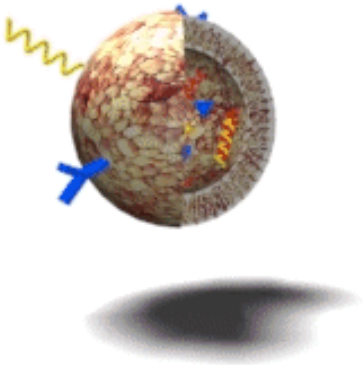
DRUG RELEASE METHODOLOGIES FOR NANOMEDICINES

ADDRESSING CHALLENGES



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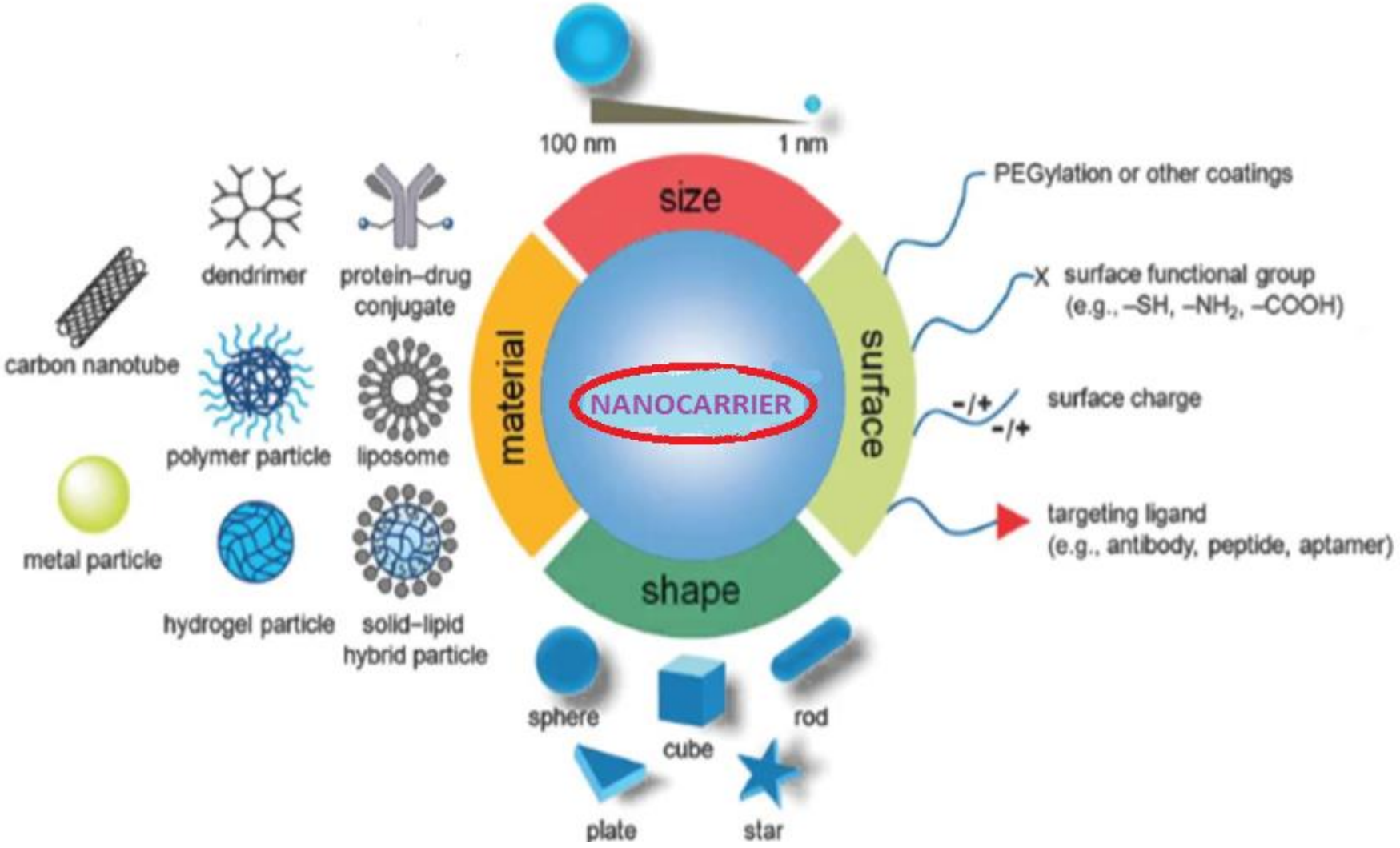
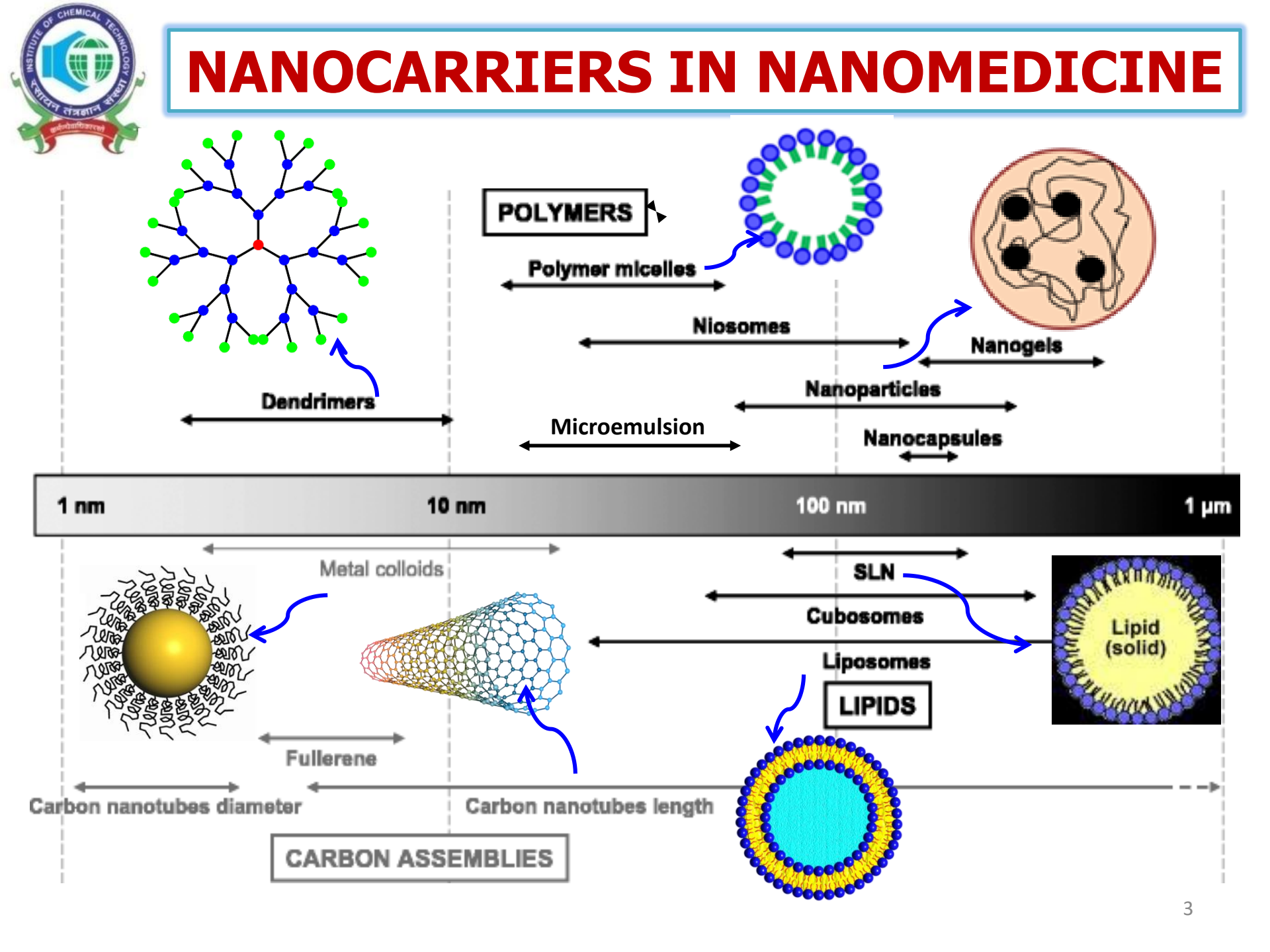
DISSO EUROPE – ROMANIA, OCTOBER 20-21, 2016

