# Molecular Sieves in Medicine

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**Abstract:** During the last few decades microporous and mesoporous materials have been considered for medical use due to biological properties and stability in biological environment. Zeolites have been investigated as drug carriers, and as adjuvants in anticancer therapy, dietetic supplements or antimicrobial agents. This review gives a brief overview of the major aspects of molecular sieves applications in medicine.

## INTRODUCTION

Molecular sieves are porous, crystalline materials usually a synthetic or natural zeolites, that contain well-defined pores of precise and uniform size. The term zeolite originally described a group of natural crystalline aluminosilicates, however nowadays the term covers many different materials such as aluminophosphates or gallium-silicalites. Because of the structure, well-defined pores and channel sizes (porosity), acidic and ion exchange properties, and thermal stability, zeolites are applied as industrial catalysts in processes such as cracking, aromatization, aromatic isomerization, and disproportionation.

Zeolite frameworks consist of $SiO_4^{4-}$ and $AlO_4^{5-}$ tetrahedral units joined by common oxygen atoms. Each $AlO_4^{5-}$ unit introduces to the molecular sieve framework negative charge which can be balanced by protons or metal cations. Si/Al ratio determines cation capacity and properties such as chemical and thermal stability or local polarity [1-4].

In 1992 the Mobile Oil Corporation discovered the M415 family of mesoporous materials. One of the most studied, MCM-41, consists of a hexagonal array of one-dimensional channels with pore diameters of 2-5 nm [5,6]. Both, zeolites and mesoporous materials have been investigated and extensively characterized by powder X-ray diffraction, nitrogen adsorption isotherms, dynamic light scattering, electron microscopy and other experimental techniques for many years [7,8].

Several excellent reviews on the synthesis, modification, and characterization of zeolites have appeared during the last few years [9-13]. Due to important technical applications, including the conversion of hydrocarbons to liquid fuel [14] and separation of xylenes [15], material science related to zeolites has drawn much attention during the last few years [16].

Due to biological properties and stability in biological environments, zeolites have been recently considered for medical use [17]. Application of zeolites as a food supplement significantly decreased the level of certain radionuclides in the liver and kidneys [18]. Because of shape selectivity, zeolites have also been investigated as carriers for a variety of drugs. Drug release can be easily controlled by chemical functionalization of a zeolite framework or chemically removable caps. Zeolites were examined as carriers for slow or delayed release anthelmintic and antitumoral drugs. The latest experimental studies, based on the results obtained in various tumor cells and in tumor bearing animals, have shown that zeolites can be successfully applied as an adjuvant in anticancer therapy [19]. Zeolite nanocrystals have been applied in the enrichment and identification of low-abundance peptides/proteins [20,21] as well as the immobilization of enzymes for biosensing [22]. The regularly distributed silanols on the surface of zeolites also allowed a uniform covalent grafting of enzymes [23]. Additionally, $Gd^{3+}$-doped zeolite nanoparticles were considered to be good contrast agents for magnetic resonance imaging in medical diagnosis [24].

The size and shape selectivity as well as encapsulation of catalysts, such as metal complexes, in zeolite-hosts led to the synthesis of zeolites that mimic enzyme functions in certain biological processes. The zeolite framework, as compared to proteins, can protect incorporated metal complexes from degradation. In many cases, the reaction rates are very slow, and pore blockage leads to a decrease in reactivity. However, these serious problems can be easily solved by designing new zeolite-hosts.

## DRUG DELIVERY SYSTEMS

Zeolites have high adsorption capacity, undergo reversible adsorption/desorption, and because of large internal surface area they are able to absorb even up to 50 % of their own weight of water or considerable quantity of different substances. The large variety in pore structures and morphologies provided by different types of molecular sieves offers unique possibilities for the design of host-guest systems with particular properties. Dyer *et al*. examines the ability of commercial zeolite Y to act as a slow release agent for various anthelmintic drugs (Fig. (**1**)). The zeolite Y with loaded pyrantel and/or fenbendazole was administrated to *Nippos-*

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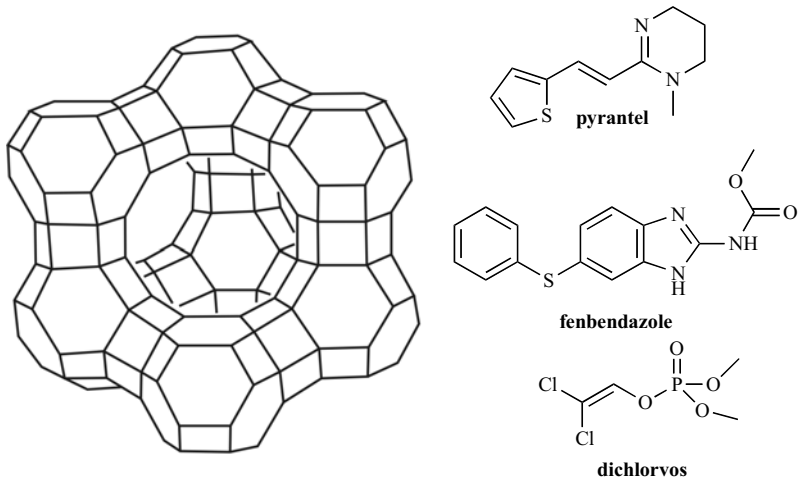



