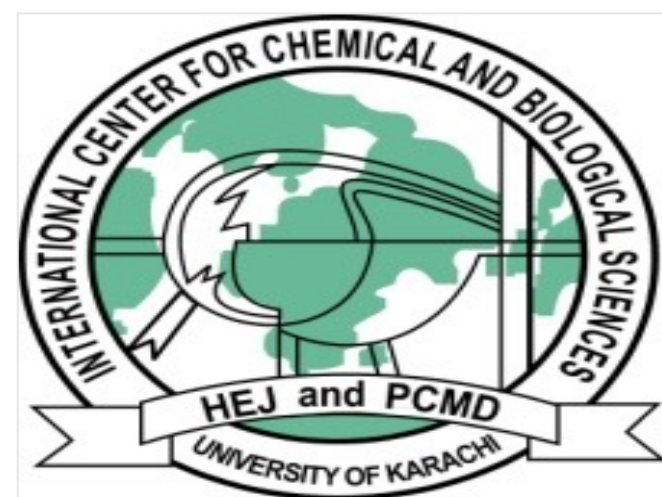




# Designing Nanoscale prodrugs of SAID's and their biological evaluation

Aqsa Arif, Saadat Hussain, and Dr. Mujeeb ur Rehman

International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan.

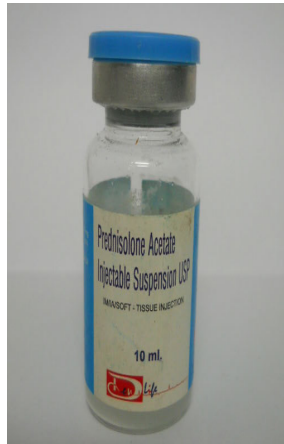
## Abstract

Inflammation is protective function of immune system against the damaging stimuli. Rheumatoid arthritis is one of the types of inflammation where stiffness, swelling and destruction of joints occur. The worse effects of RA are potential disability, reduction in life expectancy (about 10 years), enhanced angiogenesis and decreased quality of life. Steroidal anti-inflammatory drugs (SAIDs) have a long history as anti-inflammatory and immunosuppressive drugs but their use is limited by their side effects particularly during long term therapy. The encapsulation of SAIDs such as Prednisolone and Methylprednisolone, in nanoparticles (NPs) faces two main issues: a low drug loading and the destabilization of the nanoparticle's suspension due to drug crystallization. To address the issue of poor drug loading and stability of nanoparticles we designed prodrug(s)/analogues, **1,2,3, 4**, of MPD and PRD respectively. Each analogue/prodrug is then formulated into nanoparticles by using lipid polymer. The Nanoprecipitation/ethanol injection method allowed the formation of stable nanoparticles with optimized drug/lipid ratio. Nanoparticles were characterized by using DLS and size is within 110nm and 140nm with Pdl below 0.2. Owing to the presence of polymer, a high drug entrapment efficiency of  $\geq 90\%$  w/w was achieved for all nanoparticles.

## Introduction

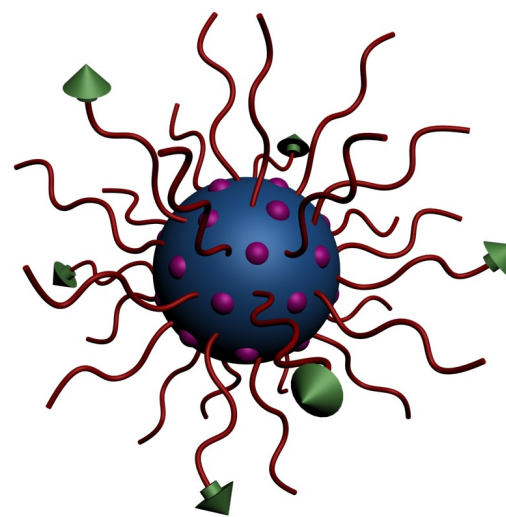
### Methylprednisolone and prednisolone

Potent Steroidal Anti inflammatory Drug (SAID) used as pain killer and anti rheumatic drug  
SAIDs lead to severe side effects due to undesirable pharmacokinetics like  
➤ Short half life  
➤ Large volume of distribution  
➤ Time dependent dosage  
➤ Lack of tissue specificity

