Microparticle Loaded Films for Drug Delivery

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Representative Publication

1. "Stabilizing Dispersions of Hydrophobic Drug Molecules Using Cellulose Ethers during Anti-solvent Synthesis of Micro-particulates". X. Meng Y. Chen , S. Chowdhury, D. Yang , and S. Mitra. *Colloids and Surfaces B: Biointerfaces*, **2009,** 70, 7-14.

2. "Simultaneous synthesis, stabilization and self assembly of micro-scale drug particles in polymer films". Xiangxin Meng , Dachuan Yang and Somenath Mitra. *J. of Appl. Polymer. Sci.* **2010**, 120, 2082–2089.

3. "Antisolvent precipitation of hydrophobic, organic functionalized multiwall carbon nanotubes in an aqueous environment". Chintal Desai, Susana Addo Ntim and Somenath Mitra, *J. of Coll. and Interface Sci.* 368, 115–120 (**2012**).

4. "Synthesis and Immobilization of Micro-scale Drug Particles in Presence of β-Cyclodextrins." Xiangxin Meng, Dachuan Yang , Golshid Keyvan, Bozena Michniak-Kohn, and Somenath Mitra. **2011**, *Colloids and Surfaces,* B: Biointerfaces http://dx.doi.org/10.1016/j.colsurfb.2011.11.043.

Dealing with Hydrophobic Molecules

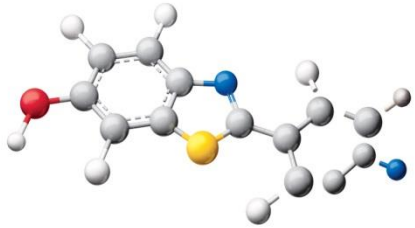
- **Hydrophobic drug molecules exhibit poor aqueous solubility, making it bioavailable has been a challenging task.**

- ***Reduction in particle size results in an increase in surface area, which can increase the solubility and bioavailability***

- ***Conventional Approach – Homogenization and Milling***

- **Simultaneous synthesis, stabilization and further processing into delivery systems, such as, thin film or liquid suspensions is possible via precipittation methods.**

Conventional Approach

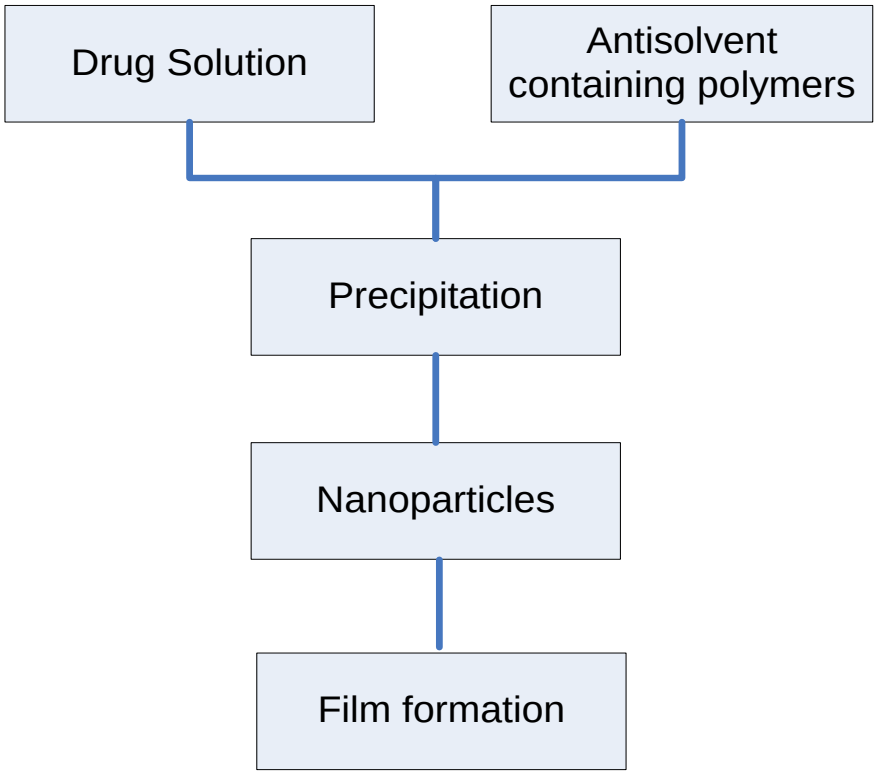


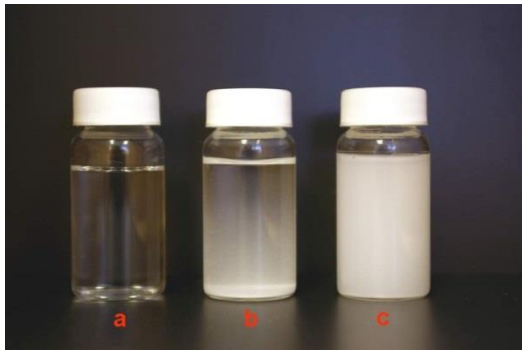
DISCOVERY

MANUFACTURE

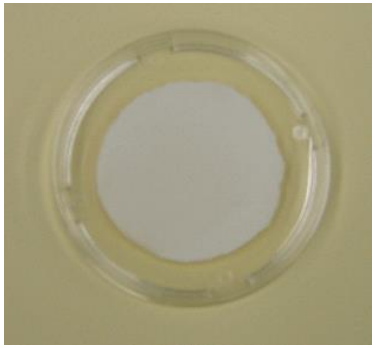
FORMULATION

Anti-solvent Particle Synthesis and Stabilization





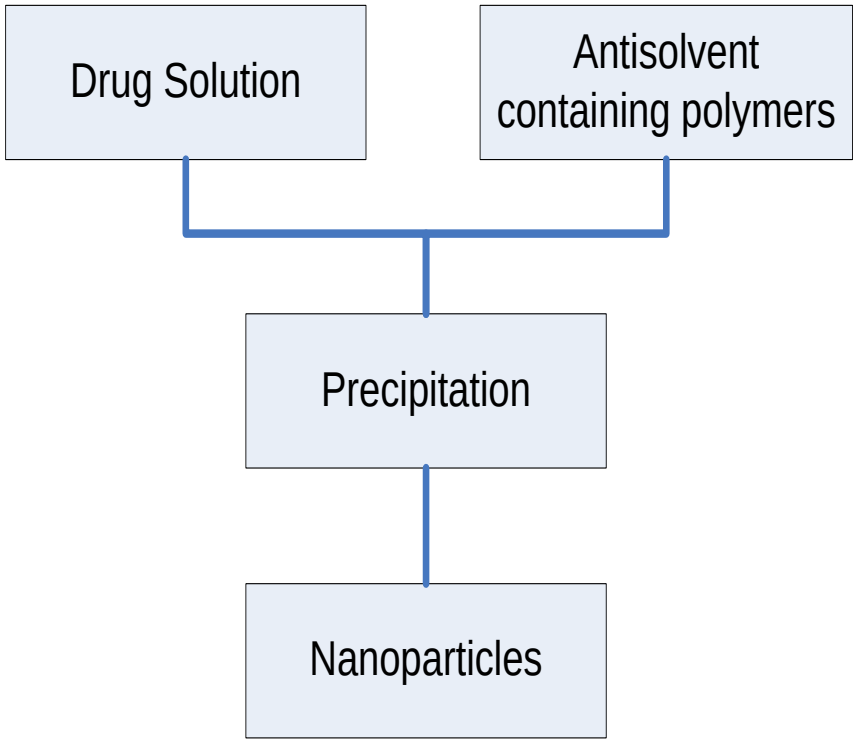
→ **Suspensions**



→ **drug film**

Combination of different cellulose and surfactants are being used to synthesize micro/nanoparticles in aqueous medium encapsulated by the polymers

Anti-Solvent Particle Synthesis and Stabilization

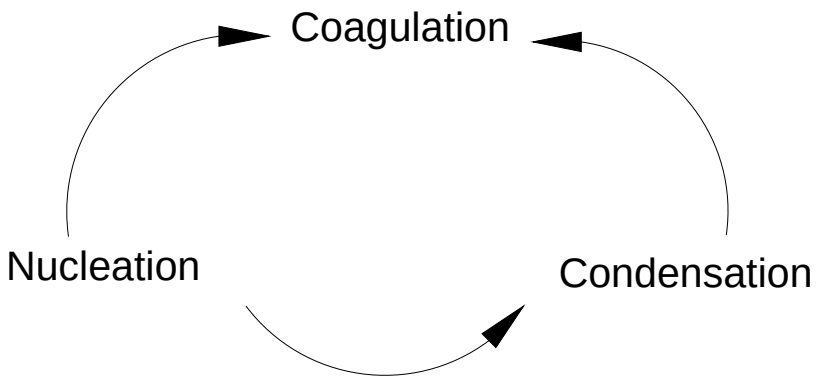


Advantages:

- **ease of use**
- **easily from uniform particles**

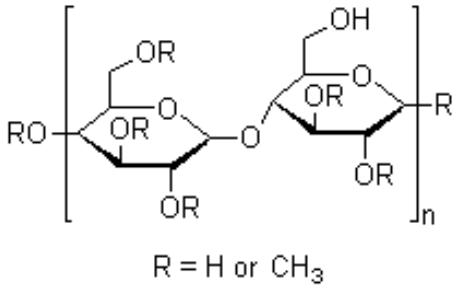
Disadvantages:

- **Water removal**
- **Scale up precipitation**

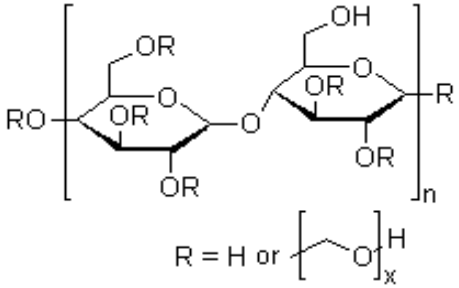


Celluloses Used

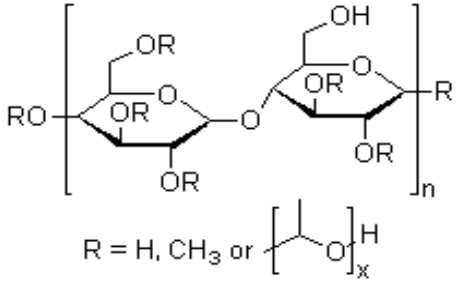
Cellulose ethers



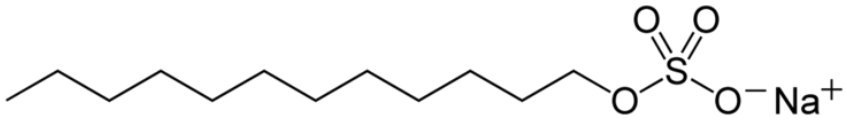
Methyl Cellulose (MC)



Hydroxyethyl cellulose (HEC)

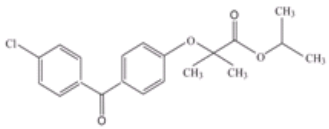
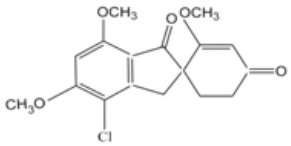


Hydroxypropyl Methyl cellulose (HPMC)

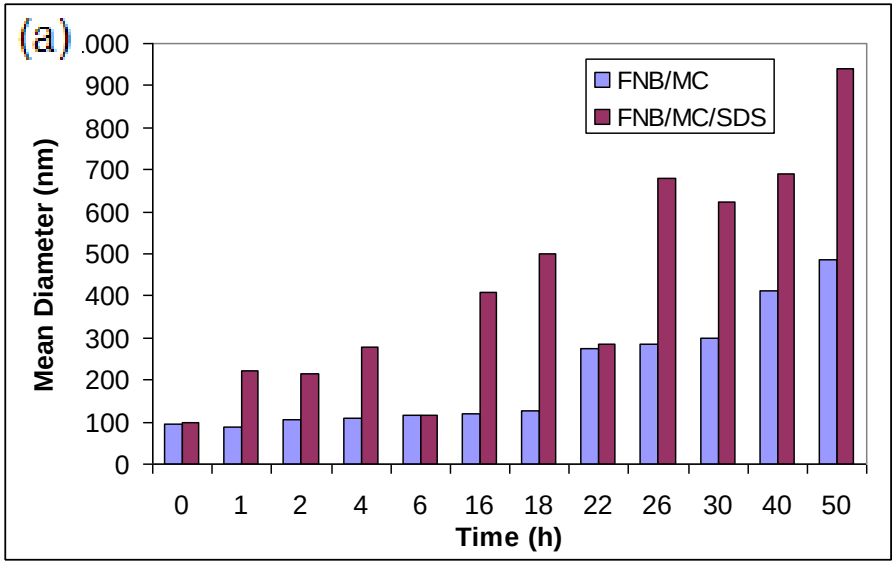


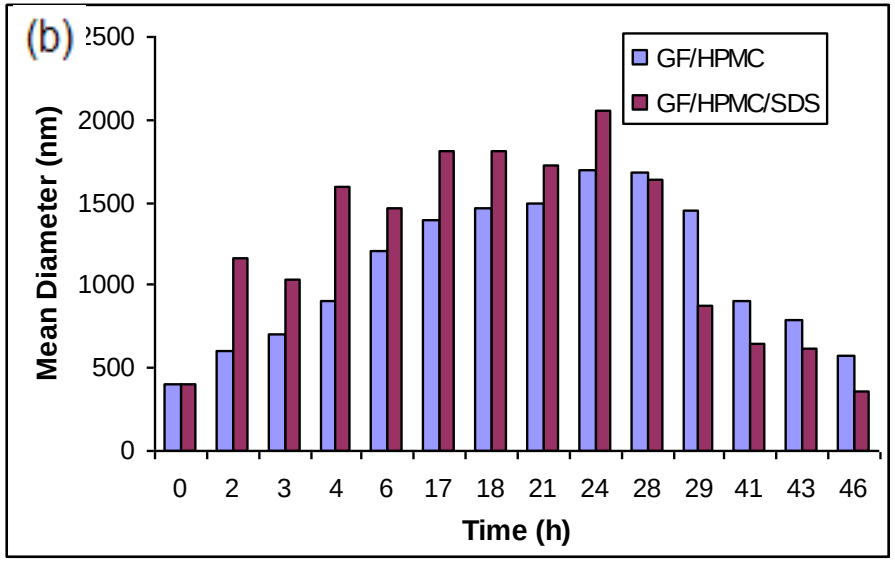
sodium dodecyl sulfate (SDS)

Drug molecules under study

	Structure	MF	FW	Water solubility (µg/ml)	ΔHf (kJ/mol)	Molar Volume (ml/gmol)	cLog P (n-Octanol Water)
Fenofibrate (FNB)		$C_{20}H_{21}ClO_4$	360.8	0.1	34.0	310.7	4.43
Griseofulvin (GF)		$C_{17}H_{17}ClO_6$	352.8	12	41.0	255.0	3.53

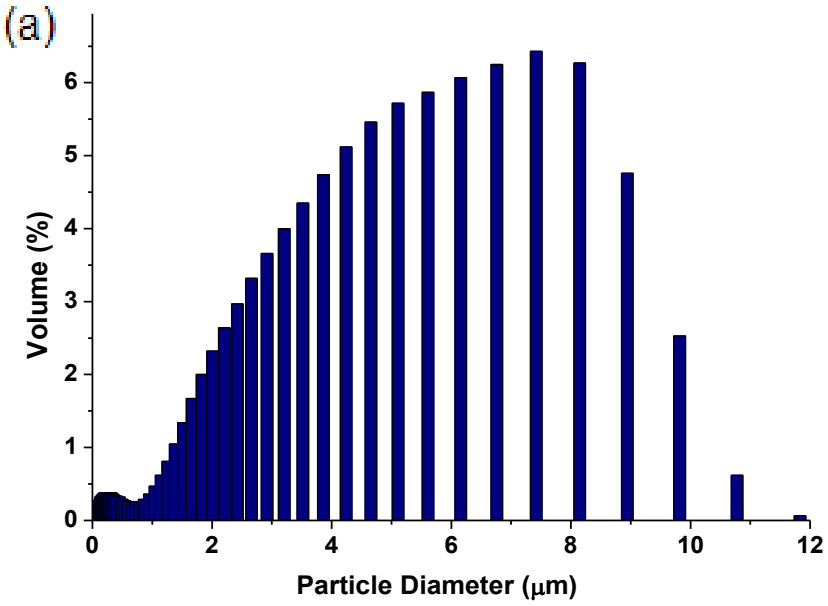
Dynamic light scattering of stabilized suspensions