**Fig. (1).** Structures of Zeolite X/Y (Faujasite FAU) and pyrantel, fenbendazole and dichlorovos drugs.

*trongylus brasiliensis* infected rats. Similarly, the zeolite Y containing dichlorvos was administrated to pigs dosed with *Ascaris* and *Oesophagostomu.* Both experiments have shown that administration of the pure drug was not as successful in killing adult worms as drugs loaded on zeolite Y [25]. The same research group demonstrated that the known beneficial effects of certain drugs, including dichlorvos, fenbendazole and pyrantel, could be enhanced by incorporating them into a zeolite matrix. They are slowly released, thus prolonging drug delivery in the therapeutic range [26].

Tetramisole, an antihelminthic drug that has been tried experimentally in rheumatic disorders where it restores the immune response by increasing macrophage chemotaxis, and T-lymphocyte activity, could also be used as zeolite Y adduct [27].

Enrofloxacin, a fluoroquinolone antibiotic, is widely used in poultry production to treat respiratory and enteric bacterial infections, Fig. (**2**) [28]. The adsorption of enrofloxacin, a veterinary antibiotic, onto natural zeolite and was investigated by Ötker *et al*. The adsorption of enrofloxacin on natural zeolite was found to be highly pH dependent, exhibiting increases correspondent to decreases in pH [29].

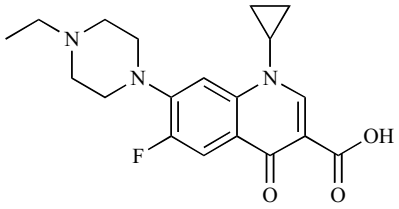


**Fig. (2).** Structure of enrofloxacin, a fluoroquinolone antibiotic.

Other very promising materials are zeolite nanocomposites consisting of magnetite and FAU (Faujasite, see Fig. (**1**)) zeolite with a high surface area and adsorption capacity which have been used to store and release substantial amounts of doxorubicin, an anticancer antibiotic belonging to tetracyclins group. In this form of drug delivery, an external or internal magnetic field can be used to direct drug-delivery particles to the proximity of the target (i.e., a tumor cells) thus enabling significant reduction of the necessary dose of medication and minimizing the side effects. The nanocomposites mentioned above are composed of commercially available magnetite nanopowder covered by a thin aluminosilicate coating [30].

Another 'magnetic zeolite' was obtained by Shan *et al*. Zeolite nanocrystals were *in situ* combined with superparamagnetic magnetite ($Fe_3O_4$) nanoparticles in the hydrothermal synthesis procedure. High amount of enzymes adsorption and a good biocatalytic performance is shown by those newly formed magnetite/zeolite composite nanoparticles [31].

Ion-exchanged zeolites have also been used as a novel approach to storage and delivery of nitric oxide (NO) [32]. Exposure of the zeolite material to NO gas results in NO binding to the metal ions within the pores facilitating highly efficient packing of NO within the solid. NO-zeolites of this type are very stable in the anhydrous state, and NO is released when zeolite is immersed in aqueous environment. Nitric oxide capacity of these materials is impressive, and the release rate can be modulated mainly by altering the porosity of zeolite [33]. The application of NO-containing zeolite ranges from antimicrobial coatings for urinary catheters and wound dressings to slow acting antithrombotic coatings for bypass tubing, stents, catheters and cannulae [34].

Another interesting application of purified natural zeolite - clinoptilolite has been explored by Rivera *et al*. It has been shown that the presence of benzalkonium chloride or another surfactant on the zeolite induces a remarkable increase in sulfamethoxazole drug incorporation, which is not adsorbed by unmodified zeolite at all. Therefore, the pre-adsorbed benzalkonium chloride works as an anchor for drug adsorption. A regular behavior is observed for the composites of natural zeolite and benzalkonium chloride and there is a direct relationship between the amount of adsorbed drug and the amount of surfactant and the mass of zeolite. Amongst the various studied surfactants, clinoptilolite shows the strongest affinity for the cationic surfactants, resulting in the new stable composites, such as with the previously mentioned benzalkonium chloride [35]. Another group has shown

that the presence of surfactant and drugs on the zeolite does not produce any structural changes but results only in a decrease of the active surface area. Additionally, when proper surfactants are used zeolitic materials are able to support drugs of a very different nature [36].

Zeolite of the CuX type has been used as a support for the antitumoral drug cyclophosphamide. The *in vivo* tests show that the intensity of the antitumoral effects of the CuX zeolite- cyclophosphamide system is similar in comparison to that achieved by cyclophosphamide alone. An important advantage of the CuX zeolite-cyclophosphamide system is the continual maintenance in the blood of a cyclophosphamide concentration ranging between 100 and 1000 ng/ml of plasma [37].

Rivera group conducted studies in order to evaluate the physicochemical interaction between zeolite and the two drugs, metronidazole and sulfamethoxazole, which cause considerable gastric side effects. It seems that both drugs remain unaltered after interaction with the zeolitic products and no degradation of drugs was observed at broad pH range. The authors prove that both zeolitic materials and drugs could be simultaneously administrated to a patient without any loss of an individual pharmaceutical effect of each product [38].

