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Review

Environmental and Pharmacokinetic Aspects of Zeolite/Pharmaceuticals Systems—Two Facets of Adsorption Ability

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Abstract: Zeolites belong to aluminosilicate microporous solids, with strong and diverse catalytic activity, which makes them applicable in almost every kind of industrial process, particularly thanks to their eco-friendly profile. Another crucial characteristic of zeolites is their tremendous adsorption capability. Therefore, it is self-evident that the widespread use of zeolites is in environmental protection, based primarily on the adsorption capacity of substances potentially harmful to the environment, such as pharmaceuticals, pesticides, or other industry pollutants. On the other hand, zeolites are also recognized as drug delivery systems (DDS) carriers for numerous pharmacologically active agents. The enhanced bioactive ability of DDS zeolite as a drug carrying nanoplatform is confirmed, making this system more specific and efficient, compared to the drug itself. These two applications of zeolite, in fact, illustrate the importance of (ir)reversibility of the adsorption process. This review gives deep insight into the balance and dynamics that are established during that process, i.e., the interaction between zeolites and pharmaceuticals, helping scientists to expand their knowledge necessarily for a more effective application of the adsorption phenomenon of zeolites.

Keywords: zeolites; drugs; adsorption; drug delivery systems; theoretical approach

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1. Introduction

Zeolites are porous, hydrated aluminosilicate minerals with a three-dimensional structure and loosely bounded cations of alkali or alkali earth metals [1–3]. Due to the progress of mineralogy, the traditional definition of zeolite as aluminosilicate frameworks was found to be too inflexible. In the definition of a zeolite mineral recommended by the International Mineralogical Association, Commission on New Minerals and Mineral Names, structures containing an interrupted framework of tetrahedra are accepted where other zeolitic properties predominate, and complete substitution by elements other than Si and Al is allowed [4]. These include the divalent cations Be^{2+} and Zn^{2+}, other trivalent cations such as B^{3+}, Ga^{3+}, and Fe^{3+}, as well as tetravalent cations such as Ti^{4+} and Ge^{4+}.

According to their origin, they can be natural and synthetic [5]. Zeolites are formed in nature in the reaction of volcanic rocks and ash with water of high pH value and a high concentration of salt [1,2,5,6]. Natural zeolites possess high selectivity for heavy metal ions and ammonium ions and are therefore important for environmental protection [6]. There are around 50 known natural zeolites, and the most important ones are clinoptilolite, mordenite, and chabazite [2]. Natural zeolites usually contain impurities of other minerals—for example, feldspar and quartz, metals, etc. [2], and, as a result, their application is limited

when it is required to use zeolites of high purity and uniformity [1]. It is important to note that zeolite deposits are a non-renewable resource. Laboratory synthesis of zeolites is based on the application of natural and synthetic silicates as carriers. Zeolites synthesised using natural substrates are never 100% pure. However, their price is significantly lower compared to zeolites obtained from synthetic substrates [6]. Studies have shown that synthetic zeolites have numerous advantages over natural zeolites. The pore size of synthetic zeolites is significantly larger than natural zeolite, which allows the adsorption of larger molecules—for example, diesel fuels and used engine oil. Also, the efficiency of removing radioactive waste and heavy metal ions from the environment is higher for synthetic zeolites [2,6].

Zeolites can be classified on the basis of their crystal structure, chemical composition, pore size, etc. [1]. The Si/Al ratio is an important characteristic of zeolites that determines their ion-exchange abilities. Increasing this ratio changes the surface selectivity from hydrophilic to hydrophobic [1,2,7]. For this reason, silicon-rich zeolites are stabilized in the synthesis process by adding various organic species to the reaction mixture [8].

Zeolites can be classified according to the Si/Al ratio as follows:

1. Low Silica Zeolites: $Si/Al \leq 2$
2. Intermediate Silica Zeolites: $2 < Si/Al \leq 5$
3. High Silica Zeolites: $Si/Al > 5$ [9].

Another classification of zeolites is based on the diameters of their pores:

1. Small-pore zeolites (8-member rings) with pore diameter of 0.3–0.45 nm
2. Medium-pore zeolites (10-member rings) with pore diameter of 0.45–0.6 nm
3. Large-pore zeolites (12-member rings) with pore diameter of 0.6–0.8 nm
4. Extremely large-pore zeolites (14-member rings) with pore diameter of 0.8–1.0 nm [1–3].

Zeolites can be represented by the structural formula based on a crystallographic unit cell:

$$M_{x/n}[(AlO_2)_x(SiO_2)_y]\cdot wH_2O$$

where n represents the valence of a cation M, w is the number of water molecules per unit cell, x and y is the number of tetrahedra per unit cell, and the y/x ratio is most often in the range of 1 to 5 [3,10].

The zeolite structure is composed of SiO_4 and AlO_4 tetrahedra interconnected through oxygen atoms [5,10]. In the zeolite structure, silicon is tetravalent and forms an electroneutral SiO_4 tetrahedron, while aluminium is trivalent and each AlO_4 tetrahedra carries a negative charge. This charge is balanced by the presence of non-framework easily exchangeable cations [10]. The connection of the SiO_4 and AlO_4 tetrahedra (both commonly marked as TO_4) leads to the formation of cavities and channels with an internal surface area that reaches several hundred square meters per gram of zeolite. This characteristic makes zeolites extraordinarily effective ion exchangers. The pore diameter is usually in the range of 0.3 nm to 1.0 nm, in the group of aluminosilicates, and extends to about 1.4 nm in the respective phosphates, and they contain water molecules and cations [11].

The primary building blocks of zeolites TO_4 tetrahedra can be assembled into secondary building units by linking through oxygen atoms, resulting in the final structures of zeolites with a regular distribution of pores and cavities [3,5,10].

These secondary building units (SBU) or blocks have various different compositions and can have up to 16 T-atoms. SBUs can be single 4-, 5-, 6-, 8-member rings or double 4-, 6-, 8-member rings, or some other complicated structures like two connected 5-member rings (5–3) or 6-member rings followed by 4-member one (6–2), etc. The space combination of these SBUs sometimes gives a rise to specific cages in structure. For example, a combination of single 6- and 4-member rings creates a well-known sodalite cage. Using different parts of this cage to connect cages, different zeolite frameworks arise. Illustrations of double 4- and 6-membered rings are presented in Figure 1. Sodalite cages directly connected through 4-member rings create a sodalite structure (Figure 2 left), while cages on some distance create a double 4-member ring giving a rise of Linde Type A structure type

(Figure 2 middle). Similarly, creating a double 6-member ring makes a Faujasite structure type (Figure 2 right). Each zeolite framework is marked using a three-letter type code assigned by the International Zeolite Association [12]. The above-mentioned zeolites have codes SOD, LTA and FAU, respectively. Silicon and aluminium could be substituted by phosphorus, gallium or germanium ions, creating aluminophosphates, galophosphates etc. In the zeolite structure, cations can be reversibly replaced with other cations from solution in contact with the zeolite in the ion exchange process, and water can be reversibly removed at temperatures usually below 400 °C, leaving the crystal structure undamaged [1,3,4,13].

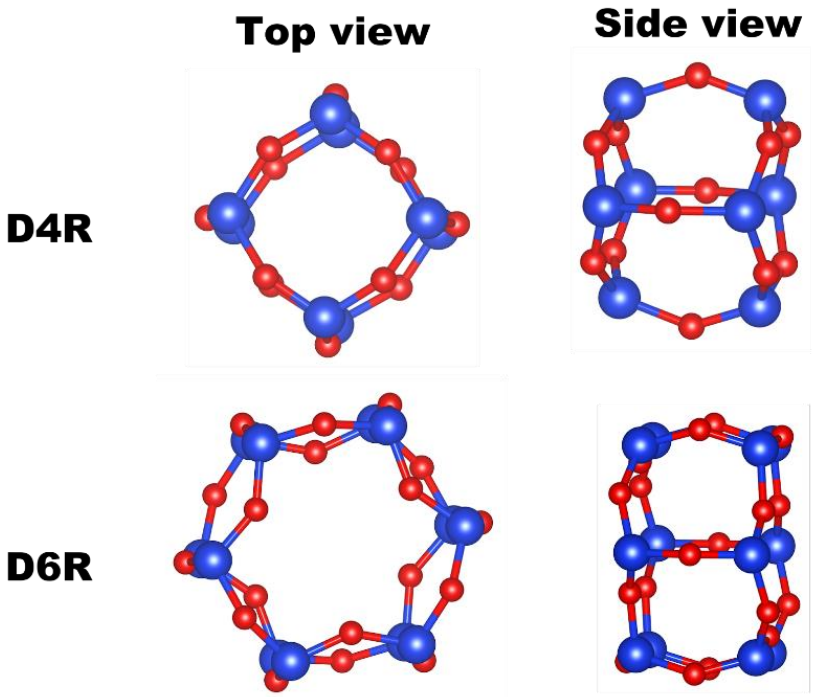


Figure 1. A double 4-members ring (D4R) and double 6-members ring (D6R) as examples of SBUs. Red atoms are oxygen and blue atoms are silicon or aluminium atoms.

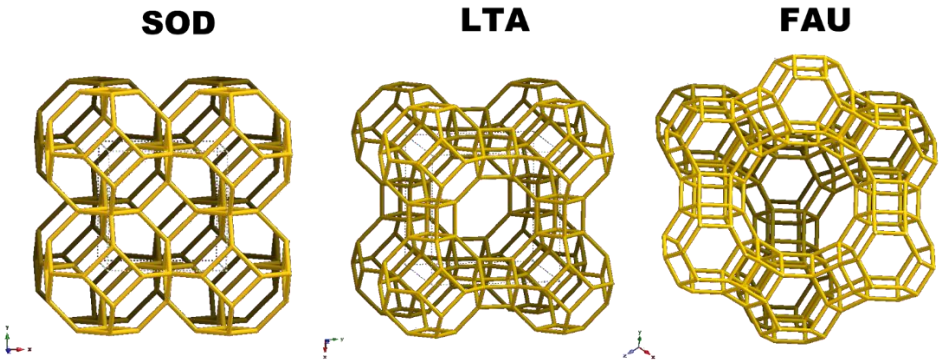


Figure 2. The framework structure for SOD (**left**), LTA (**middle**) and FAU (**right**) zeolitic network.

The wide and still not completely finished list of applications of zeolites is related mainly with their porous structure, high adsorption capacity, and ion exchange properties [14]. Zeolites are used in various technological applications, such as catalysts and as molecular sieves, including separating various molecules, as detergents, etc. [15,16].

Biotechnology and medicine are other promising fields for applications of zeolites [17]. These include detoxification of animal and human organisms, improvement of the nutrition status and immunity of farm animals, separation of various biomolecules and cells, construction of biosensors and detection of biomarkers of various diseases, controlled drug delivery systems (DDS), radical scavenging, and tissue and bone engineering. As

components of hemostatics, as gastroprotective drugs, or as antioxidative agents, zeolites can also be applied.

Zeolites can be widely applied in nowadays extremely important sustainable chemistry, including biomass conversion, exhaust post-treatment, radionuclide removal, fuel cells, thermal energy storage, CO_2 capture and conversion, air-pollution remediation, water and air purification, etc. [18]. Water purification with zeolites includes removal of radioactive contaminants, and their great efficiency in pesticide removal [19–23].

Many of these applications are based on the extraordinary adsorption capacity of zeolites. Isotherm modelling and kinetic investigation are applied in order to get insight into the main mechanisms behind the adsorption processes.

2. Zeolites in the Removal of Pharmaceuticals from the Environment

2.1. Where to Start?

Wide applications of pharmaceuticals, which are defined as substances used in the diagnosis, treatment, or prevention of disease and for restoring, correcting, or modifying organic functions, have contributed to the incredible improvement of human health and raised the quality and length of life to a great extent [24]. The most recent example is the explosion of the use of pharmaceuticals during the SARS-CoV-2 pandemic, in the treatment, but also in the prevention and diagnosis of diseases on a global scale. Despite the many benefits of modern medicine, its usage is a double-edged sword, because of the fact that a significant percentage of drugs used will end their journey in the environment.

In addition to frequently administered drugs like antidepressants, lipid-lowering agents, β-blockers, etc., very often investigated the occurrence of antibiotics, and non-steroidal anti-inflammatory drugs-NSAIDs and their residues in wastewater [25,26]. Although antibiotics levels are ng/L to μg/L, they are considered toxic compounds which contribute to the evolution of antibiotic-resistant bacteria and genes [27,28].

Ciprofloxacin, azithromycin and cephalexin, as frequently administered drugs, are suitable as markers of antibiotic pollution of the aquatic environment [25]. Interestingly, the effects on aquatic systems of birth control pills or better defined, endocrine-disrupting chemicals, are the subject of numerous reported studies for more than 40 years [29].

