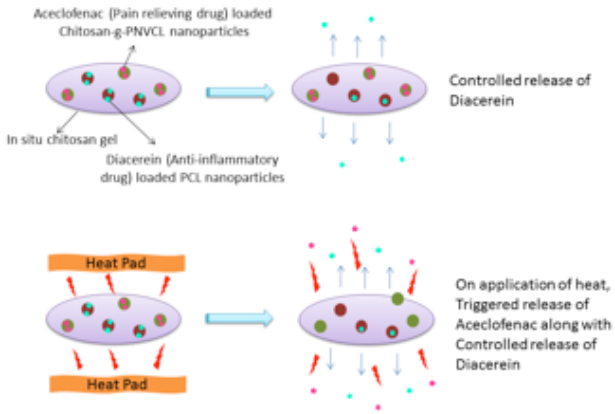
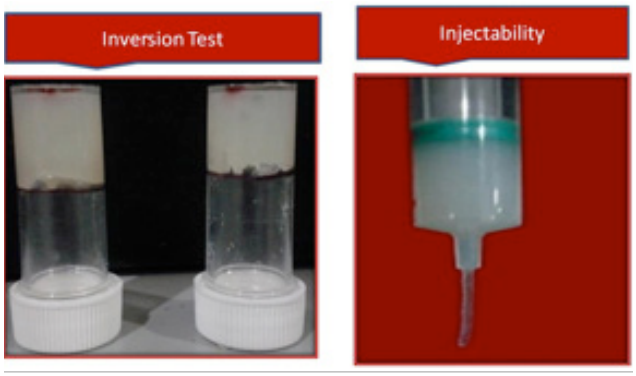
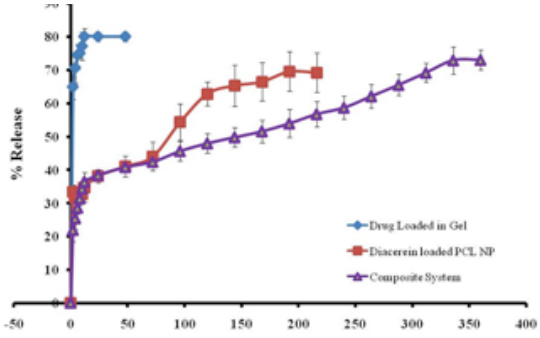
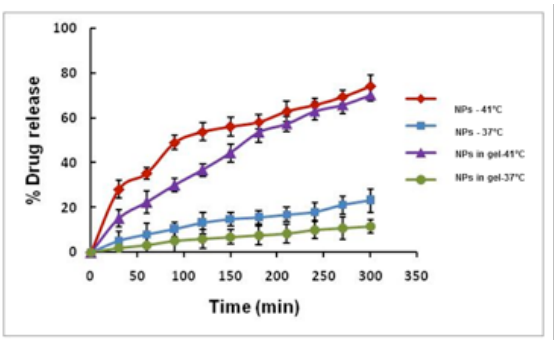
Development of nanoengineered dual release graft for pain / inflammation management in osteoarthritis



Osteoarthritis (OA) is a chronic degenerative disorder of joints, which has multi-factorial etiology. OA is the second most common rheumatological problem and is most frequent joint disease with prevalence of 22-39% in India. Injectable polymeric composite gel are synthesised with tailor-made polymeric nanoparticles to achieve both controlled release and thermo-responsive on application of a heat pad on the desired site. The main objective of the project is to develop an intra-articular drug delivery system for OA using a composite *in situ* gelling system. This system is designed in such a way that it can deliver an anti-inflammatory drug in a sustained/controlled manner, and a pain-relieving agent on response to application of heat. The composite *in situ* gelling system comprise of a thermoresponsive *in situ* gel made of chitosan.







The system will have two different sets of microparticles embedded in an *in situ* gelling system:

- PCL (Poly Caprolactone) nanoparticles: to deliver an anti-inflammatory drug (Aceclofenac) in a sustained manner for few weeks to a month.
- Chitosan-g-PNVCL (Poly-N-Vinyl Caprolactam) (CP) nanoparticles: This is a thermoresponsive polymer, which can deliver a pain-relieving agent (Diacerin) on application of the heat. The patient can apply a heat pad on the affected area to get relief from pain.
- The composite injectable gel was prepared successfully comprised of Diacerin loaded PCL nanoparticles and Aceclofenac loaded CP nanoparticles. PCL nanoparticles serves as carrier for sustained release of anti-inflammatory drug Diacerin and CP nanoparticles serves as a thermo-responsive carrier releasing the pain relieving Aceclofenac drug in response to heat.

Further characterisations such as SEM and DLS were done for the particle size analysis. Fourier transform-infra red spectroscopy analysis was performed to study the drug-carrier interaction and rheology studies to determine the mechanical strength of the composite gels. Release profiles of both the drugs were obtained from the network of composite gel structure. The release of Diacerin was found to be sustained with respect to time for a longer time period where as the release of Aceclofenac was in terms of pulsatile release with on/off mode of temperature i.e., the release was significantly high in presence of heat.

The delivery of the drugs (NSAIDs) is usually systemic accounting for their gastrointestinal toxicity. Orally administered agents depend on gastrointestinal resorption and are subject to first-pass metabolism in the liver. This intra-articular injectable thermoresponsive composite gel based delivery system provides improved stability *in vivo*, extended bioavailability, and optimised delivery to inflamed synovium resulting in non-selective immuno-suppression, have low systemic toxicity and be affordable.

The nanocomposite injectable gel was prepared and characterised for various parameters with respect to size, morphology, mechanical strength, injectability and its chemical interaction with drugs respectively. Drug release kinetics was determined for the composite system and for the nanoparticles separately. *In vitro* anti-inflammatory studies, *in vivo* compatibility, pharmacokinetics and the anti-inflammatory activity of the composite injectable gel has to be assessed in pain-induced models *in vivo*.

Prof. Rohit Srivastava, Department of Biosciences and Bioengineering, rsrivasta@iitb.ac.in