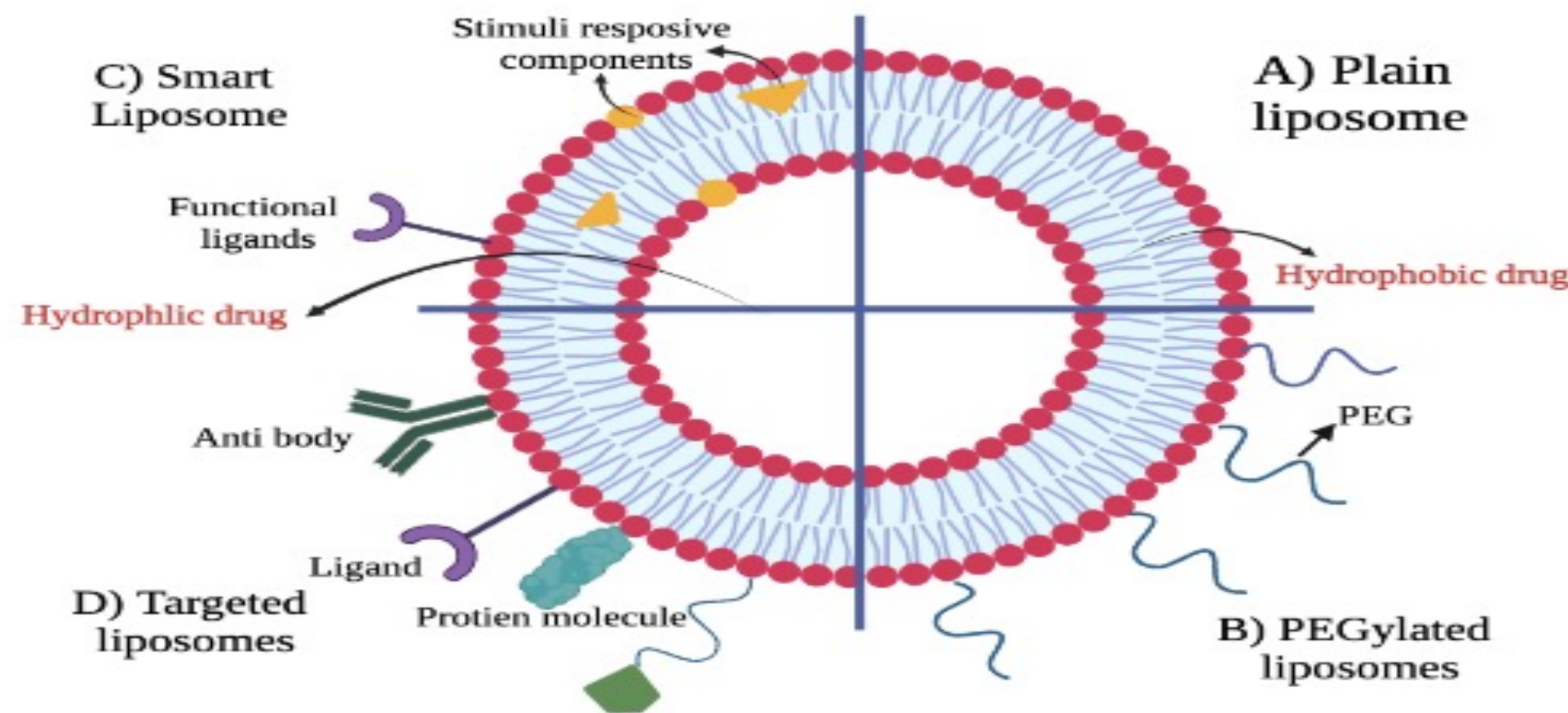


### Nanoparticles of SAIDs

- Lower dose administration
  - Limited side effects
  - Increased efficacy
- But, Nanoparticles of SAIDs have issue of
- **Limited drug loading**
  - **Premature burst release**
- Prodrugs of SAIDs & Phospholipids
- High drug loading
  - Long circulating nanoparticles
  - Passive targeting

