Effect of Polymer Type and Drug Loading on The Mechanism of Nano-species Generation During Dissolution of Amorphous Solid Dispersions of Aprepitant

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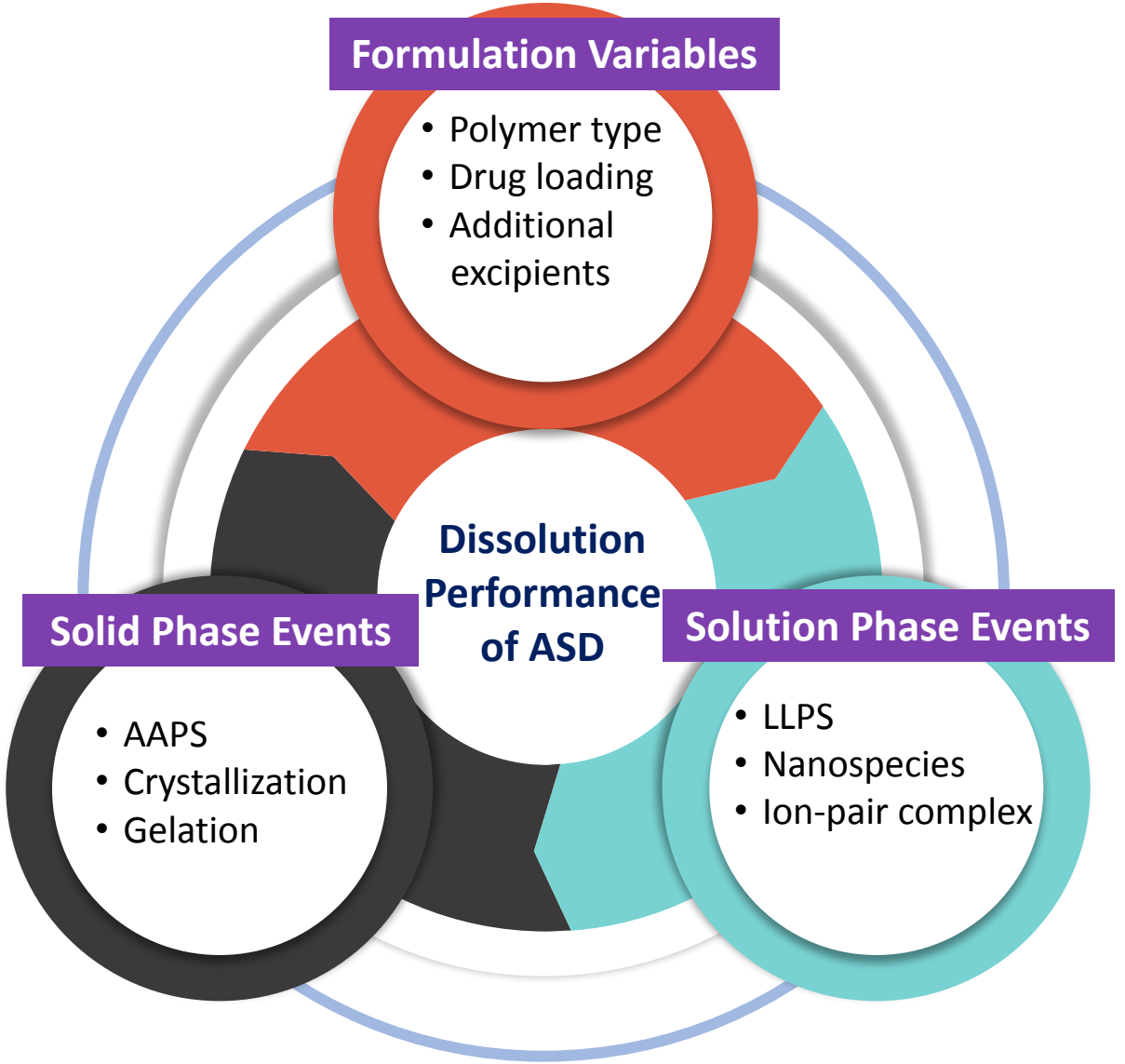
Flow of Presentation

- Introduction
- Background
- Aprepitant-PVPVA ASDs
- Aprepitant-Eudragit L100-55 ASDs
- Key Takeaways

Introduction

Introduction

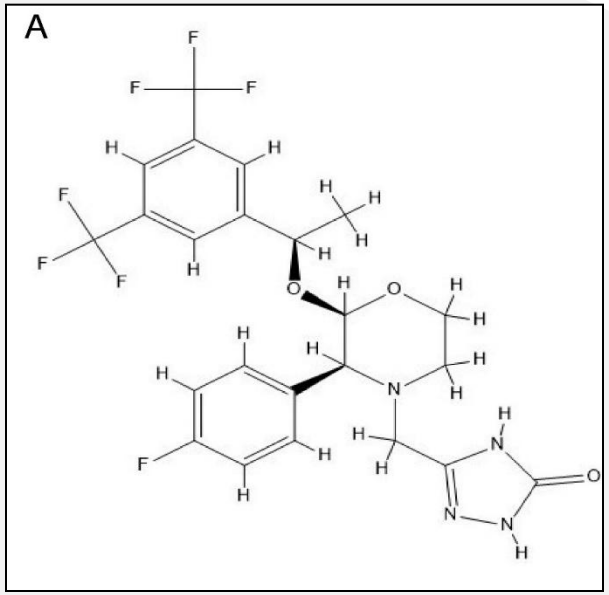


Influence of interplay of above parameters on dissolution performance is an active area of research

Background

Background

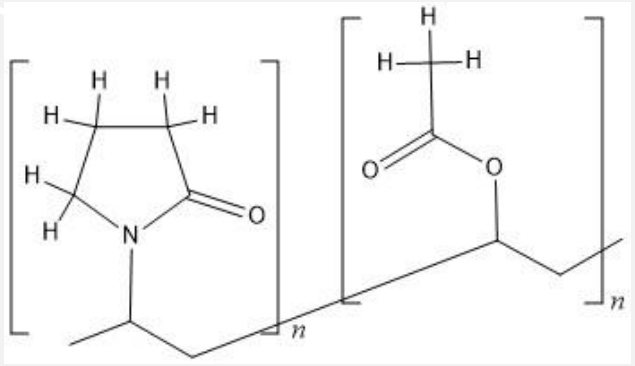
Aprepitant (APR): GFA Class 2



Crystalline solubility (µg/mL) at 37 °C[a]	0.485 at pH 6.8
Amorphous solubility (µg/mL) at 37 °C[a]	9 at pH 6.8
Melting point (°C)[a]	253.44
Glass transition temperature (°C)[a]	Onset-85.89
Log P	4.8 at pH 7
pK_a	7.14 (strongly acidic), 4.03 (strongly basic)