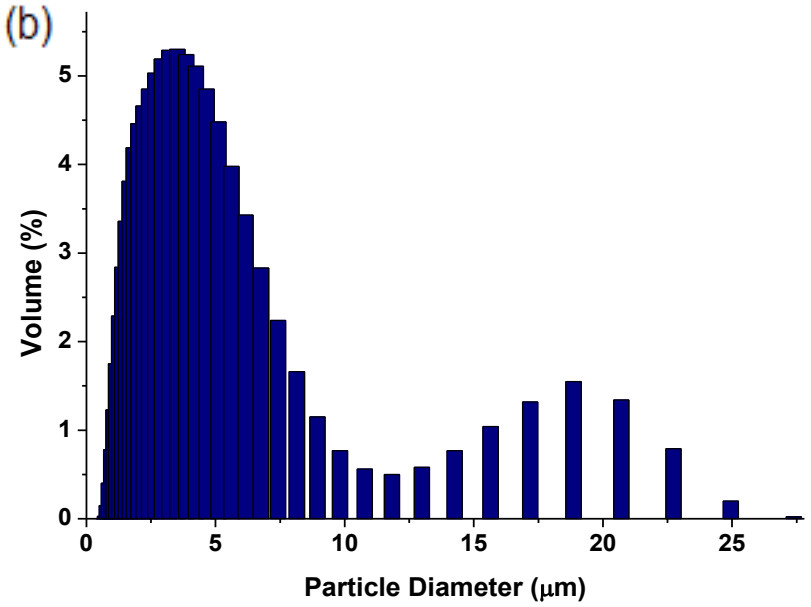




(a) FNB stabilized with MC; FNB stabilized with MC and SDS
(b) GF stabilized with HPMC; GF stabilized with HPMC and SDS

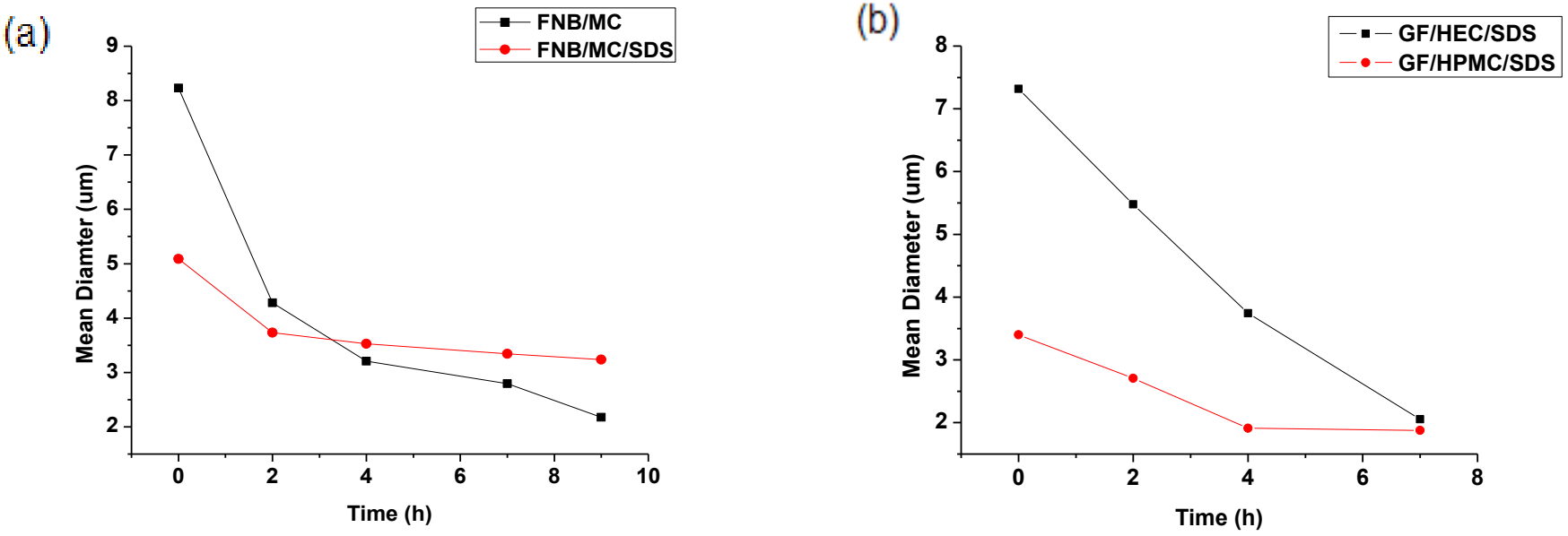
Particle Size Distribution of stabilized suspensions





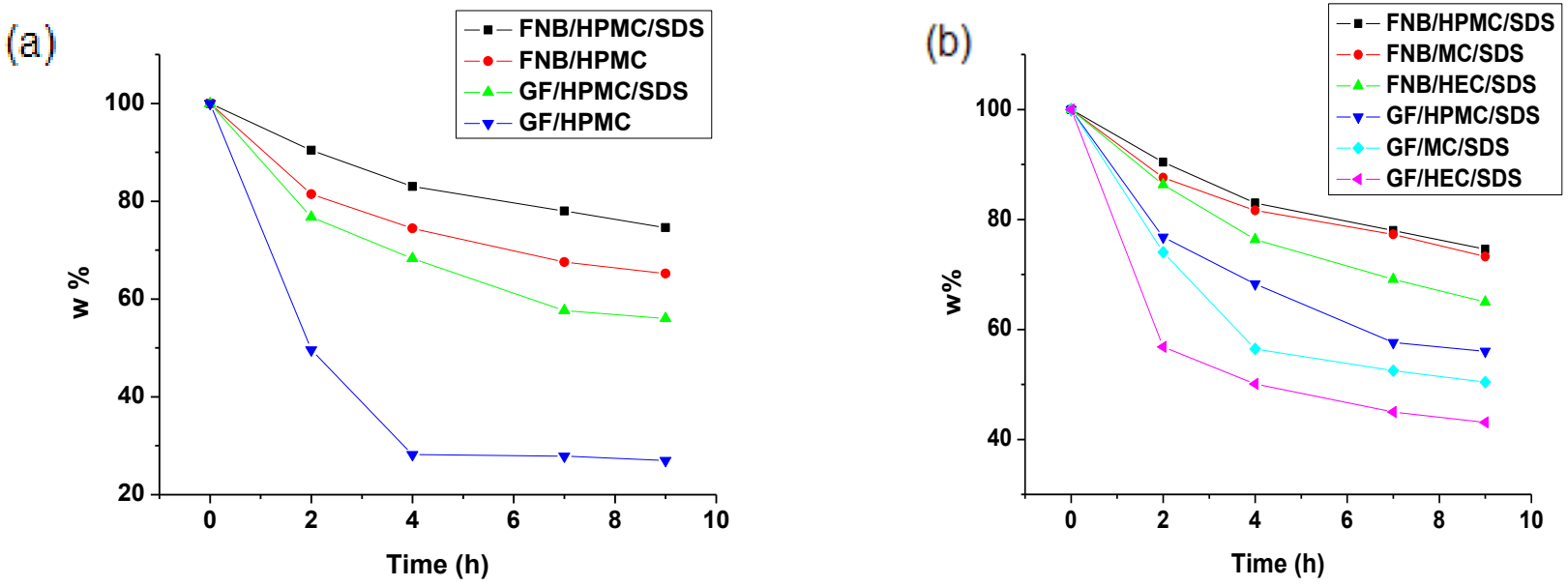
(a) FNB stabilized by HPMC and SDS (b) GF stabilized by HPMC and SDS

Mean diameter of drug particles as a function of time



(a) FNB stabilized with MC, FNB stabilized with MC and SDS
(b) GF stabilized with HEC and SDS, GF stabilized with HPMC and SDS

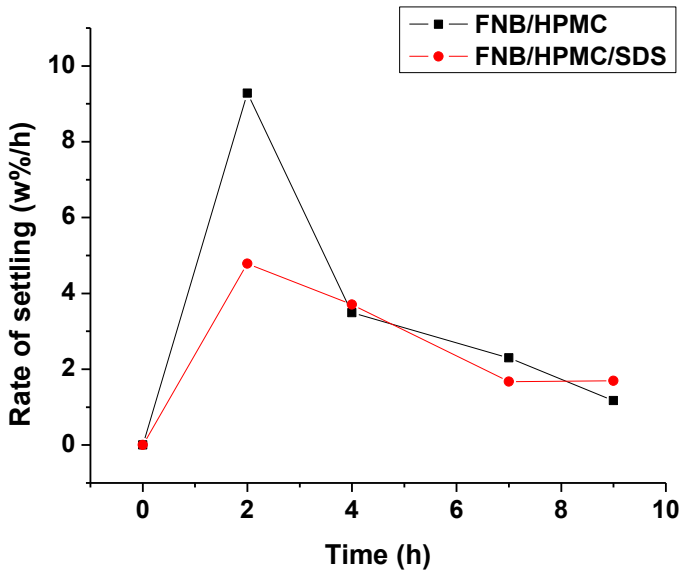
Weight percentage of stabilized drug particles in suspension

