

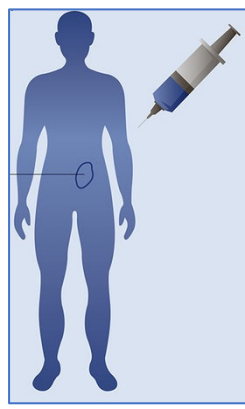


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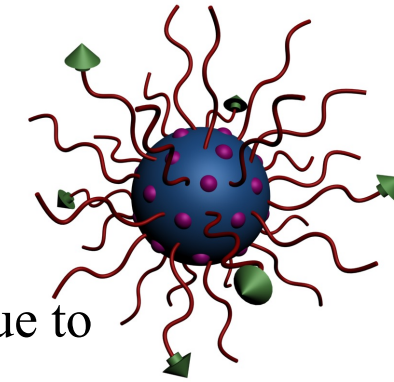
Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs known worldwide when it comes to the treatment of inflammatory diseases. NSAIDs are commonly used to cure arthritis (rheumatoid) and for pain relief. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) of phenylacetic acid class with effective activities like anti-inflammatory, analgesic and antipyretic. Diclofenac is one of the most prescribed NSAIDs, worldwide. However, the use of NSAIDs including Diclofenac in the treatment of rheumatoid arthritis is limited by some of their side effects (such as gastrointestinal issue, ulceration, even bleeding and cardiotoxicity) due to their unfavorable pharmacokinetics. Delivering NSAIDs by using nanotechnology is promising prospects but even the encapsulation of NSAIDs into nanoparticles faces issues: low drug loading, immature burst release and the destabilization of the nanoparticles suspension due to drug crystallization. To overcome these challenges we have formulated colloidal nanocarriers prodrugs (1-4) of diclofenac. We have successfully formulated prodrugs of diclofenac acid; **1**, **2**, **3**, **4**, into nanoparticles stabilized by the sole addition of polymer. Emulsion-evaporation formulation process allowed the formation of stable nanoparticles. Adjusted drug/lipid ratio and the prodrugs concentration, nanoparticles of prodrugs, with a size between 110 to 150 nm can be obtained. Moreover, the prepared nanoparticles were studied for stability at 40°C and room temperature. The designed nanoparticles were stable (over 30 days), nanosized (d_h 110 to 150 nm), displaying negative zeta potential (-29 to -49 mV), with high prodrug entrapment efficiency (90-96%). To ensure that the anti-inflammatory activity of diclofenac was preserved after formulation, in vitro and in vivo biological activities were performed and all nanoparticles were more efficacious compared to the drug diclofenac.

Potent Non Steroidal Anti inflammatory Drug (NSAID)
used as pain killer and anti rheumatic drug
Diclofenac Sodium leads to severe side due to undesirable
pharmacokinetics like

- Short half life
- Large volume of distribution
- Time dependent dosage



- Lower dose administration
 - Limited side effects
 - Increased efficacy
- Nanoparticles lack in rate of clinical translation due to
- Limited drug loading
 - Premature burst release
- Prodrugs of diclofenac & lipid polymer
- High drug loading
 - Long circulating nanoparticles



SAIDs Nanoparticles	
Hydrodynamic Diameter (nm)	140-150
PdI	<0.2
Zetapotential	-29 to -45
%EE	>90%

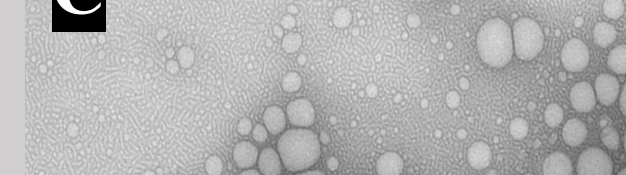


Figure 1 shows the morphology of SAIDs nanoparticles. The TEM image (C) displays numerous spherical nanoparticles of varying sizes, with a scale bar indicating 200 nm. The nanoparticles appear to be well-dispersed and have a relatively uniform spherical shape.

