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NOVEL MOF-ALGINATE AEROGEL COMPOSITES FOR DRUG DELIVERY

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ABSTRACT
Composites of Metal Organic Frameworks (MOFs) with aerogels are attractive materials for development of controlled drug delivery devices due to their high surface areas, adjustable ratio of mesoporous and microporous regions and high pore volumes. In this study, we synthesized novel composites of the MOF Fe-BTC with alginate aerogel using both the dripping method and the emulsion gelation technique. The composite aerogels were characterized by X-Ray Diffraction, Scanning Electron Microscopy and FTIR. Paracetamol (Acetaminophen) which was selected as a model drug was loaded to Fe-BTC–alginate aerogels via gas antisolvent crystallization inside the pores. The release of paracetamol from the composites were investigated. The results show that this novel aerogel composite has promising advantages for controlled drug delivery.

INTRODUCTION
Nanoporous materials have great advantages in biomedical applications such as drug storage, delivery, imaging and sensing [1]. For drug delivery, it is very important to achieve controlled release of drugs with high drug loadings and with use of non-toxic carriers [2]. Among nanoporous materials, metal organic frameworks (MOFs) and aerogels are very promising and widely studied for drug delivery applications.

Polysaccharide aerogels are especially attractive for drug delivery applications due to their biodegradable and biocompatible nature, mesoporous structure, very low density and very high surface areas [3]. Aerogels are mesoporous materials with very low densities which are generally synthesized by supercritical drying of gels synthesized by a wide variety of methods. The aerogels might be synthesized in form of monoliths, beads or small size particles.

MOFs are hybrid materials composed of inorganic nodes that are connected with organic linkers. They usually have well-defined microporous and tunable structures, high surface areas and some even has flexibility which is also called the “breathing effect” [4]. One of the factors which has prevented the use of MOFs at an industrial scale has been the difficulty in their processing and handling due to their powder form.

Aerogels are one of the best possible hosts to carry MOFs without compromising their most important features like microporosity and high surface area. MOF-aerogel composites can be composed of various MOFs and aerogels. Although research on MOF-aerogel composites has gained momentum in recent years, there has been no study in the field of drug delivery for these composites[3,5,6]. The combination of microporosity of MOFs with the mesoporous aerogels

have the opportunity to make hierarchically porous materials with very high surface areas. This way, it is possible to retard the diffusion and increase the amount of drug loaded. Therefore MOF-aerogel composite materials have great potential in drug delivery applications.

For this research, we have chosen Fe-BTC as the model MOF and alginate as the aerogel matrix. Alginates are important type of materials as they found many applications in industries such as pharmaceutical, food and cosmetics[7]. Their gel forming ability along with their non-toxic nature and biocompatibility makes them perfect candidates for drug delivery systems. Fe-BTC was chosen due to the fact that iron is highly biocompatible and has low toxicity[2,8].

Paracetamol was selected as the model drug due to the fact that it is very suitable for gas antisolvent crystallization (GAS) process inside the pores. This process enables high loadings of target molecules into the gel matrix. For GAS process, the drug is loaded at the last step of solvent exchange and then the gel containing the drug is dried supercritically so that ethanol that is miscible in $scCO_2$ is removed whereas $scCO_2$ acts as an anti-solvent for the drug. Therefore the drug precipitates inside the pores of the aerogel.

MATERIALS AND METHODS

Fe-BTC—alginate aerogel composites were synthesized using both dripping method and emulsion gelation technique. For the preparation of MOF-aerogel composites, Basolite F300 which is a commercial MOF produced by BASF and sodium alginate (*Alginic acid sodium salt from brown algae)* from Sigma Aldrich was used. Various MOF-alginate composites were synthesized with using solutions with the same alginate concentrations but different MOF contents.