Excretion is the dominant way that drugs reach the environment, sometimes in their parent form or as metabolites. The environment's physicochemical and bioconversion of excreted pharmaco-active compounds, which occurred after their biotransformation pathways, give as a result various and sometimes unpredictable products [30]. The fate of pharmaceuticals in the aquatic environment is therefore a very attractive field of study [31]. Although pharmaceuticals are generally considered as susceptible to diverse transformation reactions, the resulting products are often very stable. Such transformed hydrophilic compounds easily pass-through sewage treatment plants [32]. Anyway, the drugs of even the same pharmacology active groups possess a variety of non-predictable excretion rates, with considerable impact to the aquatic environment [33].

The importance of inadequate disposal of discarded drugs should not be neglected, although this area is officially regulated in most countries [34].

Luckily, this topic is nowadays under the watchful eye of scientists, and water is an environment of interest for monitoring pharmaceutical levels, as well as the resulting impacts it leads to. Focus is placed on surface water samples, sewage treatment plants, and drinking water [35–37].

2.2. Examples of Effective Removal of Pharmaceuticals with Zeolites

The procedures for removal of pharmaceuticals from the aquatic environment are numerous and more and more innovative. For example, pharmaceuticals can be removed from wastewater by biological processes, hydrodynamic cavitation and ultraviolet light treatment [38]. Besides the general approach, it is usually necessary to create a specific action toward targeted compounds.

Although the conventional procedures, like an advanced oxidation, hydrolysis, and photo-degradation, are usually an efficient way for removal of pollutants, these strategies applied to pharmaceutical rich waters, such as hospital waste effluents or pharmaceutical industries are, can potentially cause environmental and health harmful products [39,40], and must be considered in detail [41].

Among numerous attempts, the use of zeolite for water purification from pollutants was highlighted as a simple, efficient, low-cost, and eco-friendly procedure. Zeolites (either in pristine or modified forms), are well-known materials for the adsorption of pesticides from wastewaters [19–23].

The most important characteristic of zeolite for this application is its adsorption ability. The efforts of scientists in this field are focused on finding materials with improved adsorption capacities, appropriate kinetics, and examining the reversibility of the adsorption process, as well as the possibility of reuse.

First, investigations often start with neat structures, to elucidate key parameters, such as Si/Al ratio, surface area and extra-framework ions. The experimental design relies on sample loading optimization; however, the practical approach imposes the use of low loadings to boost adsorption capacity. To participate in this quest, researchers sometimes report loading that exceeds the starting adsorbent amount several times, although this has no physical meaning. Another challenge is to detect important parameters for efficient removal of environmentally significant concentrations, which are often for pharmaceuticals at the ng/mL level. Such a low concentration masks real adsorbent performance, and lab research usually employs mg/L concentration to boost experimental sensitivity [42].

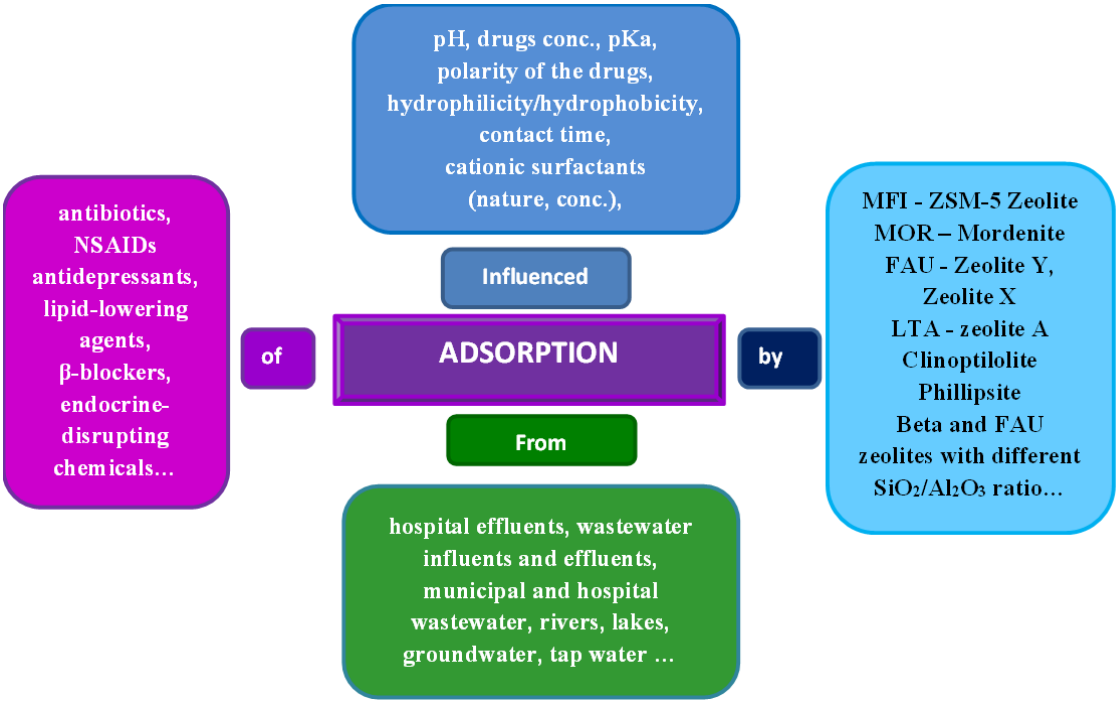
A search of the literature can reveal the published results of testing a large number of zeolite structures with the aim of testing their ability to remove drugs, i.e., their adsorption from wastewater. Table 1. gives the most explored types of zeolites for this purpose.

Table 1. Some types of zeolites.

Synthetic		Natural	
Structure	**Zeolite Type**	**Structure**	**Zeolite Type**
LTL	Zeolite L	HEU	Clinoptilolite
LTA	Zeolite A	MOR	Mordenite
MFI	ZSM-5 Zeolite	CHA	Chabazite
FAU	Zeolite X		
	Zeolite Y		
BEA	Beta Zeolite		

Among different zeolites, the FAU framework is especially present for wastewater treatment due to its substantial adsorption capacity toward different molecules. Additionally, in some cases there is no need for functionalization, and commercially available zeolite can be readily employed. Following its beneficial adsorption behaviour, FAU zeolite has been so far employed for the removal of sulfonamide [43,44] and fluoroquinolone antibiotics [45,46]. A special study was dedicated to the macrolide class representative, azithromycin removal by FAU zeolite [47]. Another reason for FAU selection lies in its fast kinetics, which takes up to several minutes for half an hour, which is of utmost importance for environmental application. Antibiotics are often oxygen and nitrogen-rich compounds whose main mechanism of interaction with the zeolite surface is hydrogen bonding. If this is the case, it is necessary to examine pH effects on the adsorption process [47]. Scheme 1 illustrates the drug removal by zeolites.

Zeolites sometimes require functionalization/composite preparation to establish new and improved features. MFI zeolite, for example, suffers from low adsorption capacity, and combination with excellent adsorbents enabled the removal technique to be extended from adsorption to catalytic degradation in the presence of suitable oxidants. For instance, composite prepared of MFI zeolite and carbon adsorbent is proposed for 150 ppm ciprofloxacin adsorption [48].



Scheme 1. Pharmaceutical adsorption by zeolites from aquatic media.

These procedures, however, sometimes tend to be costly and complicated or even pose a bigger environmental threat, due to hazardous solvents or higher toxicity, leaving of constituents, etc.

The adsorption conditions of antibiotics on zeolite are often examined, like in the study of chlortetracycline, oxytetracycline (OTC), ofloxacin, and enrofloxacin adsorption on natural zeolite [49]. The Langmuir-Freundlich sorption model was employed to estimate the maximum sorption capacity, and it was found that the capacity increased if the solution pH decreased. The presence of natural organic matter reduced the sorption of OTC but improved the sorption of the remaining antibiotics. An ofloxacin removal was additionally tested on LTA zeolite prepared from red mud/fly ash/spinel iron oxide nanoparticles [50]. Tested adsorption was investigated in different matrices—tap and river water—by spiking the samples with 10 μg/L antibiotics.

As another example, erythromycin (ERY) and levofloxacin (FLX) were almost completely adsorbed by Y zeolite (as an example of organophilic zeolite) from water samples collected at the outlet of a wastewater treatment plant [45].

The "2-in-1" idea to lower the overall costs and to use environmentally undesirable materials is reported in the study where coal fly ash (CFA) driven zeolites were applied for the adsorptive removal of ceftazidime, a broad-spectrum antibiotic [51], where CFA is a leftover product of burned coal, very harmful for the environment.

Sometimes reviews about zeolites and mesoporous silica materials as effective adsorbents of drugs, besides antibiotics, are focused on the removal of NSAIDs, as another most frequently used pharmaceuticals. The review of Grela et al. summarized available literature data and concluded that the highest concentrations of diclofenac, ibuprofen, and ketoprofen were found in wastewater influents, municipal wastewater, and hospital effluents, and gave the order of NSAIDs and antibiotics concentrations in different types of water samples: hospital effluents > wastewater influents > municipal wastewater > secondary wastewater > river water > wastewater effluents > groundwater > surface water > seawater > tap water > hospital wastewater > surface water (lakes) [52].

High concentrations of pollutants in simulations of real water samples are necessary to elucidate key parameters for adsorption and to select the best adsorbent. But, directing further research towards lower concentrations in environmental real water samples (real

effluents in environmentally relevant concentrations) and information on the practical implementation of these materials in real-life wastewater treatment is of extreme importance. Recently, Ajo et al. showed that the actual removal rates of ibuprofen cannot be accurately estimated in the context of real wastewaters without negative bias from simultaneous reformation [53]. The review by Shearer et al. focused on metformin and macrolides and assesses isotherm, kinetic and thermodynamic studies, as well as the adsorption mechanisms, with discussion on some identified mistakes and inconsistencies. The review also sought to identify gaps in knowledge, particularly real-world applications, which should be priorities for future investigations [54]. The removal of pharmaceuticals from wastewater can be challenging due to its complex matrix. The examination of removal efficiency of fluoroquinolone antibiotics, norfloxacin and ofloxacin, by using nanoscale zero-valent iron loaded zeolites modified with polyethylene glycol surfactant in samples taken from the Yellow River is directed towards such applications [55]. A similar investigation, considering real river samples, was conducted for the Photo-Fenton treatment of water sample from the Meurthe River in France for the removal of 21 different pollutants, including 17 pharmaceutical compounds such as diclofenac, erythromycin, ibuprofen, ketoprofen, and lidocaine using Faujasite Y zeolite containing iron as catalyst [56]. In an interesting study, De Sousa et al. studied wastewater effluent samples from Girona wastewater treatment plants in Spain, which included wastewater from hospitals, homes, and urban areas. Two FAU zeolites with different SiO2/Al2O3 ratios were used as adsorbents for determining the concentration of azithromycin, ofloxacin, and sulfamethoxazole [47]. However, a larger number of studies refer to the analysis of samples that do not actually contain pollutants, but real matrix (for example, river water) spiked with pollutants.

Natural zeolite, like Jordanian zeolite (Intermediate silica), was successfully applied as an adsorbent for the removal of several frequently used pharmaceuticals such as ibuprofen, diclofenac sodium, indomethacin, chlorpheniramine maleate, and paracetamol from water [57]. The study showed the optimal was pH 2 for the removal of all tested compounds, except for diclofenac sodium it was pH 6, with 80 min as the optimum adsorption time. After optimization, the highest removal was found to be 88.3% for NSAID ibuprofen, and 85.8% for antihistaminic chlorpheniramine maleate. The adsorption efficiencies were evaluated, and it turned out that Freundlich isotherm fits the experimental data for both ibuprofen and chlorpheniramine maleate. The results of a continuous flow experiment performed on ibuprofen under constant influent concentration and fixed flow rate indicated that the percentage removal of ibuprofen on zeolite was the highest after fraction 9 with 78% removal.

The introduction of cationic surfactants (cetylpyridinium chloride and Arquad® 2HT-75) into natural zeolites, such as clinoptilolite (CLI) and phillipsite, leads to a better effect of the obtained composites in the removal of ibuprofen and naproxen [58]. The zeolitic surfaces were prepared as monolayer and bilayer surfactant coverage. The Langmuir model gives the conclusion that the highest adsorption capacity for the composite characterized by a bilayered surfactant at the clinoptilolite surface was 19.7 mg/g for ibuprofen and 16.1 mg/g for naproxen. The influence of the initial drug concentrations and contact time on adsorption of ibuprofen and naproxen and zeolite clinoptilolite and phillipsite, are surely very important factors for the process of drug adsorption from buffer solutions [58].