NANOMEDICINES



NANOCARRIERS IN NANOMEDICINE



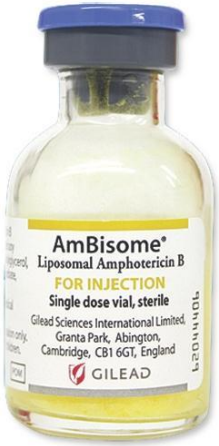
ADVANTAGE - NANOMEDICINE

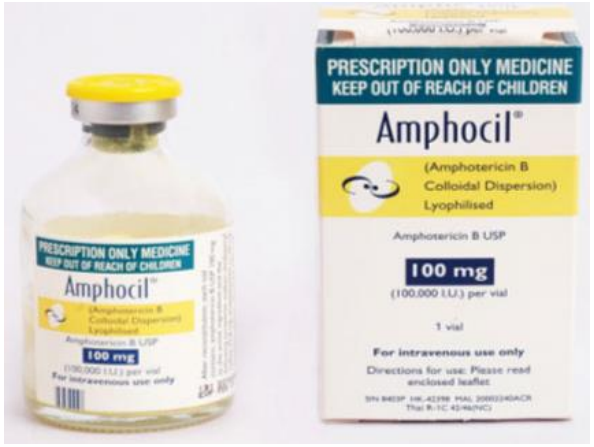
- ✓TARGETTED DELIVERY
- ✓ENHANCED EFFICACY
- ✓DECREASED SYSTEMIC TOXICITY

SUCCESS STORIES

CANCER

INFECTIOUS DISEASES





Nanosystems and Need for *in vitro* Dissolution testing

Nanosystems are promising

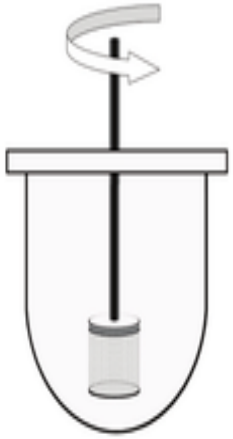
↓

Unavailability of standardized *in vitro* dissolution method

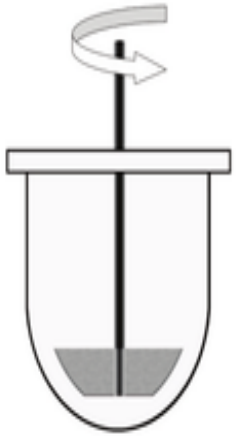
↓

Urgent Need to develop Standardized Testing Methods

OFFICIAL USP DISSOLUTION APPARATUS



Type I



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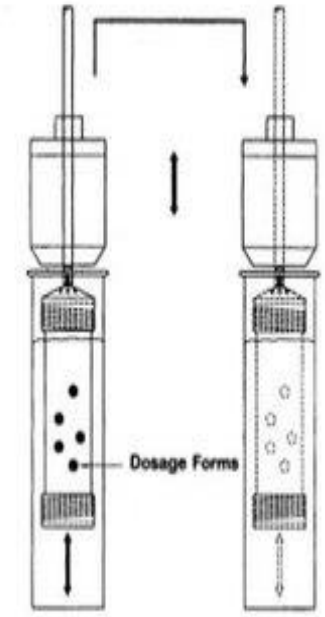


Type III

Type IV

Type VII

CHALLENGES IN DISSOLUTION METHOD FOR NANOMEDICINES

Size & Separation

- Difficulty in Separation of NP from medium

Complex System

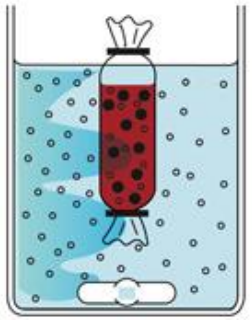
- Complexity of System type
- Target specific release
- Environment specific release (pH, temperature)
- Programmed Release

DISSOLUTION METHODS FOR NANOMEDICINES

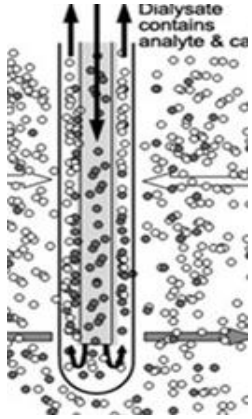
DISSOLUTION METHODS

- Sample & Separation methods

- Membrane Diffusion (Dialysis Sac) methods

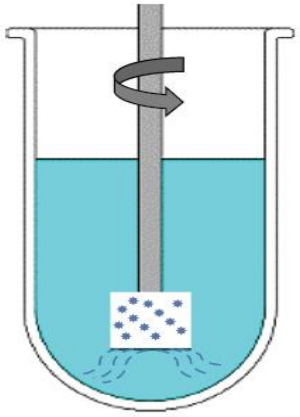


- Others (Micro dialysis, Dynamic dissolution & 2 stage reverse dialysis)



MODIFIED OFFICIAL APPARATUSES

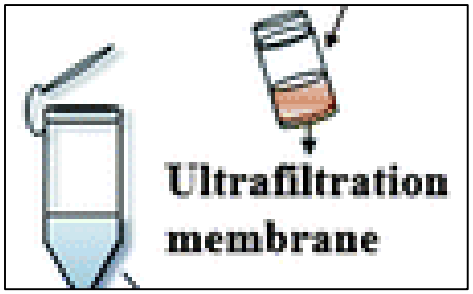
- Constant Volume



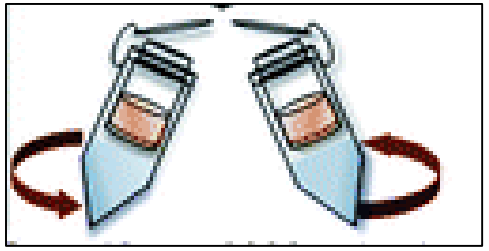
- Continuous Flow Methods

SAMPLE & SEPERATION METHODS

- NP directly added in medium & separation techniques applied
- Drug content in supernatant or filtrate is analyzed



Ultrafiltration



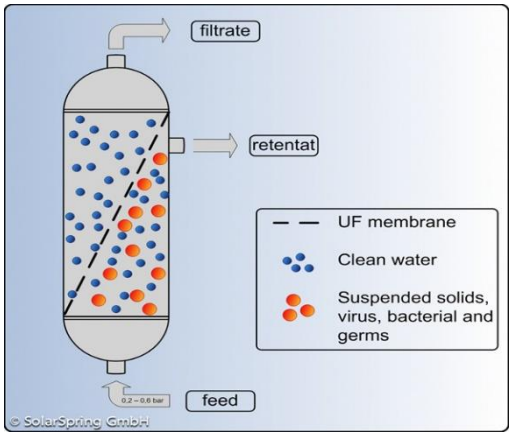
Ultracentrifugation

Key parameters : **Sample separation technique**
Agitation conditions

SAMPLE & SEPARATION METHODS

Pressure Ultrafiltration

- Completely separate Nanoparticles from release media within 5 min
- Prevent Clogging of filter pores



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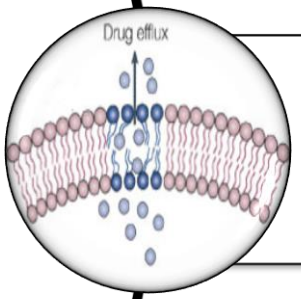
Syringe Filtration