In the dripping method, a suspension of Fe-BTC in an alginate solution was dropwise added to a solution of $CaCl_2$. The resulting spherical gel particles with an average size of 0.45 cm were then subjected to stepwise solvent exchange with ethanol. Whereas in the emulsion gelation method, a water-in-oil emulsion was produced using an alginate solution with Fe-BTC dispersed in it. After gelation, the particles were recovered by filtration and subjected to solvent exchange with ethanol. Produced composite gel particles were loaded with 0.5 M paracetamol at the last step of solvent exchange. These particles were kept overnight in a solution of paracetamol dissolved in ethanol and later supercritically dried. With this process called gas antisolvent crystallization inside the pores, paracetamol that is insoluble in $scCO_2$ precipitated inside the pores of the composites.

The paracetamol loaded composites were then subjected to release experiments. Each composite was put into a solution of fixed amount of phosphate buffered saline (PBS) with pH adjusted to 5.8. The composites were then kept under constant stirring at 310 K and samples were taken from the solution at specific time points. The samples were then analyzed with Thermo Scientific NanoDrop ND 1000 UV-Vis Spectrophotometer at 242 nm using a calibration curve prepared with solutions of paracetamol with known concentrations. Moreover, the composites were also characterized with FTIR, XRD and SEM.

RESULTS

Seven different composites were synthesized with a 2 wt% Sodium Alginate solution and different Fe-BTC concentrations. The weight fractions of Fe-BTC varied between 0.01 and 0.7. The density of the composites ranged from 0.1 g/cm^3 to 0.176 g/cm^3. As MOF content increased, it became harder to disperse MOF particles in alginate solution, therefore some MOF

agglomerates were observed. The highest MOF loaded composite (70 wt%) had agglomerates at its surface as shown in Figures 1 and cross section as shown in Figure 2.

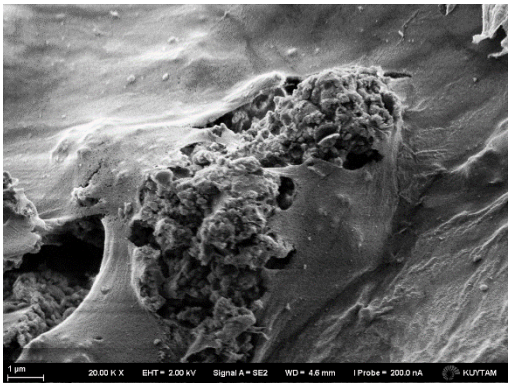

Figure 1. SEM image of surface of 70 wt% Fe-BTC-alginate aerogel composite surface with paracetamol loaded

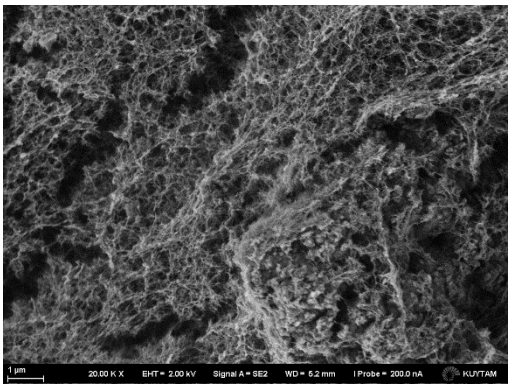

Figure 2. SEM image of cross section of 70 wt% Fe-BTC-alginate aerogel composite surface with paracetamol loaded

XRD results as seen in Figure 3 show that Fe-BTC remains intact and paracetamol is in crystal form which is very important for drug delivery purpose.

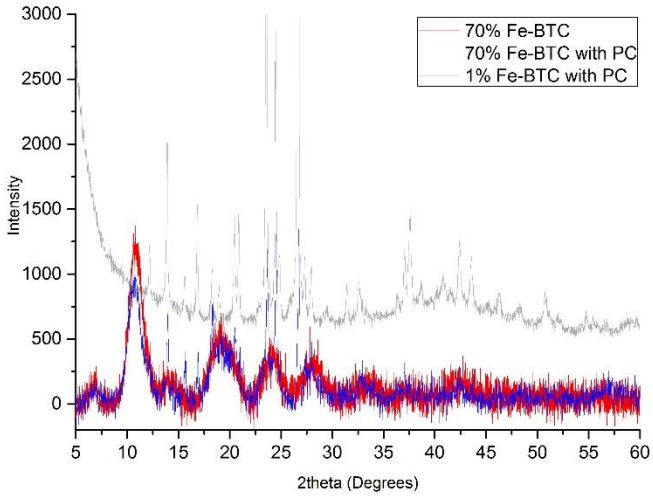

Figure 3. XRD Spectra of 70 wt% Fe-BTC-alginate aerogel with and without paracetamol

The results of the release experiments carried out with composites with different MOF contents are given in Figures 4 and 5. As Fe-BTC fraction in the composite matrix increased, the amount of paracetamol that is loaded increased as seen in Figure 4. In addition, Figure 5 shows that the initial release is slower and the time it takes to achieve full release increases with increased Fe-BTC concentrations.