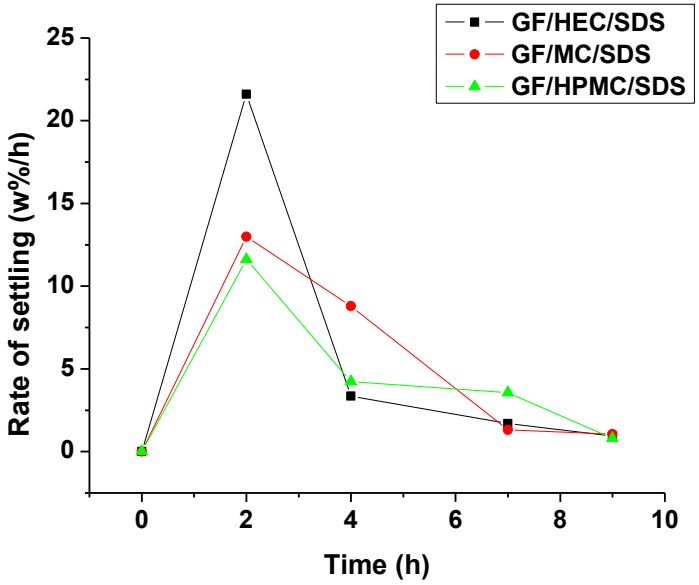


(a) FNB and GF in presence of HPMC and SDS
(b) FNB and GF in presence of different cellulose ethers and SDS

Rate of settling as a function of time for drug suspensions

(a)



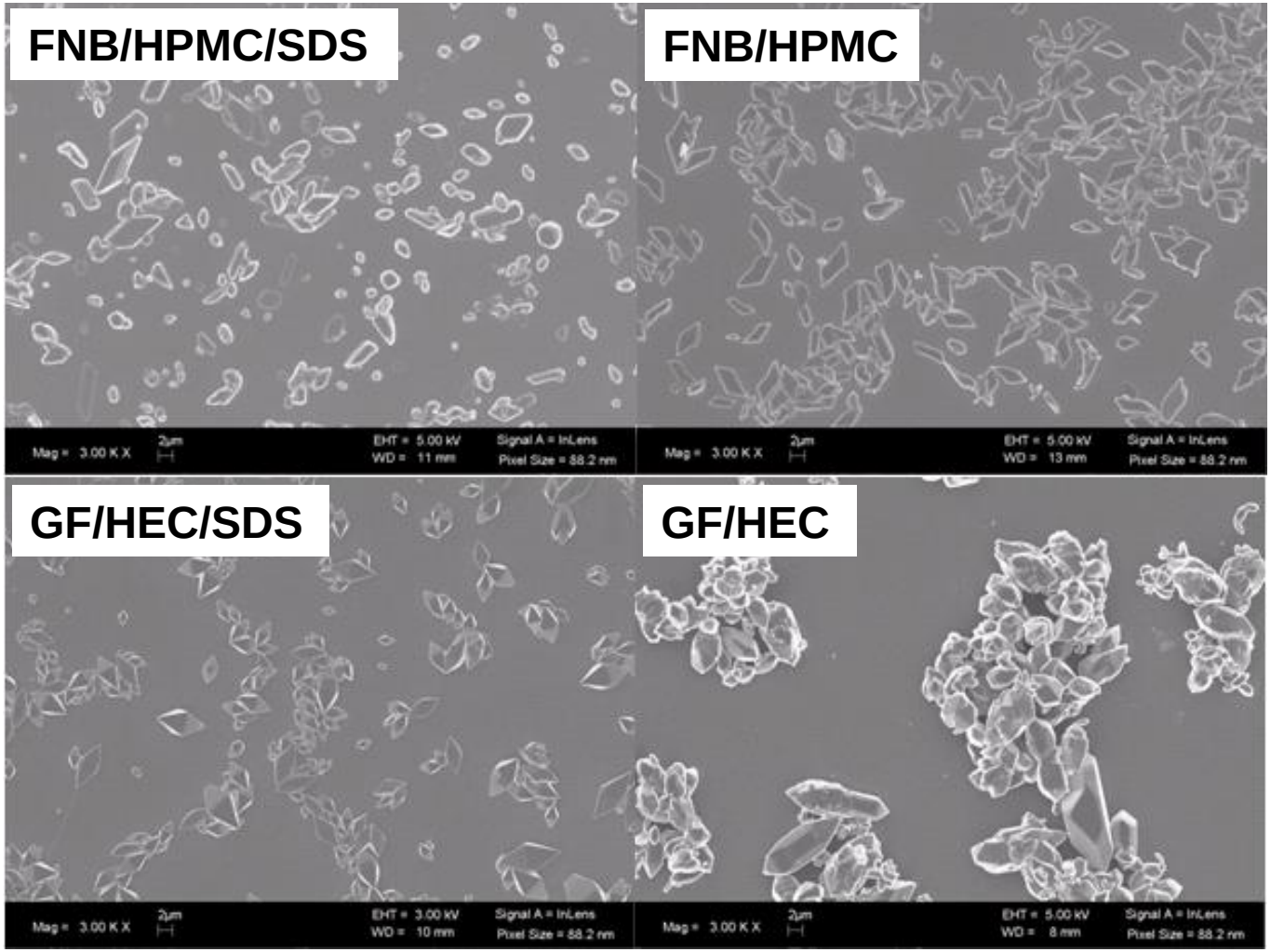


(a) FNB in presence of HPMC and SDS
(b) GF in presence of different cellulose ethers and SDS

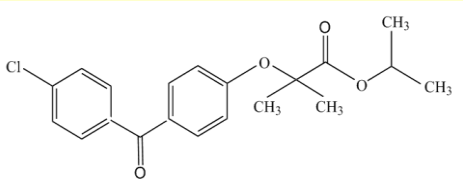
Zeta potential and Melting point analysis

Suspension	Zeta potential (mV)	Melting point (°C)
FNB/HPMC/SDS	-19.25	73
FNB/HPMC	-7.44	74
FNB/MC/SDS	-15.11	72
FNB/MC	-6.52	74
FNB/HEC/SDS	-11.55	75
FNB/HEC	-3.24	73
GF/HPMC/SDS	-15.16	201
GF/HPMC	-18.01	203
GF/MC/SDS	-13.06	200
GF/MC	-24.61	204
GF/HEC/SDS	-14.06	198
GF/HEC	-17.96	202

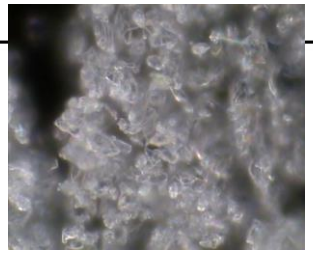
Drug Particle Morphology



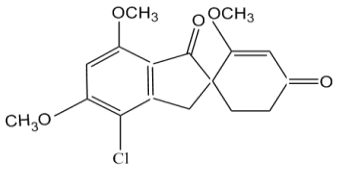
Raman spectroscopy analysis for FNB particles



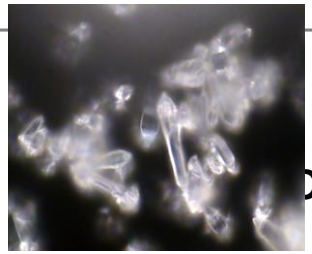
(FNB)