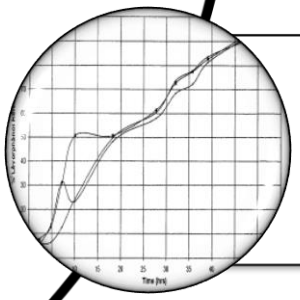
- Use of Syringe filters with smaller pore size (0.1 to 0.02 µm) has been used

DISADVANTAGES OF SAMPLE & SEPARATION METHODS

Difficulty in separation of NP from media though high external energy applied



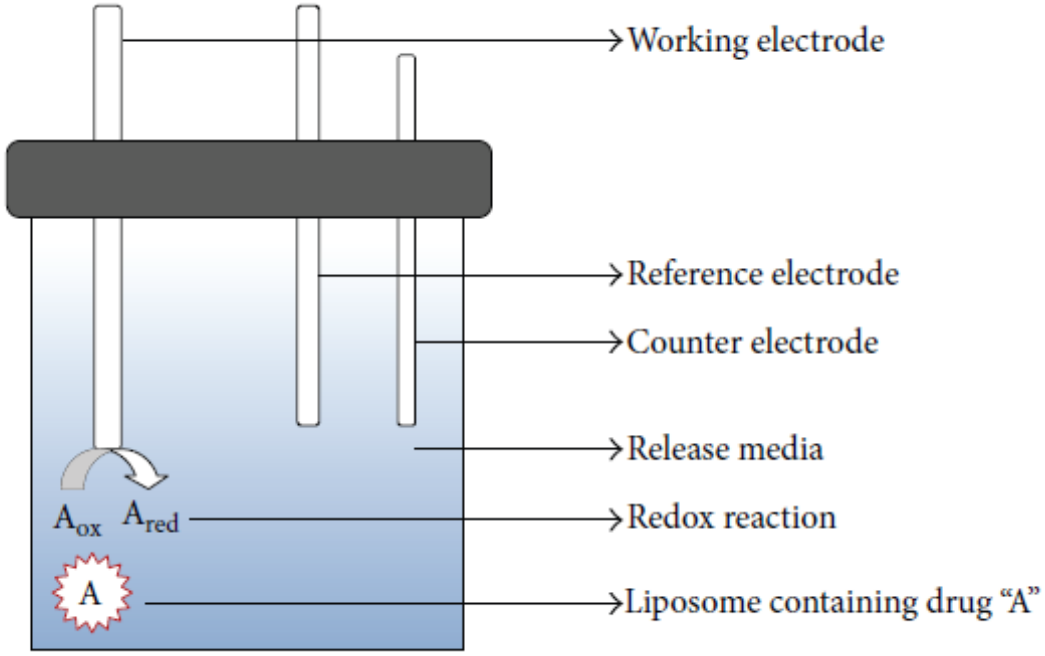
Long-time & High speed can result in destabilization of system (e. g. Nanoemulsion & Liposome)



Drug release continues during separation process, which can lead to erroneous results

DYNAMIC DISSOLUTION

ADVANCED SAMPLE AND SEPARATE METHOD



Utilize ion- or drug-selective electrodes to monitor the dissolution/release profiles of electroactive drugs

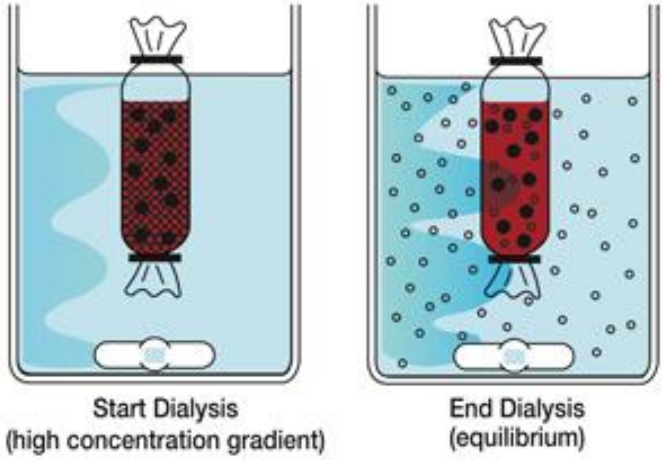
Not suitable for non-electroactive drugs

DIALYSIS METHODS

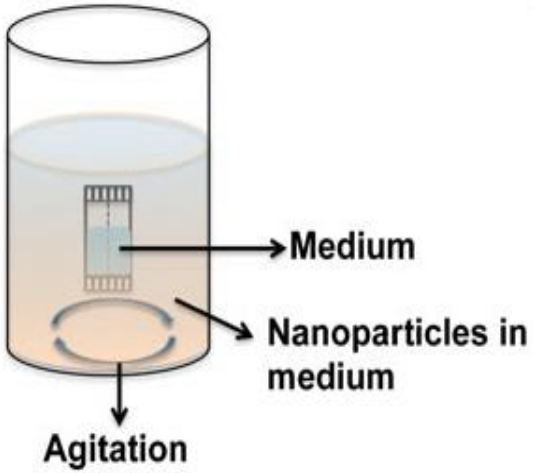
FIXED VOLUME

MEMBRANE DIFFUSION METHODS (DIALYSIS BAG)

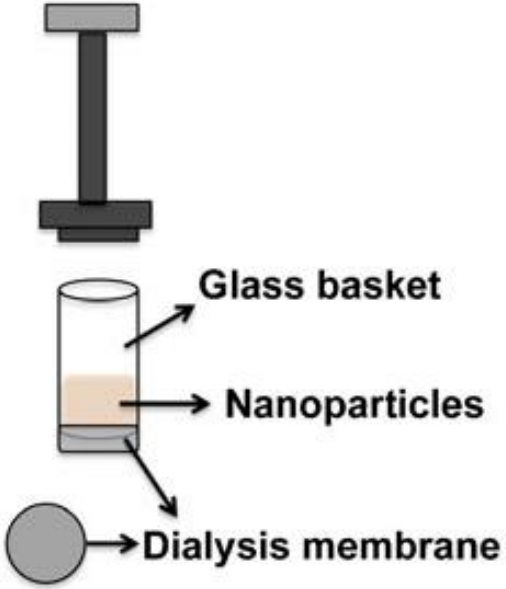
Nanosystems separated from the release medium through dialysis membranes that are permeable to the free drug but impermeable to the nanosystems