PVPVA (Kollidon VA 64)

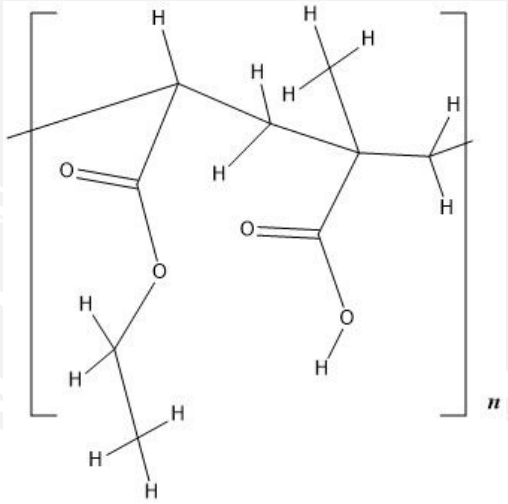
Neutral, Hydrophilic



Ratio of Contact angle (Polymer/APR)= 0.31

Eudragit L100-55

Ionic, Hydrophobic



Ratio of Contact angle (Polymer/APR)= 0.59

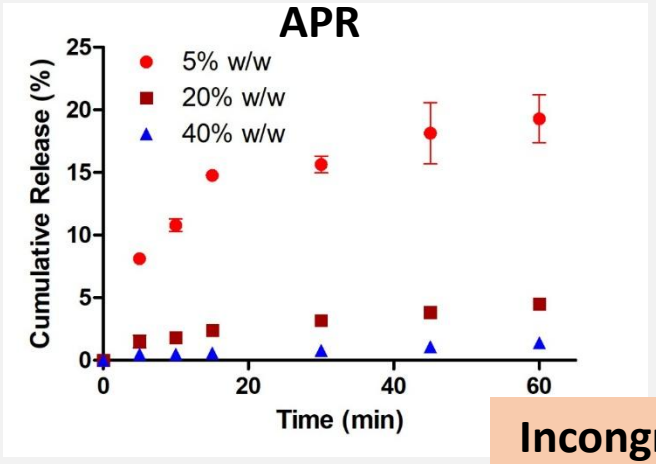
Experimental Design

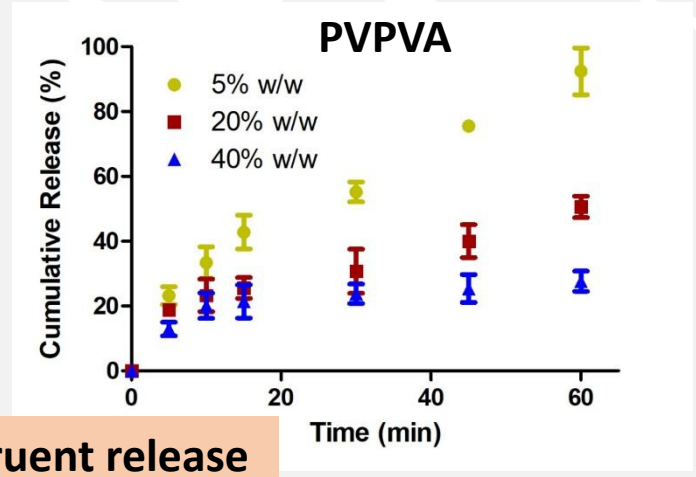
Experiment	Information
Drug loading (DL)	5, 20 and 40% w/w
Surface Normalized Release (SNR) Experiment	Release behaviour of drug and polymer Presence of nano-species and their nature
PXRD of dissolving ASD compact	Evidence of crystallization
Exposure of ASD films at 97% RH	AAPS using TEM and PLM
Unstirred water layer (UWL)	Microenvironment pH and LLPS
FTIR	Drug – polymer interactions