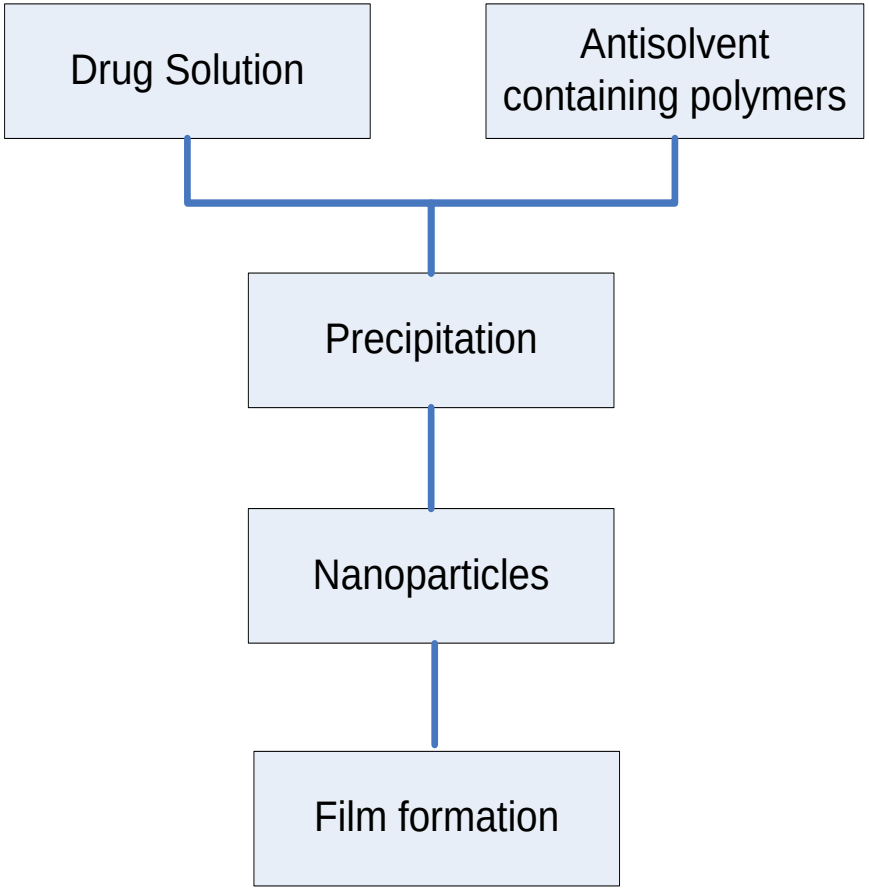
Raman spectroscopy analysis for GF particles

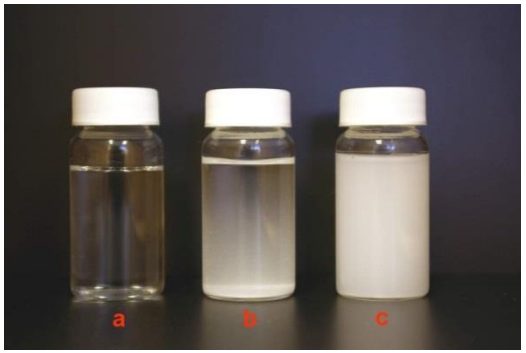


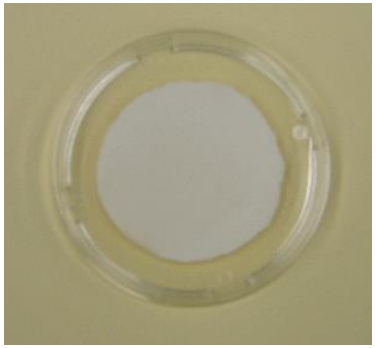
(GF)



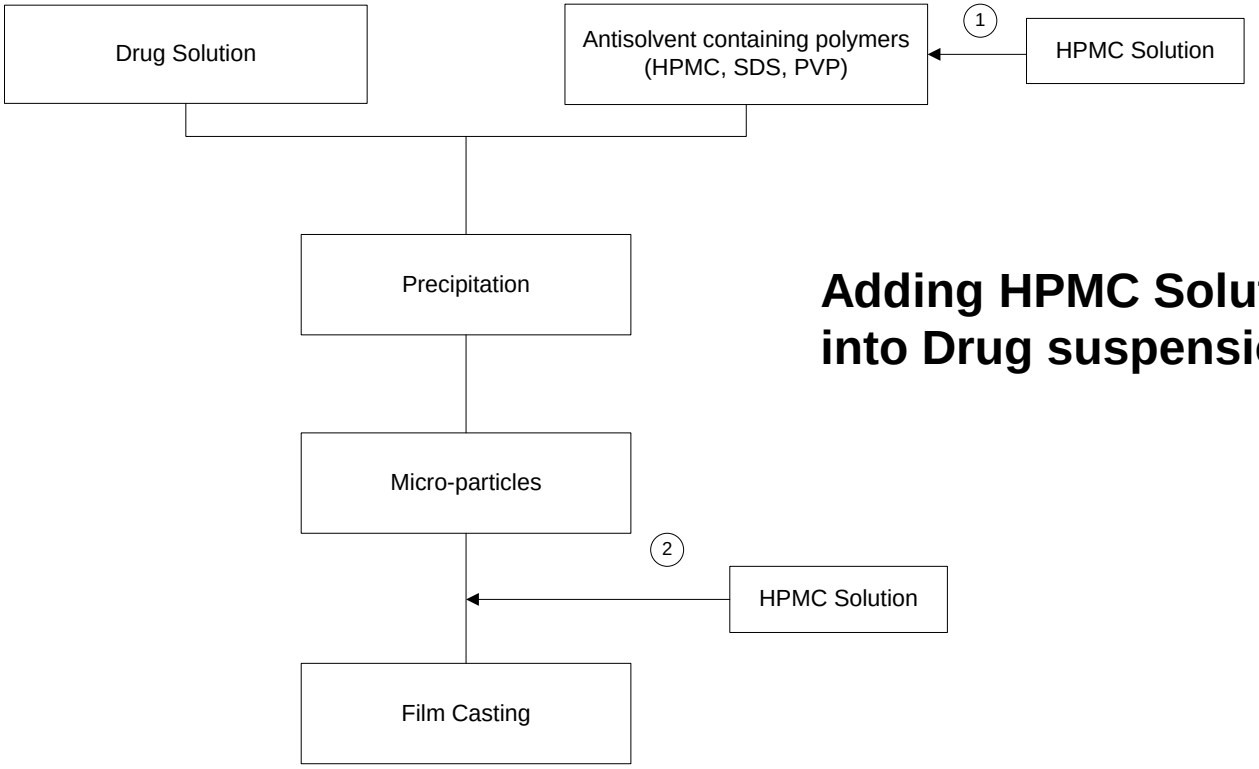
Film formation followed by anti-solvent synthesis