Dialysis Sac Method

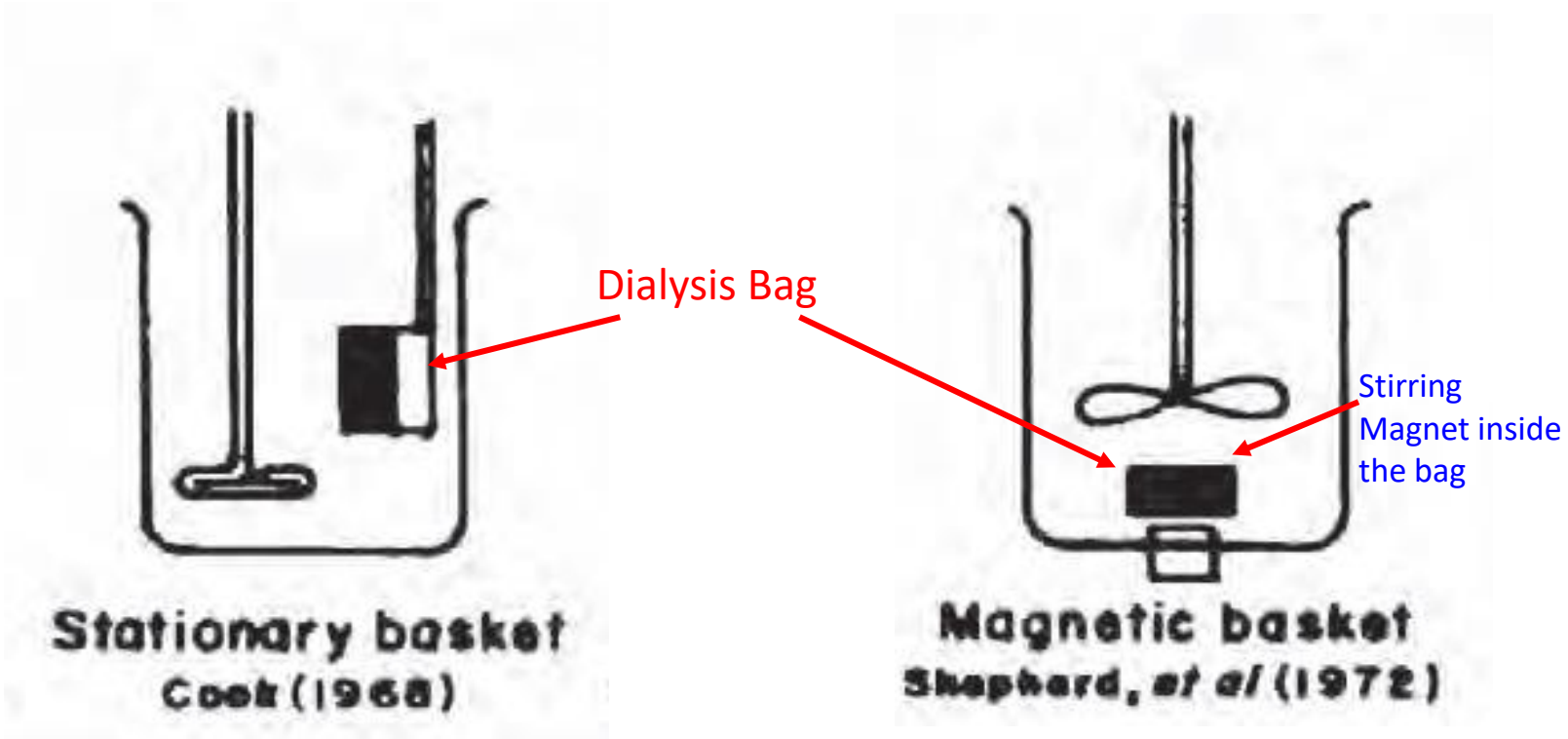


Reverse Dialysis Sac Method

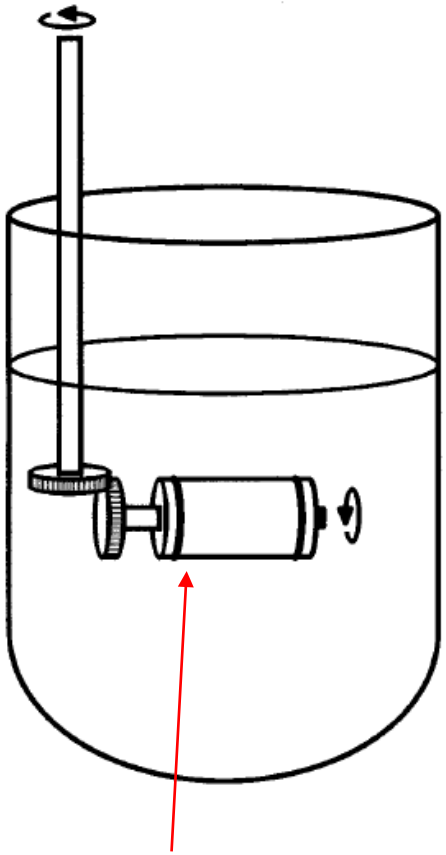


Side-by-Side-Dialysis

DEVELOPMENTS IN DISSOLUTION METHOD

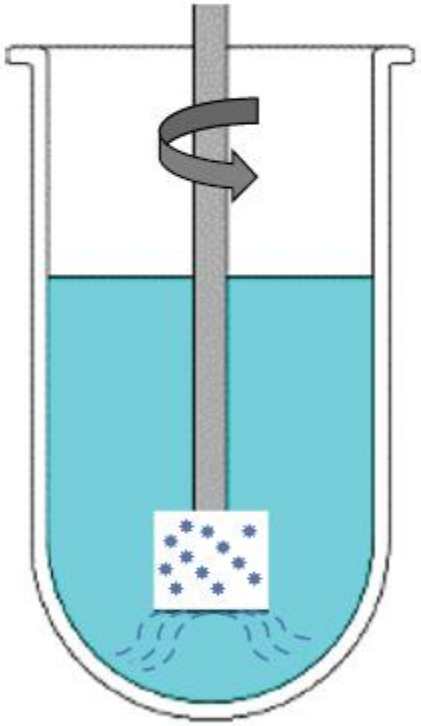


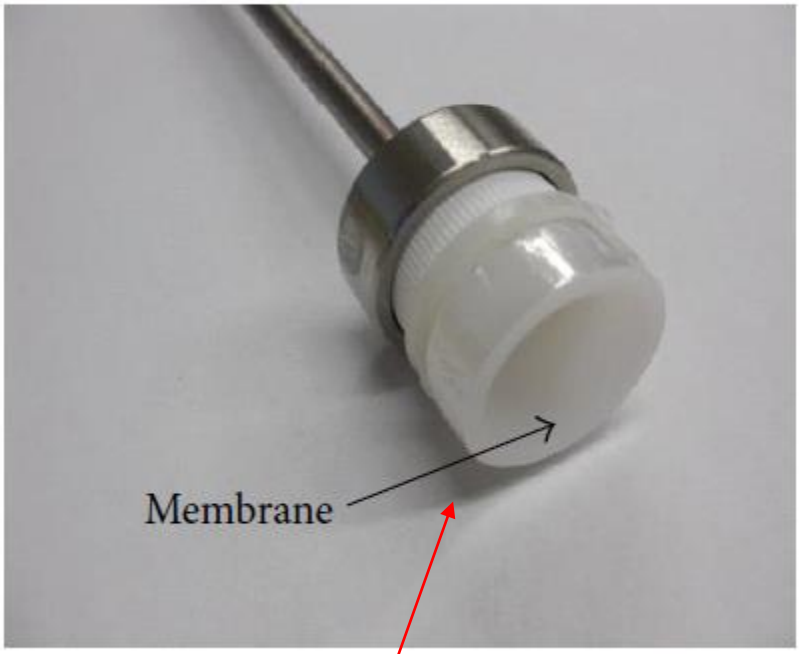
ROTATING DIALYSIS CELL FOR PARENTERAL DEPOT FORMLATIONS



BASKET MODIFIED INTO A DIALYSIS CELL

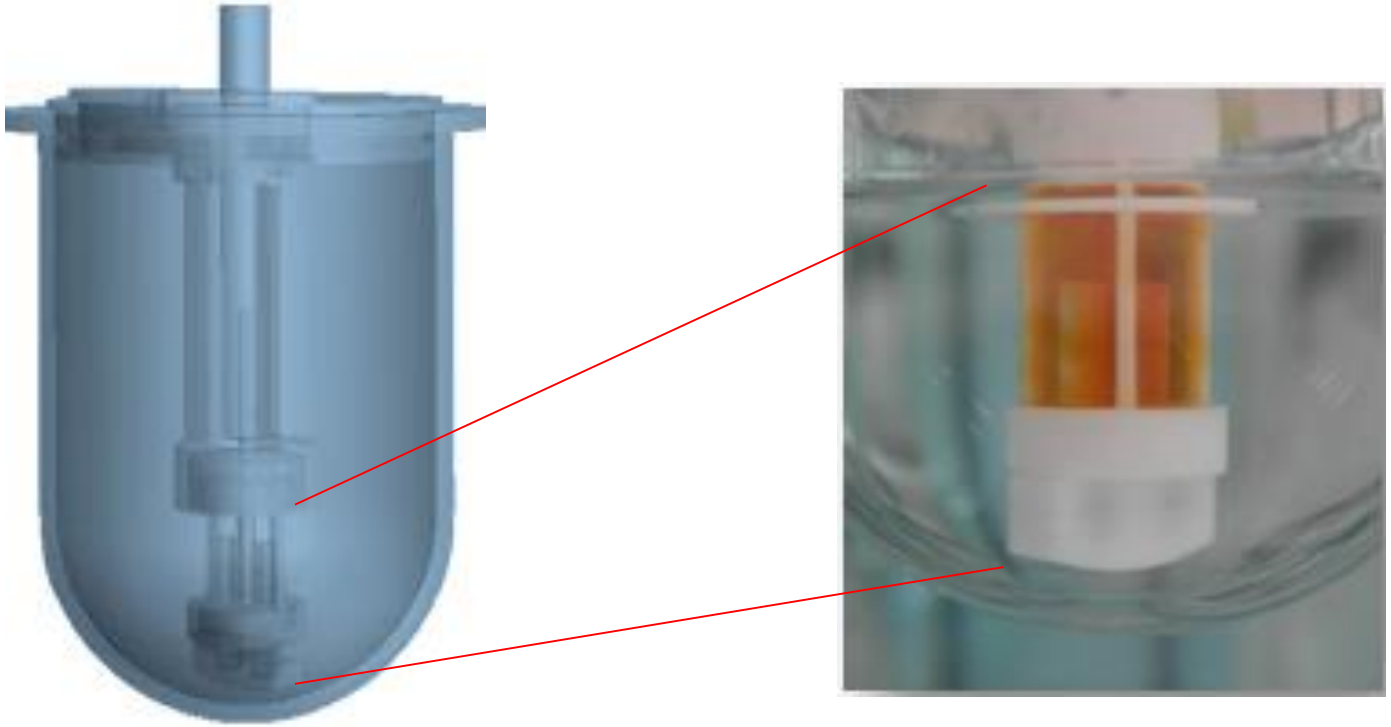
ADAPTATION OF DIALYSIS AND USP TYPE I





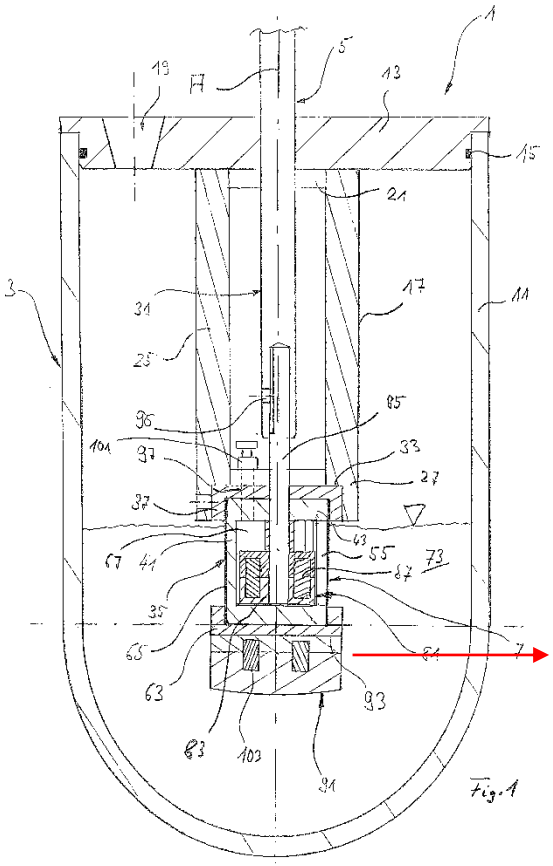
BASKET MODIFIED INTO A DIALYSIS CELL

ADAPTATION OF DIALYSIS AND USP TYPE I & II (Phamatest)