APR-PVPVA ASDs

APR Nano-species in Bulk SNR Experiment of APR-PVPVA ASDs

Release pattern of 100 mg ASD in 200 mL of 50 mM pH 6.8 phosphate buffer

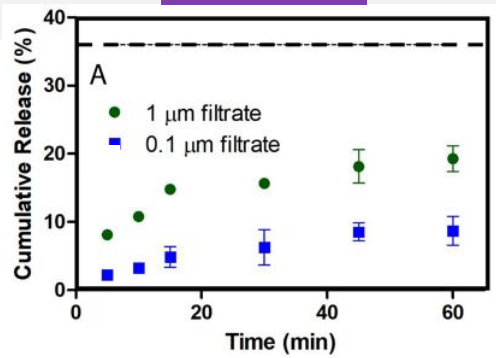




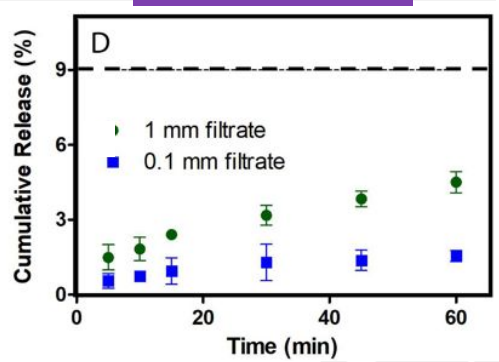
Incongruent release

Sequential Filtration through 1 µm and 0.1 µm pore size filter membrane

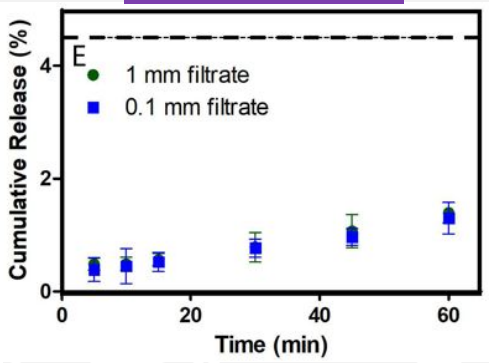
5% w/w



20% w/w

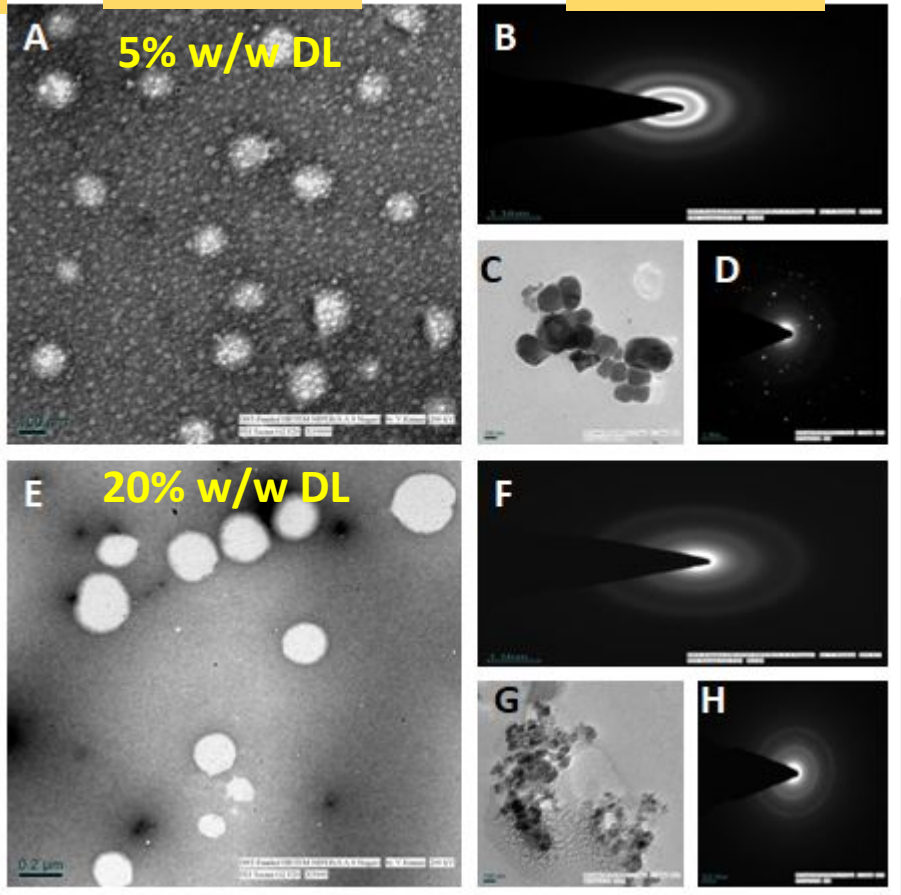


40% w/w



Nano-species formed up to 20% w/w drug loading

TEM **SAED**



- Dissolved APR concentration in bulk < $C_{amorphous}$
- SAED Analysis: Amorphous+crystalline nature
- Time-dependant size reduction of nano-species

Chakraborty, S and Bansal, AK, Surfaces and Interfaces; 69, 2025, 106763

Hydration-Induced Phase Separation in ASDs

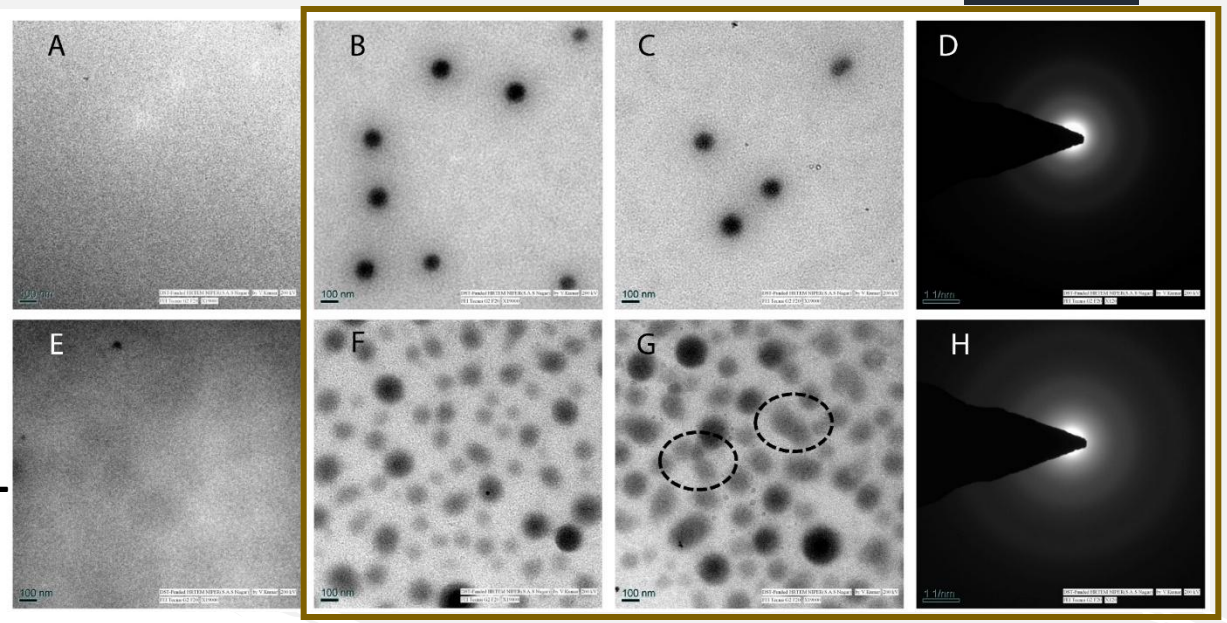
PXRD of dissolving ASD compact showed partial crystallization

Spin-coated ASD films were stored in a closed system at 97% RH

Spatial Pattern of Phase Separation (4h)

Before | TEM | After | SAED

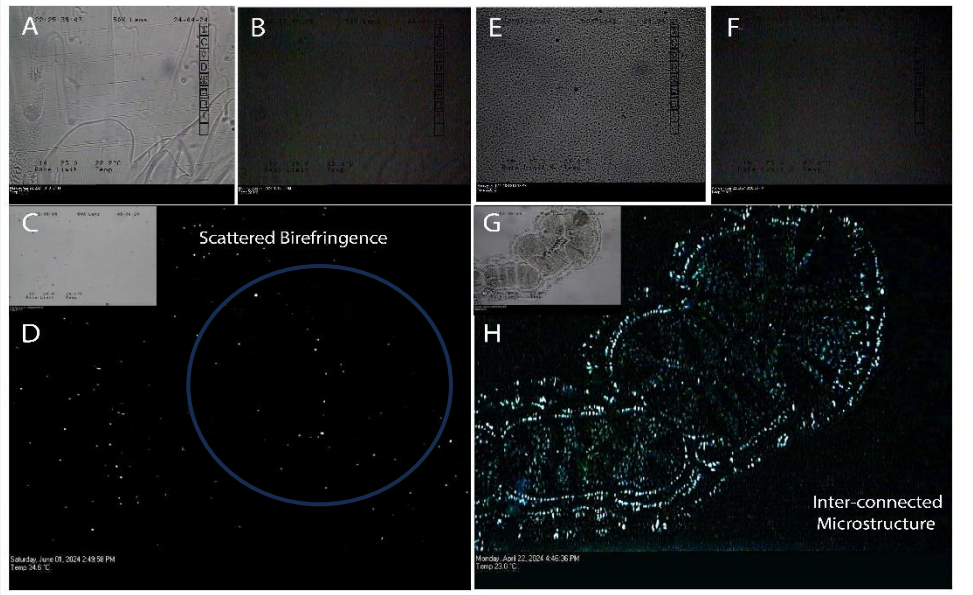
5% DL / 40% DL



Spatial Evolution of Phase Separation (24h)