Simply discovering that a certain zeolite has the ability to adsorb a pharmaceutical, so it can be used for wastewater treatment, can in no way satisfy the scientific public. It is extremely important to shed light on the adsorption process itself, e.g., to determine the factors that affect the capacity, dynamics and reversibility of this process. For this purpose, a multidisciplinary approach and a number of modern instrumental methods are used. This approach will be illustrated by citing some examples from the literature.

Adsorption isotherms and thermogravimetric analysis show that ERY, FLX and carbamazepine (CBZ) are adsorbed in remarkable amounts by Y zeolite. X-ray structure analyses carried out on zeolite after adsorption revealed the selected drugs inside the Y cage. The

study indicates that the adsorption properties of zeolitic materials do not only depend on micropore size, and that zeolite shape selectivity also depends on structural features [45].

The beta zeolites with different SiO_2/Al_2O_3 ratio (i.e., 25, 38 and 360) were tested for adsorption of ketoprofen, hydrochlorothiazide and atenolol from diluted aqueous solutions, with changing the ionic strength and the pH, before and after thermal treatment of the adsorbents [59]. The processes were followed by thermogravimetry and X-ray diffraction. The study confirmed that the adsorption capacity was dependent on both the solution pH and the alumina content of the beta zeolites. The noticed difference was explained as a function of the interactions between drug molecules and zeolite surface functional groups. Atenolol was adsorbed on the less hydrophobic zeolite, under pH conditions in which electrostatic interactions were predominant, while ketoprofen adsorption was mainly determined by hydrophobic interactions. The adsorption capability for undissociated molecules increased with the increase of hydrophobicity.

Certain studies were conducted with the aim to better understand the interaction between the natural zeolite clinoptilolite and antibiotics that caused gastric side effects, such as metronidazole and sulfamethoxazole [60]. Beside the considerable importance of pH on the adsorption process, the study reported that interaction of metronidazole and sulfamethoxazole with the clinoptilolite and its forms is fundamentally related with the polarity of the molecules and the nature of the zeolitic material.

Other agents that can modify the properties of the solid surface of zeolites and improve the adsorption of some pharmaceutics are surfactants. The study of Lam et al. reported the results of semiempirical calculations applied on the systems formed by surfactants, drugs, water and a clinoptilolite channel model [61]. Special attention was paid to the interaction of each drug molecule with the external surface of the clinoptilolite model. The cationic surfactant seems to be well adsorbed on the clinoptilolite model, contrary to the anionic surfactant. The polarity of the drugs plays a very important role in the adsorption process from the solution: the most polar studied drug, metronidazole, was best adsorbed on the zeolite model, followed by acetylsalicylic acid and sulfamethoxazole. If the same system contains the cationic surfactant, the order of the drug adsorption is opposite: the adsorption of sulfamethoxazole as a hydrophobic molecule is more pronounced. Those conclusions can help in adjusting the adsorption of certain drugs on clinoptilolite in the desired direction by the presence of surfactant on the zeolite external surface.

Zeolitic imidazolate metal organic framework group of compounds, such as ZIF-8, belongs to metal-organic frameworks (MOFs), and possess similar characteristics to zeolite, including the high adsorption capability, and therefore can be a great candidate for the testing of removal of the pharmaceuticals from wastewater. As an example, ZIF-8 exhibits ultra-high adsorption capacity to tetracycline from aquatic media [62].

2.3. Use of Theoretical Calculation for Predicting Interactions

In a well-designed experiment, theoretical calculations should precede empirical research. Afterwards, when optimizing interactions of interest is concluded, and adsorbates and adsorbents are selected, it makes sense to start an experiment. The fact is, however, that predictions do not always produce ideal results, thus the reverse order of research is resorted to. Namely, most methods include theoretical support that follows after preceedingly obtained experimental results as a form of deeper explanation of adsorption phenomena.

There is great power in using theoretical calculations like density-functional theory (DFT), semi-empirical methods or molecular dynamic simulations. These methods could be used for predicting the stability and reactivity of molecules or predicting adsorption energies.

Drugs are usually organic molecules, so HOMO and LUMO orbitals and associated energies can be calculated. HOMO energy is connected to the ability of a molecule to donate electrons, while LUMO energy is connected to the ability to accept electrons. The gap between these two orbitals helps in the description of chemical behaviour. Lower energies are correlated with higher reactivity and lower stability of molecules [63].

Modern DFT calculations can be used to predict material properties and it is a tool that is indispensable. Based on the first principal energies of the particular systems can be calculated, followed by the prediction of adsorption energies [64].

Zeolite structures are complex, so calculations of energies in systems of interest could be complicated and some approximations had to be used. Mainly, the structure of zeolite is approximated by a cluster which represents the main cage or pore, in the particular zeolite. This was done in the work of Brachi et al., where the structure of FAU zeolite was represented by the central cage [65]. Different sulfonamide antibiotic molecules were initially optimised using DFT and minimal energy conformers were found. These steps were followed by calculations of interaction energies, bond lengths and optimal dimer conformations in the FAU cage.

In their work, Hessou et al. used the primitive crystal lattice of FAU zeolite and modeled the adsorption of dibenzyl disulfide, which can be considered as a theoretical model of pollutant molecules [66]. A theoretical prediction of the interaction energy was modeled in the presence of various monovalent extra framework cations. They predicted that CsY, AgY and CuY had high adsorption energy for dibenzyl disulfide, while not favoring production of dissociated species.

While molecular mechanics/molecular dynamics calculations are widely used to investigate the adsorption of various organic molecules with different complexity on full silica zeolites, application of these calculations on drug adsorption is quite low but emerging lately.

Fatouros and his co-workers applied molecular dynamic calculations to predict interactions and adsorption of theophylline and salbutamol on beta zeolite. Theophylline and salbutamol are molecules with similar dimensions, but salbutamol is a more flexible one. Calculations predicted that salbutamol could be adsorbed into the channels and pores of beta zeolite, while theophylline could not. These theoretical findings are supported by experimental data showing the significantly less adsorbed amount of theophylline on beta zeolite, compared with salbutamol [67].

The same research group applied molecular dynamics to predict diffusion rate and release the possibility of 5-fluorouracil from beta and FAU zeolite [68]. This drug had significantly different diffusion rate coefficients in FAU and beta systems. The slower release rate from beta zeolite is a consequence of a smaller pore system, and increased van der Waals interactions with drug molecules, compared with FAU zeolite.

In the final example of using theoretical models for predicting interactions of drugs with zeolite adsorbents, the author employed molecular dynamic simulations, as well as DFT calculations. Simulations were performed for over 20 widely used drugs and two zeolites as adsorbents, mordenite and faujasite. The author showed that the interaction energy of the zeolite-drug system from minimal energy configuration could be useful for predicting the effective removal of drugs from water. The zeolite framework was kept rigid in the simulation process in order to lower system complexity. For mordenite, it was calculated that 8 out of 21 drugs (i.e., triclosan, ibuprofen, oxybenzone...) had interaction energies between 200 and 270 kJ/mol and experimentally it was found that mordenite removes quantitatively these drugs. Nine drugs (i.e., diazepam and hydrocodone) not adsorbed by mordenite had interaction energies close to zero.

The calculations take considerable time and computational resources, but this type of screening should precede experiments whenever possible [69].

3. Zeolite-Based Biomaterials for Biomedical Application

The biocompatibility and mechanical strengths of zeolite make them suitable for biomedical application as pharmaco active compounds or as biomaterial used for dental fillers, bone grafts, implant coating, or as a drug carrier agent [70].

An illustration of the positive example of application of zeolites themselves in pharmacotherapy is clinoptilolite which can stand out as a potent detoxifying, antioxidant, and anti-inflammatory agent [71,72]. Zeolites are currently regarded as dietary super-

materials [71], and this, sometimes, is an overstatement. Every drugstore is selling zeolite-based nutritional formulations enhanced with vitamins, enzymes, etc., often without any scientific basis to support the claims of high nutritional benefits. Antioxidant, antimicrobial, detoxifying, and anticancer activity is often attributed to both synthetic and natural zeolites. However, a strict survey of the available literature gives somewhat controversial findings. For instance, zeolite's ability for trapping radical species in order for them to be safely removed from the body is a cornerstone of many studies [73]. A part of this is actually true, zeolite structure does enable radical species removal [74,75], although they shouldn't be a part of a human diet in spite of being used for cattle because tightly bind mycotoxins from animal feed in the gastrointestinal tract and thereby decrease their bioavailability [76]. Concerning this, Ipek et al. assessed the effect of natural zeolite, clinoptilolite supplementation on the oxidative status in cows and concluded that it did not support cow's systems against oxidative stress [77].

3.1. Zeolites for Dental Applications

In addition to their wide application in medicine and other sciences, zeolites have also displayed a significant potential for use in the field of dentistry. Zeolites may be applied in root canal therapy, periodontics, implant and restorative dentistry, and tissue engineering [78]. Zeolites were introduced into dental practice mainly as root filler materials, based on their hemolytic and cytotoxic properties [79], or their antimicrobial and mechanical characteristics [78]. Remineralizing the ability of calcium-rich zeolite makes it a promising candidate as a dental composite filler [80]. We can say that a wide application of zeolite in dentistry is not primarily based on adsorption as a phenomenon, but certain functions of zeolite are significantly improved thanks to the adsorption effect, which will be illustrated by examples.

In general, zeolites alone have little or no effect on antimicrobial properties, unless the zeolites are doped with ions, such as silver or zinc. The ability of zeolites to uptake and release ions, combined with their exceptional biocompatibility and long-lasting effects, has been used for the antimicrobial treatment against pathogenic oral microorganisms. Regarding dental restorative materials, zeolites are generally combined with glass ionomer cements (GIC), resin cements, or bonding agents. The antibacterial effects of GIC containing silver-zeolite (AgZ) were demonstrated on *Streptococcus mutans* in vitro [81]. Similar antimicrobial results can also be found in a zinc-doped zeolite (ZnZ) against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Candida albicans* [82]. A functional dental restorative platform consisting of zeolite nanoparticles as a drug delivery carrier loaded with chlorhexidine (CHX), was incorporated into commercial dental GIC, demonstrating a stronger inhibitory effect on *S. mutans* compared to GIC alone [83]. AgZ combined with GIC sealer showed a stronger antimicrobial effect towards *E. faecalis* compared to GIC sealer alone, which was concentration- and time-independent [84].

The root canal treatment has been related to persistent periradicular lesions, including primary endodontic infections and persistent infectious progression with the *E. faecalis* as the main etiological factor in these diseases. Zeolites in endodontics were generally added to calcium hydroxide and mineral trioxide aggregate (MTA) and used as root canal irrigants to enhance their antimicrobial properties. Ghatole et al. showed that adding AgZ to calcium hydroxide enhanced the antimicrobial effect against *E. faecalis* compared to the control or when chlorhexidine is added [85]. Among the root end filling materials, MTA is regarded as biocompatible and is most commonly used in clinical applications, but with limited antimicrobial activity. The addition of AgZ to MTA enhanced antimicrobial effects toward selected oral microflora such as *E. faecalis*, *S. aureus*, and *Candida albicans* in a concentration-dependent manner throughout 72 h [86].

Two types of zeolites, Zeolite A and ZSM-5 were investigated for their potential to adsorb volatile sulphide compounds (VSC), which are produced in the oral environment by Gram-negative bacteria and cause periodontal disease and mouth odour. The amount of H_2S adsorbed on zeolite A was found to be larger than that on ZSM-5, suggesting that the

adsorptive property of zeolites depends on their Si/Al ratio. By optimising Si/Al ratio, it is expected to develop an adsorbent material, which highly adsorbs VSC, and may contribute to oral health [87].

Zeolite in prosthesis can be added to both acrylic resin and non-acrylic materials, such as ceramic. The non-acrylic materials that were tested with zeolite demonstrated that adding AgZ to soft liners enhanced its antimicrobial properties against *C. albicans* and gram-negative bacteria while also maintaining its viscoelastic properties [88]. Sodalite zeolite is a subtype of zeolite that can easily infiltrate other materials due to its selectivity and strong catalytic activity and has been often applied to ceramic prostheses to improve their mechanical properties [89]. Incorporation of Ag-Zn zeolite with acrylic resin materials showed beneficial effects by improving their surface finish and resistance to surface damage by increasing hardness [90].

Application of zeolites in dentistry can also extend to antibacterial coatings on implants since coating titanium implants with AgZ was effective in inhibiting methicillin-resistant *S. aureus* growth [91].