- Pharma Test offers the “dispersion releaser”
- High sensitivity for fluctuations in release rate
- Works well for compounds **with poor, moderate and good solubility**

ADAPTATION OF DIALYSIS AND USP TYPE I & II (Phamatest)



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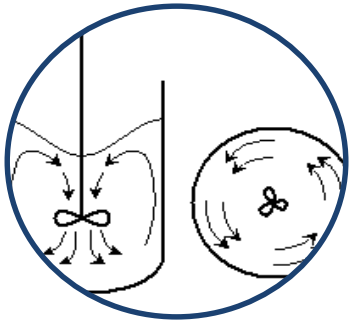
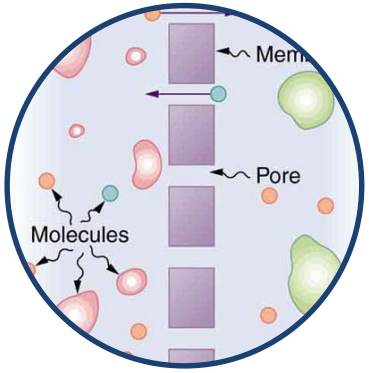
KEY PARAMETERS INFLUENCING DRUG RELEASE IN DIALYSIS METHODS



Agitation Conditions

Ratio between Donor & acceptor cell Volume

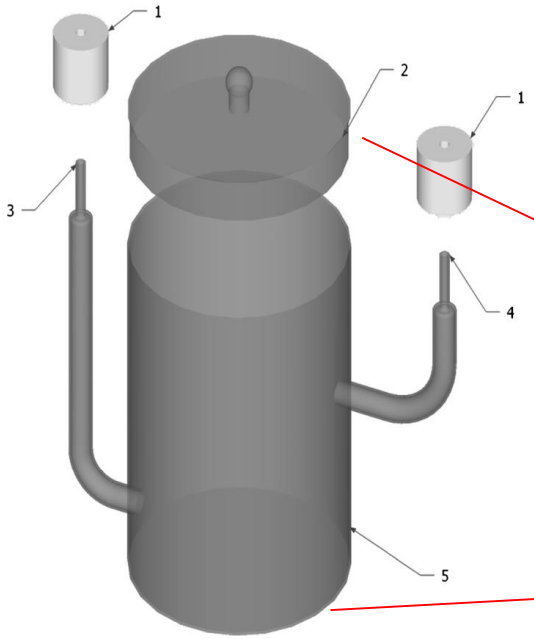
Inside Volume 6 to 10 fold less than medium volume