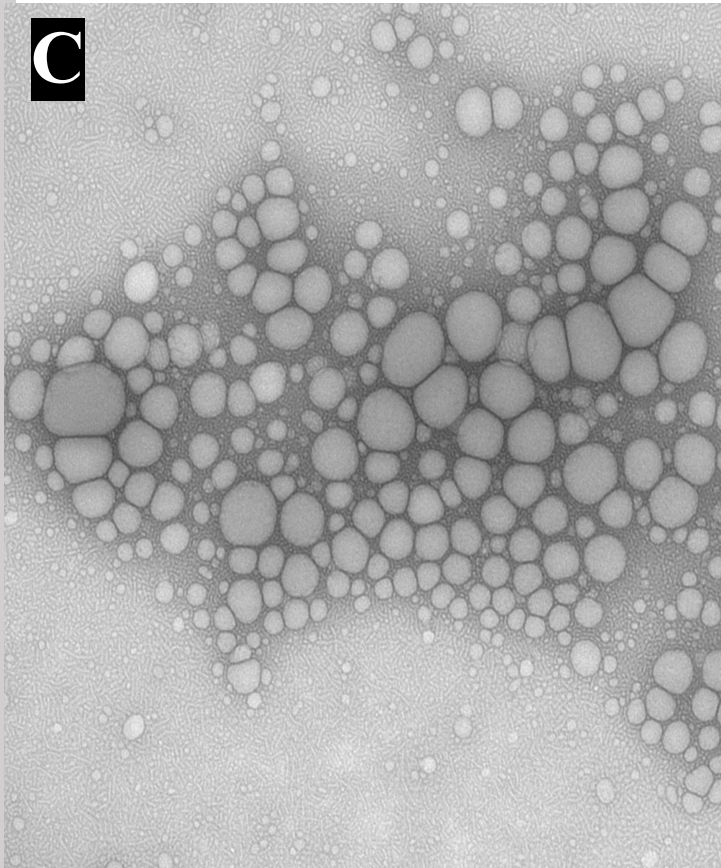
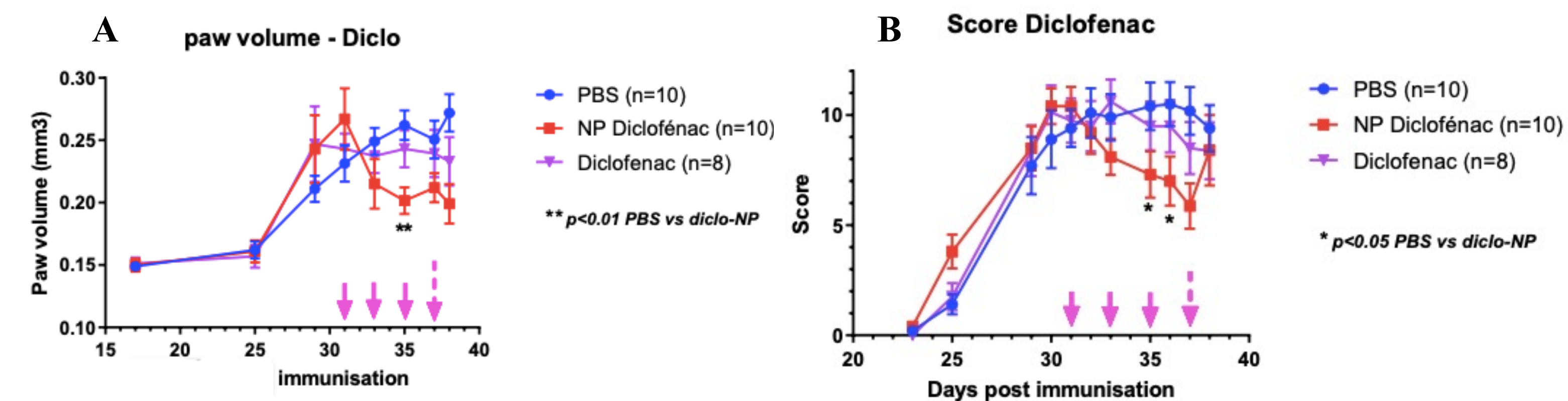
