"ZEOLITES AS POTENTIAL CANDIDATES FOR MICROENCAPSULATION DRUG DELIVERY SYSTEM"

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Abstract: The active drug molecule more often a Protein or Peptide, is very active in small doses, sensitive to unfolding by heat or organic solvents, available only in small quantities and are very expensive. Some of the new molecules have poor solubility in aqueous media and some of them have poor solubility in lipid media. New techniques are being designed for delivery of this drug molecule to the targeted area, taking into account several new requirements. The stability and biological activity of drug should not be affected during microencapsulation process, yield and drug encapsulation efficiency should be taken care of, microsphere quality and drug release profile should be reproducible, microspheres should not exhibit aggregation or adherence. The present review focuses on some of the naive qualities of zeolites like pore structure and topologies, large surface area with tunable surface properties and more over ion exchange properties, which makes them as the potential candidate for microencapsulation drug delivery system.

Keywords Drug molecule, microencapsulation, potential candidate, zeolites.

Introduction: Zeolites are crystalline hydrated alumino silicates of alkali and alkaline earth metals, forming a three dimensional network of interconnected SiO_4 and AlO_4 tetrahedra, linked to each other by sharing of all the oxygen atoms. Fundamental unit is SiO_4 tetrahedron. Substitution of Al^{3+} for Si^{4+} cation occurs forming an AlO_4 tetrahedron and producing a deficiency in electrical charge. So additional positive ions (of alkali and alkaline earth metals) are required within the interstices of the structure. The presence of aluminum in the zeolite framework gives a net negative charge to the system and thus creates the existence of charge compensating counter ions. Such counter-ions provide the zeolite with a very unique property of ion-exchange. The ion-exchange properties of the zeolites are widely used in transition metal catalysis as well as in water softening techniques. Silicate structure becomes complex due to various ways in which tetrahedral groups can link to form polynuclear complexes. The Zeolite framework contains channels and interconnected voids which are occupied by the cations and water molecules.The cations may be exchanged to varying degree by other cations.The water molecules are rather loosely bound to the framework and is removed continuously and reversibly. These dehydrated Zeolites act as "Molecular sieves" due to difference in their sizes and other structural factors. This theory was first of all explained by Mc Bain[1].The Zeolites selectively adsorb or reject different molecules. This molecular sieve action is because of the reason that Zeolites have well defined pore structures and topologies, having a large surface area with tunable surface properties This property allow the use of zeolites in the separation of small molecules from large molecules. This makes the phenomenon of shape selectivity possible in catalytic reactions .This molecular sieve action may be total or partial. These pores allow molecules smaller than its pore diameter to be adsorbed and completely exclude molecules which are larger than their diameter. High surface area and high thermal stability of Zeolites makes them highly useful for a wide range of applications such as adsorbents, detergents and catalysts [2]-[4].

zeolites as potential candidates for controlled drug delivery systems: zeolites can be the potential candidates for controlled drug delivery systems. Controlled release in zeolites has been achieved through the introduction of functional groups on the external surface of the zeolites, and by controlling a number of factors such as the pore size, the nature of intermolecular interactions, ion exchange properties and biocompatibility. The loading of the drug in zeolites can be maximized by understanding the nature of host-guest chemistry.The last few years has seen, a number of interesting drug delivery applications of zeolites and mesoporous materials.

Zeolite Pores and drug delivery: The small size of the pores confines the space of a drug and engages the effects of surface interactions of the drug molecules and the pore wall. The size of the pores and the surface chemistry of the pore walls can be easily controlled. The size and the surface chemistry of the pores, play an important role in increased or sustained release of the loaded drug. Drug loading from a solution at room temperature enables the use of zeolites also with sensitive therapeutic compounds susceptible to degradation, like peptides and proteins. .