5% DL | PLM | 40% DL

Before / After



- Nano-sized phase-separated domains in both 5% and 40% w/w DL
- 5% w/w ASD- smaller domains with low spatial density
- 40% w/w ASD- small + large domains with high spatial density and coalescence

Chakraborty, S and Bansal, AK, Surfaces and Interfaces; 69, 2025, 106763

Evaluation of LLPS in UWL

For generation of the nano-species through LLPS, the dissolved APR concentration should be equal or more than the amorphous solubility in UWL during dissolution

Samples were sequentially filtered through 1 µm pore size filter membrane and ultra-centrifuged (40000 rpm 30 min)

Drug loading	Molecularly dissolved APR Concentration	+APR nano-species concentration
5% w/w	1.15 µg/ml	92.43 µg/ml
20% w/w	2.18 µg/ml	169.03 µg/ml
40% w/w	2.87 µg/ml	2.94 µg/ml

- **In all cases, molecularly dissolved APR concentration was below amorphous solubility of APR (9 µg/ml)**
- **Thus, APR nano-species formation was not mediated by LLPS in UWL**

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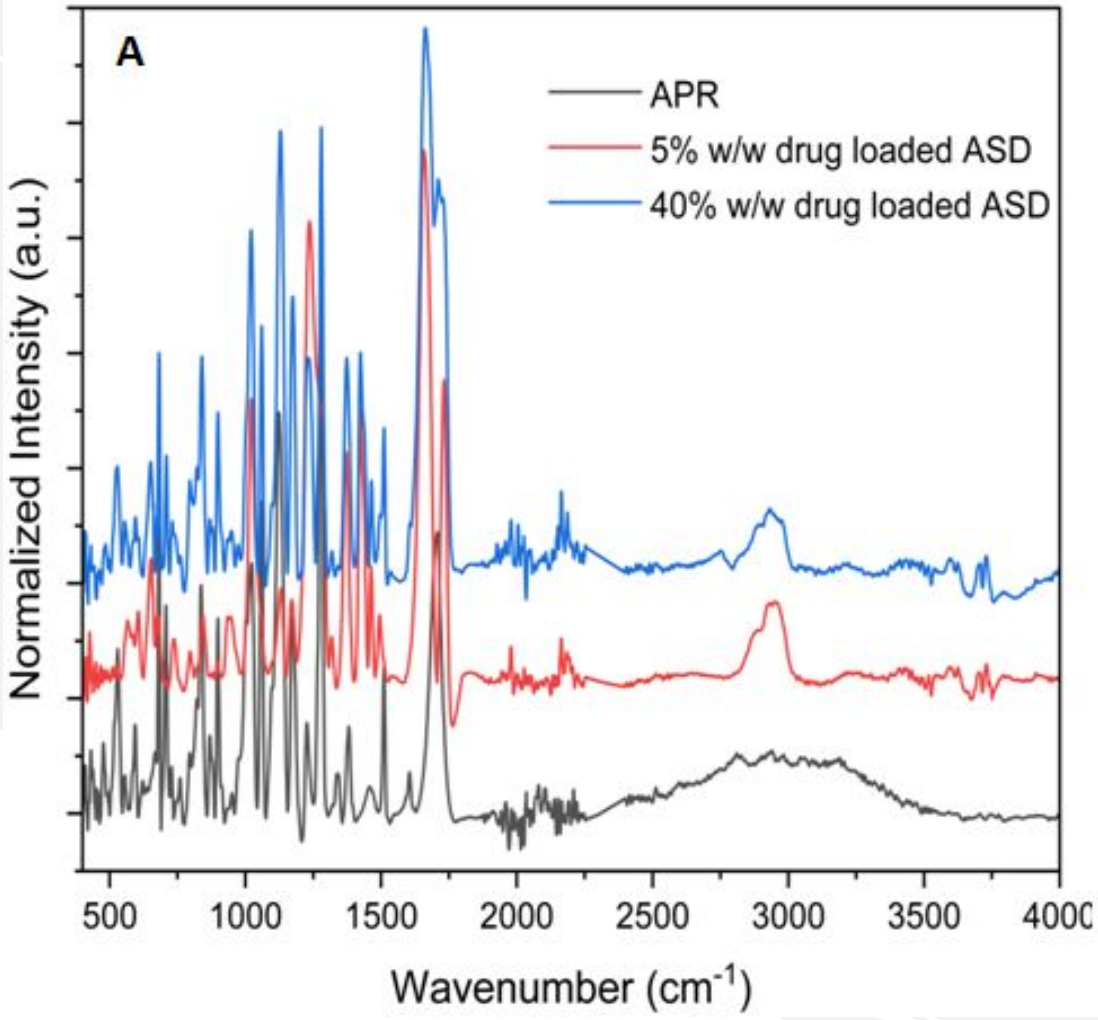
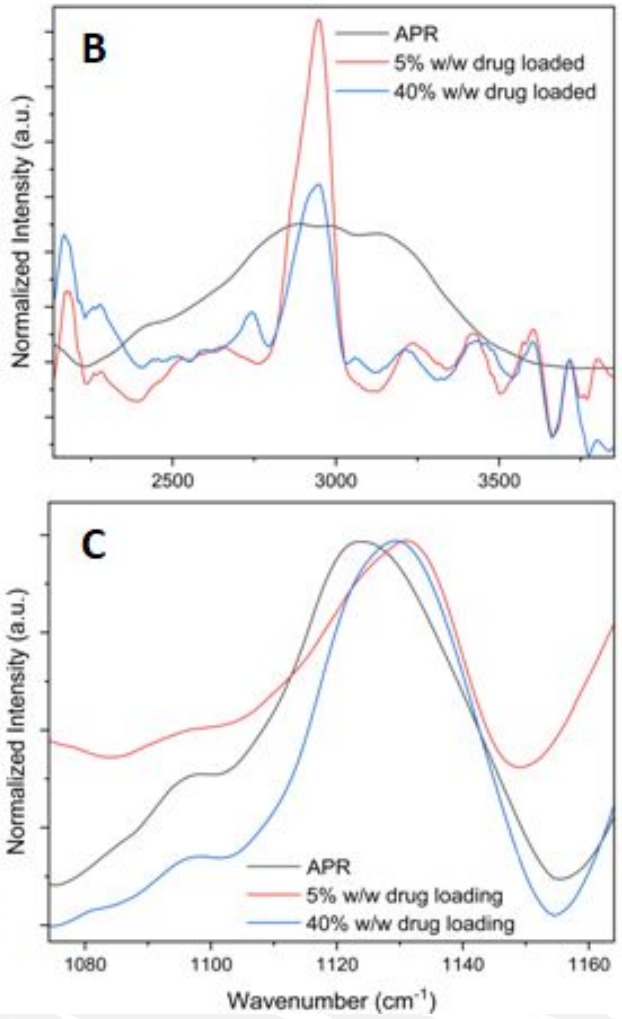
Drug-Polymer Interactions @ 5% and 40% DL