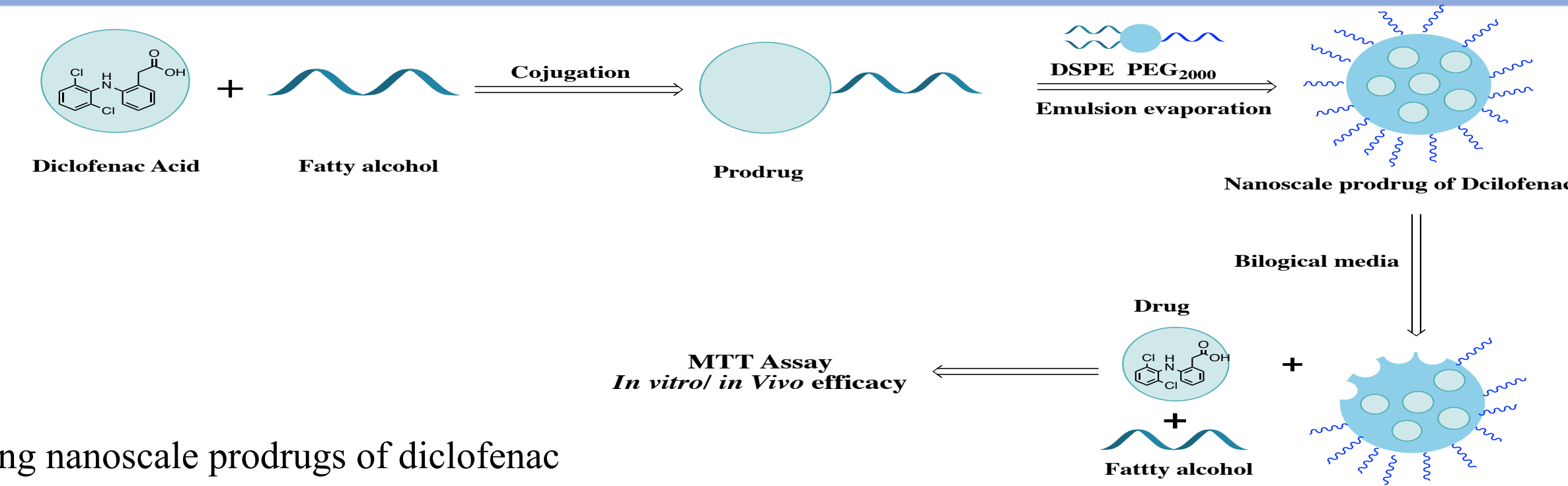
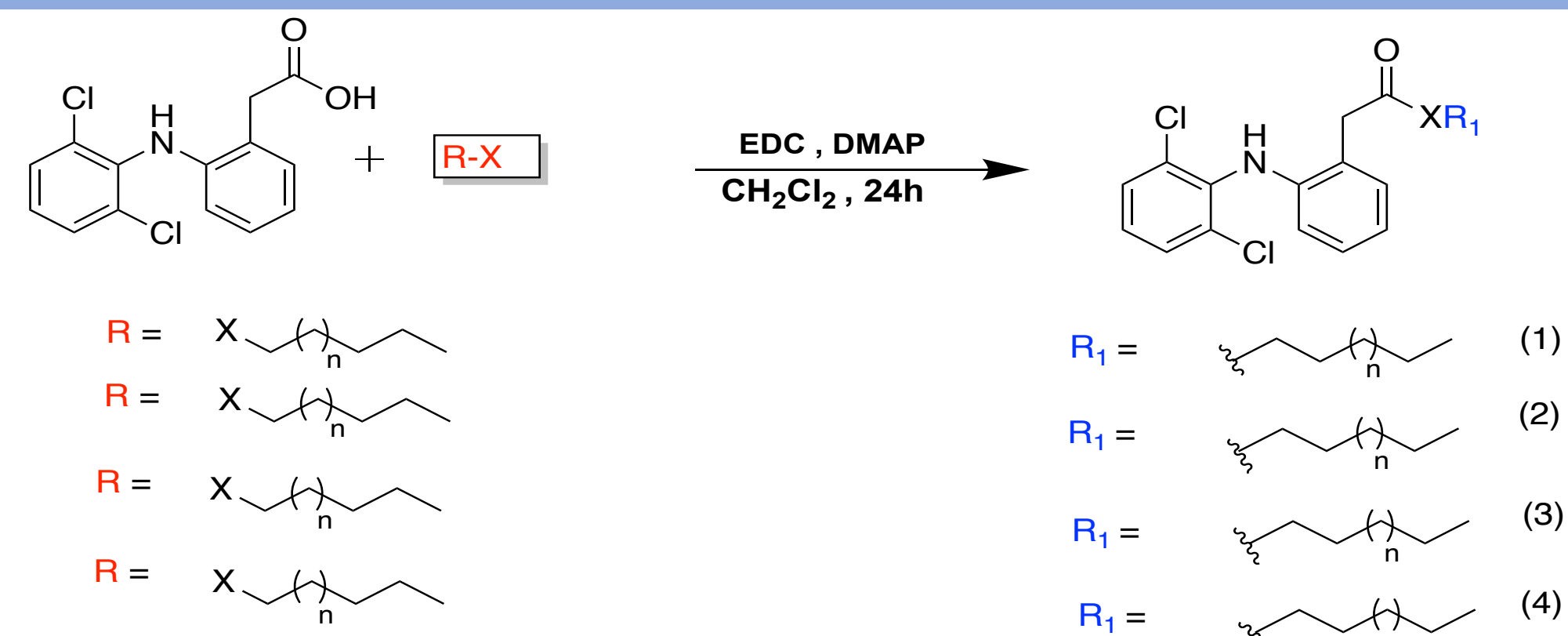