Zeolites Faujasite(FAU) and Linde type A (LTA),were studied byRicardo Amorium [5], to investigate their suitability for drug delivery systems (DDS). The

sodium form (NaY and NaA) of zeolites were used as hosts for encapsulation of an experimental anticancer drug α-cyano-4-hydroxycinnamic acid (CHC). by diffusion in liquid phase . Spectroscopic techniques (FTIR, ^{1}H NMR, ^{13}C and ^{27}Al solid-state MAS NMR, and UV–vis) chemical analysis, powder X-ray diffraction (XRD) and scanning electron microscopy (SEM) were used for the characterization of new drug delivery systems, CHC@zeolite,and the effect of the zeolites and CHC@zeolite drug deliveries on HCT-15 human colon carcinoma cell line viability was evaluated.No toxicity to HCT-15 cancer cells was revealed by both zeolites alone. CHC@zeolite exhibited an inhibition of cell viability up to 585-fold, in comparision to the non-encapsulated drug. The results strongly advocate zeolites as potential candidates for drug loading and delivery into cancer cells to induce cell death.

5-fluorouracil (5-FU), is a traditional drug used in the treatment of several cancers, including colorectal (CRC),the studies of potentiation of 5-fluorouracil were carried out with zeolites Faujasite in the sodium form, with different particle sizes (NaY, 700 nm and nanoNaY, 150 nm) and Linde type L in the potassium form (LTL) with a particle size of 80 nm by Natalia Vilaca,and Ricardo Amorim [6] .Loading was done into zeolites by liquid-phase adsorption. Characterization of drug loaded zeolite was completed by spectroscopic techniques (FTIR, ^{1}H NMR and ^{13}C and ^{27}Al solid-state MAS NMR), chemical analysis, thermal analysis (TGA), nitrogen adsorption isotherms and scanning electron microscopy (SEM).Characterization established the successful loading of 5-FU into the zeolite hosts. In vitro drug release studies (PBS buffer pH 7.4, 37 °C) were performed and studies revealed the release of 80–90% of 5-FU in the first 10 min.The release profiles were studied kinetically according to zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas and Weibull kinetic models. The efficacy of the drug delivery systems (DDS) was evaluated using two human colorectal carcinoma cell lines, HCT-15 and RKO. No toxicity was shown by Unloaded zeolites to both cancer cells, while all DDS established an important potentiation of the 5-FU effect on the cell viability.

Rimoli MG,Rabaioli MR [7]studied Synthetic zeolites, toinvestigate their ability to encapsulate and to release drugs. Zeolite X and a zeolitic product obtained from a cocrystallization of zeolite X and zeolite A were examined. Characterization of these unloaded materials was done by chemical analyses (ICP-AES), X-ray diffraction, nitrogen adsorption isotherm, scanning electron microscopy, laser diffraction, and infrared spectroscopy. Ketoprofen was chosen as a model drug for the formulation of controlled-release dosage forms, encapsulation was done by a soaking procedure. Drug-loaded matrices were then characterized for entrapped drug amount and thermogravimetric behavior. activated zeolites, Synthetic zeolite.Ketoprofen (800 mg) was encapsulated in 2 g of activated zeolite matrix.,Ketoprofen release studies were done at different pH conditions By using HPLC measurements. There was no release in acid conditions and a double phased release, at two different pH values (5 and 6.8),clearly suggest that after activation these materials have good potential for a encapsulated delivery system of Ketoprofen

Cavallaro G, Pierro [8]studied a mesoporous material based on aluminosilicate mixtureto investigate its ability to include drugs and then release them, using nonsteroidal anti-inflammatory agents such as diflunisal, naproxen, ibuprofen. The prepared mesoporous material was characterized by X-ray, N2 absorption-desorption isotherm, and thermogravimetry analysis. Drug loading was performed by a soaking procedure. The entrapped drug amount, water absorption ability, and thermogravimetric behaviour of Drug-loaded matrices were also characterized . Drug release studies were performed at pH 1.1 and 6.8 mimicking gastrointestinal fluids. Experimental results established that this type of matrix is able to trap the bioactive agents by a soaking procedure and, then, to release them in conditions mimicking the biological fluids.These matrices also showed high affinity for water making them potentially biocompatible. Release data suggested that the impregnated matrix offers good potential as a system for the modified drug release.