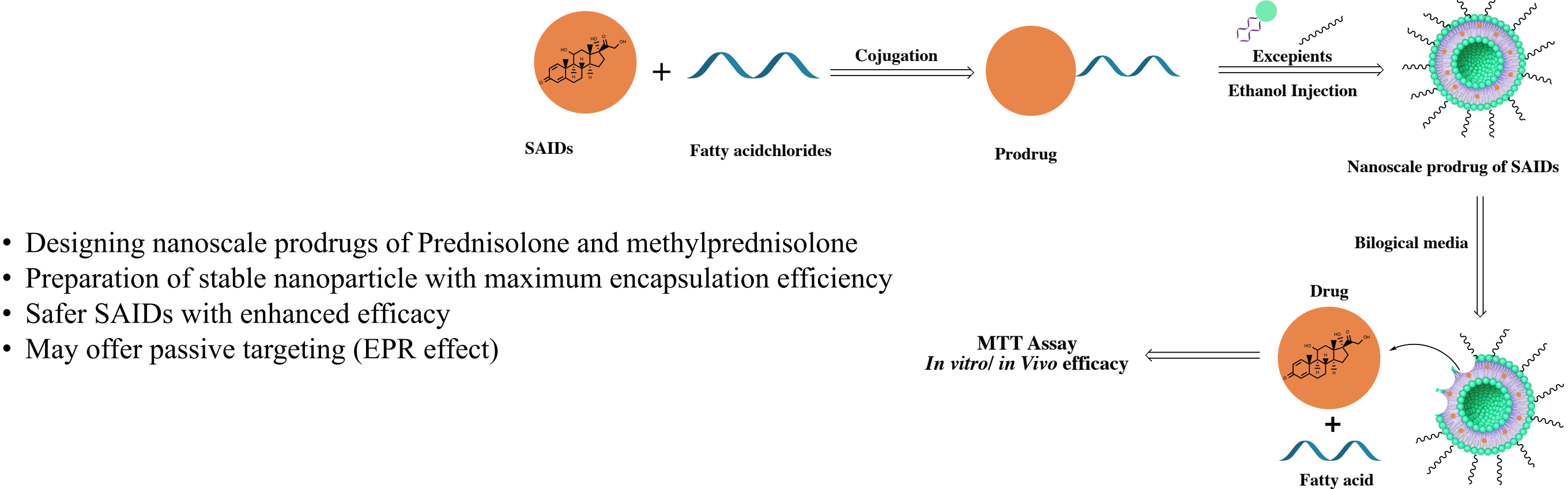


## Background



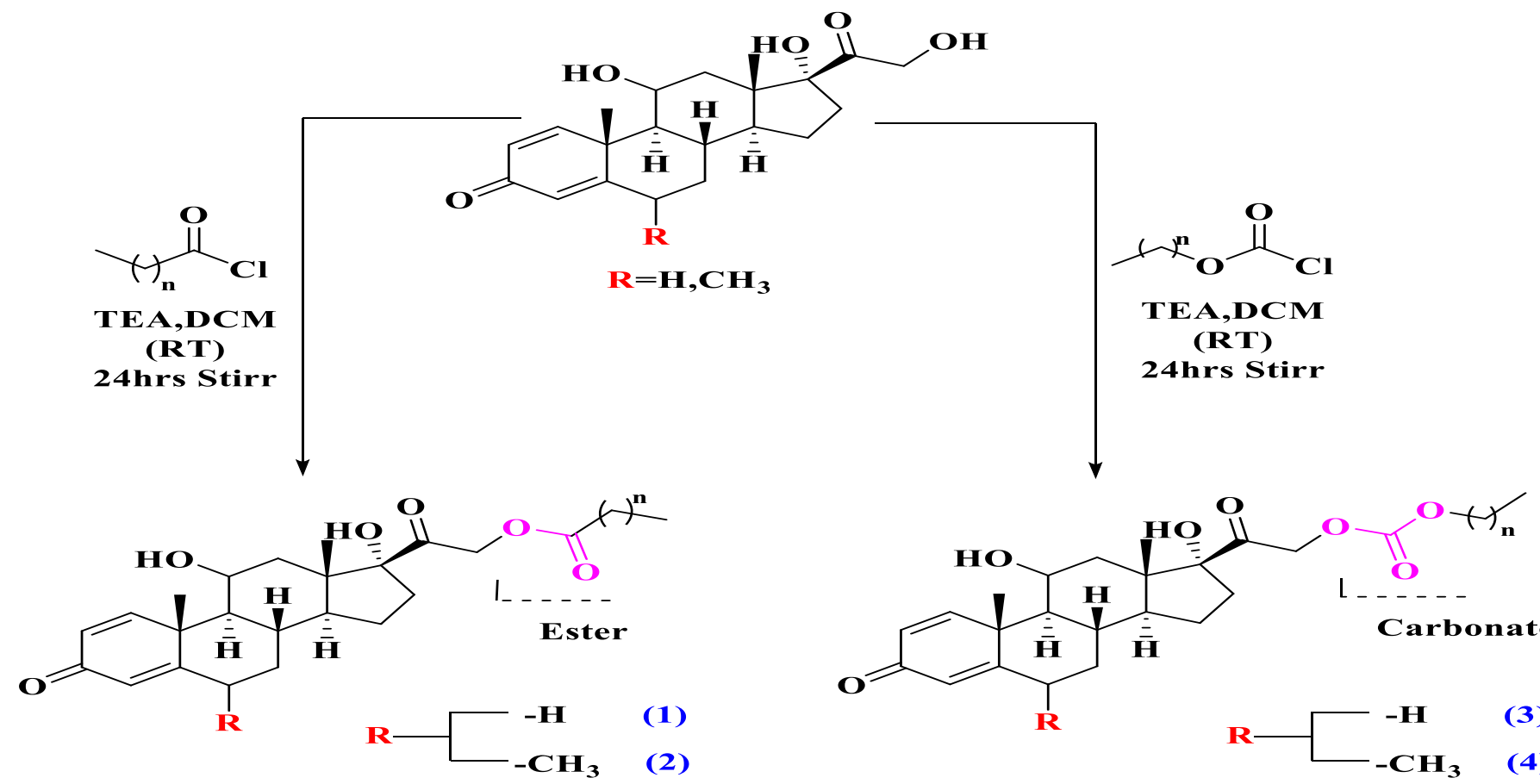
| SAIDs Nanoparticles        |            |
|----------------------------|------------|
| Hydrodynamic Diameter (nm) | 100-120    |
| PdI                        | <0.2       |
| Zetapotential              | -25 to -35 |
| %EE                        | >90%       |