Zeolites are known for their applicability in different composite materials, including dental materials. Zeolite fillers associated with phenol−formaldehyde resins and poly-(vinylidene fluoride) are often used [92]. An important fact is that zeolites have a positive impact on the mechanical properties of composites, which is combined with their ability to deliver the calcium ions (Ca^{2+}) to the tooth surface, showing the remineralizing potential of the hydroxyapatite structure of dentin and enamel [93]. FAU zeolites (X and Y type) have the highest remineralisation potential [94] and can be also used as scaffolds because they do not affect cell viability [80]. Since Gram-negative bacteria do not adhere to the type X zeolite, composite materials with zeolite X will not be sensitive to secondary caries [80].

Dental composites consist of inorganic fillers and organic resin matrix with some amounts of additives [95]. Due to the low adhesion of inorganic fillers to resins, it is often necessary to modify their surface before mixing these components. One of the main types of modifications that is used in dental fillings is silanization. This modification empowers bringing into contact the groups that are involved in cross-linking of the composite to a filler's surface [96]. Silane molecules that ensure the binding between the organic matrix and inorganic filler make the composite have a more rigid structure and improve the mechanical features of the composite, such as compressive and flexural strength, to obtain similar mechanical characteristics of the tooth structure [97]. Application of calcium-rich 13X zeolites as active fillers improved the remineralizing effect of examined composites by providing sustained release of calcium ions in conditions simulating a natural oral environment. Furthermore, the silanization of these composites significantly improved flexural strength and compressive strength values. The beneficial effects of silanization are the consequence of a stronger bond between fillers particles and resins from the organic matrix due to the introduction of methacrylic groups to the fillers' surface, which form covalent bonds between the resin and the filler [80].

Modification of the zeolite surface by a 4-(dimethylamino)benzenediazonium cation to acquire an active filler in methacrylic-resin-based composites was performed to verify some mechanical properties, as well as crosslinking ability [98]. All conducted tests proved that the addition of modified zeolite improved the compressive and flexural strength of the composite. The modification process, as well, has a crucial impact on these values. The results also show that it affected the crosslinking properties of the resin.

Soft and hard tissue engineering of the oral cavity represents the therapeutic approach with great potential. Zeolites, due to their favourable properties, have appeared promising as scaffolds in bone- and tooth-tissue engineering. The clinoptilolite-composite scaffolds enhanced mechanical, physical, and biological properties of polymer-based scaffolds, increased in vitro protein adsorption capacity of the scaffold and led to higher osteoinductivity and intracellular calcium deposition [99].

It is expected that the further research effort should focus on zeolite-based materials and concentrate on zeolite effects in response to microbial challenges in vivo, but also to

determine the proper concentration of zeolite that may be incorporated into various dental materials and establish zeolite's impact on their mechanical properties. The possibilities and beneficial effects of various surface modification methods should also be involved. Zeolite's favourable properties and wide range of the composition and hierarchical pore structure makes the zeolitic materials convenient for tissue engineering purposes.

3.2. Zeolites as Drug Carriers in Pharmacotherapy

The next logical step in the medical application of zeolites was their usage as drug carriers. That idea was surely provoked by two main groups of reasons. The first one is the reversibility of the adsorption of pharmaceuticals by zeolites, and which requires thorough studying of many important factors which influence this process. The focus, for sure, must be put on the ability to control and prolong drug release.

At the same time, scientists have made great efforts to exploit the possible synergistic bioactivities of zeolites with applied drugs. The resulting effects are often unpredictable and require detailed study, especially when cytotoxic effects on fibroblasts and tumour cells are performed in parallel.

The application of zeolites in biomedicine, as drug carriers, is based on their large specific surface area, high adsorption capacity [100], biocompactness, low toxicity [101], and microporous structure, which allows drug encapsulation within the zeolite and the ability to control and prolong drug release. Drug release is monitored in liquids with different pH values that correspond to the pH of the regions through which the drug-loaded zeolite carrier passes [102]. Drug encapsulation in drug delivery systems (DDS) eliminates side effects while maintaining treatment effectiveness [103], reduces drug concentration, and provides targeted delivery [104].

Zeolite nanocarriers enable drug delivery to a specific target and drug release without affecting surrounding healthy cells [105], and they display enhanced permeability, controlled drug distribution, and prolonged life in the blood system [106]. Synergistic effects of zeolites, such as gastroprotective influence, especially in the case of clinoptilolite DDS, could be ascribed to zeolites ability to attach to hydrogen ions and biologically active amines and nitrates [107].

The differences between the zeolite pore size and the targeted drug, and in hydrophilicity between zeolites and drugs, which are usually considered as limitation in their loading capacity, can be improved by surface modification of the zeolite [108], with the aim to adjust the surface of a zeolite depending on the delivered drug characteristics.

The efficiency of zeolites as DDS can be improved by the adsorption of cationic surfactants on the surface of zeolites through ion exchange and hydrophobic interactions, leading to the formation of monolayers or bilayers, depending on their concentration [109]. It looks that very important role here concerns the concentration of the cationic surfactant in relation to external cation exchange capacity—ECEC value, confirmed by the study performed on the natural zeolite with high clinoptilolite content with different levels of cetylpyridinium chloride (CPC) [110]. If the surfactant loading level was equal to ECEC, a monolayer of the organic phase is present at the zeolitic surface. When the amount of the CPC was above the ECEC value, a less extended bilayer is formed, while the sample with the highest surfactant content ordered bilayer or admicelles exist at the zeolitic surface. Similar results, obtained for the cationic surfactant-hexadecyltrimethylammonium bromide (HB) showed proportional increase of drug adsorption by increasing the amount of surfactant used for zeolite modification, leading to interactions between DS and HB at the zeolitic surface [111].

3.2.1. Zeolites as Carriers of Anti-inflammatory Drugs

Diclofenac and ibuprofen are the most commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) with low toxicity and thermal and chemical stability [100,112]. Due to the short half-life and the possibility of side effects [109,112], the subject of many studies is the encapsulation of drugs into systems that allow prolonged drug release, improving

therapeutic activity and reducing side effects [112]. The ability of natural zeolites as carriers of anti-inflammatory drugs can be improved by modifying their surface with different cationic surfactants [100,109].

For the sorption of diclofenac sodium (DS) as a model drug by zeolites modified with cationic surfactant cetylpyridinium chloride (CPC), the best fit to the equilibrium data over the entire tested concentration range provides the Langmuir equation [110]. The phase resulting from adsorbed CPC was the primary sorption phase for the DS, enabling the adsorption and partitioning processes at the same time.

Results of DS release in vitro of the hexadecyltrimethylammonium bromide modified zeolite composites showed that the prolonged DS release throughout 8 h was achieved, making them promise as a functional drug formulation excipient [111]. Because of the strong affinity of hexadecyltrimethylammonium bromide for DS, even corresponding physical mixtures showed prolonged DS release.

Serri et al. tested the DS delivery system using natural zeolites clinoptilolite (CLI), chabazite (CHA), and phillipsite (PHI) modified with cetylpyridinium chloride. The drug loading process took less than five minutes, with roughly equal amounts of DS in clinoptilolite and phillipsite and loading capacities greater than anion exchange capacity (AEC), while chabazite had the lowest loading capacity. The DS release process was sustained for five hours for all three zeolites, through particle diffusion for CLI and PHI, and a combination of film diffusion and particle diffusion for CHA, with a release of about 40% in the first hour. Despite the higher loading efficiency, CLI and PHI achieved a lower percentage of release compared to CHA (100%), indicating stronger interaction with the surfactant [112]. When DS was adsorbed in granulated clinoptilolite modified with cetylpyridinium chloride, the release process was extended up to 9 h, with approximately 22% of the drug released in the first 2 h in the solution at pH 1.2. The release of DS from the zeolite followed quasi-zero order kinetics for the first 8 h [108].

Considering the zeolite capability as a carrier for sustained drug release, a clinoptilolite was superficially modified with CLC and loaded with DS, to enhance its adsorption. The release profile was found to be reversible with the DS being gradually released in the presence of an ionic medium, such as simulated intestinal fluid (pH∼6.8). The results pointed out the ability of superficially modified nanozeolites to prolong DS release for 5 h. This release was predominantly governed by very fast ion exchange, while the drug diffusion through the boundary layer was the rate-controlling step of the process [100].

The modification of clinoptilolite and chabazite with cetyltrimethylammonium bromide results in higher DS adsorption capacities of 21.9% and 33.7%, respectively [113]. Diclofenac sodium was released rapidly from chabazite, with 97.7% of the drug released in the first hour and 100% released after only 3 h. In the case of clinoptilolite, an initial release of 57% was observed after one hour, followed by a prolonged release of 84% after six hours.

3.2.2. Zeolites as Carriers of Anticancer Drugs

Cancer is one of the most common diseases whose treatment includes surgery, chemotherapy, and radiotherapy [102,114]. The most frequently used anticancer drugs include doxorubicin, 5-fluorouracil, cisplatin, and cyclophosphamide, among others, which can be used alone or in combination with other drugs [114]. However, many of the drugs used in clinical practice cause undesired mutagenic and cytotoxic changes in normal cells, leading to numerous side effects. Zeolites have emerged as suitable carriers for anticancer drugs which can be encapsulated within them and hence may reduce the side effects of anticancer treatment on healthy cells, but also may provide a prolonged exposure of the drug to the cancer cell, resulting in an enhanced anticancer effect [101,106]. As the environment of tumour tissue is more acidic (5.5–6.0) compared to normal tissue (7.4), the focus of many studies is the development of DDS with pH-controlled drug release, which increases the effectiveness of therapy and reduces side effects [115]. This pH-dependent drug release can be especially important when analysing zeolite as a drug carrier for gastrointesti-

nal cancer treatment because pH values significantly vary through different parts of the digestive tract.

Polyphenol curcumin exhibits a wide range of biomedicine applications based on its anticancer, antioxidant, antifungal, and anti-inflammatory properties [105,116–119]. Encapsulation of curcumin within zeolites improves its solubility and stability in water and increases bioavailability [105]. Karimi et al. investigated the effects of surface modification with polyethylene glycol PEG on drug encapsulation and release efficiency using two synthetic zeolites, Y and ZSM-5 (PEG/Y and PEG/ZSM-5). The results of BET analysis revealed that the efficiency of curcumin encapsulation in zeolite Y (60.06%) was higher compared to ZSM-5 zeolite, while in the case of modified zeolite, the pores were partially coated with PEG, resulting in a lower encapsulation efficiency. Nitrogen adsorption-desorption analysis indicated that zeolite pore volume and surface area decreased after the encapsulation of the drug in the zeolite. In vitro release of curcumin in this study showed that more drug was released in solution with a lower pH value, with a higher amount of drug released from modified zeolites due to the increase in solubility of curcumin in the presence of PEG as well as the weakening of zeolites-curcumin interactions. A maximum drug release efficiency of 67% was achieved for PEG/Y over a period of 120 h [117]. Investigation of cyclodextrin-modified ZSM-5 zeolite for hydrothermal delivery of curcumin showed that higher efficiency was achieved in a more acidic medium (pH 5.5) compared to buffer solution at pH 7.4 [105].

Magnetite-zeolite nanocomposites (MZNC) were tested as carriers for the anticancer drug 5-fluorouracil (5-FU), with a loading capacity that increased with the concentration of 5-FU. Measuring the amount of drug released in buffer solutions showed that 90% of 5-fluorouracil was released from MZNC at pH 5.0 over 360 min. 5-FU encapsulated in MZNC showed concentration-dependent inhibitory effects on the proliferation of gastric carcinoma cells [114].

In another study, three types of micronized zeolites (ZSM-5, Zeolite A, and Faujasite NaX) were investigated and loaded with 5-FU as delivery systems to establish the drug release behaviour in a simulated gastric fluid environment, but also to reveal the cytotoxic effect of zeolites without/with 5-FU on colon cancer cells. The aluminosilicate structure was easier to be altered and decompose in a more acidic solution (pH 1.6) than in a mild acidic solution (pH 5) and the drug was released easier. Furthermore, all applied zeolites had a safe behaviour towards colon carcinoma cells, while the cytotoxic effect on these cell lines was confirmed in their 5-FU-loaded versions, showing the most potency for ZSM-5, followed by ZA and ZX [102]. Therefore, these zeolites can be used as good carriers for anticancer drugs which release in a controlled way.