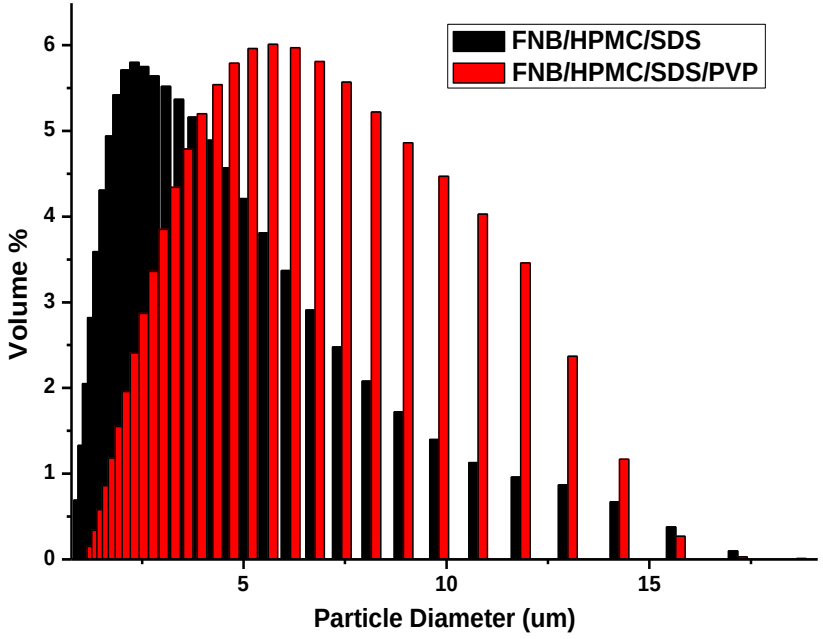


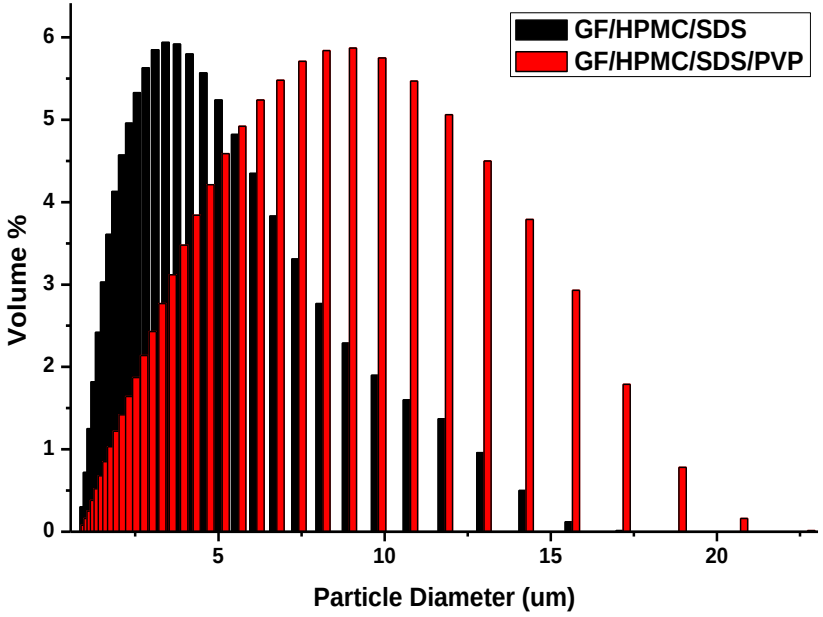
Integrating anti-solvent precipitation/film casting



Adding HPMC Solution into Drug suspensions → ***Stage 1 or Stage 2 ?***

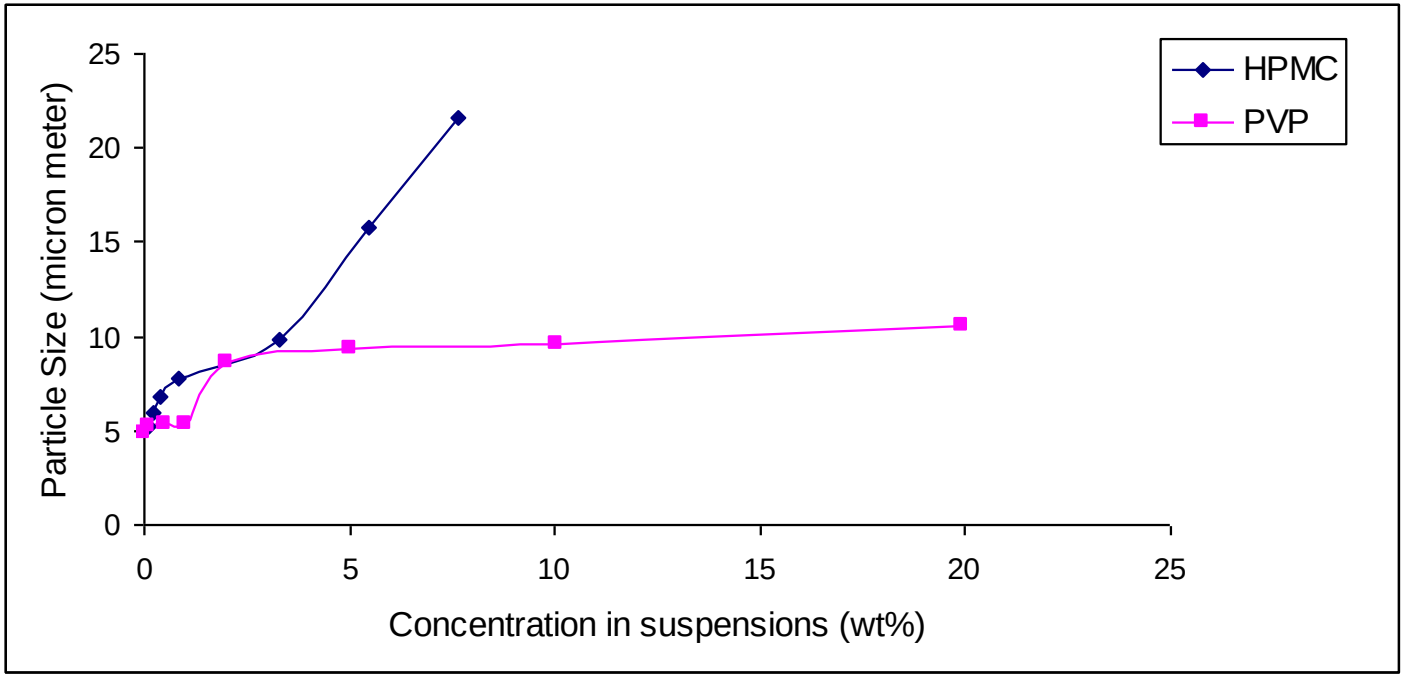
Particle Size Distribution of Drug suspensions





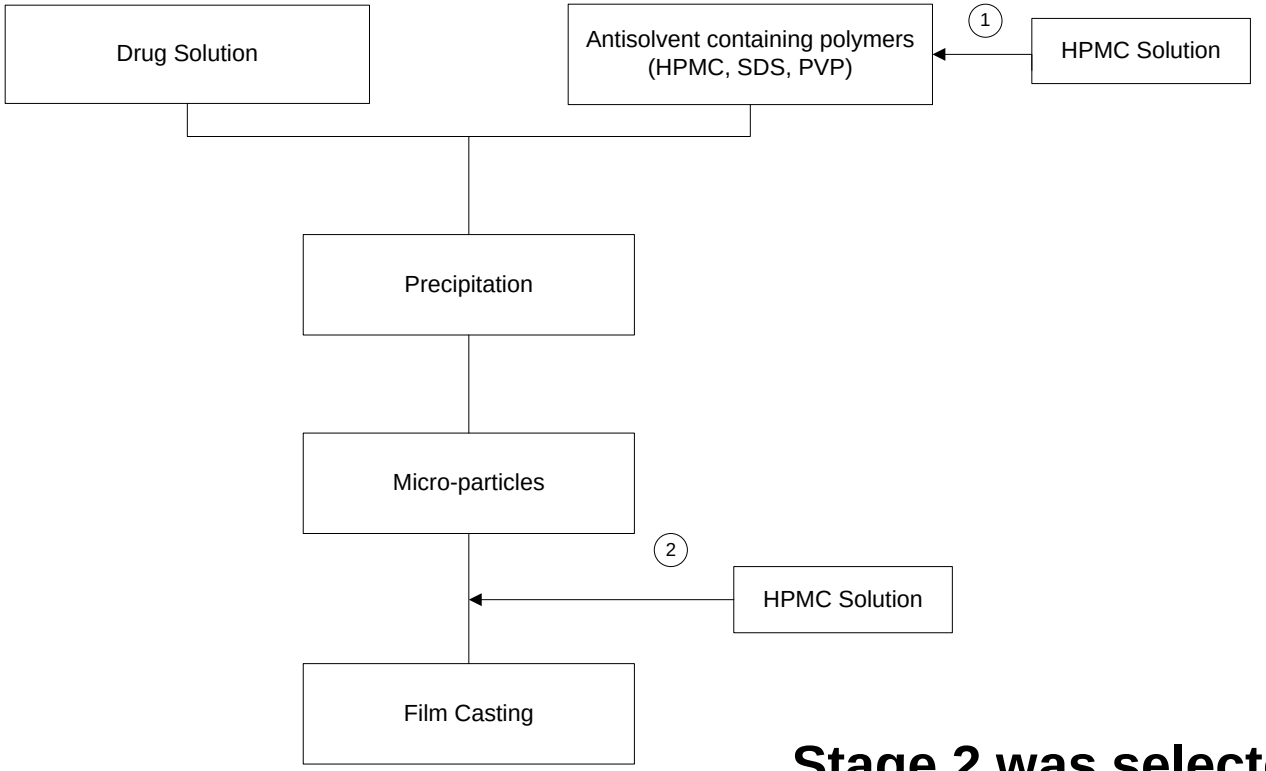
Increase in mean particle diameter is due to higher concentration of HPMC

Effect of concentration of HPMC/PVP on particle size



Mean particle Diameter increased linearly with the increase of concentration of HPMC

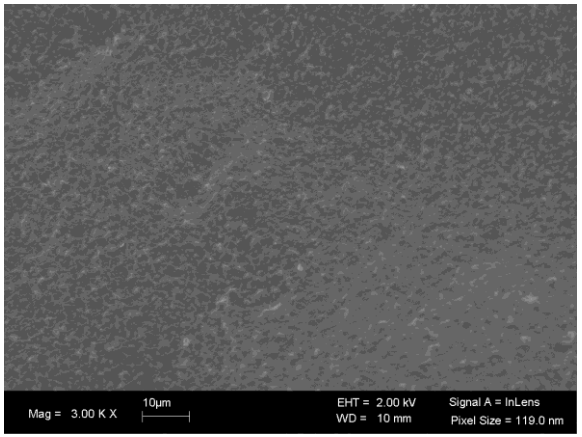
Approach to integrating anti-solvent precipitation/film casting