P. Horcajada, A. Ramila [9]studied the influence of pore size of MCM-41 materials on drug delivery rate.Small pore size MCM-41 materials have been synthesised from mixtures of two different alkyltrimethylammonium surfactants with chain length of 8 and 10 carbon atoms. The analgesic ibuprofen was introduced into the pore channels.Delivery to the media is measured and compared with the delivery from bigger pore-sized MCM-41.This study has revealed that the delivery rate of ibuprofen in a simulating body fluid solution decreases as the pore size decreases.

Ion exchange properties of zeolites and drug delivery: Zeolites show excellent ion exchange properties which arise from the positioning of aluminium in tetrahedral coordination, imposing anet negative charge of the framework counterbalanced by cations within the cavities and channels.Ionic character of bonding between interstitial cations and framework facilitates cation exchange for zeolites. The unique property of cation

exchange is exploited in number of applications like water softening, removal of waste from water,in filters for odour control and toxin removal.

Interstitial cations in zeolites can be exchanged to fine tune the pore size,thus making zeolites as a potential applicant for drug delivery.

Sarah miller[10] and colleagues have prepared multifunctional nanocontainers for imaging, targeting and drug release,they functionalized zeolite L crystals with β-cyclodextrin (CD) and obtained multifunctional systems with potential for encapsulation of drug molecule inside zeolite pores. Functionalization with CD was achieved in two steps, first of all zeolite surface was modified with aminoalkoxysilanes then 1,4-phenylene diisothiocynate was reacted with the amino monolayer to bind CD heptamine by using its remaining isothiocynate groups.The team reported that the use of APDMES and APTES drastically improved the uptake and release properties of zeolites by affecting the accessibility of the channels for cation exchange. APTES formed an impermeable layer on the surface and thus block the diffusion of thionine dye molecules inside the crystals completely,APDMES allow exchange of K^+ with charged dye molecules . This approach allows ions to be permanently trapped inside the channels by using APTES, this is very important for imaging and thus makes zeolites interesting for drug-delivery applications

Cattaneo M V, Chang T M [11] demonstrated the use of microcapsules containing a urease-zeolite preparation for urea removal., zeolite W is nonselective toward calcium ions and is stable at the high pH found in the intestinal tract. Zeolite W, when present in the sodium form, has a high ammonium capacity of 3.6 mEq NH4+/g, reactivity of zeolite to ammonium under simulated intestinal conditions;is also higher. The current in vitro study proves that microcapsules, containing a urease-zeolite preparation, remove up to 80% of urea in less than 1 hour.

Patzer JF II, Yao SJ, Wolfson SK Jr[12] reported that ammonia removal from a recirculating dialysate stream is a major challenge in developing a truly portable, regenerable hemodialysis system. Three zeolites, type F, type W, and clinoptilolite, were reported to have good ammonia ion exchange capacity with linear equilibrium ion exchange coefficients of 0.908, 0.488, and 0.075 L/g, respectively, which relates dialysate ammonia concentration (mumol/L) to the amount of ammonia absorbed by zeolite (mumol/g) at equilibrium. Ammonia uptake by zeolite powders was fast, with equilibrium reached within 15 sec. Zeolite ammonia ion exchange and regeneration was studied using an ion exchange column containing clinoptilolite pellets.

