of the treatments, the decrease of doses, the reduction of undesirable side effects, and the limitation of medical advices (4).

Many of the new drug delivery devices are polymeric. Despite of the nature of polymer backbone, both the biopolymers and the synthetic ones play an important role in pharmaceutical industry. They have been used as blood substitutes, tissue regenerators, various auxiliary materials or excipients (5).

Molecularly imprinted polymers (MIPs) are the class of new synthetic polymeric materials that provide a high selectivity towards the selected molecules (6-9). They offer high thermal, chemical and mechanical stabilities. Those advantages caused broad applications in the analytical chemistry, where they are used for the separation or detection of many compounds (10-12). They are also used in organic synthesis and catalysis (13, 14). The role of MIPs in pharmaceutical sciences, predominantly in the pharmaceutical analysis, was discussed elsewhere (15, 16). However, MIPs have a great potential in the drug delivery, where they could be used as new and selective drug dosage forms (17, 18).

In this review, the principles of molecular imprinting are highlighted, followed by the discussion on molecular recognition and release mechanisms in the imprinted systems. Detailed advantages and disadvantages for the application of MIPs as the future drug delivery devices are also discussed, as molecularly imprinted polymers, drug delivery systems, sustained/controlled release.
well as the recently published significant scientific achievements are presented. Finally, some future prospects for the imprinted polymers are outlined.

**Principle of molecular imprinting**

There are three main steps in the synthesis of MIPs. In the first step, a template molecule (an imprinted compound) creates a prepolymerization complex with selected functional monomer(s). Then, the prepolymerization complex is cross-linked during the polymerization process, and in the final stage, the template is removed from the polymeric matrix with leaving the well-defined three-dimensional cavities (19, 20). The scheme of the imprinting process is presented in Figure 1.

The selectivity of the imprinted polymer is compared with the respective non-imprinted polymer, synthesized in the same way as the imprinted one, but without the template molecule.

The preparation of a stable prepolymerization complex is the crucial stage of the whole imprinting process. The commonly used non-covalent approach has assumed that relatively weak intermolecular interactions between the template and the functional monomer(s) are used in the formation of a prepolymerization complex. The advantages are the coexistence of various intermolecular interactions, the quick formation of a complex, and the easiness of the template removing, but the main disadvantage is an unpredictable stability of the complex during the polymerization process (20).

The stable prepolymerization structure is obtained with a covalent approach. This strategy involves a chemical reaction between the template and the functional monomer(s) in order to synthesize a functionalized prepolymerization compound. The main disadvantages are a troublesome template removing process and a prolonged loading step related to the chemical reaction that should occur in the cavity (20). The covalent approach was used to produce the imprinted material for a controlled delivery of β-blockers (21). Suedee and co-workers synthesized the polymer with N-acryloylalanine. After some post-polymerization modification and the subsequent hydrolysis of L-alanine, MIP thus obtained was loaded with propranolol. In order to avoid a complicated loading step, the authors have proposed the so-called “semi-covalent” approach. This strategy assumes the covalent imprinting and non-covalent binding of the drug in the cavity during the loading procedure (22). The monomers often used in the preparation of MIPs for some drug delivery forms are presented in Figure 2.

Typical imprinting procedure has assumed that a prepared imprinted polymer is more or less cross-linked. The presence of a cross-linker provides the rigidity of material and the steric stability of the cavities. On the other hand, an obtained polymer has to

![Figure 1. Scheme of the imprinting process](image-url)
be flexible enough to ensure the easy diffusion of appropriate solvents into the matrix (19). Both highly cross-linked rigid imprinted polymers and low-cross-linked imprinted hydrogels have been investigated as the drug delivery forms. The cross-linkers frequently used in the synthesis of MIPs for some drug delivery forms are presented in Figure 3.

**Recognition and the release mechanism**

Molecular recognition in biological systems is governed by the combination of various weak interactions between the bound molecule and the binding site. This process is combined with cumulative interactions of secondary structures that involve the conformational reorganization of macromolecular environment of the binding site. An increased amount of complementary interactions enhances the strength of the binding and promotes the selectivity of the whole process (23). The stable three-dimensional cavities which exist in the polymeric matrix after the imprinting process are complementary in shape and in electrostatic potential to the template molecule. Both, the weak non-covalent interactions between different functional groups, heteroatoms or aromatic rings and the steric effects (or molecular volume) of the template govern the whole recogni-
tion mechanism. Hence, it is important that the template should provide some structural elements able to form hydrogen bonds, ionic bonds, van der Waals interactions etc. The presence of chiral atoms and a conformational stability are also crucial (6, 7).

