Title:	BIOCOMPATIBLE AND THERAPEUTIC NANOMICELLE FOR THE TREATMENT OF INFLAMMATORY DISEASE.
Authors:	Vyawahare, Akshay Raghu.
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Abstract:	Inflammation is an immune response to pathogenic, bacterial or foreign bodies which is primarily characterized by redness, swelling, heat, pain etc. Normal inflammatory stimuli temporarily upregulates the inflammatory players, however it gets resolved when threat has passed. It plays major role in defense mechanism, however if not controlled can turn into several complications called inflammatory diseases. Depending upon the course of inflammation there can be acute and chronic inflammation. Inflammatory diseases are broad list of classification which is unregulated interplay of several cytokines, chemokines as well enzymes. Inflammatory disease including Rheumatoid arthritis (RA) and Ulcerative colitis (UC) are major contributors of mortalities worldwide with no perfect cure till date. Conventional therapies are anti-inflammatory drugs involves several other complications due to its non-specific reach and low bioavailability of drugs due to lipophilic nature. Nanotechnology based drug delivery system emerged as new therapeutic alternative to overcome the drug related drawbacks. Such kind of drug delivery systems is glooming need and can be looked as an option to treat inflammatory diseases. In this thesis we have developed or synthesized nanotechnology based therapeutic nanomicelles by conjugation of active molecules with amphiphilic backbone for treatment of RA and UC. The ultimate goal of these strategic therapies was to provide relief from painful stimuli and cure from the disease as well as site specific reach avoiding non-specific effect. We have utilized chemical synthesis to conjugate an active therapeutic molecule claiming potential role against inflammation with an amphiphile which self assembles to form nanomicelles. These nanomicelles have hydrophobic core these cores can be utilized to incorporate the potent anti- inflammatory drug which are hydrophobic in nature. We have developed 3 such type of drug delivery system with different approaches and targets to treat the disease. In first work we developed nanomicelle carrier system for the delivery of anti- inflammatory drug 9-aminoacridine (9-AA) for the treatment of experimental arthritis. In this work we have synthesized Caffeic acid (CA) conjugated mPEG-b-PCL nanomicelle (NM). We anticipated that CA being potential antioxidant or anti- inflammatory against pro-inflammatory markers when combined with 9AA mightexhibit enhanced therapeutic potential. We observed that 9-AA and CA has been successfully bridged between mPEG-b-PCL nanomicelle. Further we demonstrated that nanomicelle efficiently augmented disease severity such as joint damage, swelling, cartilage erosion by inhibiting the expression of pro-inflammatory markers NF-κB and HIF-α and simultaneous activation of anti-inflammatory marker NR4A1 in Collagen induced arthritis model. In 2 nd work we synthesized chlorotoxin conjugated mPEG-b-PCL (mPEG-b-PCL- CTX) nanomicelle and incorporated Neutrophil elastase (NE) inhibitor drug sivelestat. Chlorotoxin is a MMP-2 inhibitor we anticipated bringing two potential moieties together on drug delivery platform might exhibit enhanced therapeutic outcome against Ulcerative colitis. We showed that sivelestat loaded nanomicelle (SLM) electrostatically adheres to inflamed colon of human as well as on preclinical mice model. We also showed that SLM exhibited enhanced therapeutic potential by simultaneous inhibition of MMP-2 and NE by chlorotoxin and sivelestat. In 3 rd work we explored the therapeutic potential of Sivelestat loaded nanomicelle (SLM) against collagen induced arthritis model. We observed promising results against UC hence we further extended its potential to treat RA. We showed that SLM provided significant anti-inflammatory potential by reducing the joint damage, cartilage erosion and swelling. The mechanistic exploration of SLM showed that it is acting by the inhibition of proteolytic enzymes such as MMP-2 and NE. The 4 th work comprised of conjugation of chlorogenic acid with PLGA which self- assembles to form nanomicelles when immersed in aqueous medium. This assembly was incorporated with Methotrexate (MTX) which is potent anti-arthritis drug but due to hydrophobic nature and collateral side effects used inefficiently. Chlorogenic acid earlier showed potential anti-inflammatory as well as anti-oxidant effect. We observed that site specific delivery of MTX along with carrier exhibiting its own therapeutic effect showed enhanced potential against collagen induced arthritis by inhibiting the RANKL, NF-κB which augments the joint damage and cartilage erosion. These drug delivery systems were characterized with different nanotechnology based characterization techniques for their shape, size, charge, synthesis characterization, cytocompatibility, in-vitro characterization, along with in-vivo evaluation on animal models. We observed that bridging two different therapeutic molecules on nanomicelle drug deliveryplatform efficiently worked and ultimately showed enhanced therapeutic potential against DSS induced colitis model as well as Collagen induced arthritis model.
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