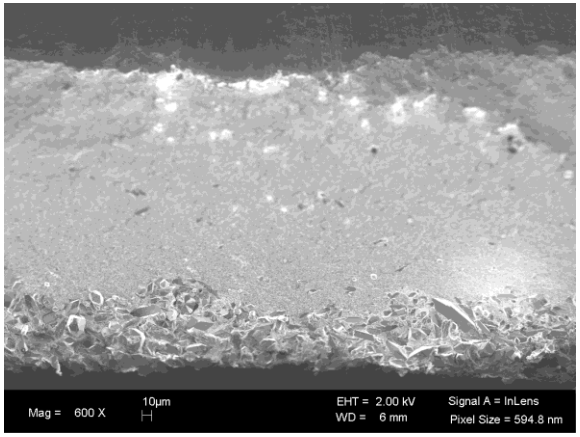
Stage 2 was selected because it led to smaller particle size

Film formation followed by anti-solvent synthesis

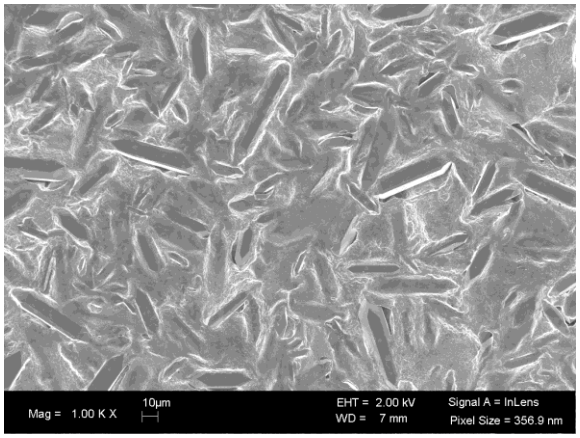
GF-loaded polymer film with high concentration of HPMC (84 wt%)



Top surface



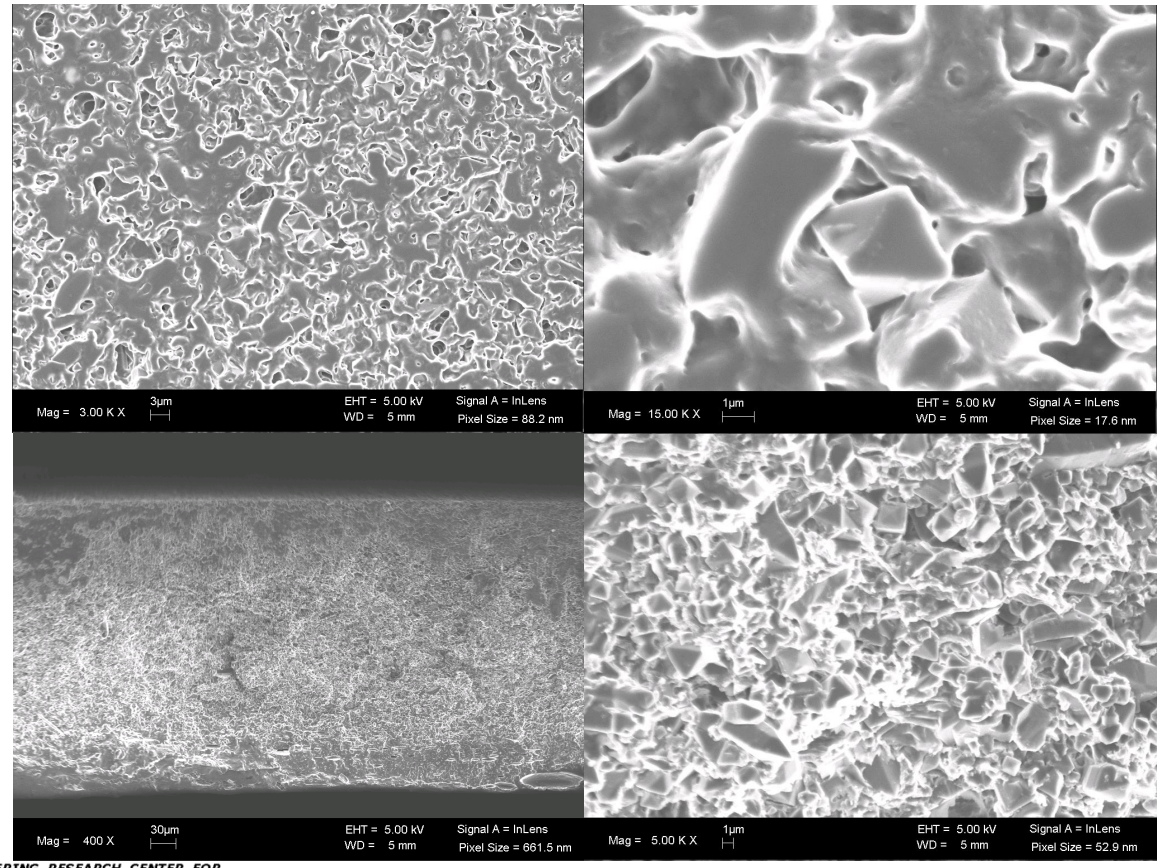
Cross section



Bottom surface

Film Formation Followed by Anti-solvent Synthesis

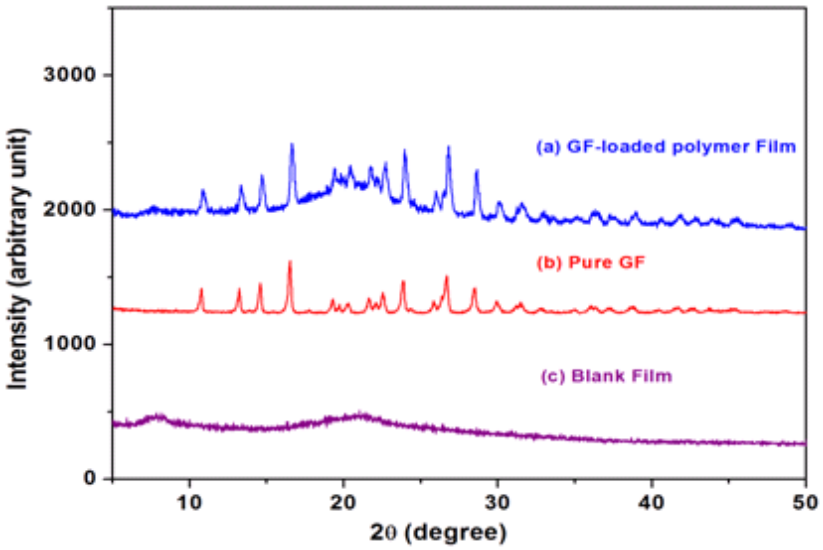
GF-loaded polymer film (GF: 28.4%, HPMC: 50.6%, PVP: 13.1%, SDS: 7.9%)