The release of the selected drug from the carrier is performed in different routes (24-26). The most common releasing process, which occurs, for instance, in hydrogels, can be induced by the external fluids that promote the solvent penetration and relaxation of the polymer network. Hence, the drug transport is controlled by the swelling degree of the polymer (27). In the imprinted systems, the numerous complementary or sterically oriented functionalities interact with the drug. The stronger interactions in the cavities slowed or delayed the release of the drug from the polymer network, despite of the swelling degree of the polymer (28). In another mechanism, the competitive binding of a structurally related compound present in external fluids will promote the release of the drug. This mechanism was investigated with a hydrocortisone imprinted polymer. This imprinted system showed an ability to adsorb a considerable amount of testosterone, due to a structural similarity of the both compounds. The release of testosterone in water was very slow, but in the presence of hydrocortisone, the competitive binding promoted a rapid release of testosterone from the binding sites of MIP (29). Those imprinting systems are extremely interesting as the drug carriers, because they can respond or release the drugs, when the concentration of certain bioanalytes is increased (30). There is also the mechanism that involved a hydrolytically induced releasing. This approach required the use of the erodible imprinting system from which the drug cannot be released unless the whole (or a part of) the polymer degrades. Preliminary investigations have been carried out for some imprinted hydrogels designed for the release of p-aminobenzoic acid (31). The last one and the most sophisticated mechanism of release is the stimuli sensitive mechanism which allowed to release the drug after the response to changes in the physicochemical properties of external fluids. This mechanism has recently been described in a pH-responsive S-omeprazole imprinted drug delivery system (32), and in a low cross-linked insulin imprinted drug delivery system (33).

Applications of the molecularly imprinted polymers as the future drug delivery systems

It is necessary to discuss additional precautions related to the applications of MIPs as the drug delivery devices. Those are biocompatibility and toxicity, homogeneity of the matrix, uniformity of the particles, selectivity and capacity of the formulation, reproducibility and stability of the imprinted material.

Synthetic monomers and cross-linkers used to prepare the MIPs for the dosage forms have to be biocompatible, because they are in contact with sensitive tissues. This requirement significantly reduces the choice of effective functional monomers for the imprinting process, because many of them are toxic ones. Only the application of the well-known and tested reagents could prevent any unexpected incompatibility. The reagents of interest are methacrylic acid and ethylene glycol dimethacrylate or their analogues (34). They are commonly used in the preparation of MIPs, and they are used for producing some pharmaceutical formulations, for instance a trademark Eudragit is a copolymer of ethyl acrylate, methyl methacrylate and a low-content of methacrylic acid ester with quaternary ammonium groups (35).

It should be kept in mind that the polymerization which finally resulted in the imprinted material is predominantly carried out in organic solvents (19). The presence of trace amounts of organic impurities could evoke the living cell destruction. The application of water as the polymerization medium is limited, because the aqueous environment considerably reduces the stability of prepolymerization complex and causes the lost of selectivity of MIPs, but the recent progress in water compatible MIPs would contribute to overcome this problem (36, 37). Residual impurities in the polymeric matrix could be derived also from the polymerization initiators and other reagents, such as surfactants etc. Hence, the careful purification and precise control is required to ensure the lack of any contaminants.

The monomers and cross-linkers constitute the backbone of a polymer. This composition is also important, because it should reveal a hydrophilic character, the property that enhances biocompatibility and prevents from the adsorption of proteins and microorganisms (38).

Synthesis of MIPs assumes the use of the proper template to create a three-dimensional cavity. The template can be the drug itself or its structural analogue (39). This latter so-called “pseudo-template” approach is very helpful, when the drug is unstable during the polymerization, expensive or difficult to obtain. In both cases the template removal step is obligatory unless an in situ loading procedure (described below) is performed. It should be mentioned that quantitative template removal is a very difficult and time-consuming process. The template leaching problem is well characterized, when MIPs are used in an analytical field, and new methodolo-
Molecularly imprinted polymers as the future drug delivery devices