ATR-FTIR





- **2956 cm^{-1}: secondary amine stretching band of APR increased in intensity in ASD, due to hydrogen bonding with PVPVA.**

5% DL: ↑↑

40% DL: ↑

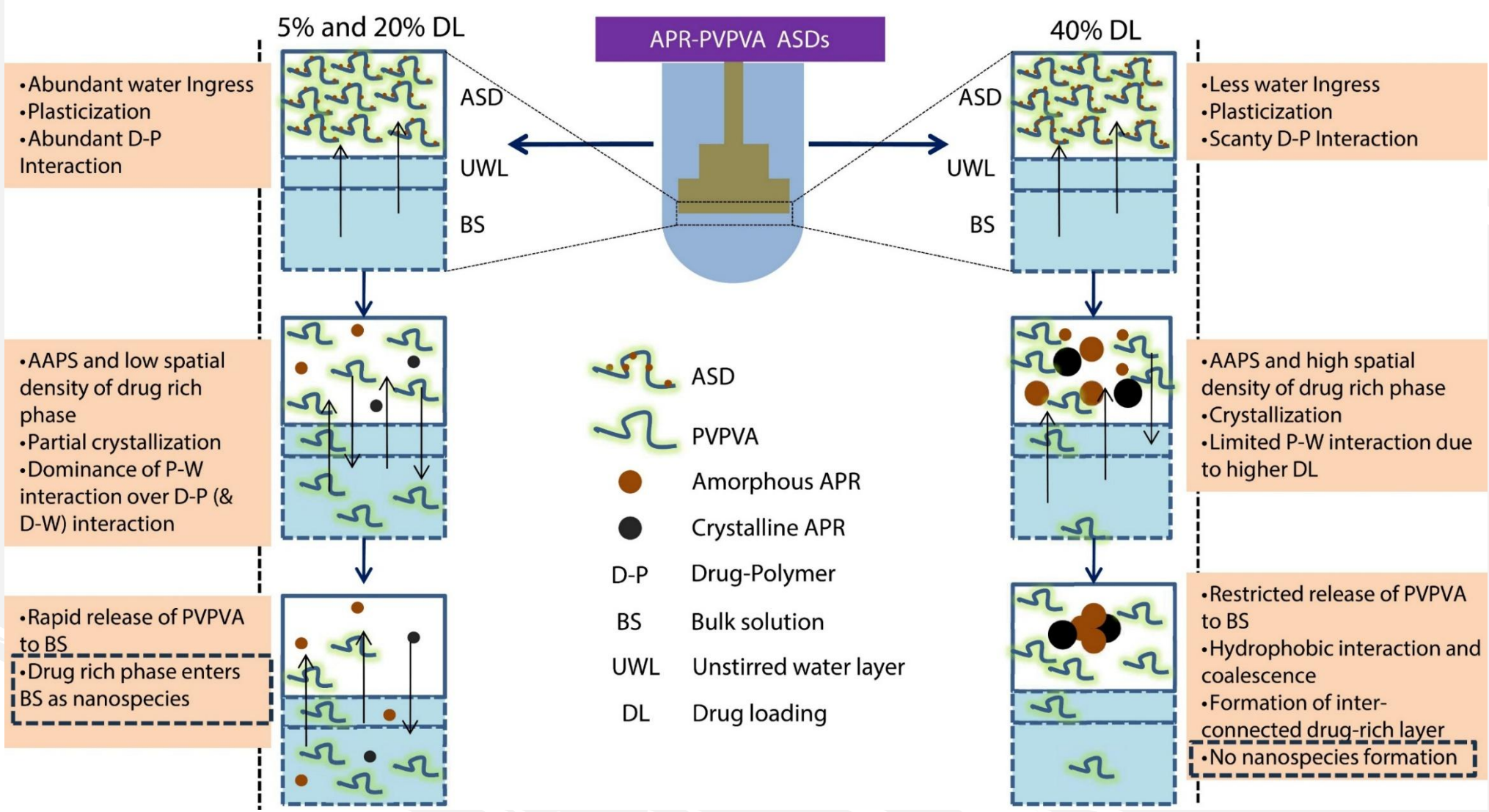
- **1124 cm^{-1}: C-F stretching band of APR shifted to higher wavenumber in ASD due to formation of halogen bond with PVPVA.**

5% DL: +6 cm^{-1}

40% DL: +4 cm^{-1}

Abundance of interaction was higher in 5% w/w drug loaded ASD than 40% w/w drug loaded ASD

Effect of Drug Loading on Origin of Nanospecies Formation from APR-PVPVA ASDs



•No LLPS either in UWL or bulk medium.
•AAPS was responsible for generation of nano-species
•Drug loading has a profound influence on solid phase events at the dissolving ASD interface.