It was shown that synthetic zeolites can also be used as drug carriers. The commercially available synthetic zeolites Vegobond 13X and Vegobond AX (SASOL, Italy) were tested as carriers of the anti-inflammatory drug ketoprofen. It could be possible to encapsulate 400 mg of the drug in 1 g of activated zeolite matrix. Ketoprofen release studies were performed at various pH conditions to mimic gastrointestinal fluids. No release of the drug was observed in acidic environment [39]. Other studies of the hydrolytic stability of drugs were performed for aspirin/zeolite system. The mineral materials used were of cancrinite-type zeolites. These studies demonstrated that the two drugs (one from antacid family and aspirin) may be used together without annulling their medical activity. The hydrolysis rate of aspirin loaded into zeolites was compared to the similar system where aspirin was hosted by synthetic hydrotalcites. The hydrolysis process was superior in the cases of aspirin loaded into zeolite, because of the more basic character of hydrotalcite [40].

Zeolite matrix has also been used to stabilize erythromycin solutions. An existing commercial product based on diisopropylsebacate/ethanol solution of 4% erythromycin and zinc acetate (Zineryt®, Yamanouchi Pharma) has been compared to analogical systems where active compounds are loaded into porous material. A zeolite carrier for the erythromycin of this kind releases zinc *via* ionic exchange after contact with the skin salts and is stable and easy to handle. Moreover, apart from the expected therapeutic effects of chemicals hosted by zeolite material, an additional wound healing action has been observed for natural zeolites, but the mechanism of this last effect is not known yet [41,42].

Since the MCM-41 mesoporous material was invented by Mobil researchers at the beginning of the 1990's, syntheses and applications of mesoporous molecular sieves have drawn much attention [5,43]. The structure of the MCM-41 molecular sieve consists of a hexagonal array of one-dimensional channels with pore diameters of 2-5 nm, Fig. (**3**). Typically, this molecular sieve is synthesized by a templating mechanism. The channel diameter basically depends on the surfactant used in the synthesis [43-47].

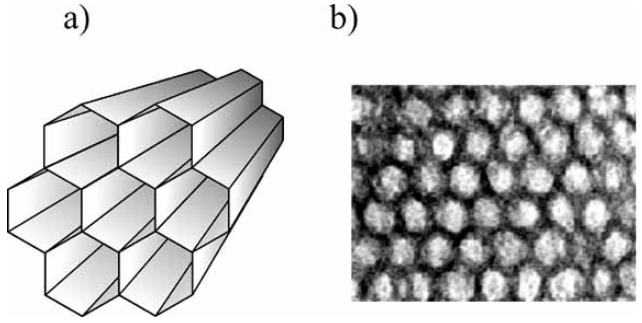



**Fig. (3).** Structure of MCM-41 mesoporous material (a) schematic view and (b) TEM image.

The invention of this material has opened new possibilities for their use as supports or adsorbents. Well defined periodic nanostructure of zeolites suggest that they can be used as a host for many organic molecules or optically active materials. Much research focused on preparing the organic/inorganic hybrids by functionalization of the surface of molecular sieves suggest utilization of MCM-41 in many areas.

Vallet-Regi *et al.* proposed the use of MCM-41 mesoporous material for drug delivery applications [48,49]. MCM-41 was loaded with ibuprofen, an anti inflammatory drug. (Fig. (**4**)). It has been shown that the weight percent ratio of ibuprofen/MCM-41 was 30%. Whereat, the drug release depends on the impregnation method.

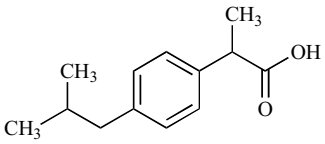



**Fig. (4).** Structure of ibuprofen - an anti inflammatory drug.

In order to control delivery rate, the surface of the molecular sieves can be modified (functionalized) with different organic groups [50-54]. Munoz *et al.* investigated MCM-41 a molecular sieve modified with aminopropyl groups [51]. The delivery rates were obtained in by soaking the samples in a solution simulating body fluids (SBF) at 37ºC and at physiological pH of 7.4 [55]. In the case of ibuprofen, which contains a carboxylic group, the functionalization with aminopropyl groups decreases delivery rate. It has been demonstrated that the functionalization method can determine adsorption of the drug on a molecular sieve and finally affects the delivery rate. However, different pore diameters of the host material do not affect delivery rate in the case of ibuprofen.

Manzano *et al.* investigated MCM-41 functionalized with 3-aminopropyltriethoxysilane as a potential drug carrier [56]. Powder and monodispersed spheres (490-770 nm in diameter) were investigated in SBF solution [55]. It was found that amine-functionalized spheres of MCM-41 show much slower

ibuprofen release than powdered MCM-41, which could make possible the control of the drug delivery over a longer time.

The modification of the MCM-41 with 3-glycidoxypropylsilane leads to higher drug bonding to a molecular sieve [52]. In such functionalized MCM-41, ibuprofen can form covalent bonds with the molecular sieve walls (Fig. (**5**)). Loading of ibuprofen, determined with different experimental methods, can vary from 27.4% up to 33 % weight percent. Impregnation of MCM-41 with a solution of ibuprofen in ethanol results in the improvement of drug loading. X-ray diffraction data show that the encapsulated ibuprofen remains in the molecular and amorphous phase and only a small fraction (about 0.2%) was found in crystalline form on the surface of host material [57].