Molecularly imprinted polymers (MIPs) can be defined in terms of its molecular composition, distribution of the binding sites and morphological uniformity. Despite of the nature of the polymer (highly cross-linker rigid imprinted polymers or imprinted hydrogels) there are various instrumental methods for the analysis of the polymers, viz. FT-IR and Cross-Polarization Magic Angle Spinning (CP/MAS) $^1$C NMR spectroscopy, X-ray diffraction (XRD) or scanning electron microscopy (SEM) (41). The necessity of determination of molecular composition of the imprinted polymers arises from the fact that different monomers can be used in the imprinting process, which is in fact a free radical polymerization. Relative reactivities between the constituent monomers can be varied, forming thus the polymers with different chemical composition and different distribution of the monomer units within the copolymer, which can be predicted on the basis of the monomer feed composition alone (19, 42). Multi-functional monomers used in the synthesis of MIPs produce a non-linear architecture of the resulted copolymer. This fact also can affect the drug release rate (43). Investigations have been carried out to obtain the tacticity-controlled poly(N-isopropylacrylamide) (Fig. 2), which is frequently used as a monomer in the imprinted hydrogels (44). Particular attention has to be directed to the distribution of binding sites inside the polymer matrix. MIPs prepared via the covalent approach are characterized by a single population of the binding sites. In contrary, MIPs prepared via the non-covalent approach are generally characterized by different populations of the binding sites. Heterogeneity resulted from the insufficient stability of prepolymerization complex and from the polymer composition that is often responsible for the hydrophobic forces. Usually, there are two populations of the binding sites with a high-affinity and a low-affinity towards the template (45-47). Those latter can lead to a non-specific adsorption of the drug during the loading procedure and to unexpected expulsion of medication during the initial release process. The simple and excellent method to overcome this problem is to produce a restricted access material combined with MIPs (48). That material was produced from glycidyl methacrylate (Fig. 2) as a pro-hydrophilic monomer carrying an epoxide ring, and was treated in acidified medium after the polymerization in order to hydrolyze the epoxide ring. The restricted access imprinted material show a drastically lower hydrophobic non-specific adsorption of the polymer. The release profile of $\alpha$-acetaminophenol from such MIP was evaluated, and its ability to serve as the drug dosage form was confirmed. Finally, the morphological homogeneity of MIPs should be carefully determined. The highly cross-linked polymers could be prepared using various polymerization techniques and different methods of their surface analysis are described (41, 49). The most common format of MIPs is the bulk polymer. This format is easy-to-prepare and cheap-to-prepare, but the post polymerization preparation is time-consuming, and the obtained particles are irregular in size and shape. Better defined and more uniform are the particles obtained when the precipitation or the suspension polymerization techniques are involved (50). Novel formats of MIPs, such as supermacroporous cryogels or highly cross-linked nanospheres with their diameter below 200 nm have been investigated (51, 52). Recently, the polymerization with supercritical carbon dioxide has been proposed (53). This technique looks to be very promising to form MIPs for the drug delivery, because it excludes the use of organic solvents and produces more regular particles of the imprinted material.

MIPs provide a high selectivity towards a particular drug, despite the stereoisomeric character. Even while the imprinting process is performed towards the drug without stereoeactive site, the resulted imprinted polymer provides high selectivity with respect to non-imprinted counterpart. Moreover, they show also a high stereoselectivity, which is extremely important, when considering their application as the drug delivery form. A majority of the drugs have chiral atoms and their pharmacological activity is exhibited only by one isomer, or only one isomer show a significantly higher activity. The ability to maximize the delivery of given isomer, the isomer of interest and reduce or even eliminate the delivery of the diisomer, the undesirable isomer, is an enormous advantage of MIPs (54). Predominantly MIPs reveal quite selective binding only when low concentrations of the analytes are applied. The result is a low capacity of the imprinted polymer. This problem is very important, when MIPs are considered as the drug dosage forms, because it could considerably limit their utility. The sufficient loading capacity is necessary to ensure a prolonged release of the drug. Typically, the imprinted polymer is drug loaded by its soaking in

Molecularly imprinted polymers as the future drug delivery devices

Molecularly imprinted polymers as the future drug delivery devices

Molecularly imprinted polymers as the future drug delivery devices
an equilibrium dependent procedure. Otherwise, the loading can be performed *in situ* during the preparation of MIPs, introducing the drug as a part of the prepolymerization complex. The latter procedure increases the capacity of MIPs, but it is limited to drugs which can survive the polymerization process. Another problem arises from the fact, that there is no guarantee that the whole amount of the drug was introduced to the polymer network during the preparation of MIPs (55). The precise determination of the amount of the drug after the polymerization and post-polymerization preparation may be difficult to perform. Recently, significant efforts have been made to overcome the problem of a low capacity of MIPs and the use of a living/controlled polymerization technique, instead of a free radical polymerization looks to be very promising (56).

Preparation reproducibility is a very important factor for ensuring the robustness and practicability of MIPs. It has to be very high in order to predictable behavior of the imprinted dosage formulae. Although many authors confirmed that MIPs prepared for analytical applications showed good reproducibility (57), there are reports that a low reproducibility affected the release profiles (58). The stability of MIPs in term of time is very high, and they could be used even after a long time without any loss of its properties. They are also stable under harsh conditions, such as low pH or elevated temperature (59).

