Brief Summary

Rheumatoid arthritis (RA), the most common form of inflammatory arthritis that mainly affects the diarthrodial joint, has a substantial socio-economic burden in terms of cost, functional disability, and lost productivity. Although, with the new treatment strategies, many patients achieve remission, management of RA is still challenging because of unfavorable properties of existing drugs such as instability, poor solubility, low cell permeability, rapid metabolism, and indiscriminate systemic distribution all contributing towards the low bioavailability of drug at the target site, thereby require 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 developed. However, these advanced delivery systems themselves lead to an increase in cost and possess certain limitations like difficulty of scaling-up, poor drug-loading, leakage, and stability issues. Prodrug strategy has emerged as major toolbox to modify the physicochemical properties of drugs, however, many approved small-molecule prodrugs still show unfavourable pharmacokinetic and pharmacodynamic properties, thereby restrict their clinical applications.

Self-assembling prodrugs, a new paradigm in drug delivery, offer the key benefits of both prodrug design and nanotechnology, thereby exhibit high drug loading, less premature drug leakage, improve pharmacokinetic/pharmacodynamic parameters and targeting ability. In aqueous environment, these amphiphilic molecules form supramolecular nanostructures, which by virtue of their size decreases the renal clearance rate, thereby extending circulation time and increased accumulation at disease site. Notably, selection of suitable linkers offers temporal/spatial controlled-release of drugs in arthritic joints that have specific pathophysiological characteristics including aberrant enzymes, low pH, and oxidative stress state.

Sulfapyridine, that has been reported to be equally effective to that of methotrexate, leflunomide, hydroxychloroquine, and intramuscular gold, 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 sulfapyridine 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 sulfapyridine i.e., disassembly of nanostructures and endogenous-stimuli triggered release of drug.

Working in this direction, our team has successfully synthesized the amphiphilic prodrugs of sulfapyridine using *p*H and 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 appearance of amide protons in the range of 8-10 ppm in proton NMR indicated the successful synthesis of prodrugs. The aromatic protons were found to be deshielded to a higher value (6–8 ppm) due to the electron-withdrawing nature of the amide bond. Signals observed in the range of 1-2 ppm in proton NMR were attributed to the aliphatic protons of the alkyl chain. In ^{13}C NMR,

the appearance of signal around 170-172 ppm indicated the presence of carbonyl carbon in prodrugs. The signals due to the alkyl chain were observed at a value less than 40 ppm. The appearance of molecular ion peak in mass spectrum also confirmed the successfully synthesis of prodrugs. In IR spectra, C=O amide band appeared at approximately 1695 cm^{-1}. The UV absorption maxima of all the prodrugs were found to be the same, *i.e.*, 265 nm, which is due to the similarity in the chromophore. The percentage purity of the synthesized prodrugs, as determined by HPLC, was found to be greater than 94%. Currently, we are doing the validation of HPLC method as per ICH guidelines. One of the parameters i.e., linearity has been determined and the coefficient of determination were found to be more than 0.99.

Further, we will develop and characterize the self-assembled nanoparticles, followed by pharmacological evaluation.

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