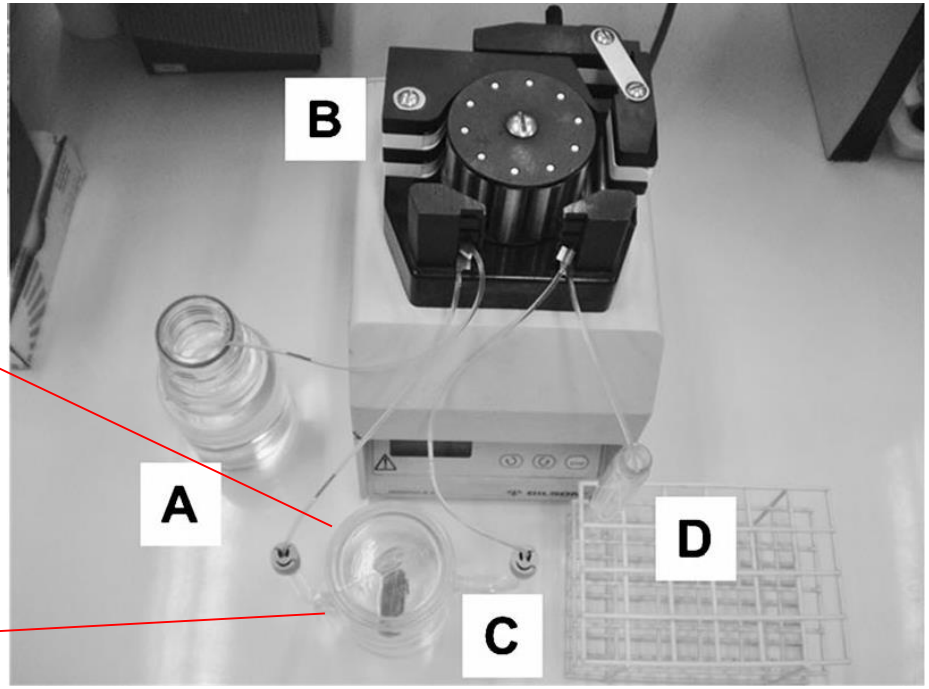


Molecular Weight Cut-Off (MWCO) of membrane

MWCO 100 times more than drug MW

ADAPTATION OF DIALYSIS AND CONTINUOUS FLOW CELL



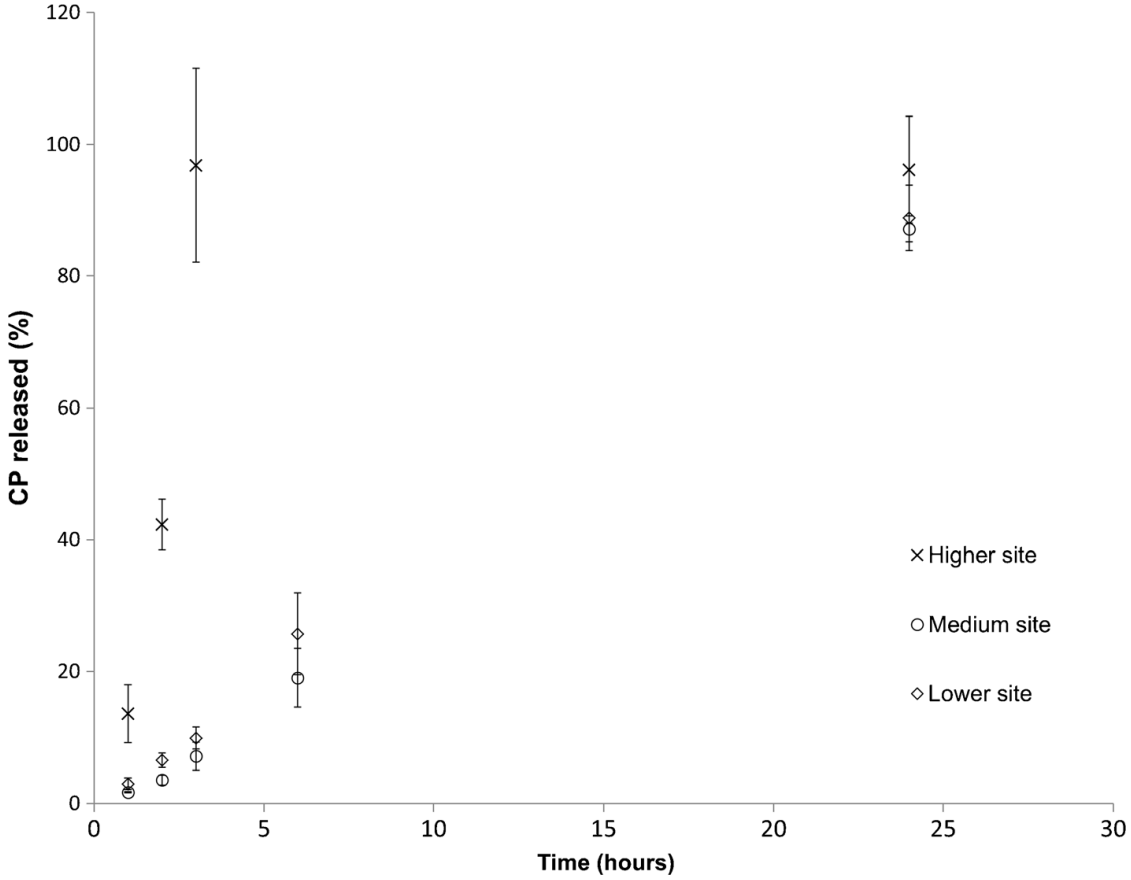


1 rubber seals
2 glass lid
3 release medium outlet
4 release medium inlet
5 release device

A a flask containing fresh release medium
B a peristaltic pump
C the proposed release device
D a sampling flask

ADAPTATION OF DIALYSIS AND CONTINUOUS FLOW CELL FOR NLC

Conventional Dialysis bag method with Proposed flow apparatus

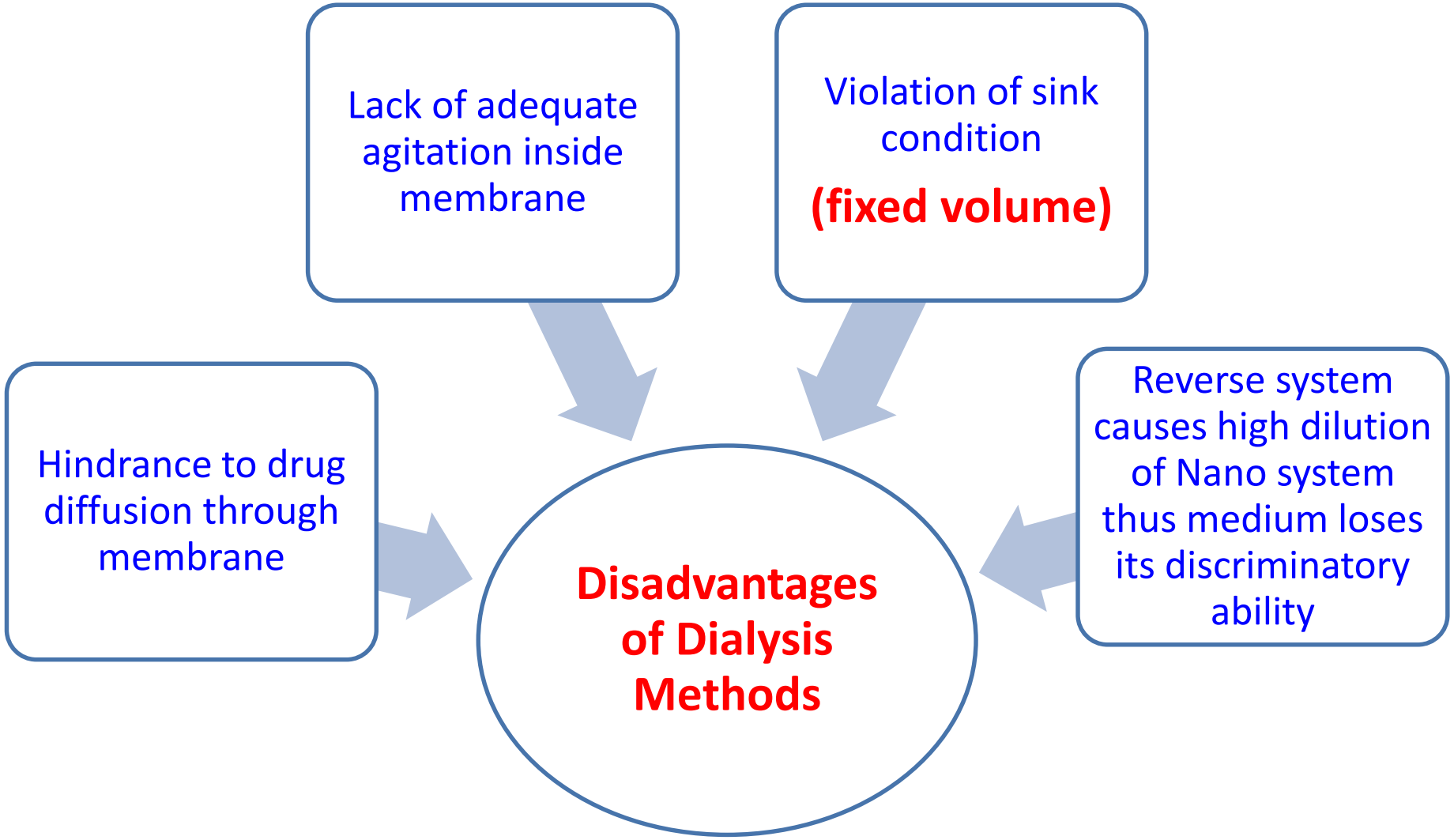


In vitro CP (Clobetasol Propionate) release

CONVENTIONAL DIALYSIS SAC TECHNIQUE

SIGNIFICANT DIFFERENCE BASED ON SITE OF SAMPLING

DISADVANTAGES OF DIALYSIS METHODS



CONTINUOUS FLOW THROUGH CELL TYPE IV

This method has been widely used to investigate drug release from microspheres

But Nanoparticulate systems have very small particle size (<100nm), challenging to test their release in USP IV.