When compared to Linde Type L (LTL) zeolite, which has monodimensional nanochannels, drug delivery systems based on NaY zeolite showed higher loading efficiency for 5-FU due to the three-dimensional structure. Both NaY and LTL were nontoxic to three cell lines analysed (breast cancer, colon cancer, and melanoma cell lines), even when applied in the highest concentrations. On the other hand, both host zeolites combined with 5-FU exerted toxic effects on all three cell lines and these effects were concentration- and cell type-dependent, with 5-FU/LTL showing a stronger inhibitory effect on cell viability compared to 5-FU/NaY. The toxic effect was more prominent on breast cancer and colon carcinoma cells. In vivo results also showed cell-specificity and led to a higher tumour reduction in breast cancer cells [120]. Encapsulation of 5-FU in LTL zeolite modified with positive amino groups leads to increased DDS internalisation by breast cancer cells and MCF-10 non-cancer epithelial mammary cells, with a more prominent effect in cancer cells compared to normal, which can be attributed to the higher metabolic and growth rates present in malignant cells compared to healthy ones. The results of this study showed that the surface nanoparticle functionalization with positive charges enhanced their internalisation and improved the zeolite efficacy as DDS, by improving their electrostatic interactions with the negatively charged cell membrane of the chosen cell lines. Furthermore, this effect was achieved with the application of a lower drug amount. Overall, these findings emphasise the importance

of zeolite structures as DDS and the significance of surface modification in enhancing their efficacy as anti-cancer agents.

Linde type A zeolites and their magnetite nanocomposites can be used for efficient loading and slow-release applications. While the zeolites and their nanocomposites were nontoxic to breast cancer cell lines, the loading of zeolites with doxorubicin (DOX) enhanced cell growth inhibition along with the increase in concentration compared to non-encapsulated DOX, with the highest efficiency for DOX-4A and magnetic DOX-4A [121].

Doxorubicin loaded on ZSM-5/chitosan core-shell (ZSM-5/CS) nanodisks was examined as pH-sensitive DDS for the treatment of osteosarcoma. Its mesoporous structure contributed to the high loading efficiency of 97.7% while chitosan core-shell layers on the surface improved drug delivery efficiency and controlled DOX release. After 7 days of incubation, the maximum cumulative release ratio of DOX was 71% in solutions at pH 5.5. The cytotoxic effect on osteoblastic human osteosarcoma-derived cell line (MG63) cells showed that ZSM-5/CS/DOX toxicity was higher at lower pH (5.5), causing inhibition of cell growth more than free DOX [122].

In research by Abasian et al., chitosan/PLA/NaX/Fe_3O_4/DOX nanofibers obtained by an electrospinning method were tested as a carrier for doxorubicin. The loading efficiency of the NaX-DOX system reached a maximum of 97%, while the loading efficiency of the DOX-loaded chitosan/PLA/NaX/Fe_3O_4 nanofiber was reduced to 92% due to DOX release during the electrospinning process. The prolonged release of doxorubicin in two steps consisted of release from NaX, followed by release from nanofibers. The presence of magnetic nanoparticles in the fibers contributed to slowing down the process of drug release, while the presence of a magnetic field showed the opposite effect. The main drug-release mechanism was Fickian diffusion of DOX into buffer solution, as described by Korsmeyer-Peppas kinetics. The maximum death of the human lung epidermoid carcinoma cell line after 7 days of treatment was 82% for DOX-loaded composite nanofibers in the presence of an external magnetic field [123].

Cisplatin (CIS) has been used for the treatment of numerous human cancers, with limited application due to its numerous and serious side effects, extensive resistance, and toxicity [124,125]. Furthermore, because of the drug's non-specific delivery, high doses are required for treatment, which are very toxic to healthy cells [123–126]. Investigating the delivery of CIS on synthesized zeolite Y nanoparticles revealed that this DDS was pH-, concentration- and time-dependent. In vitro drug release assessment showed that CIS release from ZC-NPs was faster in an acidic environment (pH 5.4) with a maximum drug release of 93.8%. The zeolites alone increased the viability of MG63 cells, while the CIS incorporated within zeolite decreased cell viability, but to a less extent compared to CIS alone [124].

Similar results were obtained in a study that investigated a polycaprolactone-zeolite (PCL-Z) nanocomposite Y-scaffold as a drug delivery system for CIS in the treatment of osteosarcoma. The release rate of a CIS from the zeolite carrier was pH-dependent, showing that 87.6% of the drug was released at pH 5.4 during 28 days of incubation. The presence of the zeolite in the PCL-Z scaffold increased MG63 cell viability, while the release of CIS from this nanocomposite showed a cytotoxic effect on these cells [125].

Two synthetic zeolites FAU and LTA in their sodium forms (NaY and NaA) were used for the encapsulation and controlled release of an anticancer agent, α-Cyano-4-hydroxycinnamic acid (CHC). The zeolite NaA adsorbed 67–76% of the CHC in solution, while the adsorption capacity of the NaY zeolite was 85%. Both applied zeolites exerted no toxic effect on cancer cells. On the other hand, a significant increase in the drug effect on the human colon cancer cells was observed when applying CHC in the zeolite system compared to CHC alone, and this effect was concentration-dependent and more prominent in zeolite combination with NaY compared to NaA. CHC-zeolite combination led to an inhibition of cell viability up to 146-fold (CHC/NaA) and even 585-fold (CHC/NaY) when compared to the non-encapsulated drug. These results could be attributed to the

more open structure of NaY that allows drug diffusion, making it a more efficient drug delivery system [103].

The current challenge in treating cancers is to replace conventional chemotherapy with an in-situ drug delivery system to enhance drug efficiency. Currently, zeolites as pH-sensitive delivery systems with their exceptional physiological stability are very promising contestants in cancer treatment procedures and the development of a new delivery system with multifunctional activity. In experimental models in vivo and in vitro, the use of zeolites as scaffolds for anticancer drugs, can provide effective and sustained drug release and may aggravate the inhibitory effect on various cancer cells compared to the anticancer drug applied alone. Zeolites are denoted as a promising system for targeted delivery of chemotherapeutic agents by promoting their therapeutic efficiency, reducing undesired side effects, and diminishing their toxicity on the healthy surrounding tissue.

Besides zeolites, metal-organic frameworks (MOFs) possess certain advantages compared to other DDSs such as definite crystalline structure and flexibility in creating them from scratch [127]. Zeolitic imidazolate frameworks (ZIFs) seem to be nowadays the most frequently studied MOFs as DDSs, especially because of their biocompatibility, and simple synthesis procedures [128]. ZIFs have especially harvested interest as pH-sensitive drug carriers with high drug loading capacities and biodegradability, which remains stable in neutral and basic media, but quickly collapses in the strong acidic aqueous solution [129]. ZIFs were particularly successfully confirmed as anticancer DDS [130].

Hao et al. reported the evaluation of the possible beneficial applications of zeolites and ZIFs as DDS for anticancer drugs, including doxorubicin (DOX), 5-fluorouracil (5-FU), curcumin, cisplatin, and others [131]. Following PRISMA guidelines, after screening the full texts published till August 2021, 53 articles remained and were included in the analysis. Clinoptilolite is currently the only zeolite registered in the EU as a medical device, and can be used in oral treatment, as drug carriers and delivery systems. Despite that fact, CLI was included as anticancer DDS in only three studies. The study claimed that 35 studies included ZIFs based supports for DDSs, of which in 31 considered particularly ZIF-8. FAU types of zeolites follow in the number of reported results as DDS carriers, i.e., 19 studies included NaX, NaY, or nano NaY zeolites.

What is the secret of such an interest in ZIF-8 as a carrier in anticancer DDS? Computer simulations and molecular modelling helped to clarify that the diffusion of 5-fluorouracil (5-FU) and caffeine (CAF), model drugs, between neighbouring pores in ZIF-8 is strictly restricted due to large energy barriers. The study of Proenza and Longo shows that the inner pores of ZIF-8 surface model were inaccessible to the 5-FU and CAF, but accessible to the solvents (methanol or water) [132]. The outstanding reliability of the ZIF-8 surface model relies in its appropriate explanation of the surface and by exposing adsorption sites such as undercoordinated zinc ions to interactions with large molecules, achieved by changing the periodic conditions from the atomistic level to a higher molecular level, such as a ZIF-8 nanocrystal. Perhaps future considerations of zeolites as drug carriers should take into account the comparative advantages demonstrated by ZIF, modifying them to be more suitable, reliable and effective.

Current research trends in the adsorption phenomenon using porous materials [133,134] along with innovative adsorbent characterization [135] reveal the utmost importance of the subject in both medical and environmental areas and offer novel and comprehensive ideas and solutions which may further assist drug/carrier design.

4. Conclusions

As a conclusion, here are listed some of the perspectives that may be addressed in future zeolite use as a removal tool of pharmaceuticals and/or other pollutants from the aquatic environment:

- main interactions in the pollutant-zeolite system assisted by spectroscopic methods, especially in post-adsorption studies;

- targeted interactions lead to a comprehensive understanding of the adsorption mechanism. Once we know the mechanism in detail, we can elucidate a number of target pollutants. If a designed zeolite adsorbent shows substantial adsorption capacity for one species, can it be applied for the other or their occurring mixtures?
- sometimes zeolites are designated as costly materials, and novel routes for synthesis, from waste materials, are beneficial;
- what to do with the spent adsorbent, does this impose a significant shortcoming of mainly physical removal techniques? Some innovative solutions are offered, mostly in the pyrolysis of the spent adsorbents and subsequent employment as electrode materials;
- environmentally relevant concentrations and/or flow techniques may be employed in the second step of the adsorption test aimed at pharmaceuticals removal. This requires HPLC/UPLC techniques, preferably with sensitive detection such as mass spectrometry. For volatile pharmaceuticals, GC/MS methods are also available.
- a focus needs to be shifted to real effluents, with a range of concurrent adsorbing ions, mostly metals, and organic matter;
- test whether the adsorption, as a removal technique, leaves the environment more toxic than the pollutant itself;
- apply a range of quantum mechanical calculations to guide future adsorbent design as this state-of-the-art calculation can point out exactly what to expect from your adsorption system and enable future predictions.

If we talk about zeolites as drug carriers in pharmacotherapy, the above listed considerations are more or less appropriate for this application of interaction between zeolites and pharmaceuticals. Future directions of investigations must cover several important issues:

- first, there is a need to study and ensure the lowest possible level of toxicity;
- expand the therapeutic range of DDS, improving more benefits and less side effects of pharmacological active compounds;
- raise the specificity of targeted sensitive sites of DDS action;
- work to achieve appropriate kinetics of release of pharmacologically active components. Parallel development of reliable, sensitive and specific analytical methods for following such a low concentration level of drugs in situ are more than desired.

This is certainly a topic within which researchers will be motivated to shed more light in the future, because of its important potential benefits, and as to a final conclusion—adsorption does matter.

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References

1. Ramesh, K.; Reddy, D.D. Zeolites and Their Potential Uses in Agriculture. *Adv. Agron.* **2011**, *113*, 219–241. [CrossRef]
2. Cataldo, E.; Salvi, L.; Paoli, F.; Fucile, M.; Masciandaro, G.; Manzi, D.; Massini, C.M.; Mattii, G.B. Application of Zeolites in Agriculture and Other Potential Uses: A Review. *Agronomy* **2021**, *11*, 1547. [CrossRef]
3. Jacobs, P.A.; Flanigen, E.M.; Jansen, J.C.; van Bekkum, H. *Introduction to Zeolite Science and Practice*; Elsevier: Amsterdam, The Netherlands, 2001.

