Brief Summary

Rheumatoid arthritis (RA), the most common form of inflammatory arthritis that mainly affects the diarthrodial joints, has a substantial socio-economic burden in terms of cost, functional disability, and lost productivity. Although many patients achieve remission, with the existing treatment strategies, management of RA still remains a challenge. This is attributed to certain unfavorable properties of existing drugs such as instability, poor solubility, low cell permeability, rapid metabolism, and indiscriminate systemic distribution. These, in turn, lead to low bioavailability of drug at the target site, thereby requiring high and frequent dosing, which may lead to extra-articular adverse effect. To overcome these limitations, a number of novel drug delivery systems have been reported. However, due to the expensive specialized additives and sophisticated processing, their production cost goes up. Other limitations of these advanced delivery systems include difficulty of scaling-up, poor drug-loading, leakage, and stability issues. Prodrug strategy has emerged as major approach to modify the physicochemical properties of such drugs. However, many approved small-molecule prodrugs still show unfavourable pharmacokinetic and pharmacodynamic properties, thereby restricting their clinical applications.

Self-assembling prodrugs, a new paradigm in drug delivery, offer the key benefits of both prodrug design and nanotechnology, thereby exhibiting high drug loading, less premature drug leakage, improving pharmacokinetic/pharmacodynamic parameters and targeting ability with no added cost of additives and processing. In aqueous environment, amphiphilic molecules of prodrugs form supramolecular nanostructures, endowing all the favourable characteristics of nano-drug delivery systems. Targeting can be further enhanced by selection of suitable linkers offering temporal/spatial controlled-release of drugs in arthritic joints exploiting specific pathophysiological characteristics including aberrant enzymes, low *p*H, and oxidative stress state.

Sulfapyridine (SP), that has been reported to be equally effective as methotrexate, leflunomide, hydroxychloroquine, and intramuscular gold in RA, has not enjoyed much success due to various formulation and therapeutic challenges. Therefore, the present study proposes to develop enzyme-responsive self-assembled nanomedicines of amphiphilic SP prodrugs. Intra-articular injection of these nanostructures is anticipated to exhibit longer retention in synovial joints by virtue of their size and two-step release of SP i.e., disassembly of nanostructures and endogenous-stimuli triggered release of drug.

In the present research work, we have successfully synthesized the amphiphilic prodrugs of SP using enzyme-responsive amide linker. Promoieties such as fatty acids of variable carbon chains as well as Boc-protected amino acids were used to synthesize amphiphilic derivatives. All the synthesized prodrugs were characterized by IR, NMR, and mass analysis. The percentage purity of the synthesized prodrugs, as determined by HPLC, was found to be greater than 97%. Furthermore, we had fabricated the self-assembled nanoparticles of SP prodrugs. Based on the morphology, stability, and hydrodynamic diameters of self-assembled particles, SP-LLEU was

found to form stable nanostructures of optimum size, thus selected for *in vivo* evaluation. Intra-articular injection of nanoparticles to rats with adjuvant-induced arthritis mitigated the inflammation, demonstrated by decreased levels of inflammatory arthritis, thus offering a cost effective, safe and therapeutically effective approach in the treatment of RA.

Signature of Nominator

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