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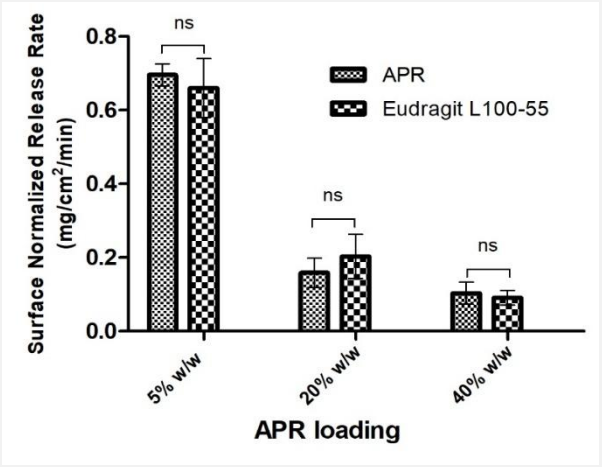
APR-Eudragit L100-55 ASDs

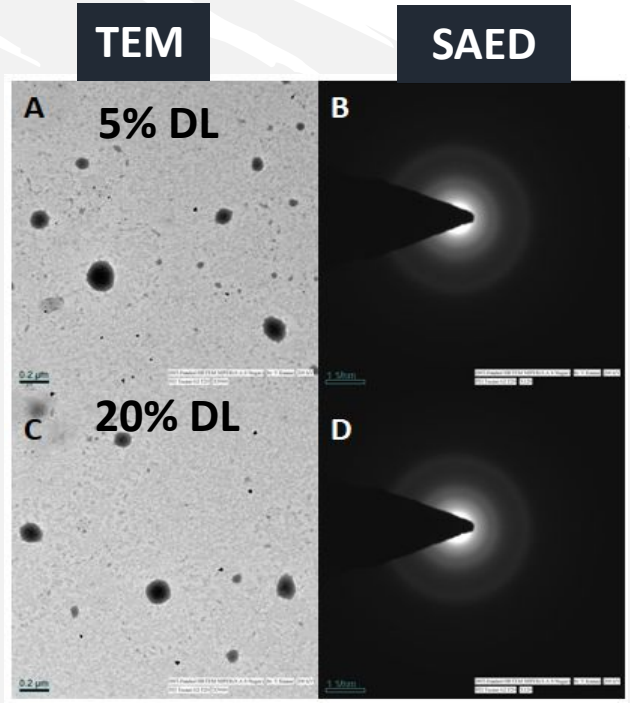
Eudragit L100-55: Copolymer of Methacrylic acid and Ethyl acrylate

APR Nanospecies in Bulk During SNR of APR-Eudragit L100-55 ASDs

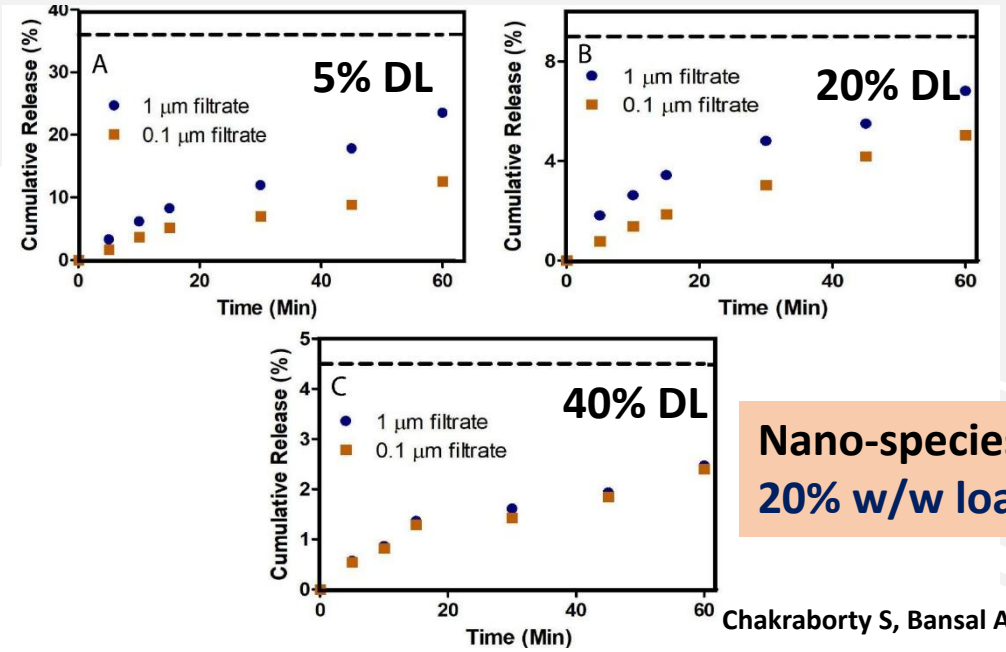
Release pattern of 100 mg ASD in 200 mL of 50 mM pH 6.8 phosphate buffer



Congruent Release



Sequential Filtration through 1 µm and 0.1 µm filter membrane



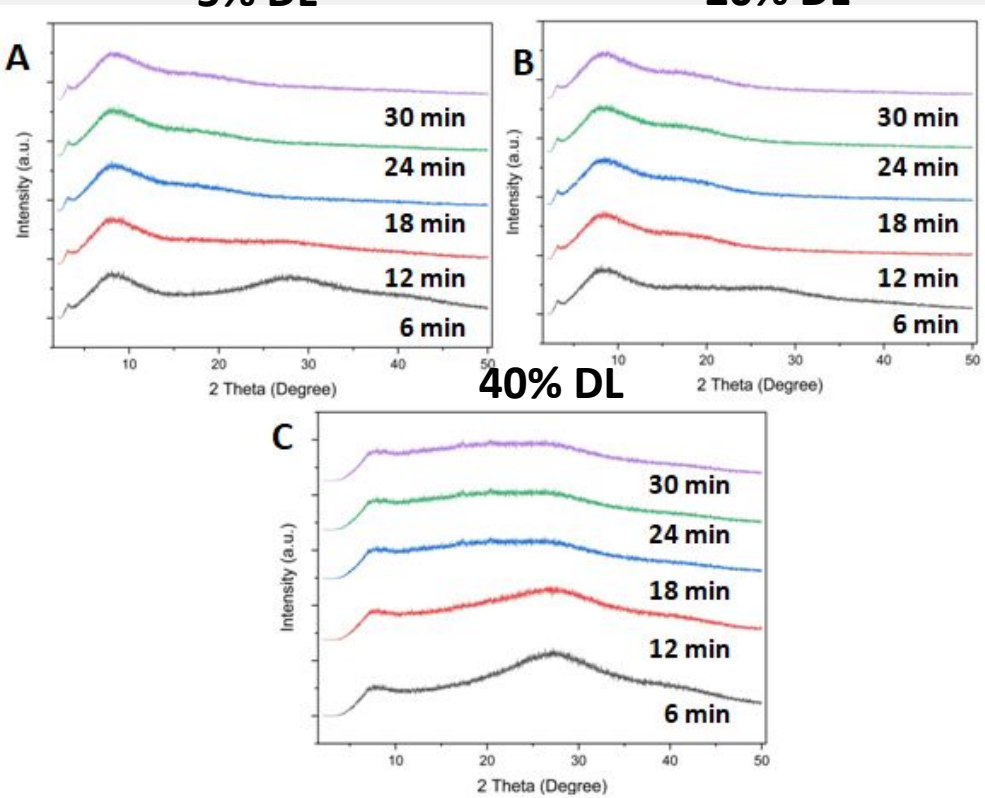
Nano-species up to 20% w/w loading

Dissolved drug conc. was < $C_{Amorphous}$ at bulk pH (6.8)
SAED Analysis: Amorphous in nature