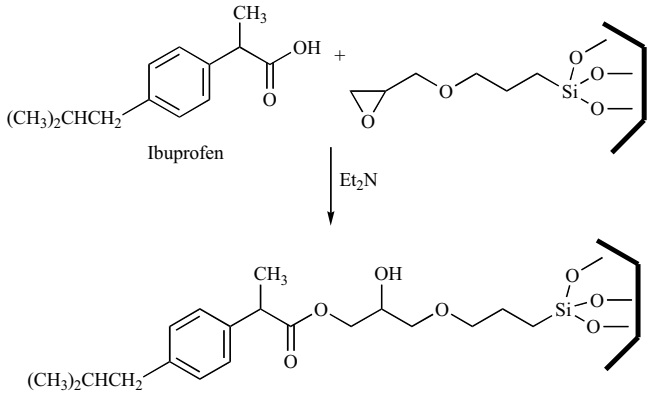


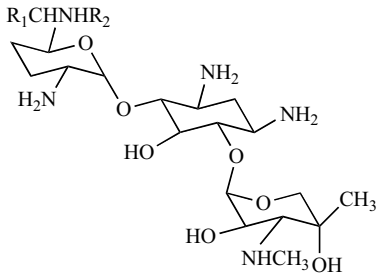

**Fig. (5).** Chemisorption of ibuprofen on MCM-41 mesoporous material functionalized with 3-glycidoxypropylsilane.

The drug adsorption effectiveness depends not only on the specific interaction between zeolite and guest molecule but also on the pore size and the active surface area [58-60]. This can be explained by a change of intermolecular interaction in ibuprofen. Larger pore diameter/volume leads to higher drug adsorption. This factor is also critical for drug release rate. NMR studies of ibuprofen encapsulated in MCM-41 with 35 and 116 Å pore diameters show that at ambient temperature ibuprofen molecules are extremely mobile with higher mobility in silica with greater pore diameter. It seems that high mobility of ibuprofen is a result of a weak host-guest interaction that leads to high release rate [61].

Fisher *et al.* compared adsorption and release rates of the drug model fluorescein and its analogues for NaX zeolite and MCM-41 mesoporous material. Adsorption of 9 and 14 % of the sodium salt of fluorescein on NaX zeolite and MCM-41 respectively suggests relatively low penetration of the pores. A higher adsorption was obtained when acetone was used as a loading solvent. Basically, a large initial fluorescein release was observed from the surface of zeolites with very little further increase over time. The presence of esterase enzyme in release solvent significantly increased release rate from MCM-41 but does not affect release from zeolite X. Generally, the adsorption of fluorescein strongly depends on the applied solvent However, release rates also depends on pH and the presence of enzymes in a release medium [62].

The work published by Tang *et al.* presents another type of chemically modified mesoporous silicate. The silicate was modified by reaction with 2-cyanopropyltriethoxysilane, and the product containing cyano groups was hydrolyzed in acidic conditions. Newly formed silicate containing carboxylic groups was used as a carrier of model drug famotidine. Three kinds of release fluids including simulated gastric, intestinal and body medium were used to test the famotidine release rate from the modified silicate material [63].

Synthesis of SBA-15, well ordered mesoporous silica with uniform tunable pores (up to 300 Å) open new possibilities for drugs delivery [64,65]. A large pore size allowed drug storing with relatively larger molecules. Doadrio *et al.* conducted research on controlled delivery of gentamicin – an antibiotic for infection (Fig. (**6**)) [66]. The SBA-15 silica was charged with gentamicin sulphate and experiments were carried out *in vitro*. No significant difference in release profile was observed in the tests between disk and powdered samples.




**Gentamicin $C_1$: $R_1 = R_2 = CH_3$**
**Gentamicin $C_{1A}$: $R_1 = R_2 = H$**
**Gentamicin $C_2$: $R_1 = CH_3 R_2 = H$**

**Fig. (6).** Structure of gentamicin.

SBA-15 functionalized with amine groups has been found to be very effective in model drugs adsorption (ibuprofen and bovine serum albumin). The adsorption capacities and release profiles of these two model drugs are strongly dependent on the surface modification of SBA-15. Due to the ionic interaction between adsorbed drug, carboxyl groups of unmodified SBA-15 and amine groups of functionalized SBA-15, the release profile of ibuprofen from SBA 15 modified by postsynthesis has been found to be effectively controlled [67].

A delivery system based on the SBA-15 mesoporous material, with magnetic particles formed *in situ* and thermosensitive poly(*N*-isopropyl acrylamide), as a controlled switch, was designed and synthesized by Zhu *et al*. An adsorption and release test of ibuprofen shows that this system has potential use for thermo-responsive controlled release [68].