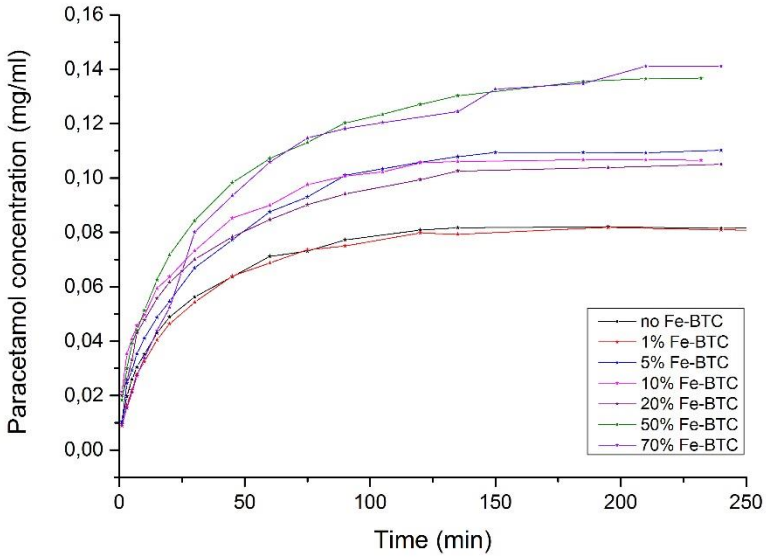

Figure 4. Concentration of paracetamol in PBS over time (pH 5.8, 310 K, under stirring)

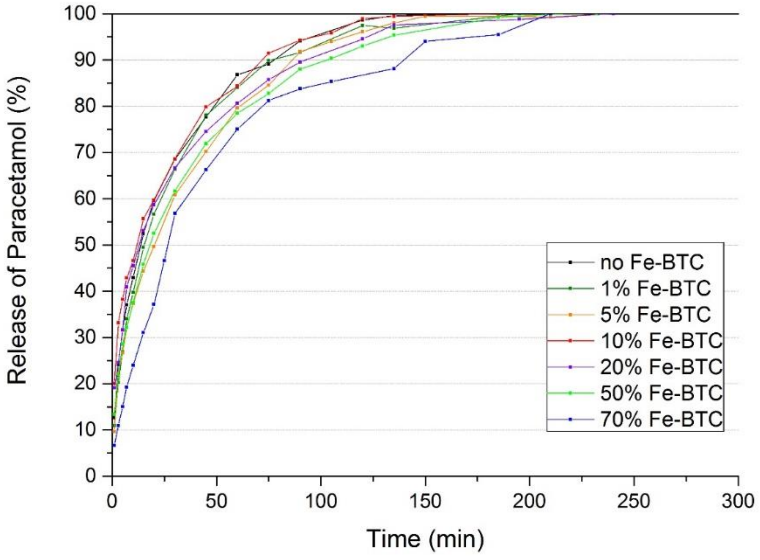

Figure 5. Release of paracetamol from composites into PBS

CONCLUSION

The results show that the MOF Fe-BTC stays intact inside an alginate gel matrix leading to formation of nanoporous composites suitable as hosts. Delivery of a model drug from these

materials was investigated experimentally. As Fe-BTC concentration in the composite matrix increased, the amount of paracetamol that could be loaded increased due to increased surface area. Moreover, the initial release rate was slower and the time it took to achieve full release increased presumably due to the slow diffusion from the micropores of Fe-BTC. Therefore, these composites are very promising for both drug storage and controlled drug delivery applications.

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