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

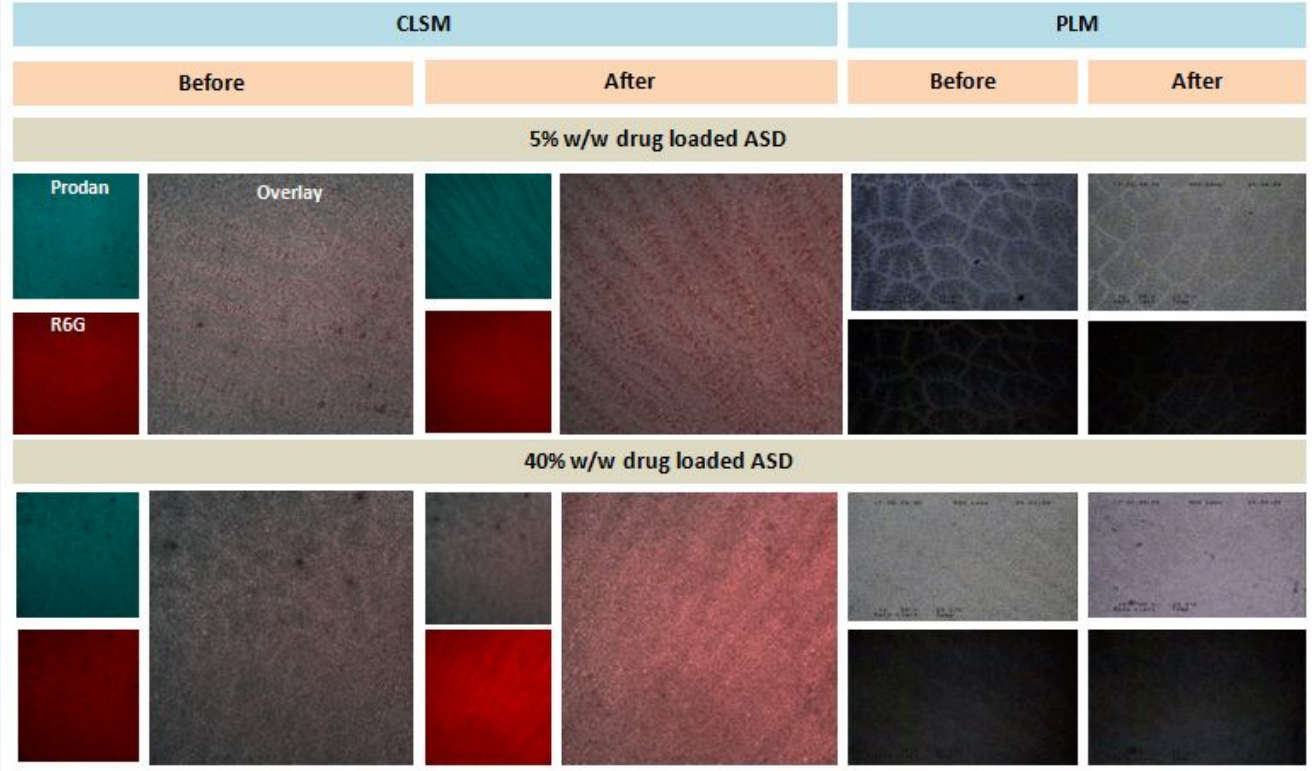
Hydration-Induced Phase Separation in ASDs

pXRD of Dissolving ASD Interface



No crystallization on ASD compact surface

Spin-coated ASD films were stored in 97% RH for 48 h



No hydration-induced AAPS

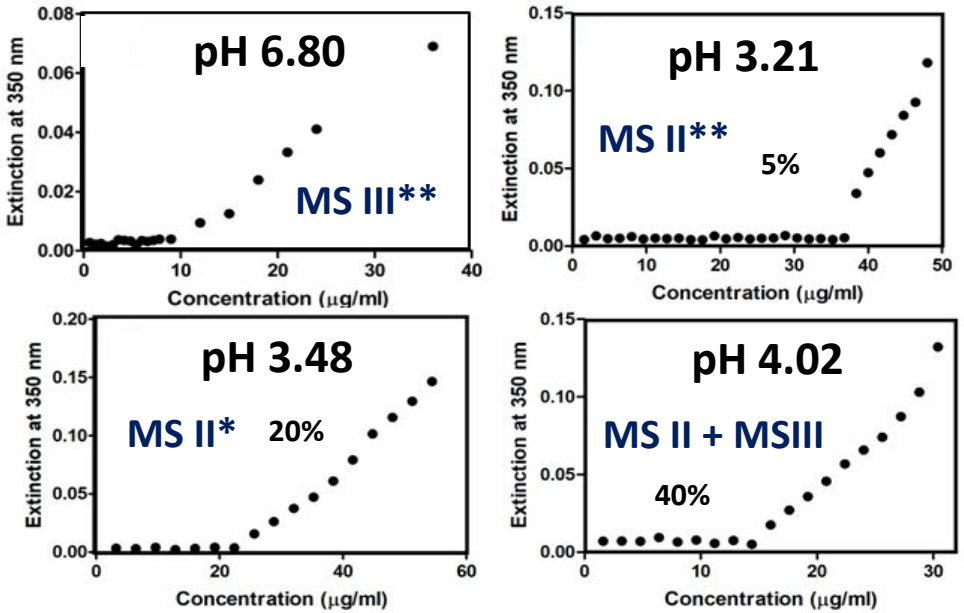
Nano-species did not originate from AAPS in solid ASD

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

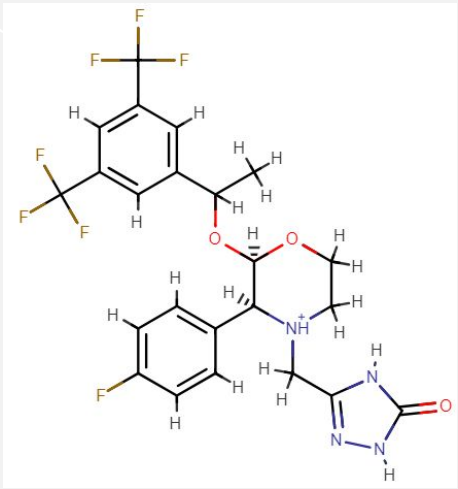
Events in Unstirred Water Layer (UWL)