## TISSUE ENGINEERING

Since the discovery of Bioglass in 1971 [69] various materials containing $CaO\text{-}SiO_2$ or $CaSiO_3$ have been investigated as potential materials for tissue regeneration or replacement. Recently, the porous materials have been considered for biomaterials science applications such as bone tissue regeneration. Due to high stability over time, zeolites are commonly used as root filler base paste [70]. Silanol groups

located on the surface of mesoporous silica are able to react with physiological fluids and form hydroxycarbonapatite.

Watanabe *et al.* reported preparation of hydroxyapatite on 4A zeolite (Fig. (**7**)). A thin layer of hydroxyapatite was obtained during hydrothermal synthesis based on cation exchange reaction. The hydroxyapatite needle-like crystals were grown under reaction between discharged $Ca^{2+}$ ions from zeolite and $PO_4^{3-}$ ions in $(NH_4)_3PO_4$ solution. The crystal structure of the zeolite was not destroyed under reaction conditions. However, the morphology was changed only with complete covering of scaly hydroxyapatite particles. The obtained nanocomposite exhibits properties of both hydroxyapatite and zeolite [71,72].

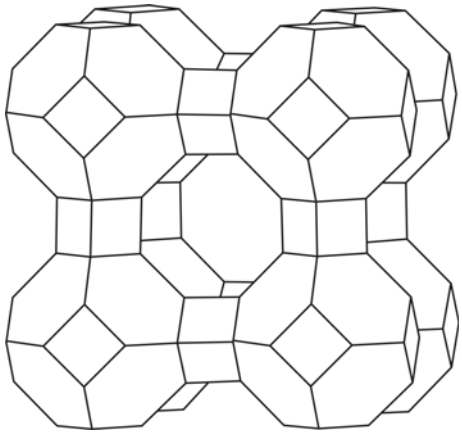


**Fig. (7).** Structure of zeolite 4A (LTA).

*In vitro* bioactivity studies of the SBA-15, MCM-41 and MCM-48 mesoporous materials soaked with simulated body fluid, which has a composition and ionic concentration similar to that of human plasma, show that the apatite layer is formed on the surface of SBA-15 and MCM-48 after 30 and 60 days, respectively, allowing application of these materials for bone regeneration. The experimental results clearly show bioactivity of SBA-15 and MCM-48. However, MCM-48 mesoporous material exhibits slower growth kinetics when compared to SBA-15. No evidence was found for formation of apatite on MCM-41 after soaking for 60 days. This can be explained on the basis of differences in morphology and chemical properties of the investigated materials [73]. Doping MCM-41 mesoporous material with 10 wt % of glass induces formation of apatite on the surface of MCM-41 after only 7 days [74]. The bioactivity of MCM-41 mesoporous material can also be improved by incorporation of phosphorous in the structure of the molecular sieve. In contrast to unmodified, pure MCM-41 material, the phosphorous containing MCM-41 exhibits bioactive response in *in vitro* studies after 13 days. It seems that doping MCM-41 with small amount of phosphorus can play a crucial role in the improvement of bioactive properties [75]. Compared to the hydroxyapatite from bovine bone, calcium phosphate and commercial eugenol paste zeolites 4A do not affect cellular proliferation. It also does not affect collagen production [76]. The good biocompatibility of this material can be explained by silicon content. Schutze *et al.* suggests that zeolite A reduces bone resorption [77]. The presence of zeolite A reduced the osteoclast and secreted cathepsin B enzyme activity. This might indicate a potential bioactivity of zeolite A or a partial substructure of zeolite A on bone turnover.

Mesoporous amorphous calcium silicate exhibits high bioactivity in *in vitro* studies. Due to specific surface area and pore volume mesoporous amorphous calcium silicate shows significant improvement of bone forming activity compared to other materials. The formation of carbonate containing hydroxyapatite layer and near-spherical hydroxyapatite nanoparticles on the surface of mesoporous amorphous calcium silicate was observed during soaking in simulated body fluid (tris-(hydroxymethyl)-aminomethane $[(CH_2OH)_3CNH_2]$ and hydrochloric acid (HCl), at a concentration of 1 mg/mL at 37ºC, buffered at pH 7.4) for only 4 h. After longer soaking time, the number of hydroxyapatite increased [78].

The literature data univocally suggest good bone-forming bioactivity of porous materials however, the employment of zeolites as scaffolds for bone engineering is still in preliminary stages of study.