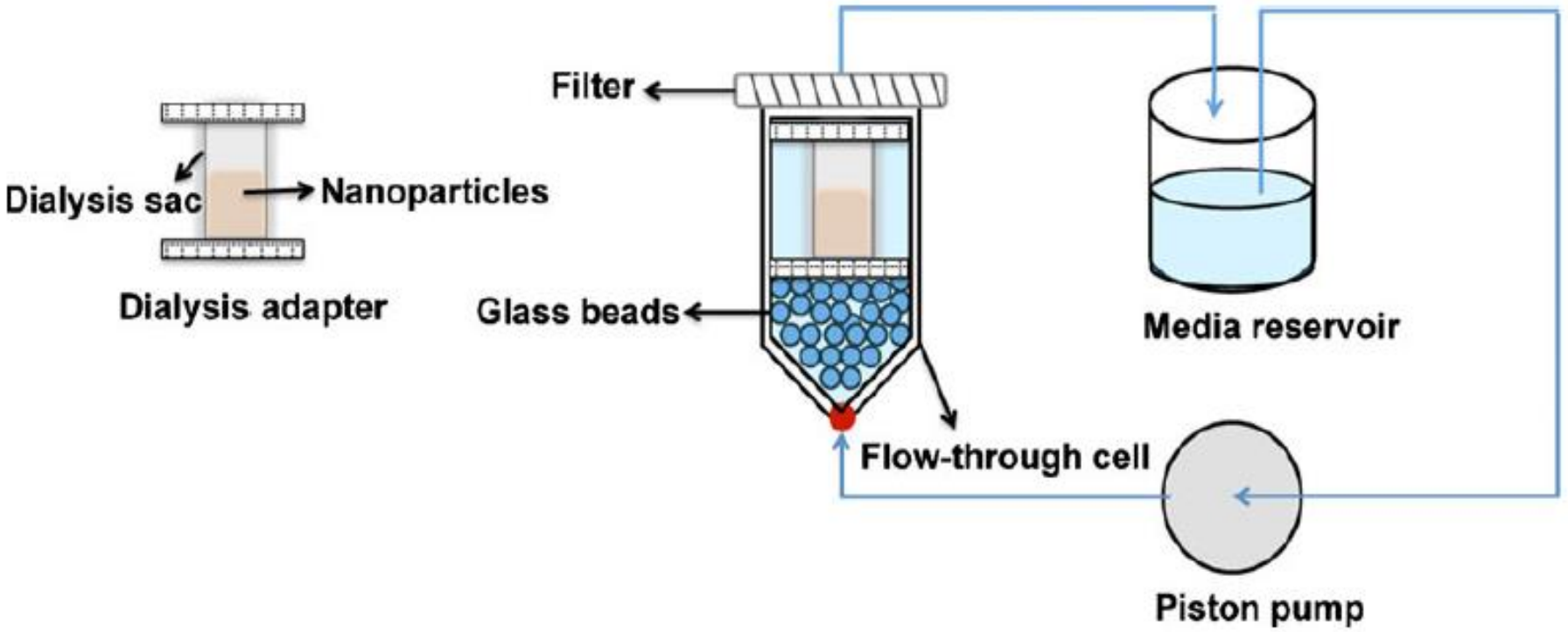
CHALLENGE:

- NP clog the filter leading to slow flow rates and high pressure build-up in the system

- Pass through filters, thus resulting in erroneous data.

SOLUTION: novel Dialysis Adaptor is introduced in USP type IV

CONTINUOUS FLOW THROUGH CELL TYPE IV



CONTINUOUS FLOW THROUGH CELL TYPE IV

CONTINUOUS FLOW THROUGH CELL TYPE IV - DIALYSIS CELL

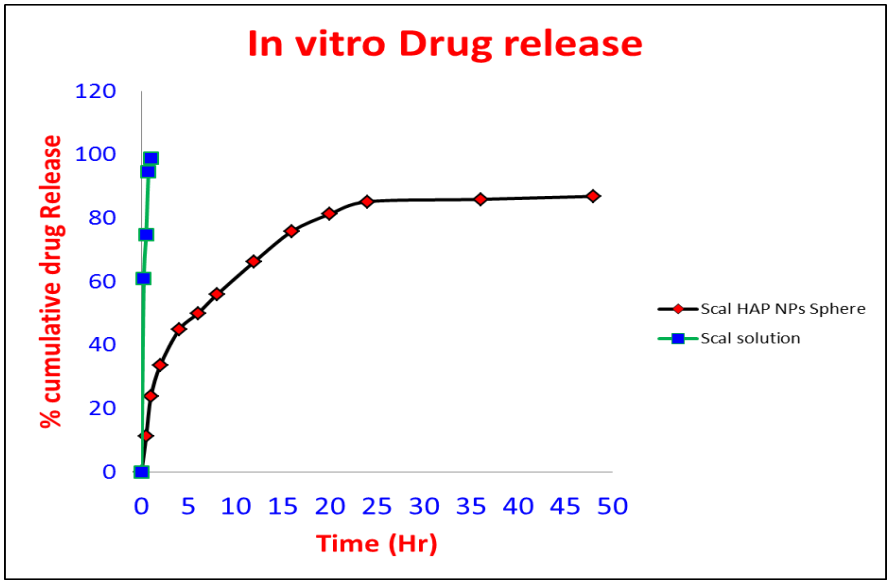
- ✓High Discriminative power
- ✓Avoided Filter clogging
- ✓Avoided violation of sink conditions
- ✓Avoided lack of agitation

