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Magnetite nanoparticle polymer composites for prolonged and controlled drug release

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Hydrogel samples that contain drug-loaded magnetite particles exhibit good release characteristics in both the presence and absence of a magnetic field.

To date, magnetic nanoparticles (NPs) have been successfully used for numerous applications (e.g., magnetic drug targeting, magnetic fluid hyperthermia, magnetic resonance imaging, drug delivery systems, enzyme immobilization, protein purification, diagnosis, imaging, and therapy). Moreover, using magnetic NPs as targeted nanoparticles has huge potential for the diagnosis and treatment of tumors. In such targeted drug delivery systems, nanoparticles loaded with a drug are transported to specific sites within the human body with the use of an external magnetic field (see Figure 1). In this way, targeted materials (i.e., containing magnetic NPs) can be rapidly and easily isolated within a magnetic field.[1] In addition, this process can prevent the accumulation of drugs and non-specific toxicity in normal cells (because of their strong magnetic susceptibility). The small size of NPs, however, means that large quantities of them are required for these therapeutic purposes, and the large concentrations of NPs in organisms can give rise to a number of problems.[2] In particular, the high concentrations of NPs can have toxicological significance (i.e., the cell's or organism's defenses are overwhelmed when the NPs interact with cells and subcellular components). For example, high doses of a persistent particulate material have been found to consistently cause the formation of granulomas.[3]

To solve these problems, several previous studies have been conducted on the polymeric matrices of hydrogels (networks of hydrophilic polymer chains). Hydrogels have several intrinsic characteristics—such as the ability to manipulate their network design, controllable hydrophilicity/hydrophobicity, porosity, the possibility of chemical functionalization, and low cost—that make them ideal drug delivery systems. Furthermore, the period of drug release and the delivered dose from hydrogels can be controlled with environmental factors (e.g., time, temperature, pH, as well as electrical and magnetic fields).

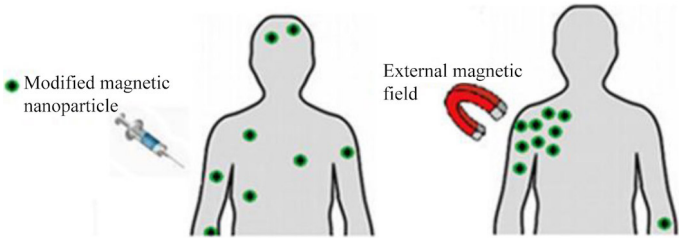

Figure 1. *Schematic illustration of the general procedure for targeted drug delivery systems, in which magnetic nanoparticles (NPs)—loaded with a drug—are used. In the first step, the NPs are injected into the body. An external magnetic field is then used to induce transportation of the NPs to a specific site in the body.*

In our previous studies we have thus investigated a number of macroporous thermosensitive cryogels that were embedded with NPs (unmodified or modified silica).[4] We have also investigated the drug delivery behavior of synthesized smart hydrogels, acrylamido-2-methyl-1-propanesulfonic acid-based microgels,[5] 4-acryloylmorpholine-based hydrogels,[6] and biodegradable hydrogels that contain β-cyclodextrin.[7] From these different studies, we concluded that the hydrophilic character of the gel matrix increases the level of drug loading and release. In addition, we found that amphiphilic systems—e.g., poly(caprolactone)-poly(ethylene glycol)—can self-assemble into micelles, and that two or more drugs can be conjugated into one polymer carrier for combined delivery. Many drugs can thus be loaded easily within the hydrophilic and hydrophobic domains of the gel matrix.

Several methods for obtaining magnetic NP polymer hydrogels have also previously been developed. Such NPs can either be directly introduced into the matrix or they can be covalently bonded to the matrix. An advantage of the covalent bond strategy is that uncontrolled release of NPs from the hydrogel matrix can be avoided.[2] In our most recent work,[8] we therefore designed composite magnetite-biodegradable

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Table 1. *Results from experiments used to investigate the effect of a magnetic field on drug loading and release from hydrogel composites. Tamoxifen and clarithromycin were loaded onto the magnetite NPs (at different concentrations) and the rate of release—both in the presence and absence of a magnetic field—was measured.*

	Absence of magnetic field		Presence of magnetic field	
	Tamoxifen (%)	**Clarithromycin (%)**	**Tamoxifen (%)**	**Clarithromycin (%)**
Drug loading	90	70	90	70
Drug release	58	64	64	67

polymer hydrogel nanocarriers for targeted drug delivery system applications. Unlike in the previous studies, we prepared our magnetite polymer hydrogel so that it can be rapidly polymerized to a 3D crosslinked hydrogel network (via a UV-mediated thiol-ene reaction). We wanted to continue using biodegradable polymer hydrogels as a key part of our drug delivery system because of their tailorable properties for organisms. With these aims in mind, we used a typical co-precipitation method to prepare our magnetite NPs. We then modified the surfaces of these NPs with the crosslinkable organic groups that provided the covalent bonding with the polymeric hydrogel matrix (see Figure 2). It was thus possible for the small magnetite NPs to be easily transferred into the biodegradable hydrogel matrix.