## ZEOLITES MIMIC ENZYMES

With the advent of bionanotechnology [79,80], the desire to mimic enzymatic systems has prompted an extensive area of research into synthetic enzymes that can be utilized mainly in the manufacture of fine chemicals with medical application, but also in other medicine related areas such as molecular diagnostics [22]. Zeolites-crystalline aluminosilicates with a microporous structure were first used as catalysts in early sixties of the twentieth century. Ever since then the attention has been focused on developing zeolite-based catalysts that mimic the excellent activity and selectivity of natural enzymes [81]. Based on observations from soluble and zeolite-based catalysts, high selectivity of the catalyst (a main goal of catalysis) can be correlated to structural uniformity. It can be quite easy to obtain due to the modern zeolite synthesis methods available these days [82-88]. However, when attempting to imitate the enzymes, it is useful to keep in mind that their efficiency, selectivity, and stability arises not only from the steric effects imposed by the environment of the enzyme active site upon substrate approach, but also from specific binding at the active site [89]. The enzymes bind to and stabilize the short-leaving transition state for a particular reaction, whereas artificial enzyme-like systems are known to bind the ground state. Even if the artificial enzyme deals with a stable transition state analogue, it is still only an analogue and not the real transition state. Therefore, even catalytic monoclonal antibodies give several orders of magnitude lower enzymatic activity than the corresponding native enzymes [90]. The prevailing view is that rate enhancements comparable to those of enzymes could be achieved if the substrate groups and the catalytic site are brought together in an intramolecular reaction. However, intermolecular catalysis of a similar performance requiring selective binding and precise orientation of substrate and catalytically active groups, remains elusive [90-92]. Therefore, the imitation of enzyme action is especially valuable in all the cases where there is a lack of the corresponding enzyme equivalent (such as the Diels-Alder in organic synthesis [90]), or potential *in situ* production of drugs, hormones, enzyme critical cofactors etc. in artificial tissues of secreting organs. The other cases that might come to mind are closely

related to the drug delivery systems mentioned earlier. Sometimes the enzyme, its active center, cofactor, substrate or inhibitor requires enhanced stability which can be secured by encapsulation in the aluminosilicate framework [93,94].

The size and shape selectivity and encapsulation of biocatalysts in zeolite-host can lead to synthesis of systems that mimic enzyme functions in certain biological processes. Natural zeolites (microporous aluminosilicates) have pores of diameters roughly of the size of small molecules (3 to 10 Å). The aluminum in the silicalite lattice induces a negative charge on the oxide framework. This charge is balanced by positively charged ions such as $Na^+$, $K^+$ and $H^+$ in the pores. These cations, which are accessible through the pores, give zeolites their large ion exchange capacity and their usefulness as size- or shape-selective catalysts. Therefore, the zeolite framework (similarly to proteins) can incorporate small, preferentially charged, molecules such as metal complexes thus protecting them from degradation [89], whereas, large macromolecules can be embedded in the frameworks of synthetic mesoporous aluminosilicates. For example, hydrothermally stable and structurally ordered mesoporous and microporous aluminosilicates: (MAS-9, MCM-48-S and MCM-41-S) with different pore sizes 90 Å, 27 Å, 25 Å respectively, have been synthesized to immobilize Cytochrome C [94]. At an earlier stage of the synthetic procedure the introduction of aluminum into the framework of pure silica materials, which increases unbalanced charge, causes an increased amount of Cytochrome adsorption. Interestingly, among these mesoporous silicalites those with the highest loading capacity, due to their large pore dimensions, are not the optimal ones for the encapsulation of the enzyme. The quite large size of the pores in MAS-9 allows conformational changes of the protein which undergo facile unfolding during hydrothermal treatments. Therefore, MCM-48-S and MCM-41-S aluminosilicates, having the pore sizes that match well the size of Cytochrome C (25 x 25 x 37 Å), manifest the highest hydrothermal stability and overall catalytic activity. On the other hand, the pore size of NaY zeolite (7.4 Å) is so small that Cytochrome C is mostly adsorbed only on the outer surface and loses its enzymatic activity rapidly [94].

Cavities of both zeolites and synthetic aluminosilicates have the potential to serve as hosts for active-sites of natural enzymes. This idea can be rationalized by the assumption that the inorganic materials would provide the best arrangement for the catalytically active centers directing the substrate towards these centers. Such an approach has been developed based on the replacement of the protein portion of natural enzymes by a size- and shape-selective framework of a mineral matrix. Intense efforts have also been undertaken in order to mimic the protein cavity of natural enzymes by designing synthetic superstructured porphyrin models with a controlled steric environment such as picnic-basket porphyrins, strapped porphyrins, etc.; phthalocyanine and Schiff-base models of enzyme active sites, especially for monooxygenase enzymes of the cytochrome P-450 family (see review [95]).

As we mentioned earlier, the immobilization of organic molecules (including enzymes or their active centers) into nanochannels of molecular sieves can be carried out by several different approaches [62,95-100]. Especially, significant developments in chemical functionalization of zeolites that introduces organic groups to a lattice, making zeolites more "biocompatible," is very promising for building new enzyme-mimic systems. These days inorganic-organic aluminosilicates-based hybrid materials, which can be used to provide a support for the organic functional groups attached as active catalytic sites, have become available [50,81,101-103].

## ANTICANCER PROPERTIES

More recently, zeolites as a clinoptilolite have been considered as a potential adjuvant in anticancer therapy for animals [104]. Pavelic *et al.* suggests that orally administered natural clinoptilolite treatment of mice and dogs suffering from a variety of tumor types led to improvement of overall health, prolongation of life-span and decrease of tumor size. Tumor formation and growth have been reduced by applying clinoptilolite to skin cancers of dogs and no negative side effects were observed. *In vitro* tissue culture studies showed that clinoptilolite in the form of fine powder inhibits protein kinase B (c-Akt) and induces expression of p21WAF1/CIP1 and p27KIP1 tumor suppressor proteins and blocks tumorous cell growth. The range of these effects was diverse, ranging from negative antitumor response to normalization of biochemical parameters, prolongation of life span and decrease of tumor size [105].