CASE STUDIES

USP APPARATUS IV WITH DIALYSIS CELL

INORGANIC NANOPARTICLES OF SALMON CALCITONIN

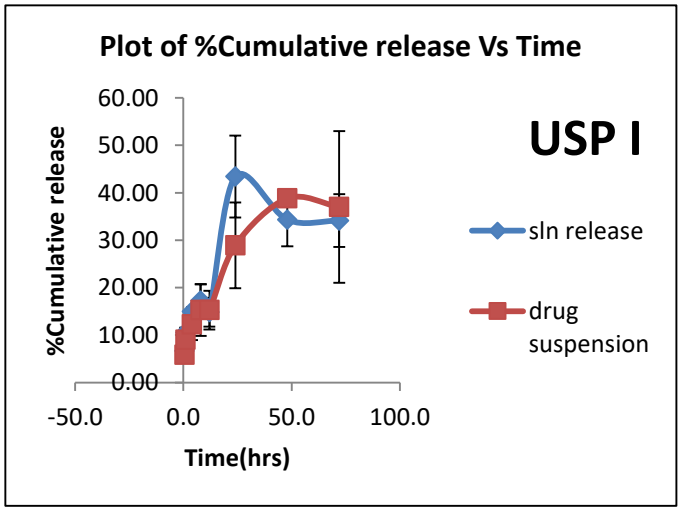
USP IV

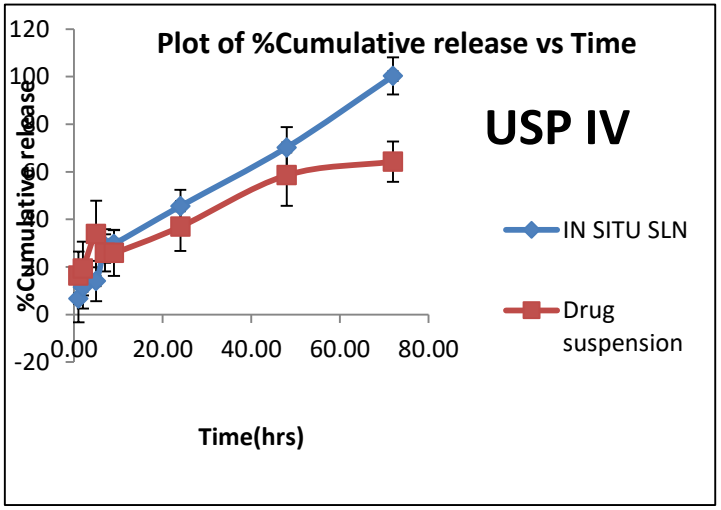


- 98 % of SCT high molecular weight drug (MW ~3000) in 1 hr indicates dialysis membrane not rate limiting
- Sustained release seen with SCT NPs

BUPARVAQUONE SLN
USP TYPE I vs IV

Parameters	USP IV	USP I
Volume of media(5%sls)	100ml	500ml
Speed	120rpm	100rpm
Flow rate	6ml/min	-
Sample volume	1ml	5ml
Aliquot volume	1ml	5ml





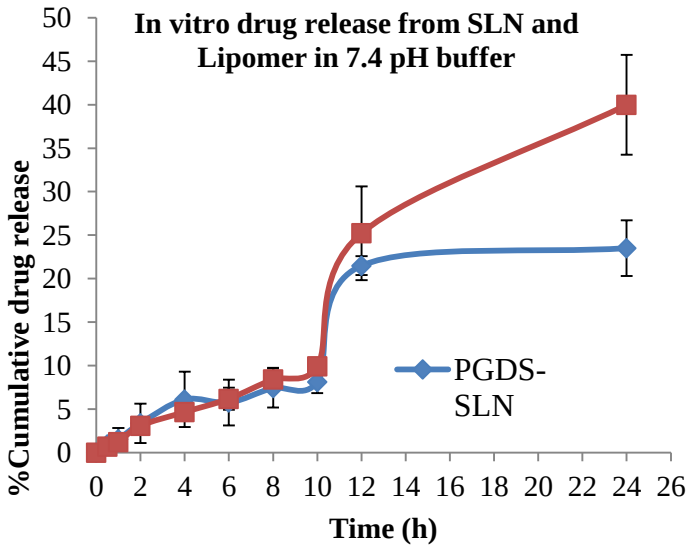
USP I – LOWER DRUG RELEASE DUE TO ABSENCE OF SINK CONDITION

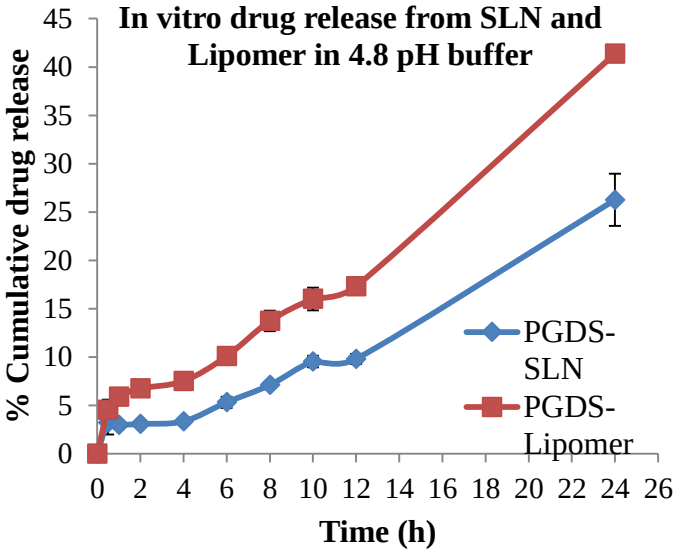
USP IV – COMPLETE RELEASE AND LOWER STANDARD DEVIATIONS

AMPHOTERICIN B NANOSYSTEM USP TYPE IV- LIPOMER vs SLN

Volume of Media-100mL
Flow rate-6mL/min

Sample volume-1mL
Aliquot volume-1mL





- SLN - 23.50±3.22% AmB release after 24h
- Lipomer - 39.98±5.74 % AmB release after 24h

- SLN - 26.26±2.70% AmB release after 24h
- Lipomer - 41.38±0.45% AmB release after 24h

DISCRIMINATION BETWEEN TWO NANOSYSTEMS OBSERVED

FUTURE PERSPECTIVES

- USP IV WITH DIALYSIS CELL APPEARS PROMISING
- USP II MODIFIED APPARATUS ALTHOUGH PROMISING COULD LACK SINK CONDITION FOR POORLY SOLUBLE DRUGS

FUTURE PERSPECTIVES

- SYSTEMS THAT ADDRESS SPECIFIC REQUIREMENTS OF NANOSYSTEMS
  - No release in circulation
  - Release prediction at site of delivery

- COST EFFECTIVE STRATEGIES MAY BE EXPLORED

PROF. DEVARAJAN'S RESEARCH GROUP

INSTITUTE OF CHEMICAL TECHNOLOGY

Deemed University , Elite status and Centre of Excellence (GOM)

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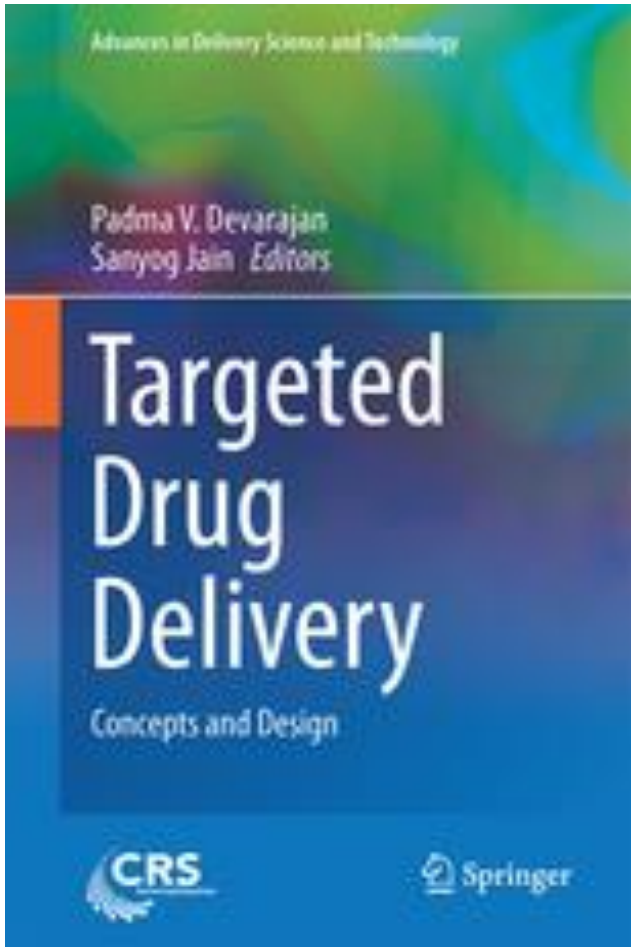
- WORLD BANK – TEQIP- ICT, FOR FINANCIAL SUPPORT
- SOTAX INDIA PVT. LTD., FOR USP IV WITH DIALYSIS CELL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