## Objectives

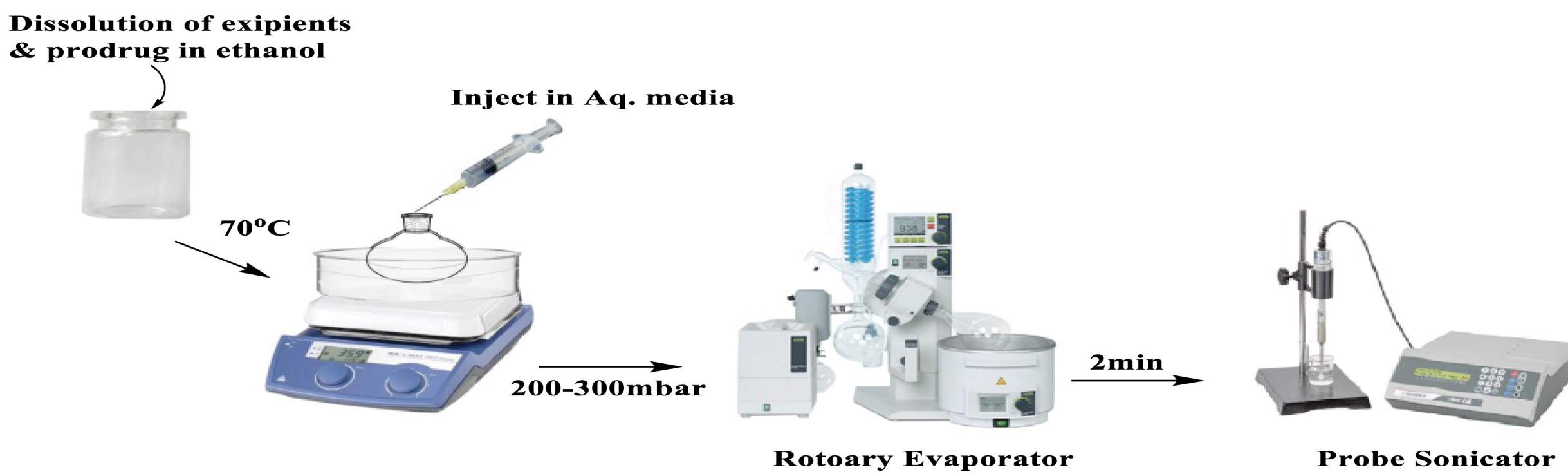


- Designing nanoscale prodrugs of Prednisolone and methylprednisolone
- Preparation of stable nanoparticle with maximum encapsulation efficiency
- Safer SAIDs with enhanced efficacy
- May offer passive targeting (EPR effect)