Figure-1: A. Statistical analysis of hind paw volume of mice compared to PBS. **B.** Arthritic score, **C.** TEM image of prodrug 3 NPs



- Designing nanoscale prodrugs of diclofenac
- Preparation of stable nanoparticle with maximum encapsulation efficiency
- Safer NSAIDs with enhanced efficacy
- May offer passive targeting (EPR effect)



X represents Nitrogen, Sulphur or Oxygen atom

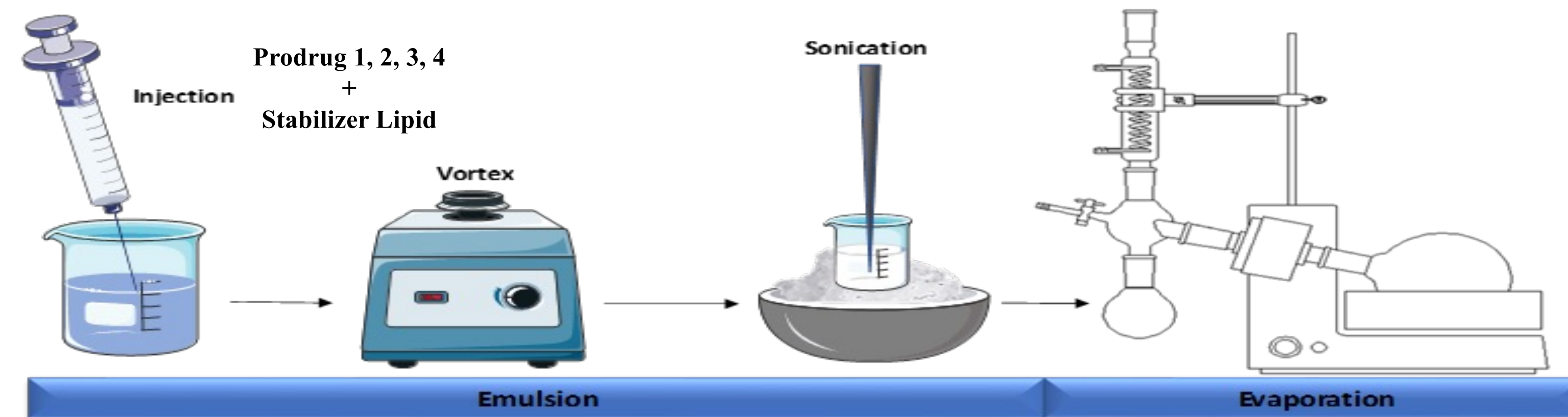
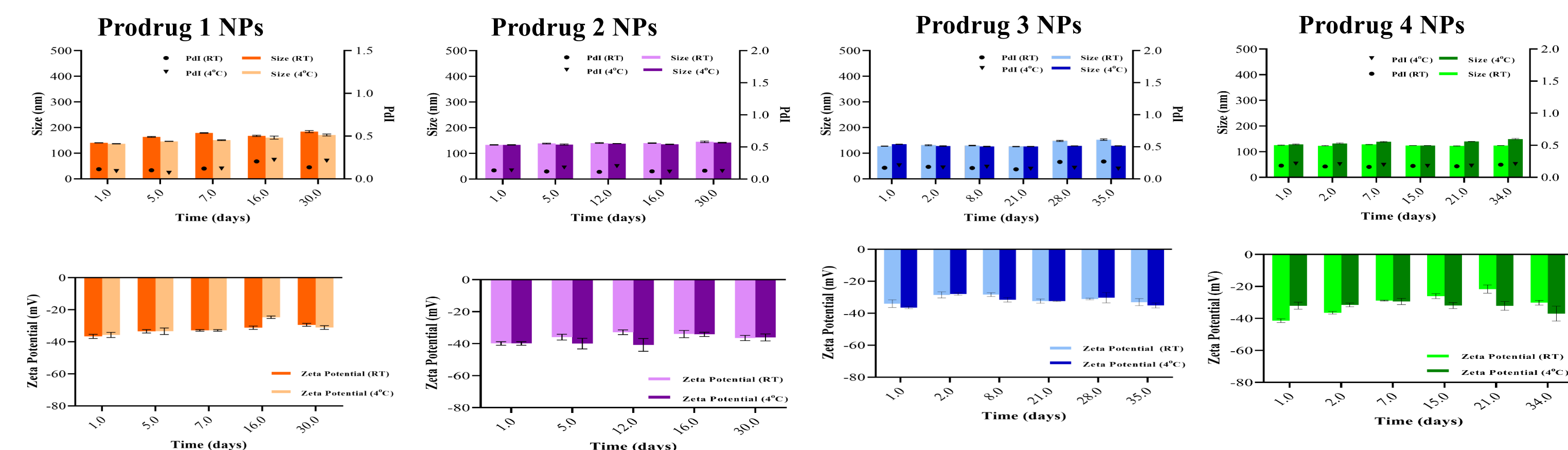
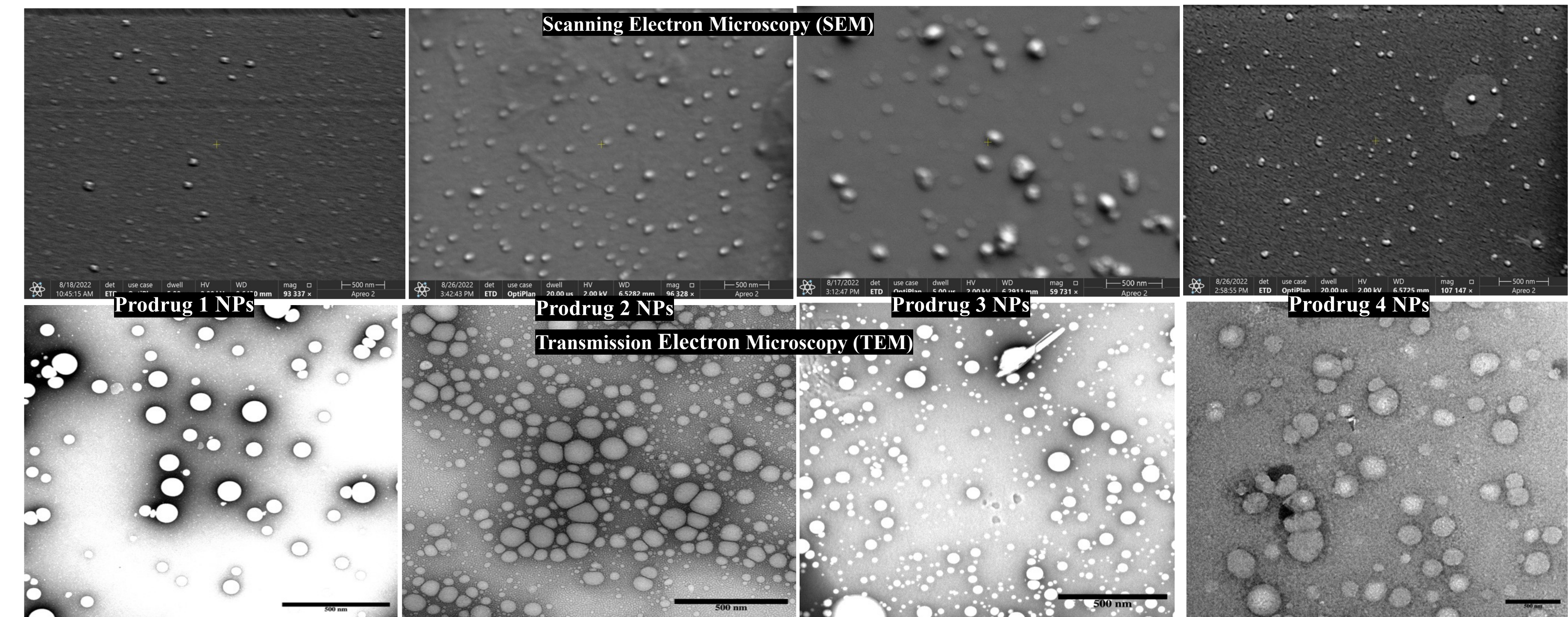
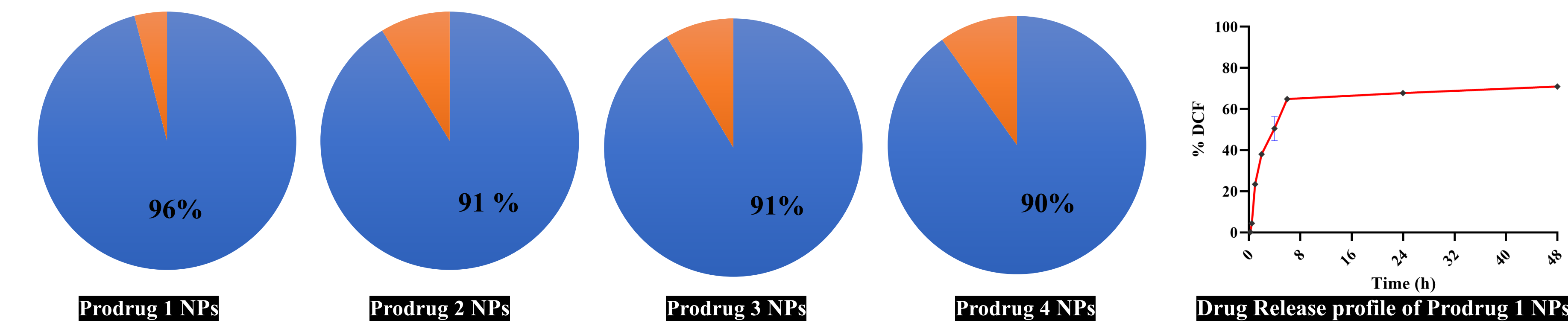