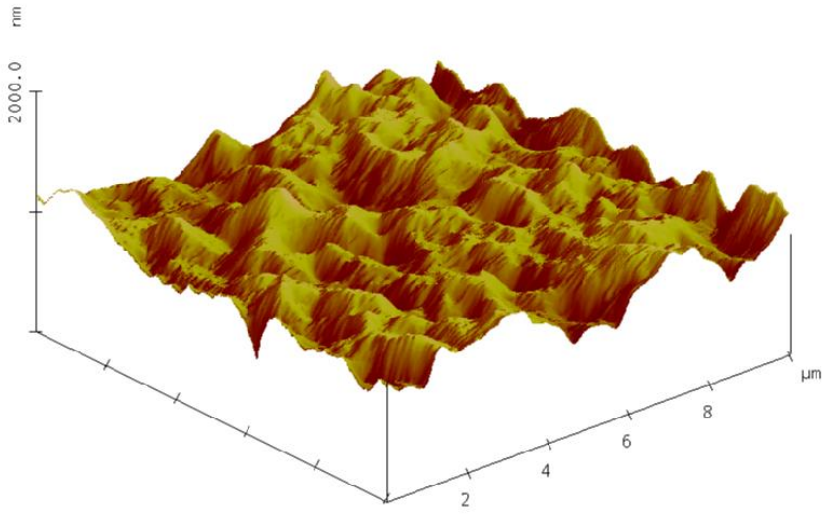
Top surface

Cross section

XRD and AFM Analysis of Films

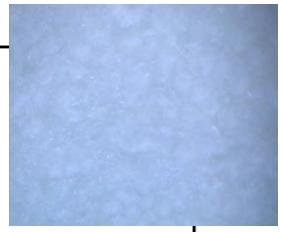


XRD analysis

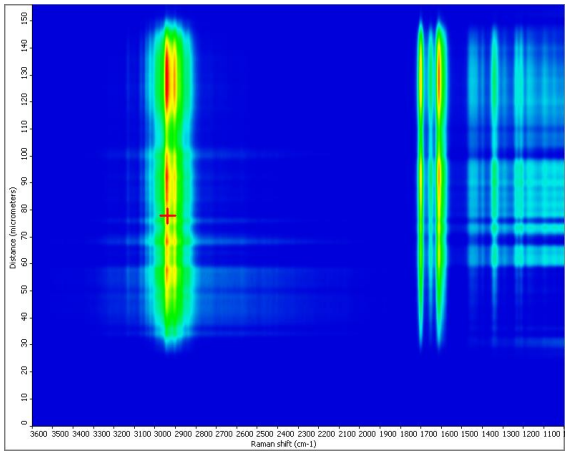


AFM surface Topography

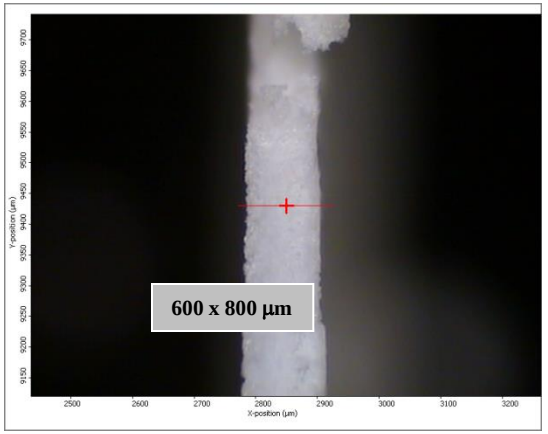
Raman Spectroscopy of Films



Raman mapping analysis

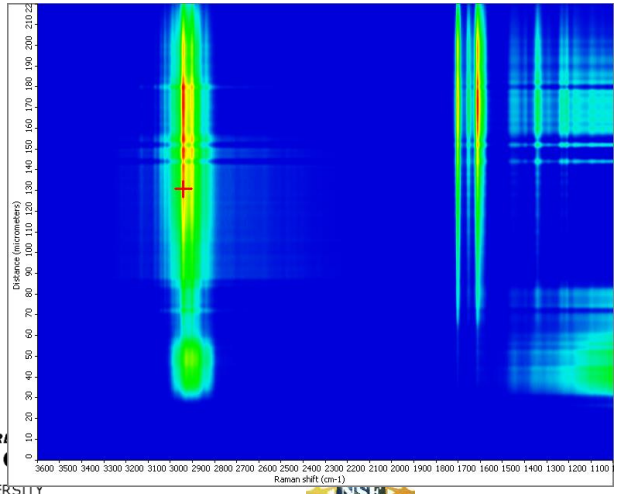


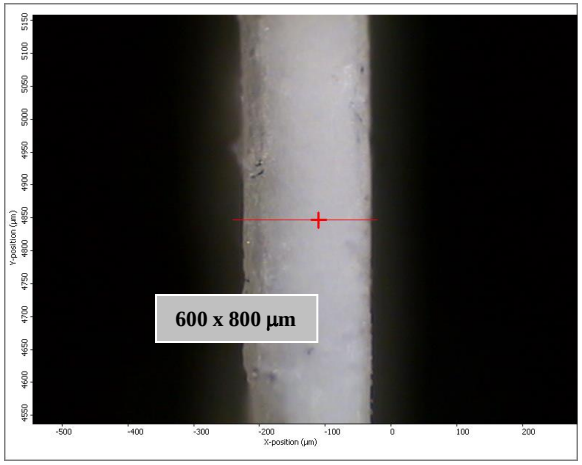
Chemical Imaging GF 28.4 wt%



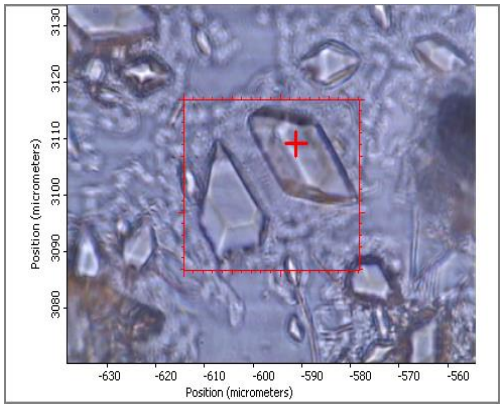
Optical Imaging GF 28.4 wt% Cross Section

GF 36.5 wt%

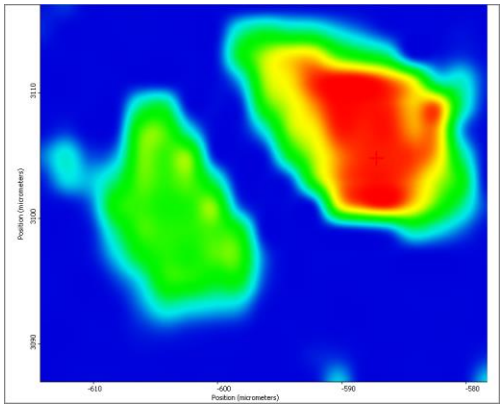




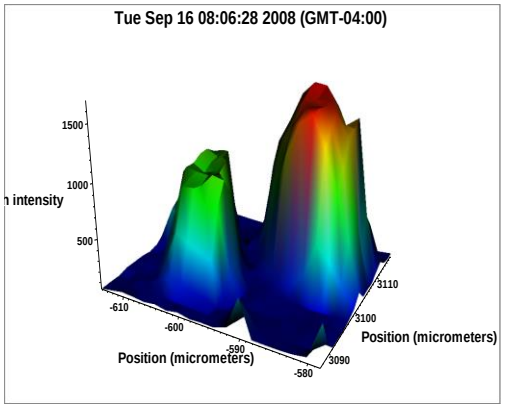
Raman Mapping



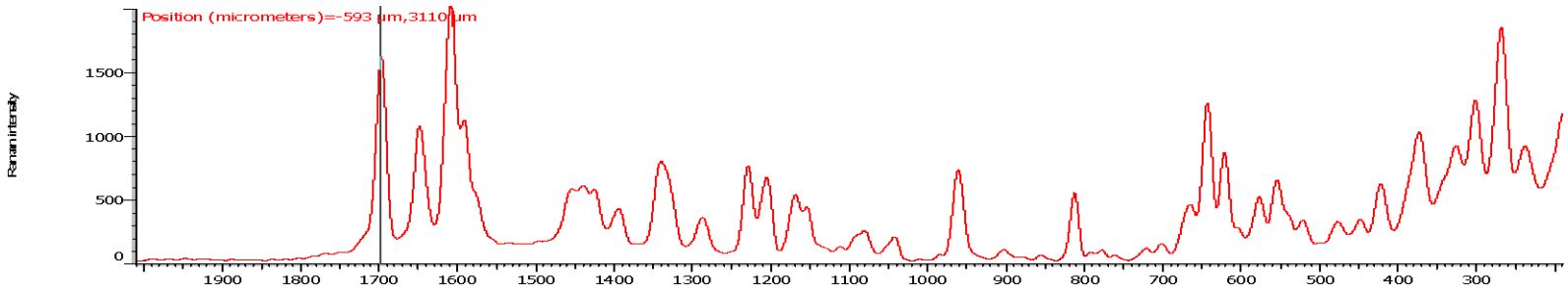
Real Imaging 60 x 80 μm



2D Chemical Imaging



3D Chemical Imaging



Raman Spectra of GF

Summary

- **Anti-solvent synthesis of micro scale drug particles with simultaneous stabilization with cellulose ether and SDS reduced the average particle size**

- **Zeta potential measurements showed that the suspensions were close to agglomeration rather than thermodynamically stable.**

- **API encapsulated films were cast from stabilized suspensions**

Acknowledgements: NSF ERC, NSF IGERT