Another study from the same group shows that micronized zeolite, combined with a standard chemotherapy treatment (Doxorubicin), reduced the metabolic rate of cancer cells, significantly reduced the amount of metastasis to the lungs and increased the anticancer effects of the chemotherapy treatment. The treatment of cancer-bearing mice and dogs with micronized zeolite clinoptilolite led generally to the enhancement of the health status and also reduction of tumor size. Reduction of lipid peroxidation in the liver of mice was noticed. Micronized zeolite clinoptilolite reduced the metabolic rate of cancer cells and increased binding of 4-hydroxy-2-nonenal (HNE) to albumin *in vitro*. Clinoptilolite selectively reduced production of HNE *in vivo* in tumor stroma after Doxorubicin treatment, leaving onset of lipid peroxidation intact in malignant cells. Combined treatment with Doxorubicin and micronized zeolite reduced the pulmonary metastasis count and moderately increased anticancer effects of Doxorubicin [19].

Activated TMA-zeolite shows ability to reduce oxidative stress in patients suffering from malignant disease or diabetes. Preliminary data also indicate an association between a decrease in oxidative stress and general improvement of health status [106]. It has been demonstrated that 4 weeks of oral supplementation of activated TMA-zeolite resulted in restoration of previously increased antioxidant levels and decrease of the level of free radicals in the plasma of cancer patients. Activated zeolite also demonstrated anticancer activity in *in vitro* tissue cultures by inhibition of protein kinase B (c-Akt) and induction of expression of p21WAF1/CIP1 and p27KIP1 tumor suppressor proteins, independently from p53 protein. In addition, activated TMA-zeolite treatment of mice and dogs generally led to improvement in health status, prolongation of survival and decrease of tumor size [107].

However, although the mechanism of action of natural zeolites on tumors is still unknown, the results presented so far are very promising.

## ANTACID

The new antacid drug Neutacid® is based on the neutralizing capacity of the purified natural zeolite - clinoptilolite from the Tasajera deposit (Cuba) for therapy of patients suffering from hyperacidity produced by gastric dyspepsia and gastric-duodenal ulcer. The excess of HCl in gastric juice is neutralized by zeolite preserving the structural stability of pepsin. The Neutacid® is manufactured in form of tablets and chewing tablets. Patients did not indicate such side effects as acid rebound or constipation because the structure of pepsin in the gastric juice remained stable. The physical and chemical properties of the antacid tablets remain unaltered after three years of storage at room conditions [108]. Sodium carbonate loaded into natural zeolite matrix is another promising drug for hyperacidity [109]. Apart from the beneficial attributes of zeolite carriers, it should be noticed that synthetic zeolites may undergo structural changes resulting in the release of small Al-containing ions that interferes with dietary phosphates [110]. Tillan *et al*. conducted a subchronic toxicological study of purified natural clinoptilolite for 12 weeks. It resulted in conclusion that the natural zeolite did not have toxic effects or caused biological damages in animals [108].

Further cation exchange modifications of natural zeolite in hydrothermal conditions were conducted to develop other zeolitic active materials with specific pharmacological action: the zinc exchanged form named ZZ has a microbicide effect against yeast, bacteria and protozoa; the calcium enriched form named Colestina adsorbs biliar acids from biliar juice in the intestine producing a hypo-cholesterolemic action and the Fe(II) form (FZ) is a selective adsorber of glucose in the intestine controlling the transport of this molecule to the blood, recognized as anti-hyperglycemic action [108].

## COATINGS AND POLYMERIC FILMS

Since the mid nineties, thin zeolite films and powdered coatings with antimicrobial properties are receiving increased interest as a biomaterials. Antimicrobial properties of zeolite coatings were additionally improved by exchange of zeolite with silver ions. Silver ions dispersed in the zeolitic lattice are more effective compare to bulk. Silver ion exchanged zeolites A coating on stainless steel are hydrophilic and antimicrobial and are useful in water condensers. The powder coating process results in higher activity and durability. The zeolite A coatings exhibits no loss of antimicrobial activity after submersion in water for over 8 weeks [111, 112]. Rusin *et al.* reported rapid reduction of *Legionella pneumophila* on stainless steel coated with zeolite containing silver and zinc ions compare to plain steel [113]. Zeolite X exchanged with silver ions show antimicrobial actions against *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* [114].

In 2001 Ciba Specialty Chemicals (Basel, Switzerland) introduced to the market IRGAGUARD B 5000 inorganic silver zeolite based antimicrobial agent. Special zeolite design allows controlled release of silver ions. IRGAGUARD B 5000 inhibits the growth of micro-organisms such as bacteria, moulds, mildew and fungi that can cause deterioration. These material can be incorporated into various polymer materials such as plastic films, sheets, slabs and molded plastic parts, coatings, laminates or sealants (see: www.cibasc.com/plasticadditives).

Transparent zeolite – polymer hybrid materials and polymer covered zeolites can be used as a material for packing food or medical equipment. Properties of such material can be modified by introduction of active compounds into the system. [115].