Figure-2: Size (d_H), Polydispersity index (Pdl) and Zeta potential of Prodrug 1(Orange colour), Prodrug 2(Purple), Prodrug 3 (blue) and prodrug 4(green) overtime (30 days) at Room temperature and 4°C storage conditions.



$$\% \text{ Encapsulation Efficiency} = \frac{\text{Amount of prodrug in NPs} - \text{Amount of free prodrug in NPs}}{\text{Weight of drug in NPs}} \times 100$$



In progress; prepared nanoparticle will be subjected to cell viability assay (MTT Assay) and anti-inflammatory activity would be tested against proinflammatory cytokines

All the nanoscale prodrugs of diclofenac Acid led to successful nano-formulations of spherical morphology having d_h 140 to 150 nm and polydispersity index less than 0.2. Zeta Potential of all nanoparticles were -29 to -45 mV. All nanoparticles showed drug entrapment of greater than 90%. Prodrug 1 NPs was selected as candidate for drug release studies. Drug release studies carried out in Mice plasma confirmed the enzymatic cleavage of the prodrug and liberation of active drug, almost 70% of entrapped drug was released in 8 hours and maintained till 48h. Prodrug 3 NPs were selected for in vivo studies against Collagen Induced Arthritis in mice and It showed better suppression of Arthritis compared to free drug. This is encouraging for our future aspect of in vivo and in vitro studies of all NPs which are yet to be performed.