

## Sustained Release of Minocycline Hydrochloride from Biomaterials

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### Editorial

Minocycline Hydrochloride (MH) is a second-generation, semi-synthetic tetracycline antibiotic derivative (Figure 1). It blocks the association of aminoacyl-tRNA with the bacterial ribosome and thus inhibits the bacterial protein synthesis. Independent of its antibacterial property, MH also exhibits potent anti-inflammatory effects, which makes it a promising drug candidate to combat implant-associated infection and inflammation [1-5]. In addition, MH can inhibit smooth muscle cell proliferation and neointimal hyperplasia after arterial injury [5] and reduce tumor expansion and migration [6]. MH also demonstrated cytoprotective properties in the cardiovascular, renal, and Central Nervous Systems (CNS) via its anti-oxidative and anti-apoptotic properties. MH protects neurons from oxidative stress by scavenging free radicals [7], prevent excitotoxicity by diminishing Ca<sup>2+</sup> influx and uptake [8], and suppress activation of caspases [9]. As a result, MH has been shown to provide neuroprotection in a variety of Central Nervous System (CNS) injuries and neurodegenerative diseases, such as Spinal Cord Injury (SCI) [10], traumatic brain injury [9], stroke [11], Parkinson's disease [12], Alzheimer's disease [13], multiple sclerosis [14], and amyotrophic lateral sclerosis [15], etc.

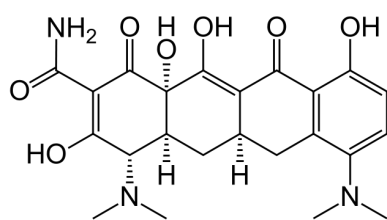


Figure 1: Chemical structure of MH.

However, many of these diseases require continuous high concentrations of MH at the injury site for effective treatment. For example, to inhibit tumor growth in mice, the maintenance of 60-120 mg/kg MH is needed for 4 weeks [16], which is much higher than the standard human dose of 3 mg/kg [17]. Systemic administration of high doses of MH for extended period of time has been shown to cause side effect, such as morbidity, liver toxicity, and even death in experimental animals. Thus, a localized delivery of MH is needed to deliver high concentrations of MH to the injury sites continuously without causing significant side effects.

The challenges related to drug delivery of MH is that MH is a small molecule (Mw = 494 Da) with high water solubility, so that MH was generally released quickly from current hydrophilic drug delivery systems [18], such as MH loaded in Poly(Vinyl Alcohol) (PVA)

hydrogel with chitosan [19]. As a result, current drug delivery systems are not ideal for localized delivery of high concentration of MH over an extended period of time.

There is a need to develop drug delivery mechanisms for sustained and controlled delivery of MH. Several strategies have been implemented and are still under investigation.

1. Hydrophobic polymers have been used to increase the loading efficiency of MH. As one example, Poly (Lactic-co-Glycolic Acid) (PLGA) nanoparticles [20] demonstrated sustained release of MH, although the loading efficiency of MH in the PLGA particles was low (less than 1%). Adding Dextran Sulfate (DS) into the system could reduce the solubility of MH so that the diffusion of MH into external medium would be slowed down to improve the encapsulation of MH in polymers or nanoparticles. The results showed that addition of DS solution increased the loading efficiency 1.92% [20].

2. MH can also chelate multivalent metal ions such as Ca<sup>2+</sup> and Mg<sup>2+</sup> to form chelate complexes without affecting its biological activities [21]. For example, MH-Ca<sup>2+</sup> chelate has encapsulated into polyion complex micelle of Carboxymethyl-dextran-block-poly (Ethylene Glycol) (CMD-PEG) so that the positively charged MH-Ca<sup>2+</sup> chelate could be entrapped in a negatively charged micelle for drug delivery [22]. Drug loading efficiency in this system is high (50%). However, MH release from the PIC micelles only lasted for 24 hours, possibly because the electrostatic interaction is not strong enough for supporting sustained drug release.

3. Metal ion-assisted complex formation. Both DS and MH have high binding affinity for metal ions (M<sup>+</sup>) such as Ca<sup>2+</sup> and Mg<sup>2+</sup>. When mixing the three components together, an insoluble complex of MH-M<sup>2+</sup>-DS can be obtained. In this system metal ions play a critical role in complex formation and MH release by binding to both DS and MH molecules simultaneously. The metal ion-mediated interaction is strong but reversible, which enables high drug loading efficiency (45%) and sustained release of MH [23].

4. Drug delivery through complex coacervation. Coacervation is a phase separation of polymer solution into two phases. One of them with concentrated polymer is the coacervate and the other is an equilibrium solution [24]. Commonly caused by electrostatic interaction between oppositely charged polymers, complex coacervation is formed and usually leads to precipitation [25], which is also called polyelectrolyte complex. One of the advantages of complex coacervation is the mild environment for preparation of drug delivery system. The electrostatic interaction between two polymers is the most critical factor of forming complex coacervation. Thus, the complex formation can be affected by various parameters, including charge density, polymer concentration, ionic strength, pH, and temperature,

since these factors will affect the electrostatic interaction [26]. Drugs, such as MH, can be loaded in complex coacervation by different ways such as physical incorporation in complex, or as one component of complex [27]. MH is the example that may be used as one of the components of complex coacervation.

5. MH-loaded complexes may not stay in local injured/diseased site and diffuse away over time. In order to selectively deliver the MH-containing complexes at the injury site, it is preferable to encapsulate the complexes into injectable hydrogel [28,29]. The injectable properties enable the hydrogel to be delivered at the injury site in human body with minimal surgical wounds. Hydrogels are ideal candidates to load and deliver drugs due to its porous and biocompatible nature. However, since the pore size of hydrogels is usually too large to slow down the diffusion of drugs, drug delivery systems are generally incorporated into the injectable hydrogels by simply mixing before injection, and will be immobilized at certain positions in the body for localized drug delivery.

Injectable hydrogels can be formed by different mechanisms, including chemical crosslinking and physically crosslinking. For the chemical crosslinking, since the exposure of drugs to free radicals potentially affects drug activity [30], initiator-free approach to prepare chemical crosslinking hydrogel would be a better choice [31]. Besides chemically crosslinking hydrogel, physically crosslinking hydrogels are also popular for drug delivery. Comparing to chemical crosslinking, physical crosslinking avoids the biocompatibility issue of residue initiators or monomers. The driving force of physical crosslinking is usually the phase transition on a change of environmental conditions, such as salt, temperature and etc [32-40].

This editorial briefly summarized a couple of methods related to drug delivery of MH for biomedical applications. These methods may be used for drug delivery of other drug molecules. Work in drug delivery is a strong component of this journal and manuscripts in this area are strongly encouraged to submit.

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