## Synthesis of Prodrugs



## Formulation (Ethanol Injection)



## Physicochemical characterization

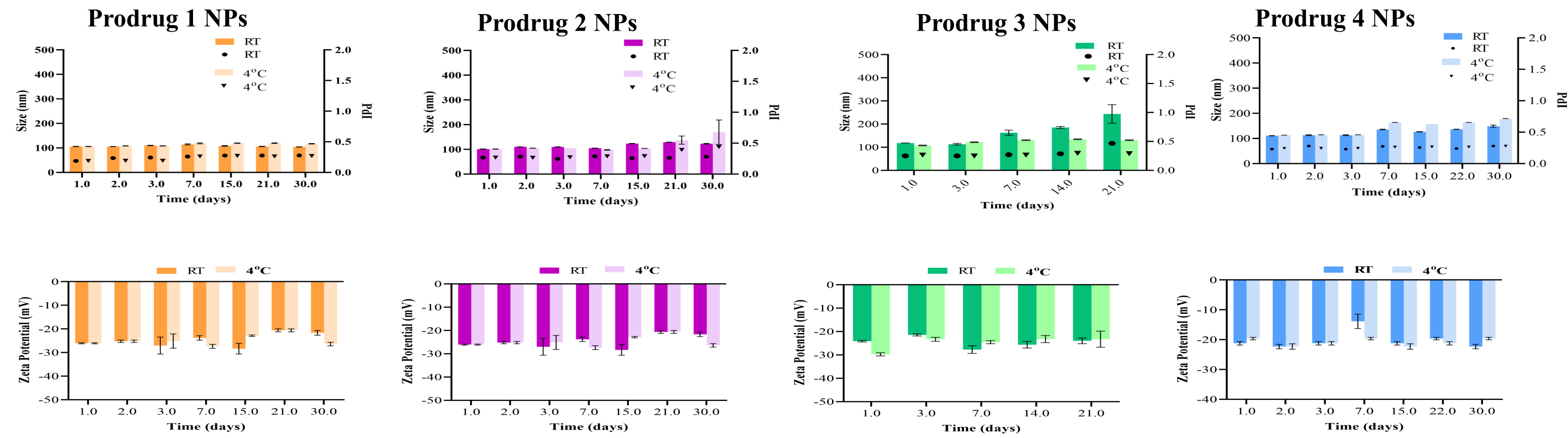
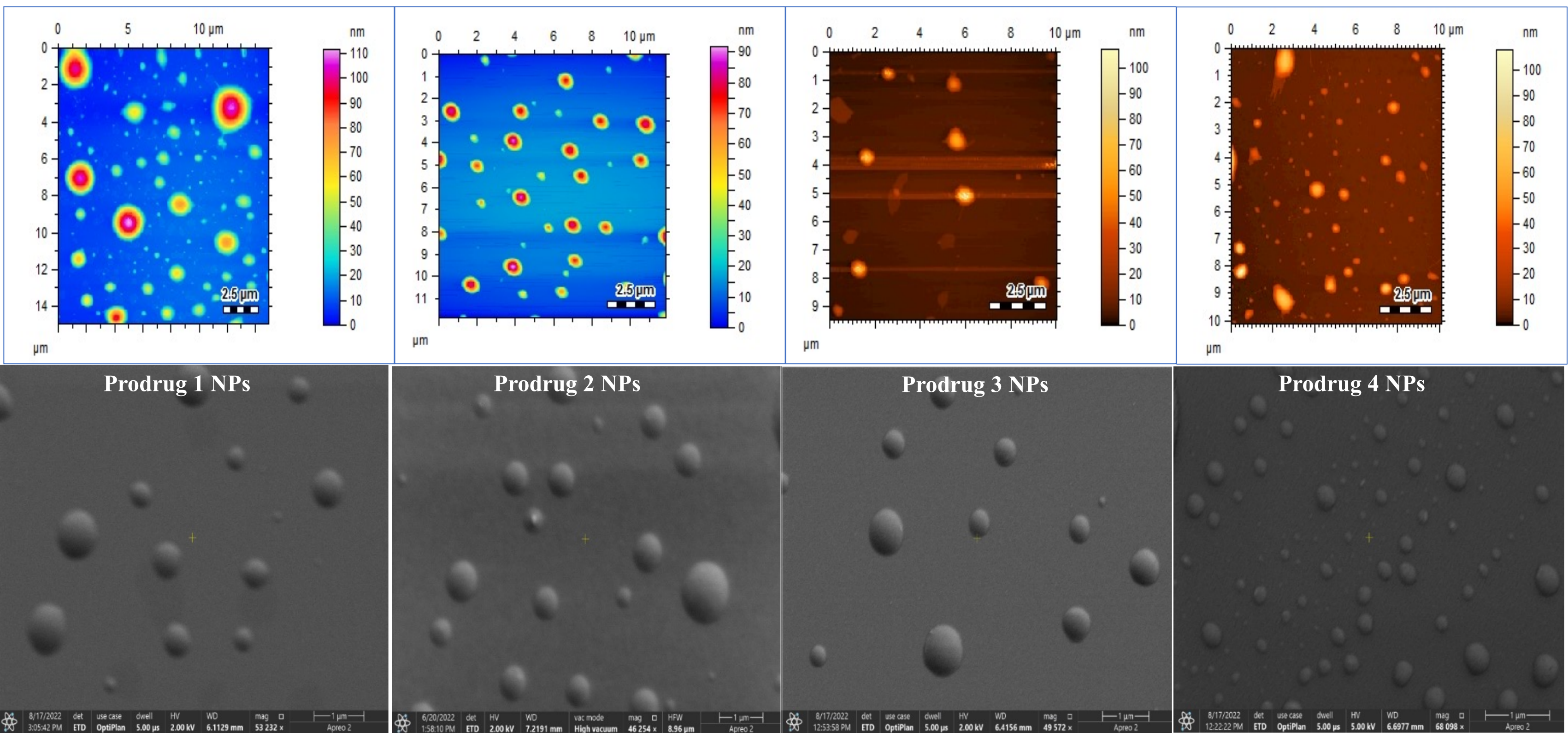
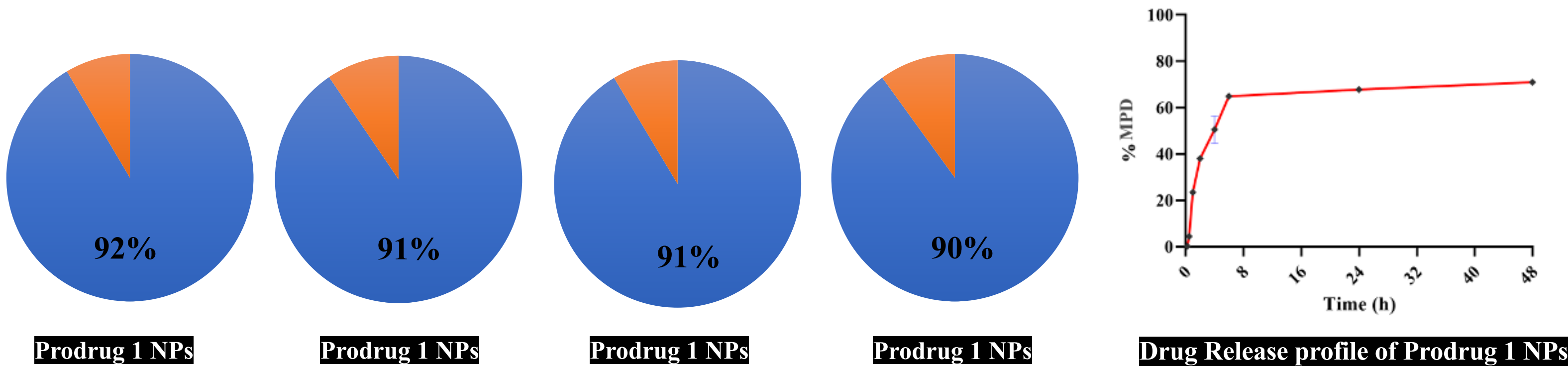


Figure-2: Size ( $d_1$ ), Polydispersity index (PdI) and Zeta potential of Prodrug 1 (Orange colour), Prodrug 2(Purple), Prodrug 3 ( green) and prodrug 4(blue) overtime at room temperature and 4°C storage condition



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



## In vitro and In vivo Studies

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

## Conclusion

All prepared prodrugs of SAID's led to successful nanoparticles of spherical morphology, having  $d_1$  from 100- 120 nm and polydispersity index less than 0.2. Zeta Potential of all nanoparticles were -29 to -35 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. Biological studies against proinflammatory cytokines would be carried out in near future.