4. Coombs, D.S.; Alberti, A.; Armbruster, T.; Artioli, G.; Colella, C.; Galli, E.; Grice, J.D.; Liebau, F.; Mandarino, J.A.; Minato, H.; et al. Recommended Nomenclature for Zeolite Minerals: Report of the Subcommittee on Zeolites of the International Mineralogical Association, Commission on New Minerals and Mineral Names. *Can. Mineral.* **1997**, *35*, 1571–1606.
5. Derbe, T.; Temesgen, S.; Bitew, M.A. Short Review on Synthesis, Characterization, and Applications of Zeolites. *Adv. Mater. Sci. Eng.* **2021**, *2021*, 6637898. [CrossRef]
6. Król, M. Natural vs. Synthetic Zeolites. *Crystals* **2020**, *10*, 622. [CrossRef]
7. Yazdi, M.K.; Zarrintaj, P.; Hosseiniamoli, H.; Mashhadzadeh, A.H.; Saeb, M.R.; Ramsey, J.D.; Ganjali, R.M.; Mozafari, M. Zeolites for theranostic applications. *J. Mater. Chem. B* **2020**, *8*, 5992–6012. [CrossRef] [PubMed]
8. Barrer, R.M. Porous crystals: A perspective. *Pure Appl. Chem.* **1986**, *58*, 1317. [CrossRef]
9. Kianfar, E. Zeolites: Properties, Applications, Modification and Selectivity. In *Zeolites: Advances in Research and Application*; Mahler, A., Ed.; Nova Science Publishers, Inc.: Hauppauge, NY, USA, 2020.
10. Bacakova, L.; Vandrovcova, M.; Kopova, I.; Jirka, I. Applications of zeolites in biotechnology and medicine—A review. *Biomater. Sci.* **2018**, *6*, 974. [CrossRef]
11. Möller, K.; Bein, T. Mesoporosity—A new dimension for zeolites. *Chem. Soc. Rev.* **2013**, *42*, 3689. [CrossRef]
12. Database of Zeolite Structures. Available online: http://www.iza-structure.org/databases/ (accessed on 5 July 2022).
13. Coombs, D.S.; Alberti, A.; Armbruster, T.; Artioli, G.; Colella, C.; Galli, E.; Grice, J.D.; Liebau, F.; Mandarino, J.A.; Minato, H.; et al. Recommended nomenclature for zeolite minerals: Report of the subcommittee on zeolites of the International Mineralogical Association, Commission on New Minerals and Mineral Names. *Mineral. Mag.* **1998**, *62*, 533–571. [CrossRef]
14. Rhodes, C.J. Properties and applications of zeolites. *Sci. Prog.* **2010**, *93*, 223–284. [CrossRef]
15. Li, Y.; Yu, J. Emerging applications of zeolites in catalysis, separation and host–guest assembly. *Nat. Rev. Mater.* **2021**, *6*, 1156–1174. [CrossRef]
16. Zhang, Q.; Yu, J.; Corma, A. Applications of Zeolites to C1 Chemistry: Recent Advances, Challenges, and Opportunities. *Adv. Mater.* **2020**, *32*, 2002927. [CrossRef] [PubMed]
17. Serati-Nouri, H.; Jafari, A.; Roshangar, L.; Dadashpour, M.; Pilehvar-Soltanahmadi, Y.; Zarghami, N. Biomedical applications of zeolite-based materials: A review. *Mater. Sci. Eng. C* **2020**, *116*, 111225. [CrossRef]
18. Li, Y.; Li, L.; Yu, J. Applications of Zeolites in Sustainable Chemistry. *Chem* **2017**, *3*, 928–949. [CrossRef]
19. Vasiljević, B.N.; Obradović, M.; Bajuk-Bogdanović, D.; Milojević-Rakić, M.; Jovanović, Z.; Gavrilov, N.; Holclajtner-Antunović, I. In Situ synthesis of potassium tungstophosphate supported on BEA zeolite and perspective application for pesticide removal. *J. Environ. Sci.* **2019**, *81*, 136–147. [CrossRef]
20. Janićijević, D.; Uskoković-Marković, S.; Ranković, D.; Milenković, M.; Jevremović, A.; Nedić Vasiljević, B.; Milojević-Rakić, M.; Bajuk-Bogdanović, D. Double active BEA zeolite/silver tungstophosphates—Antimicrobial effects and pesticide removal. *Sci. Total Environ.* **2020**, *735*, 139530. [CrossRef]
21. Jevremović, A.; Vasiljević, B.N.; Popa, A.; Uskoković-Marković, A.; Ignjatović, L.; Bajuk-Bogdanović, D.; Milojević-Rakić, M. The environmental impact of potassium tungstophosphate/ZSM-5 zeolite: Insight into catalysis and adsorption processes. *Microporous Mesoporous Mater.* **2021**, *315*, 110925. [CrossRef]
22. Jevremović, A.; Božinović, N.; Đorđević, D.; Marmakov, S.; Vasiljević, B.N.; Uskoković-Marković, S.; Bajuk-Bogdanovic, D.; Milojević-Rakić, M. Modulation of cytotoxicity by consecutive adsorption of tannic acid and pesticide on surfactant functionalized zeolites. *Environ. Sci. Process. Impacts* **2020**, *22*, 2199. [CrossRef]
23. Milojević-Rakić, M.; Bajuk-Bogdanović, D.; Vasiljević, B.N.; Rakić, A.; Škrivanj, S.; Ignjatović, L.; Dondur, V.; Mentus, S.; Ćirić-Marjanović, G. Polyaniline/FeZSM-5 composites—Synthesis, characterization and their high catalytic activity for the oxidative degradation of herbicide glyphosate. *Microporous Mesoporous Mater.* **2018**, *267*, 68–79. [CrossRef]
24. Lichtenberg, F.R. How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000–2013. *Int. Health* **2019**, *11*, 403. [CrossRef] [PubMed]
25. Rodriguez-Mozaz, S.; Vaz-Moreira, I.; Giustina, S.V.D.; Llorca, M.; Barceló, D.; Schubert, S.; Berendonk, T.; Michael-Kordatou, I.; Fatta-Kassinos, D.; Martinez, J.L.; et al. Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. *Environ. Int.* **2020**, *140*, 105733. [CrossRef] [PubMed]
26. Thalla, A.K.; Vannarath, A.S. Occurrence and environmental risks of nonsteroidal anti-inflammatory drugs in urban wastewater in the southwest monsoon region of India. *Environ. Monit. Assess.* **2020**, *192*, 193. [CrossRef] [PubMed]
27. European Commission. Communication from the Commission to the European Parliament, the Council, and the European Economic and Social Committee: European Union Strategic Approach to Pharmaceuticals in the Environment. *Communication* **2019**, *128*, 1–12. Available online: https://www.eumonitor.eu/9353000/1/j9vvik7m1c3gyxp/vkwpg8sb9wx8 (accessed on 5 July 2022).
28. Merlin, C. Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment? *Front. Microbiol.* **2020**, *11*, 33. [CrossRef]
29. Kidd, K.A.; Paterson, M.J.; Rennie, M.D.; Podemski, C.L.; Findlay, D.L.; Blanchfield, P.J.; Liber, K. Direct and indirect responses of a freshwater food web to a potent synthetic oestrogen. *Phil. Trans. R. Soc. B* **2014**, *369*, 20130578. [CrossRef]
30. Heberer, T. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: A review of recent research data. *Toxicol. Lett.* **2002**, *131*, 5–17. [CrossRef]

31. Khetan, S.K.; Collins, T.J. Human pharmaceuticals in the aquatic environment: A challenge to green chemistry. *Chem. Rev.* **2007**, *107*, 2319–2364. [CrossRef]
32. Halling-Sørensen, B.; Nielsen, S.N.; Lanzky, P.; Ingerslev, F.; Lützhøft, H.H.; Jørgensen, S. Occurrence, fate and effects of pharmaceutical substances in the environment—A review. *Chemosphere* **1998**, *36*, 357–393. [CrossRef]
33. Jelic, A.; Gros, M.; Ginebreda, A.; Cespedes-Sánchez, R.; Ventura, F.; Petrovic, M.; Barceló, D. Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. *Water Res.* **2011**, *45*, 1165–1176. [CrossRef]
34. Safe Disposal of Medicines. Available online: https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-disposal-medicines (accessed on 5 July 2022).
35. Nikolaou, A.; Meric, S.; Fatta, D. Occurrence patterns of pharmaceuticals in water and wastewater environments. *Anal. Bioanal. Chem.* **2007**, *387*, 1225. [CrossRef] [PubMed]
36. der Beek, T.A.; Weber, F.-A.; Bergmann, A.; Hickmann, S.; Ebert, I.; Hein, A.; Küster, A. Pharmaceuticals in the environment-Global occurrences and perspectives. *Environ. Toxicol. Chem.* **2016**, *35*, 823. [CrossRef] [PubMed]
37. Heberer, T. Tracking persistent pharmaceutical residues from municipal sewage to drinking water. *J. Hydrol.* **2002**, *266*, 175. [CrossRef]
38. Zupanc, M.; Kosjek, T.; Petkovšek, M.; Dular, M.; Kompare, B.; Širok, B.; Blažeka, Ž.; Heath, E. Removal of pharmaceuticals from wastewater by biological processes, hydrodynamic cavitation and UV treatment. *Ultrason. Sonochem.* **2013**, *20*, 1104. [CrossRef] [PubMed]
39. Li, W.C. Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. *Environ. Pollut.* **2014**, *187*, 193. [CrossRef] [PubMed]
40. Jaseem, M.; Kumar, P.; John, R.M. An overview of waste management in pharmaceutical industry. *Pharma Innov.* **2017**, *6 Pt C*, 158–161.
41. Rojas, M.R.; Leung, C.; Bonk, F.; Zhu, Y.; Edwards, L.; Arnold, R.G.; Sáez, A.E.; Klečka, G. Assessment of the effectiveness of secondary wastewater treatment technologies to remove trace chemicals of emerging concern. *Crit. Rev. Environ. Sci. Technol.* **2013**, *43*, 1281. [CrossRef]
42. Baresel, C.; Cousins, A.P.; Hörsing, M.; Ek, M.; Ejhed, H.; Allard, A.-S.; Magnér, J.; Westling, K.; Wahlberg, C.; Fortkamp, U. Pharmaceutical Residues and Other Emerging Substances in the Effluent of Sewage Treatment Plants. IVL Svenska Miljöinstitutet. 2015. (B-Rapport). Available online: http://urn.kb.se/resolve?urn=urn:nbn:se:ivl:diva-2969 (accessed on 5 July 2022).
43. Fukahori, S.; Fujiwara, T.; Ito, R.; Funamizu, N. pH-Dependent adsorption of sulfa drugs on high silica zeolite: Modeling and kinetic study. *Desalination* **2011**, *275*, 237–242. [CrossRef]
44. Blasioli, S.; Martucci, A.; Paul, G.; Gigli, L.; Cossi, M.; Johnston, C.T.; Marchese, L.; Braschi, I. Removal of sulfamethoxazole sulfonamide antibiotic from water by high silica zeolites: A study of the involved host–guest interactions by a combined structural, spectroscopic, and computational approach. *J. Colloid Interface Sci.* **2014**, *419*, 148–159. [CrossRef]
45. Martucci, A.; Pasti, L.; Marchetti, N.; Cavazzini, A.; Dond, F.; Alberti, A. Adsorption of pharmaceuticals from aqueous solutions on synthetic zeolites. *Microporous Mesoporous Mater.* **2012**, *148*, 174–183. [CrossRef]
46. Genç, N.; Dogan, E.C. Adsorption kinetics of the antibiotic ciprofloxacin on bentonite, activated carbon, zeolite, and pumice. *Desalin. Water Treat.* **2013**, *53*, 785–793. [CrossRef]
47. de Sousa, D.N.R.; Insa, S.; Mozeto, A.A.; Petrovic, M.; Chaves, T.F.; Fadini, P.S. Equilibrium and kinetic studies of the adsorption of antibiotics from aqueous solutions onto powdered zeolites. *Chemosphere* **2018**, *205*, 137–146. [CrossRef]
48. Al-Jubouri, S.M.; Al-Jendeel, H.A.; Rashid, S.A.; Al-Batty, S. Antibiotics adsorption from contaminated water by composites of ZSM-5 zeolite nanocrystals coated carbon. *J. Water Process Eng.* **2022**, *47*, 102745. [CrossRef]
49. Lee, B.Y. Removal of Antibiotics from Contaminated Waters Using Natural Zeolite. Master's Thesis, CUNY City College, New York, NY, USA, 2012.
50. Belviso, C.; Guerra, G.; Abdolrahimi, M.; Peddis, D.; Maraschi, F.; Cavalcante, F.; Ferretti, M.; Martucci, A.; Sturini, M. Efficiency in Ofloxacin Antibiotic Water Remediation by Magnetic Zeolites Formed Combining Pure Sources and Wastes. *Processes* **2021**, *9*, 2137. [CrossRef]
51. Tumrani, S.H.; Soomro, R.A.; Zhang, X.; Bhutto, D.A.; Buxa, N.; Ji, X. Coal fly ash driven zeolites for the adsorptive removal of the ceftazidime drug. *RSC Adv.* **2021**, *11*, 26110. [CrossRef]
52. Grela, A.; Kuc, J.; Bajda, T. A Review on the Application of Zeolites and Mesoporous Silica Materials in the Removal of Non-Steroidal Anti-Inflammatory Drugs and Antibiotics from Water. *Materials* **2021**, *14*, 4994. [CrossRef]
53. Ajo, P.; Preis, S.; Vornamo, T.; Mänttäri, M.; Kallioinen, M.; Louhi-Kultanen, M. Hospital wastewater treatment with pilot-scale pulsed corona discharge for removal of pharmaceutical residues. *J. Environ. Chem. Eng.* **2018**, *6*, 1569–1577. [CrossRef]
54. Shearer, L.; Pap, S.; Gibb, S.W. Removal of pharmaceuticals from wastewater: A review of adsorptive approaches, modelling and mechanisms for metformin and macrolides. *J. Environ. Chem. Eng.* **2022**, *10*, 108106. [CrossRef]
55. Zhao, J.; Yang, X.; Liang, G.; Wang, Z.; Li, S.; Wang, Z.; Xie, X. Effective removal of two fluoroquinolone antibiotics by PEG-4000 stabilized nanoscale zero-valent iron supported onto zeolite (PZ-NZVI). *Sci. Total Environ.* **2019**, *710*, 136289. [CrossRef]
56. Ayoub, H.; Roques-Carmes, T.; Potier, O.; Koubaissy, B.; Pontvianne, S.; Lenouvel, A.; Hamieh, T. Iron-impregnated zeolite catalyst for efficient removal of micropollutants at very low concentration from Meurthe river. *Environ. Sci. Pollut. Res.* **2018**, *25*, 34950–34967. [CrossRef]