In our study, we used scanning electron microscopy (SEM) to investigate the size, morphology, and dispersion (within the hydrogel matrix) of our surface-modified magnetite NPs. With these measurements, we confirmed that the NPs had a diameter of less than 100nm and that they were roughly spherical in shape. Our SEM images (see, e.g., Figure 3) also showed that the NPs were distributed within the hydrogel matrix without signs of agglomeration.

We also evaluated the effect of a magnetic field on the drug loading and release of the our hydrogel samples. For these tests we used a small magnet, and we chose tamoxifen and clarithromycin as our model drugs. In the first stage of the experiments, we loaded different concentrations of the drugs on to the NPs and then evaluated the rate of drug release. We observed that the in vitro release of tamoxifen and clarithromycin from the crosslinked hydrogels occurred in an initial burst and then followed a slow-release profile. These styles of drug release correspond to initial water absorption by the hydrogel matrix, before degradation of the polymer matrix began to dominate. In addition, hydrolysis of the biodegradable groups of magnetite NPs can contribute to the degradation of the composite hydrogels.

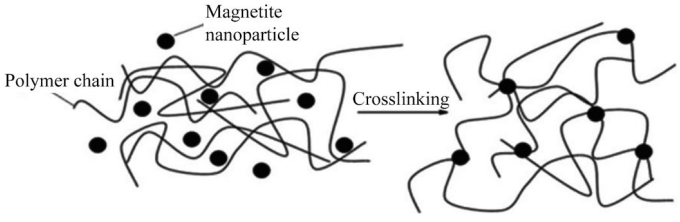

Figure 2. *Illustration of the preparation process for the magnetite NP/polymer hydrogel composites. A typical co-precipitation method is used to form the magnetite NPs, whose surfaces are then modified with crosslinkable organic groups. The modified NPs can then be easily transferred into the polymer matrix.*

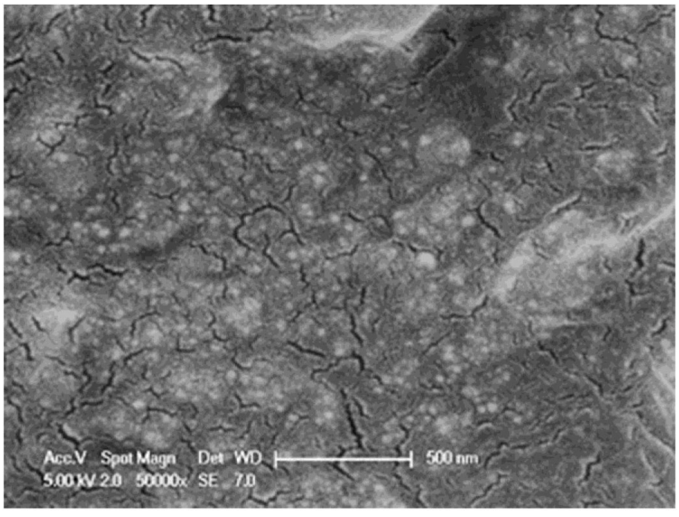

Figure 3. *Scanning electron image of magnetite NPs (bright spots) dispersed within a hydrogel matrix.*

In the second stage of our drug loading/release tests, we compared the drug release profiles in the presence and absence of the magnetic field. Our results (see Table 1) indicate that the amount of drug released from the hydrogels in the presence of a small magnetic field is higher than in the absence of the field. Although the total release profiles in the presence/absence of the magnetic field were similar, the initial burst of drug release was faster and was followed by a more sustained/controlled release in the absence of the field. We can explain

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these results by the fact that diffusion of the drugs from the hydrogels increased in the presence of the magnetite NPs when the magnetic field was absent.

In summary, we have investigated the use of magnetite nanoparticles as drug carriers in hydrogel composites. Our results show that hydrogels containing magnetite NPs exhibit controlled release of drugs over prolonged periods of time. For this reason, such composite hydrogels are suitable for use in reducing the toxicity of drugs and for improving the therapeutic efficacy of anticancer drugs (i.e., as a targeting carrier). In our future work, we will aim to study the use of NPs as imaging and therapy agents. We will also investigate how changing the size/surface modifications (e.g., polymer surface coatings for higher biocompatibility) of the particles may lead to improved magnetic behavior, as well as the transport of drug-loaded polymer hydrogels within the human body.

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