Guo X,Chang R K,Hussain M A.[13] discussed the use of ion-exchange resin (drug-resinate)in the drug delivery area. Ion-exchange resin complexes, they studied the properties of ion-exchange resins, selection of drugs that lend themselves to such an approach, selection of the appropriate resin, preparation of drug-resinate, evaluation of drug release, recent developments of drug-resinates, and their applications

Zeolites as Biomaterials*:* Taskin Ceyhan,Melkon Tatlier and Handan Akcakaya [14] studied the biological viability of zeolites.Various zeolites were kept in simulated body fluid (SBF) for different periods of time. The crystalline structures of zeolites and the chemical composition of SBF were determined by various analysis techniques and changes were noted after this treatment. The possible effects of zeolites on the morphology and viability of chronic myelogeneous leukemia and swiss albino fibroblast culture cells were also studied. It was found that when zeolites were kept in the SBF for up to 14 days, their crystal structures were not affected ,however detectable amounts of Si were found in the SBF samples after their treatment withl the zeolites.There was the increase of about 10% in the K content of SBF,after the treatment carried out by using clinoptilolite. The zeolites, which allowed the lowest and highest amount of silicon transfer into the SBF, were observed not to have any significant biological effect on the two different cell generations investigated.

The adsorption of cytochrome c on to zeolite crystals and membranes with different chemical composition and structure was studied by Palmira Tavolaro, Adalgsia Tavolaro, Guglielmo Martino [15]. The structure and texture characterization of zeolite materials were done by X-ray diffraction (XRD) and scanning electron microscopy (FESEM), and the variation of protein conformation was studied by Fourier transform infrared attenuated total reflectance (FTIR-ATR) analysis.A through analysis of the cytochrome c adsorption was done on different crystals by varying several conditions like: pH value, protein amount, structure of zeolite and chemical compositions, In order to separate the influence of zeolite structures from the effect of composite membranes,. It is observed that the electrostatic type of interaction seems to be of the utmost importance to govern the immobilization, while the zeolite Brönsted acidity is the subordinate parameter which differentiate between the adsorption performances of different zeolite structures

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A new antimicrobial material, Ag-zeolite (Zeomic°), was combined with a commercial tissue conditioner (GC-Soft Liner (GC); 1–5%) and, through monitoring the pH of the growth medium, H. Nikawa,T. Yamamoto16]examined the effects on the *in vitro* growth and/or acid production of *Candida albicans* on protein-free and saliva-coated specimens. The effect of incorporation on the physical property of the lining material was also observed according to the ISO penetration test. Comparison studies were carried out with the use of GC, Coe Comfort (CC) or undecylenate combined GC (1–5%) specimens. The results taken together affirm that an antimicrobial zeolite-combined tissue conditioner would be a potential aid in denture plaque control.

Neethu Ninan, Muthunarayanan Muthiah[17] explored the possibility of using inorganic faujasites in tissue engineering scaffolds and prepared novel gelatin/hyaluronic acid (HA)/faujasite porous scaffolds with low surface energy by lyophilization. The pore size of gelatin/HA scaffold was 50–2000 μm, after incorporation of 2.4% (w/w) of faujasites in polymer matrix, GH(2.4%) it was greatly reduced to 10–250 μm.Porosity of GH(2.4%) was 90.6% as established by micro computed tomography analysis. Embedded faujasites maintained their crystallinity in the polymer matrix as revealed by XRD analysis ,though they interacted with the polymers as indicated by FT-IR analysis.Controlled swelling and degradation, allowing sufficient space for tissue regrowth is also exibited. The latter is further supported by capability of faujasites to provide efficient oxygen supply to fibroblast cells. The in vivo studies on Sprague–Dawley rats proved its ability to enhance wound healing by increasing rate of re-epithelization and collagen deposition. These findings proved its potential as excellent wound dressing material

Koki Namekawa, Makoto Tokoro Schreiber[18] studied and developed a zeolite–polymer composite nanofiber mesh to remove uremic toxins for blood purification. The nanofiber composes of blood compatible poly(ethylene-*co*-vinyl alcohol) (EVOH) as matrix polymer and zeolites which can selectively adsorb uremic toxins such as creatinine, produced by a cost-effective electrospinning method.The SEM showed that over 90% of zeolites in the solution were successfully incorporated into the EVOH nanofibers. The adsorption capacity of nanofibres was still 67% of the free zeolites. The proposed composite fibers have the potential to be utilized as a new approach to removing nitrogenous waste products from the bloodstream without any specialized equipment.