57. Al-rimawi, F.; Daana, M.; Khamis, M.; Karaman, R.; Khoury, H.; Qurie, M. Removal of Selected Pharmaceuticals from Aqueous Solutions Using Natural Jordanian Zeolite. *Arab. J. Sci. Eng.* **2019**, *44*, 209–215. [CrossRef]
58. Smiljanić, D.; de Gennaro, B.; Daković, A.; Galzerano, B.; Germinario, C.; Izzo, F.; Rottinghaus, G.E.; Langella, A. Removal of non-steroidal anti-inflammatory drugs from water by zeolite-rich composites: The interference of inorganic anions on the ibuprofen and naproxen adsorption. *J. Environ. Manag.* **2021**, *286*, 112168. [CrossRef] [PubMed]
59. Pasti, L.; Sarti, E.; Cavazzini, A.; Marchetti, N.; Dondi, F.; Martucci, A. Factors affecting drug adsorption on beta zeolites. *J. Sep. Sci.* **2013**, *36*, 1604–1611. [CrossRef] [PubMed]
60. Farias, T.; Ruiz-Salvador, A.R.; Rivera, A. Interaction studies between drugs and a purified natural clinoptilolite. *Microporous Mesoporous Mater.* **2003**, *61*, 117–125. [CrossRef]
61. Lam, A.; Rivera, A. Theoretical study of the interaction of surfactants and drugs with natural zeolite. *Microporous Mesoporous Mater.* **2006**, *91*, 181–186. [CrossRef]
62. Wu, C.-H.; Xiong, Z.-H.; Lia, C.; Zhang, J. Zeolitic imidazolate metal organic framework ZIF-8 with ultra-high adsorption capacity bound tetracycline in aqueous solution. *RSC Adv.* **2015**, *5*, 82127–82137. [CrossRef]
63. Wanyonyi, F.S.; Pembere, A.; Mutua, G.K.; Orata, F.; Louis, H. Computational screening of zeolites for the adsorption of selected pharmaceutical pollutants. *SN Appl. Sci.* **2020**, *2*, 1901. [CrossRef]
64. Makkar, P.; Ghosh, N. A review on the use of DFT for the prediction of the properties of nanomaterials. *RSC Adv.* **2021**, *45*, 27897–27924. [CrossRef]
65. Braschi, I.; Gatti, G.; Paul, G.; Gessa, C.; Cossi, M.; Marchese, L. Sulfonamide Antibiotics Embedded in High Silica Zeolite Y: A Combined Experimental and Theoretical Study of Host−Guest and Guest−Guest Interactions. *Langmuir* **2010**, *26*, 9524–9532. [CrossRef]
66. Hessou, E.P.; Ponce-Vargas, M.; Mensah, J.-B.; Tielens, F.; Santos, J.C.; Badawi, M. Dibenzyl Disulfide Adsorption on Cationic Exchanged Faujasites: A DFT Study. *Nanomaterials* **2019**, *9*, 715. [CrossRef]
67. Fatouros, D.; Douroumis, D.; Nikolakis, V.; Ntais, S.; Moschovi, A.; Trivedi, V.; Khima, B.; Roldo, M.; Nazar, H.; Cox, P. In Vitro and In Silico investigations of drug delivery via zeolite BEA. *J. Mater. Chem.* **2011**, *21*, 7789–7794. [CrossRef]
68. Spanakis, M.; Bouropoulos, N.; Theodoropoulos, D.; Sygellou, I.; Ewart, S.; Moschovi, A.; Siokou, A.; Niopas, I.; Kachrimanis, K.; Nikolakis, V.; et al. Controlled release of 5-fluorouracil from microporous zeolites. *Nanomed. Nanotechnol. Biol. Med.* **2014**, *10*, 197–205. [CrossRef] [PubMed]
69. Fischer, M. Simulation-based evaluation of zeolite adsorbents for the removal of emerging contaminants. *Mater. Adv.* **2020**, *1*, 86–98. [CrossRef]
70. Purnomo; Setyarini, P.H.; Sulistyaningsih, D. Zeolite-based biomaterials for biomedical application: A review. *AIP Conf. Proc.* **2018**, *1977*, 030013. [CrossRef]
71. Mastinu, A.; Kumar, A.; Maccarinelli, G.; Bonini, S.A.; Premoli, M.; Aria, F.; Gianoncelli, A.; Memo, M. Zeolite Clinoptilolite: Therapeutic Virtues of an Ancient Mineral. *Molecules* **2019**, *24*, 1517. [CrossRef] [PubMed]
72. Pavelić, S.K.; Medica, J.S.; Gumbarević, D.; Filošević, A.; Pržulj, N.; Pavelić, K. Critical Review on Zeolite Clinoptilolite Safety and Medical Applications In Vivo. *Front. Pharmacol.* **2018**, *9*, 1350. [CrossRef] [PubMed]
73. Rininingsih, E.M.U. Correlation between Antioxidant Activity of Synthetic Zeolites Pillared Titanium Dioxide and Iron (III) Oxide with Adsorption DPPH. Master's Thesis, IPB University, Bogor, Indonesia, 2014. Available online: http://repository.ipb.ac.id/handle/123456789/68404 (accessed on 5 July 2022).
74. Janićijević, D.; Jevremović, A.; Ležaić, A.J.; Vasiljević, B.N.; Uskoković-Marković, S.; Bajuk-Bogdanović, D.; Milojević-Rakić, M. Comparative assessment of pesticide adsorption capacity and antioxidant activity of Silver Dodecatungstophosphate/HBEA Zeolite composites. *J. Environ. Chem. Eng.* **2021**, *9*, 106341. [CrossRef]
75. Milojević-Rakić, M.; Popadić, D.; Ležaić, A.J.; Jevremović, A.; Vasiljević, B.N.; Uskoković-Marković, S.; Bajuk-Bogdanović, D. MFI, BEA and FAU zeolite scavenging role in neonicotinoids and radical species elimination. *Environ. Sci. Process. Impacts* **2022**, *24*, 265–276. [CrossRef]
76. Tomašević-Čanović, M.; Daković, A.; Rottinghaus, G.; Đuričić, M. Surfactant modified zeolites—New efficient adsorbents for mycotoxins. *Microporous Mesoporous Mater.* **2003**, *61*, 173–180. [CrossRef]
77. Ipek, H.; Avci, M.; Aydilek, N.; Yerturk, M. The effect of zeolite on oxidant/antioxidant status in healthy dairy cows. *Acta Vet. Brno.* **2012**, *81*, 43–47. [CrossRef]
78. Hao, J.; Lang, S.; Mante, F.; Pavelić, K.; Ozer, F. Antimicrobial and Mechanical Effects of Zeolite Use in Dental Materials: A Systematic Review. *Acta Stomatol. Croat.* **2021**, *55*, 76–89. [CrossRef] [PubMed]
79. Thom, D.C.; Davies, J.E.; Santerre, J.P.; Friedman, S. The hemolytic and cytotoxic properties of a zeolite-containing root filling material In Vitro. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2003**, *95*, 101–108. [CrossRef] [PubMed]
80. Buchwald, Z. Calcium-Rich 13X Zeolite as a Filler with Remineralizing Potential for Dental Composites. *ACS Biomater. Sci. Eng.* **2020**, *6*, 3843–3854. [CrossRef] [PubMed]
81. Lee, J.H.; Lee, S.B.; Kim, K.N.; Kim, K.M.; Lee, Y.K. Antibacterial Effect of Silver-Zeolites in Glass-Ionomer Cements. *Key Eng. Mater.* **2007**, *330–332*, 831–834. [CrossRef]
82. Mabrouk, M.; Selim, M.; Beherei, H.H.; El-Gohary, M.I. Incorporation effect of silver and zinc-zeolites into commercial glass ionomer cement. *Int. Ceram. Rev.* **2013**, *62*, 50–54.