MIPs as the drug delivery devices have yet not found any commercial applications. There is still a lot of research that should to be carried out to overcome some of the problems stated above. However, interesting investigations are in progress to apply MIPs as the drug dosage forms for transdermal, ocular or oral routes of the drug administration. The most advanced and recent results are discussed below.

**Transdermal systems**

Skin is a widely used route of the delivery for local and systemic drugs. Transdermal route could be also an alternative for the oral drugs characterized by a low adsorption from gastrointestinal tract and/or extensive first-pass metabolism of the drug. The advanced investigations are under way to introduce an efficient transdermal delivery of propranolol to enhance its therapeutic effect (60, 61).

Introduction of stereoselective devices into the transdermal delivery of propranolol eutomer is required, because *S*-enantiomer provides more than 100 times higher pharmacological activity. MIPs became a potential material for such purpose. Bodhibukkana and co-workers (62) obtained membranes for the stereoselective delivery of *S*-propranolol. The membrane was a composite of MIP integrated with a bacterially derived cellulose. The cellulose membrane is a biocompatible and biodegradable material with good mechanical properties. The surface of the cellulose membrane was modified with a thin layer of *R*-propranolol or *S*-propranolol imprinted copolymer additionally anchored with 3-methacryloxypropytrimethoxisilane. The characterization of the composite membranes included their surface morphology analysis, evaluation of their mechanical properties, determination of the imprinting effect and selectivity of the membranes. The authors found the evident pH dependency in swelling ratio, which was predominantly governed by the cellulose membrane and affected its imprinting ratio of *S/R* enantiomer. The enhanced enantioselectivity of the *S*-propranolol imprinted copolymer membrane at a higher pH (7.4) have to be related with an increased binding of the favored *S*-enantiomer in the cavity of the polymer. Finally, *in vitro* percutaneous permeation studies of *R/S*-propranolol were performed. The results revealed that the *S*-propranolol imprinted polymer composite of cellulose membrane showed an enantioselectively controlled release of eutomer of the drug, but the enantioselectivity was decreased with an increased concentration during the loading procedure. In the recent study, Suedee and co-workers (63) have applied optimized composite of *S*-propranolol imprinted polymer and cellulose membrane into transdermal patches, and evaluated them in *in vivo* studies. Plasma concentration *versus* time dependence was analyzed after the administration of investigated transdermal patches. For sake of comparison, they also evaluated gels containing the racemic drug. Calculated values of AUC were as follows: 715 (for *R*) and 3928 (for *S*) for the imprinted patches and 2568 (for *R*) and 2394 (for *S*) ng h/mL for the gels. The significant difference in concentration of the eutomer after administration of the imprinted transdermal patch confirmed the utility of so prepared material. In order to enhance the homogeneity of the membrane, the same research group has developed *S*-propranolol imprinted polymer nanoparticles on microspheres (64). This material was characterized by *in vitro* study, showing its ability to a controlled release of *S*-propranolol.

**Ocular route and the imprinted contact lenses**

Bioavailability of the ophthalmic drugs from eye drops is low, because of some protective mechanisms from a lacrimal apparatus. Application of the
Rearrangement of polymeric regions was related to combined effects of the supercritical carbon dioxide on the plasticization and the imprinting effect of flurbiprofen. Comprehensive analysis of the structure and binding experiments with some structurally related compounds revealed the recognition ability and a higher affinity for flurbiprofen in aqueous solutions. The release profiles were investigated. The mechanical parameters of the imprinted commercial soft contact lenses were not affected during the impregnation process, and were satisfactory. The imprinted soft contact lenses were also investigated for norfloxacin delivery systems (73).

