On demand drug delivery from self-assembled hydrogel of methotrexate for treatment of rheumatoid arthritis

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Abstract

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints, which in turn cause swelling, pain, stiffness and redness in the joints. Methotrexate is immunosuppressant and inhibiting proliferation of the lymphocytes through to be responsible for synovial inflammation in rheumatoid arthritis. Local delivery of drugs offers the potential for high local drug concentration while minimizing systemic toxicity, which often observed with oral dosing. However, local depots are typically administered less frequently and include an initial burst followed by a continuous release. To maximize efficiency of therapy, it is critical to ensure that drug is only released when needed. An optimal system would be nontoxic and only release drugs during the period of exacerbation, self-titrating in response to the level of inflammation. The aim of present investigation was to develop and characterize on demand drug delivery from self-assembled hydrogel of methotrexate for rheumatoid arthritis. Development of an injectable self-assembled fibrous hydrogel, from a generally recognized as safe material, which is capable of encapsulation and release of agents in response to specific enzyme lipase that are significantly upregulated in a diseased state. Drug excipients compatibility was determined using FTIR. Self-assembled hydrogel was prepared using amphiphilic polymer ascorbyl palmitate. Batches were prepared by taking various concentrations of amphiphilic polymer. Optimized batch of self-assembled hydrogel containing methotrexate (2 mg), ascorbyl palmitate (1%w/v) and phosphate buffer saline pH 7.4 (2 ml) was characterized for sol to gel time, drug content, clarity, pH, viscosity and

rheology. Optimized self-assembled hydrogel was also evaluated Scanning electron microscopy, X-ray diffraction, syringeability, texture analysis and sterility test. *In-vitro* drug release study was performed in presence and absence of lipase enzyme to evaluate on demand drug release. Stability study was performed at room temperature and accelerated condition. FTIR study confirms absence of incompatibility between drug and excipients.

Sol to gel time and drug content of optimized batch was found to be 4.5±0.41 min, 95.83±0.59 % respectively. Rheological characterization showed thixotropic behavior of prepared self-assemble fibrous hydrogel suitable for injection in intra articular space. Scanning electron microscopy and X-ray diffraction confirms the fibrous structure of self-assembled-fibrous hydrogel. Syringeability was found to be optimum to pass solution from 22-25 gauge needles. Higher value of adhesiveness measured by texture analysis confirms intimate contact with surface like tissues. Absence of microbial growth was confirmed by sterility testing. *In vitro* drug release study reveals that self-assembled fibrous hydrogel showed drug release in presence of lipase up to 7 days. Stability study results indicated that self-assembled hydrogel stored at room temperature remains stable with almost no change in evaluated parameter. This novel approach represents a next-generation therapeutic strategy for localized treatment of rheumatoid arthritis with reduced systemic toxicity associated with certain drug like methotrexate.

Keywords: Self-assembled hydrogel, Rheumatoid arthritis, Methotrexate, Systemic toxicity