83. Hyun-Jin, K.; Sik, S.J.; Kyo-Han, K.; Tae-Yub, K. Antimicrobial Activity of Glass Ionomer Cement Incorporated with Chlorhexidine-Loaded Zeolite Nanoparticles. *J. Nanosci. Nanotechnol.* **2016**, *16*, 1450–1453. [CrossRef]
84. Patel, V.; Santerre, J.P.; Friedman, S. Suppression of Bacterial Adherence by Experimental Root Canal Sealers. *J. Endod.* **2000**, *26*, 20–24. [CrossRef]
85. Ghatole, K.; Gowdra, R.; Azher, S.S.; Sabharwal, S. Enhancing the antibacterial activity of the gold standard intracanal medicament with incorporation of silver zeolite: An In Vitro study. *J. Int. Soc. Prev. Community Dent.* **2016**, *6*, 75–79. [CrossRef]
86. Odabaş, M.E.; Çinar, Ç.; Akça, G.; Araz, I.; Ulusu, T.; Yücel, H. Short-term antimicrobial properties of mineral trioxide aggregate with incorporated silver-zeolite. *Dent. Traumatol.* **2011**, *27*, 189–194. [CrossRef]
87. Yokogawa, Y.; Sakanishi, M.; Morikawa, N.; Nakamura, A.; Kishida, I.; Varma, H.K. VCS Adsorptive Properties in Ion Exchanged Zeolite Materials in Gaseous and Aqueous Medium. *Procedia Eng.* **2012**, *36*, 168–172. [CrossRef]
88. Saravanan, M.; Kumar, V.; Padmanabhan, T.; Banu, F. Viscoelastic properties and antimicrobial effects of soft liners with silver zeolite in complete dental prosthesis wearers: An in vivo study. *Int. J. Prosthodont.* **2015**, *28*, 265–269. [CrossRef] [PubMed]
89. Naji, G.A.; Omar, R.; Yahya, R. Influence of sodalite zeolite infiltration on the coefficient of thermal expansion and bond strength of all-ceramic dental prostheses. *J. Mech. Behav. Biomed. Mater.* **2017**, *67*, 135–143. [CrossRef]
90. Aljafery, A.M.; Al-Jubouri, O.M.; Wally, Z.J.; Almusawi, R.M.; Abdulrudha, N.H.; Haider, J. The Effects of Incorporating Ag-Zn Zeolite on the Surface Roughness and Hardness of Heat and Cold Cure Acrylic Resins. *J. Compos. Sci.* **2022**, *6*, 85. [CrossRef]
91. Wang, J.; Wang, Z.; Guo, S.; Zhang, J.; Song, Y.; Dong, X.; Wang, X.; Yu, J. Antibacterial and anti-adhesive zeolite coatings on titanium alloy surface. *Microporous Mesoporous Mater.* **2011**, *146*, 216–222. [CrossRef]
92. Lopes, A.C.; Ribeiro, C.; Sencadas, V.; Botelho, G.; Lanceros-Mendez, S. Effect of filler content on morphology and physical–chemical characteristics of poly(vinylidene fluoride)/NaY zeolite-filled membranes. *J. Mater. Sci.* **2014**, *49*, 3361–3370. [CrossRef]
93. Dorozhkin, S.V. Calcium orthophosphates in dentistry. *J. Mater. Sci. Mater. Med.* **2013**, *24*, 1335–1363. [CrossRef] [PubMed]
94. Sandomierski, M.; Buchwald, Z.; Koczorowski, W.; Voelkel, A. Calcium forms of zeolites A and X as fillers in dental restorative materials with remineralizing potential. *Microporous Mesoporous Mater.* **2020**, *294*, 109899. [CrossRef]
95. Pratap, B.; Gupta, R.K.; Bhardwaj, B.; Nag, M. Resin based restorative dental materials: Characteristics and future perspectives. *Jpn. Dent. Sci. Rev.* **2019**, *55*, 126–138. [CrossRef] [PubMed]
96. Matinlinna, J.P.; Lung, C.Y.K.; Tsoi, J.K.H. Silane adhesion mechanism in dental applications and surface treatments: A review. *Dent. Mater.* **2018**, *34*, 13–28. [CrossRef]
97. Aydınoğlu, A.; Yoruç, A.B.H. Effects of silane-modified fillers on properties of dental composite resin. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *79*, 382–389. [CrossRef] [PubMed]
98. Sandomierski, M.; Okulus, Z.; Voelkel, A. Active diazonium-modified zeolite fillers for methacrylate-based composites. *Compos. Interfaces* **2019**, *26*, 643–657. [CrossRef]
99. de Gennaro, B.; Catalanotti, L.; Cappelletti, P.; Langella, A.; Mercurio, M.; Serri, C.; Biondi, M.; Mayol, L. Surface modified natural zeolite as a carrier for sustained diclofenac release: A preliminary feasibility study. *Colloids Surf. B Biointerfaces* **2015**, *130*, 101–109. [CrossRef]
100. Pazarçeviren, E.; Erdemli, Ö.; Keskin, D.; Tezcaner, A. Clinoptilolite/PCL–PEG–PCL composite scaffolds for bone tissue engineering applications. *J. Biomater. Appl.* **2017**, *31*, 1148–1168. [CrossRef]
101. Al-Thawabeia, R.A.; Hodali, H.A. Use of Zeolite ZSM-5 for Loading and Release of 5-Fluorouracil. *J. Chem.* **2015**, *2015*, 403597. [CrossRef]
102. Abd-Elsatar, A.G.; Farag, M.M.; Youssef, H.F.; Salih, S.A.; Mounier, M.M.; El-Meliegy, E. Different zeolite systems for colon cancer therapy: Monitoring of ion release, cytotoxicity and drug release behavior. *Prog. Biomater.* **2019**, *8*, 101–113. [CrossRef]
103. Amorim, R.; Vilaça, N.; Martinho, O.; Reis, R.M.; Sardo, M.; Rocha, J.; Fonseca, A.M.; Baltazar, F.; Neves, I.C. Zeolite Structures Loading with an Anticancer Compound as Drug Delivery Systems. *J. Phys. Chem. C* **2012**, *116*, 25642–25650. [CrossRef]
104. Paradee, N.; Sirivat, A. Encapsulation of Folic Acid in Zeolite Y for Controlled Release via Electric Field. *Mol. Pharm.* **2015**, *13*, 155–162. [CrossRef]
105. Amani, S.; Garmarudi, A.B.; Rahmani, N.; Khanmohammadi, M. The β-cyclodextrin-modified nanosized ZSM-5 zeolite as a carrier for curcumin. *RSC Adv.* **2019**, *9*, 32348–32356. [CrossRef] [PubMed]
106. Wen, X.; Yang, F.; Ke, Q.-F.; Xie, X.-T.; Guo, Y.-P. Hollow mesoporous ZSM-5 zeolite/chitosan ellipsoids loaded with doxorubicin as pH-responsive drug delivery systems against osteosarcoma. *J. Mater. Chem. B* **2017**, *5*, 7866–7875. [CrossRef]
107. Potgieter, W.; Samuels, C.S.; Snyman, J.R. Potentiated clinoptilolite: Artificially enhanced aluminosilicate reduces symptoms associated with endoscopically negative gastroesophageal reflux disease and nonsteroidal anti–inflammatory drug induced gastritis. *Clin. Exp. Gastroenterol.* **2014**, *7*, 215–220.
108. Serri, C.; de Gennaro, B.; Quagliariello, V.; Iaffaioli, R.V.; de Rosa, G.; Catalanotti, L.; Biondi, M.; Mayol, L. Surface modified zeolite-based granulates for the sustained release of diclofenac sodium. *Eur. J. Pharm. Sci.* **2017**, *99*, 202–208. [CrossRef]
109. Pasquino, R.; Di Domenico, M.; Izzo, F.; Gaudino, D.; Vanzanella, V.; Grizzuti, N.; de Gennaro, B. Rheology-sensitive response of zeolite-supported anti-inflammatory drug systems. *Colloids Surf. B Biointerfaces* **2019**, *146*, 938–944. [CrossRef]
110. Krajisnik, D.; Dakovic, A.; Milojevic, M.; Malenovic, A.; Kragovic, M.; Bogdanovic, D.B.; Dondur, V.; Milic, J. Properties of diclofenac sodium sorption onto natural zeolite modified with cetylpyridinium chloride. *Colloids Surf. B Biointerfaces* **2011**, *83*, 165–172. [CrossRef] [PubMed]

111. Krajisnik, D.; Dakovic, A.; Malenovic, A.; Milojevic-Rakic, M.; Dondur, V.; Radulovic, Z.; Milic, J. Investigation of adsorption and release of diclofenac sodium by modified zeolites composites. *Appl. Clay Sci.* **2013**, *83–84*, 322–326. [CrossRef]
112. Serri, C.; de Gennaro, B.; Catalanotti, L.; Cappelletti, P.; Langella, A.; Mercurio, M.; Mayol, L.; Biondi, M. Surfactant-modified phillipsite and chabazite as novel excipients for pharmaceutical applications? *Microporous Mesoporous Mater.* **2016**, *224*, 143–148. [CrossRef]
113. Vargas, A.M.; Cipagauta-Ardila, C.C.; Molina-Velasco, D.R.; Ríos-Reyes, C.A. Surfactant-modified natural zeolites as carriers for diclofenac sodium release: A preliminary feasibility study for pharmaceutical applications. *Mater. Chem. Phys.* **2020**, *256*, 123644. [CrossRef]
114. Sağir, T.; Huysal, M.; Durmus, Z.; Kurt, B.Z.; Senel, M.; Isık, S. Preparation and in vitro evaluation of 5-fluorouracil loaded magnetite–zeolite nanocomposite (5-FU-MZNC) for cancer drug delivery applications. *Biomed. Pharmacother.* **2016**, *77*, 182–190. [CrossRef]
115. Sun, C.-Y.; Qin, C.; Wang, X.-L.; Yang, G.-S.; Shao, K.-Z.; Lan, Y.-Q.; Su, Z.-M.; Huang, P.; Wang, C.-G.; Wang, E.-B. Zeolitic imidazolate framework-8 as efficient pH-sensitive drug delivery vehicle. *Dalton Trans.* **2012**, *41*, 6906. [CrossRef] [PubMed]
116. Tiwari, A.; Singh, A.; Garg, N.; Randhawa, J.K. Curcumin encapsulated zeolitic imidazolate frameworks as stimuli responsive drug delivery system and their interaction with biomimetic environment. *Sci. Rep.* **2017**, *7*, 12598. [CrossRef]
117. Karimi, M.; Habibizadeh, M.; Rostamizadeh, K.; Khatamian, M.; Divband, B. Preparation and characterization of nanocomposites based on different zeolite frameworks as carriers for anticancer drug: Zeolite Y versus ZSM-5. *Polym. Bull.* **2018**, *76*, 2233–2252. [CrossRef]
118. Chen, J.; He, Z.-M.; Wang, F.-L.; Zhang, Z.-S.; Liu, X.; Zhai, D.-D.; Chen, W.-D. Curcumin and its promise as an anticancer drug: An analysis of its anticancer and antifungal effects in cancer and associated complications from invasive fungal infections. *Eur. J. Pharmacol.* **2016**, *772*, 33–42. [CrossRef] [PubMed]
119. Abadeh, Z.A.; Saviano, G.; Ballirano, P.; Santonicola, M.G. Curcumin-loaded zeolite as anticancer drug carrier: Effect of curcumin adsorption on zeolite structure. *Pure Appl. Chem.* **2019**, *92*, 461–471. [CrossRef]
120. Vilaça, N.; Bertão, A.R.; Prasetyanto, E.A.; Granja, S.; Costa, M.; Fernandes, R.; Figueiredo, F.; Fonseca, A.M.; De Cola, L.; Baltazar, F.; et al. Surface functionalization of zeolite-based drug delivery systems enhances their antitumoral activity In Vivo. *Mater. Sci. Eng. C* **2020**, *120*, 111721. [CrossRef]
121. Divband, B.; Rashidi, M.R.; Khatamian, M.; Eslamian, G.R.K.; Gharehaghaji, N.; Tabriz, F.D. Linde Type A and nano magnetite/NaA zeolites: Cytotoxicity and doxorubicin loading efficiency. *Open Chem.* **2018**, *16*, 21–28. [CrossRef]
122. Yang, F.; Wen, X.; Ke, Q.-F.; Xie, X.-T.; Guo, Y.-P. pH-responsive mesoporous ZSM-5 zeolites/chitosan core-shell nanodisks loaded with doxorubicin against osteosarcoma. *Mater. Sci. Eng. C* **2018**, *85*, 142–153. [CrossRef]
123. Abasian, P.; Radmansouri, M.; Habibi, M.; Ghasemi, M.V.; Mohammadi, A.; Irani, M.; Jazi, F.S. Incorporation of magnetic NaX zeolite/DOX into the PLA/chitosan nanofibers for sustained release of doxorubicin against carcinoma cells death in vitro. *Int. J. Biol. Macromol.* **2018**, *121*, 398–406. [CrossRef] [PubMed]
124. Zakeri, N.; Rezaie, H.R.; Javadpour, J.; Kharaziha, M. Effect of pH on cisplatin encapsulated zeolite nanoparticles: Release mechanism and cytotoxicity. *Mater. Chem. Phys.* **2021**, *273*, 124964. [CrossRef]
125. Zakeri, N.; Rezaie, H.R.; Javadpour, J.; Kharaziha, M. Cisplatin loaded polycaprolactone—Zeolite nanocomposite scaffolds for bone cancer treatment. *J. Sci. Adv. Mater. Devices* **2021**, *7*, 100377. [CrossRef]
126. Dasari, S.; Tchounwou, P.B. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur. J. Pharmacol.* **2014**, *740*, 364–378. [CrossRef]
127. Lázaro, I.A.; Lázaro, S.A.; Forgan, R.S. Enhancing anticancer cytotoxicity through bimodal drug delivery from ultrasmall Zr MOF nanoparticles. *Chem. Commun.* **2018**, *54*, 2792–2795. [CrossRef]
128. Yan, J.; Liu, C.; Wu, Q.; Zhou, J.; Xu, X.; Zhang, L.; Wang, D.; Yang, F.; Zhang, H. Mineralization of pH-Sensitive Doxorubicin Prodrug in ZIF-8 to Enable Targeted Delivery to Solid Tumors. *Anal. Chem.* **2020**, *92*, 11453–11461. [CrossRef]
129. Zheng, C.C.; Wang, Y.; Phua, S.Z.F.; Lim, W.O.; Zhao, Y.L. ZnO-DOX@ZIF-8 core-shell nanoparticles for pH-responsive drug delivery. *ACS Biomater. Sci. Eng.* **2017**, *3*, 2223–2229. [CrossRef]
130. Li, X.; Hou, S.; Chen, J.; He, C.E.; Gao, Y.E.; Lu, Y.; Jia, D.; Ma, X.; Xue, P.; Kang, Y.; et al. Engineering silk sericin decorated zeolitic imidazolate framework-8 nanoplatform to enhance chemotherapy. *Colloids Surf. B Biointerfaces* **2021**, *200*, 111594. [CrossRef]
131. Hao, J.; Milašin, I.S.; Eken, Z.B.; Mravak-Stipetic, M.; Pavelic, K.; Ozer, F. Effects of Zeolite as a Drug Delivery System on Cancer Therapy: A Systematic Review. *Molecules* **2021**, *26*, 6196. [CrossRef]
132. Proenza, Y.G.; Longo, R.L. Simulation of the Adsorption and Release of Large Drugs by ZIF-8. *J. Chem. Inf. Model.* **2020**, *60*, 644–652. [CrossRef]
133. Jevremović, A.; Stanojković, A.; Arsenijević, D.; Arsenijević, A.; Arzumanyan, G.; Mamatkulov, K.; Petrović, J.; Vasiljević, B.N.; Bajuk-Bogdanović, D.; Milojević-Rakić, M. Mitigating toxicity of acetamiprid removal techniques—Fe modified zeolites in focus. *J. Hazard. Mater.* **2022**, *436*, 129226. [CrossRef]
134. Popadić, D.; Gavrilov, N.; Ignjatović, L.; Krajišnik, D.; Mentus, S.; Milojević-Rakić, M.; Bajuk-Bogdanović, D. How to Obtain Maximum Environmental Applicability from Natural Silicates. *Catalysts* **2022**, *12*, 519. [CrossRef]
135. Gildernew, E.; Tareq, S.; Yang, S. Three-Dimensional Graphene with Preserved Channeling as a Binder Additive for Zeolite 13X for Enhanced Thermal Conductivity, Vapor Transport, and Vapor Adsorption Loading Kinetics. *Catalysts* **2022**, *12*, 292. [CrossRef]