Guo Y P,Long T,Song Z F, Zhu Z A.[19] In their study, fabricated ZSM-5 zeolites for drug delivery systems by hydrothermal method, to avoid bone implant failures. They investigated structure, morphology, biocompatibility, drug delivery property, and bactericidal property of the ZSM-5 zeolites The biocompatibility tests proved the better spreading and proliferation of human bone marrow stromal cells on the surfaces of the ZSM-5 zeolites, the ZSM-5 zeolites showed greater drug loading efficiency and drug sustained release property owing to ordered micropores, large Brunauer-Emmett-Teller (BET) surface areas, and functional groups. The gentamicin-loaded ZSM-5 zeolites, allowed the sustained release of gentamicin, which significantly minimized bacterial adhesion and prevented biofilm formation against Staphylococcus epidermidis. The excellent biocompatibility, drug delivery property, and bactericidal property of the ZSM-5 zeolites proved their potentials for treating implant-associated infections.

Bedi R S, Beving DE, Zanello L P, Yan Y [20] proposed Zeolite coatings to prevent the release of the toxic ions into human tissue and for the enhancement of osteointegration , in place of traditionally used titanium alloy, Ti6Al4V for dental and orthopedic implants. They successfully synthesized Zeolite MFI coatings are on commercially pure titanium and Ti6Al4V for the first time. The coating demonstrated excellent adhesion by incorporation of titanium from the substrate within the zeolite framework,and also showed higher corrosion resistance than the bare titanium alloy in 0.856M NaCl solution at pHs of 7.0 and 1.0. Zeolite coatings also eliminated the release of cytotoxic Al and V ions over a period of 7 days, indicating that the zeolite coatings are highly biocompatible.

Nida Iqbal,Mohammad Rafiq, Abdul Kadir,Nasrul Humaimi Bin Mahmood[21] successfully synthesized , bioactive composites composed of hydroxyapatite (HA) and zeolite-Y by using a cost-effective microwave-assisted wet precipitation method. The composite materials were characterized by X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), field emission scanning electron microscopy (FESEM), and energy dispersive X-ray spectroscopy (EDX), respectively. The in vitro bioactivity assay using simulated body fluid (SBF) confirmed the better ability of silica-based materials to support and accelerate the formation of dense layer. Cytotoxicity assay confirmed the cell viability of normal human osteoblast (NHOst) cells on the composites. In addition, FESEM results proved that the material supported adhesion of NHOst cells on its

surface. In conclusion, the nano-structured zeolite–HA composites good bioactivity and in vitro cell compatibility, and, proved themselves as a potential candidate for bone tissue engineering applications.

Conclusion: The literature precedent shows that the controlled release of drug molecules from zeolite systems was achieved either by surface modification or by changing the polarity of the system. By changing the physicochemical properties of the host materials the nature of interactions of the guest (drug) molecules can be changed and as a result of which better control over the loading and release properties of drug can be achieved. The advantages of using zeolites for biomedical applications, like the delivery of small drug molecules, are the biocompatibility and low toxicity of zeolites, tunable smaller pore size, which closely matches the drug molecule size relative to other mesoporous materials ,ability to tune the zeolite properties by varying the SiO_2/Al_2O_3 ratio, the exchangeable cation and the surface functional group. The several examples of biomedical applications of zeolites reported in the literature including imaging, wound treatment, drug delivery, nanocomposites, bioimplants establishes the claim of zeolites as the potential candidates for drug delivery. Further research is needed to understand fundamental zeolite and drug molecule interactions so that the loading and release of the drug molecules can be better understood and controlled.

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