Molecularly imprinted hydrogels were extensively investigated as the ocular drug delivery forms with a hope to overcome existing problems. In their early works, Alvarez-Lorenzo and co-workers (66) prepared the imprinted soft contact lenses able to a sustained delivery of timolol. The authors evaluated the influence of composition of the matrix and the loading capacity of 2-hydroxyethyl methacrylate (Fig. 2) hydrogels weakly cross-linked with ethylene glycol dimethacrylate (Fig. 3) and with the presence or the absence of methacrylic acid and methyl methacrylate (Fig. 2). The dry hydrogels were clear and smooth with their poreless surface, and presented desirable properties required for the contact lenses. Timolol diffusion into the physiological saline from the both, 2-hydroxyethyl methacrylate and combined 2-hydroxyethyl methacrylate-methacrylic acid hydrogels was slow. The latter hydrogel presented the highest loading capacity equal to 12 µg of timolol in 1 mg of dry hydrogel. In the later study, the groups of Hiratani and Alvarez-Lorenzo (67-70) investigated the effects of different monomers in order to improve their capacity. They also evaluated the impact of the stoichiometry of reagents and polymerization conditions. Finally, they optimized dissolution of timolol in a mixture of monomers, which allowed to exclude organic solvents at the minimum of cross-linking agent necessary to secure memorable cavities in the hydrogel network. Profound analysis of the imprinted hydrogels was performed and in vivo experiments of releasing timolol from the imprinted contact lenses instilled in cornea were carried out (70). Timolol was detected in the tear fluid for a period of 180 min, which was twofold longer than that from the non-imprinted counterparts. Comparative analysis of timolol released from the eye drops containing 0.068% and 0.25% of timolol, showed the presence of the drug in the tear fluid for only 60 min. The authors found also that the timolol ocular bioavailability from the eye drops only slightly depended on the dose, but the corresponding bioavailability from the presoaked imprinted soft contact lenses increased significantly (for 34 µg of timolol the AUC values were 1.24 and 10.76 mmol min/L, respectively). In order to improve the loading capacity, the Alvarez-Lorenzo group has developed an innovative method using a supercritical fluid technology (71, 72). They used some commercial soft contact lenses which were impregnated using the supercritical carbon dioxide technology. The impregnation-imprinting procedure can be introduced to some highly water-soluble drugs. The sequential impregnation and extraction steps were carried out with flurbiprofen as the template drug. Rearrangement of polymeric regions was related to combined effects of the supercritical carbon dioxide on the plasticization and the imprinting effect of flurbiprofen. Comprehensive analysis of the structure and binding experiments with some structurally related compounds revealed the recognition ability and a higher affinity for flurbiprofen in aqueous solutions. The release profiles were investigated. The mechanical parameters of the imprinted commercial soft contact lenses were not affected during the impregnation process, and were satisfactory. The imprinted soft contact lenses were also investigated for norfloxacin delivery systems (73).

Oral systems

Oral route of the administration represents the most common and most convenient way for the drug delivery. Development of a satisfactory oral drug delivery form is still challenging, because of physiology of the gastrointestinal tract. Novel polymeric particles are investigated to improve the oral bioavailability of some drugs, and MIPs would play an important role in those investigations (74).

New polymeric imprinted devices were prepared with 5-fluorouracil. This anticancer agent is widely used in the clinical treatment, but it is quickly metabolized in the body. An insufficient level of the drug in serum decreased the therapeutic activity and prolonged the treatment. On the other hand, the continuous administration provoked severe toxic effects. Puoci and co-workers (75) synthesized a 5-fluorouracil imprinted polymer and evaluated its ability for sustained release in in vitro experiments. They used methacrylic acid (Fig. 2) and ethylene glycol dimethacrylate (Fig. 3) to form the copolymer. The in vitro release studies were performed in both gastrointestinal and in plasma simulating fluids. The imprinted polymer bounds considerably more 5-fluorouracil than the non-imprinted one, and shows a sustained release for the period of 30 h. In the further study over the application of MIP technology to an efficient delivery of the 5-fluorouracil, Singh and Chauhan (76) synthesized imprinted hydrogels containing 2-hydroxyethyl methacrylate, acrylic acid (Fig. 2) and N,N-methylelenbisacrylamide (Fig. 3). Authors carefully analyzed the drug release patterns.

in vivo experiments.
They found that the non-Fickian type diffusion mechanism is responsible for the diffusion of the 5-fluorouracil from the imprinted hydrogel. Preliminary experiments were also performed in order to evaluate the ability of MIPs serving as the delivery devices for tramadol (77), glycyrrhizic acid (78), tetracycline (79), and molsidomine (80), showing thus the fast development of this field in the application of MIPs.

CONCLUSIONS

Molecularly imprinted polymers (MIPs) are versatile tools in the modern materials science. They have the properties that can be used in construction of the future drug delivery devices by providing some improved delivery profiles, prolonged releasing times and extended residency of the drug. Moreover, MIPs can release the drugs in the feedback regulated way, which is extremely advanced and currently required in modern drug delivery systems. But most importantly they are highly selective materials with an ability to provide an appropriate enantiomeric form of the drug. Future perspectives for MIPs applications as the drug delivery forms are very promising. Combining the both, fast development in the field of molecular imprinting and current requirement of the drug delivery form, it could be possible soon to create the imprinted drug delivery devices more sophisticated, with a capability either for personalized or for individual treatment.

REFERENCES


Received: 07. 11. 2012