Zeolite containing antibiotic and antimicrobial orthopedic agents were reported in recent patents. Zeolite coatings containing therapeutic material housed within pores have been recently researched [116]. The therapeutic material loaded zeolites may be suspended or dispersed within a bioerodible polymer matrix to provide controlled delivery of the therapeutic material from various medical devices. The coating may include an outer layer of a bioerodible polymer having zeolite drug carriers with first a pharmaceutical compound and also an inner layer of a polymer matrix having zeolite drug carriers with a second pharmaceutical compound.

Antibiotic zeolite-containing films exhibit excellent antibiotic action although it contains relatively small amount of antibiotic (10 -100 mg per 1 $m^2$) [117]. Antibacterial protection an orthopedic surgical implants having contact with body tissue or body fluid can be obtained by coating with natural or synthetic zeolites exchanged with gold, silver, copper or zinc ions [118].

## OTHER PERSPECTIVES APPLICATIONS

Zeomic (Sinamen-Zeomic, Nagoya, Japan), the silver containing zeolite material, has been shown to have very wide spectrum of use. Except for the most important application as an ingredient of antibacteriostatic stomatological sealants, the possible applications include water purification filters, food packaging films, or as an ingredient of bio-resistant polymers. Zeomic shows antimicrobial effect against a wide spectrum of pathological microorganisms including Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, Gram-positive bacteria such as *Staphylococcus aureus* and also fungi such as *Aspergillus niger* and *Penicillium nigricans* [119].

Zeolites have also been used as antibacterial agents. They have been used in the control of urinary tract infections against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*, which has been demonstrated *in vitro* [120].

Innovatory application of natural zeolite – clinoptilolite as an antiviral agent has been shown by Grce *et al*. Human adenovirus 5, herpes simplex virus type 1 (HSV 1) and human enteroviruses (coxsackievirus B5 and echovirus 7) were used in the antiviral assay. The significant inhibitory effect upon viral proliferation was observed above concentrations of 12mg of zeolite/ml. It seems that the antiviral effect of zeolite is non-specific and is probably based on the absorption of viral material into pores of zeolite. This effect is not related to the ion exchange properties of this zeolite. The

possible applications mentioned in the work include purification of drinking water from different viruses [121].

Clinoptilolite is the main and active component of the antidiarrheal drug Enterex (Victus, Inc., USA). Originally, the natural zeolite - clinoptilolite enriched tuff was used for the prevention of diarrhea in calves. The therapeutic doses used were quite large, up to 2 g/kg of body weight. The effectiveness of zeolite in preventing diarrhea was of approx. 70% as compared to 18% in the control group. Authors considered adsorption of bile acids, Aflatoxine B and Glucose as a possible antidiarrhea action mechanisms [122].

Pavelic *et al.* suggest that zeolites play an important role in regulation of the immune system and similar to the silica, silicates and aluminosilicates act as non-specific immunostimulators similarly to superantigens (SAG). Superantigens are a class of immunostimulatory and disease-causing proteins of bacterial and viral origin with the ability to activate relatively large fractions (5–20%) of the T cell population. Activation of superantigen requires simultaneous interaction with the Vβ domain of T cell receptors and with histocompatibility complex class II molecules on the antigen presenting cells. It was shown that micronized zeolite administered by gastric intubation to mice injected with melanoma cells significantly reduced the number of melanoma metastases [123].

Mycotoxins comprise a family of fungal toxins. Many of them have been implicated as chemical progenitors of toxicity in men and animals. The most thoroughly studied are the aflatoxins. The recent approach to the problem has been the addition of nonnutritive sorbents to the animal's diet that sequester mycotoxins and reduce their gastrointestinal absorption. Ramos *et al.* focused on comparison of aflatoxin bonding efficiency between different porous materials - activated charcoal, bentonite, zeolite, hydrated sodium calcium aluminosilicate and a variety of clays and ion-exchange resins [124].

Zeolites are the main ingredient of commercially available anti-bleed agent QuikClot (Z-Medica Corporation, USA). The QuikClot is a granular product applied directly on wounds to stop bleeding. The mechanism of anti-bleed action is based on adsorbing water from the blood, concentrating the clotting factors, activating platelets, and promoting steps in the coagulation cascade. The water-zeolite bond formation generates heat which has been a drawback to the previous generation QuikClot product. The development of the latest versions were focused on the elimination of exothermic reaction with water [125].

## CONCLUDING REMARKS

Molecular sieves have a great potential to be applied in particular areas of medical treatment. Owing to chemical and physical properties and stability in biological environments, microporous and mesoporous materials have found application as alternative drug delivery systems. MCM-41 mesoporous material, due to the pore size tunability and functionalization possibilities, can especially encapsulate a variety of different drug molecules and release them in controlled ways.

Biocompatibility studies of zeolites clearly show that hydroxyapatite can be formed on the external surface of the zeolite after immersing in simulated body fluids. These new composite materials exhibit characteristics of zeolites and, as well as hydroxyapatite, can be seriously considered as scaffolds in tissue regeneration or bone formation.

Zeolites surface coating offer antimicrobial protection though the controlled release of antimicrobial agent and can be applied to different types of surfaces or incorporated in many types of polymers.

Recent studies on natural clinoptilolite show that this material can be utilized as an adjuvant in anticancer therapy. So far, zeolites have been successfully applied as dietetic supplements, root filler base cement and as antimicrobial agents for dental treatment.

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