It was hypothesized that deprotonation of methacrylic acid may reduce microenvironmental pH

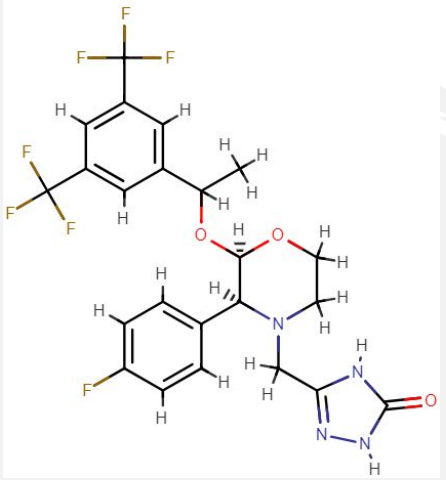
UV-Extinction



MS II (+1)



MS III (0)



* Predominant micro-species

APR loading (%)	Microenvironmental pH	Microspecies Distribution (%)		Amorphous Solubility (µg/ml)
		MS II (+1)	MS III (0)	
5	3.21	86.7	13.2	38.0
20	3.48	77.6	22.3	25.6
40	4.02	49.5	50.4	14.4

Microenvironmental pH induced change in speciation profile of APR changed the amorphous solubility of APR in UWL

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

Solution Phase Distribution of APR in UWL

Samples were sequentially filtered through 1 µm µm pore size filter membrane and ultra-centrifuged (40000 rpm 30 min)

Drug loading	Microenvironmental pH	Amorphous Solubility (µg/mL)	Molecularly dissolved APR concentration	+ APR nano-species concentration
5% w/w	3.21	38.0	50.4 µg/ml	277.44 µg/ml
20% w/w	3.48	25.6	72.42 µg/ml	342.6 µg/ml
40% w/w	4.02	14.4	4.28 µg/ml	4.50 µg/ml

- At 5 and 20% DL, molecularly dissolved APR concentration was above the amorphous solubility at the corresponding microenvironmental pH. Thus nano-species were formed via LLPS in UWL.
- At 40% DL APR concentration higher than amorphous solubility was not be achieved.

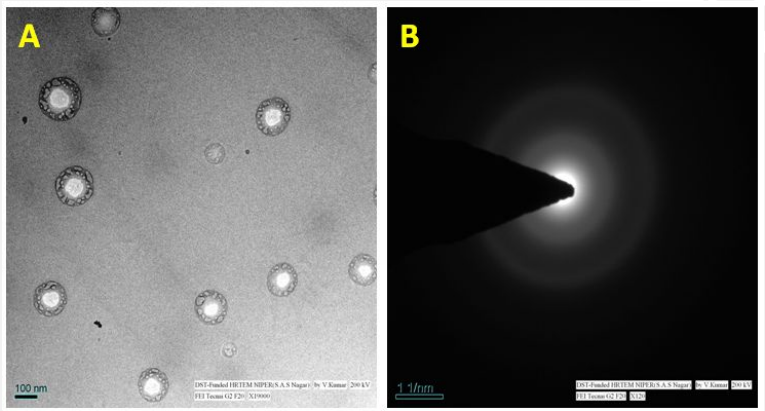
Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

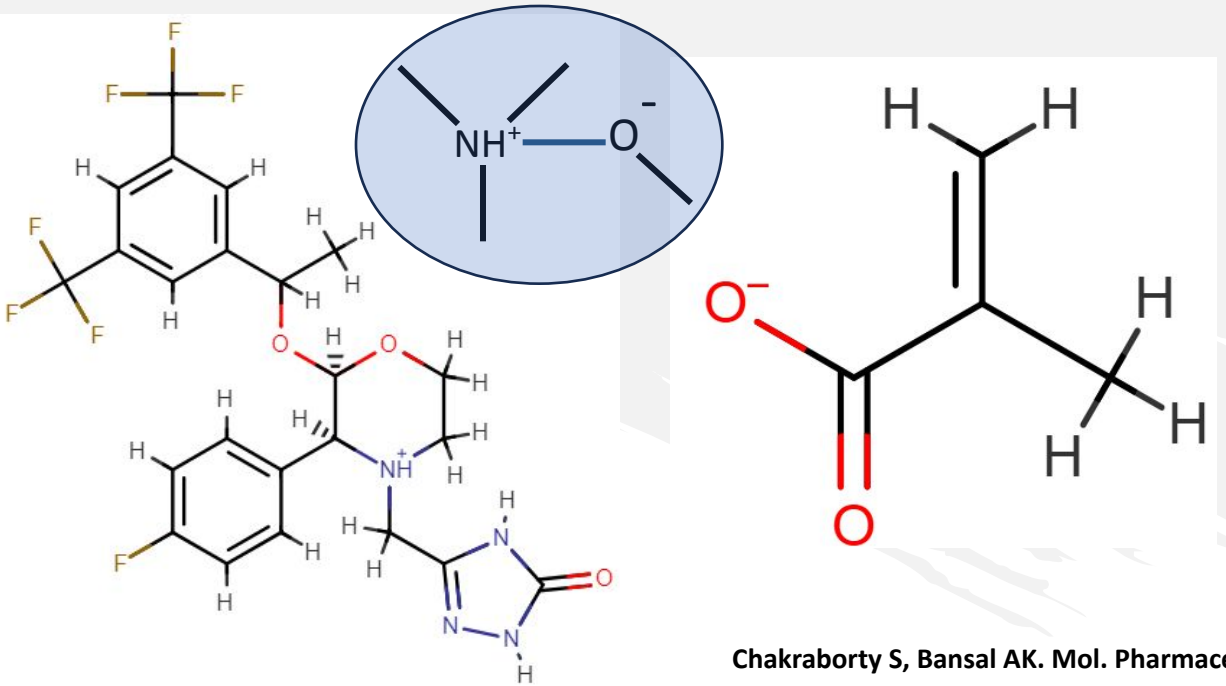
Alternative Mechanism : Ion-Pair Complexation

10 µL of APR solution in methanol (400 µg/mL) was added in 1 mL of saturated solution of Eudragit L100-55 in pH 6.8 phosphate buffer, and stirred for 15 min (Resultant concentration 4 µg/mL)

Separation Method	APR Concentration (µg/ml)
Filtration (1 µm pore)	3.39
Ultracentrifuge (40000 rpm/30 min)	1.44

TEM-SAED

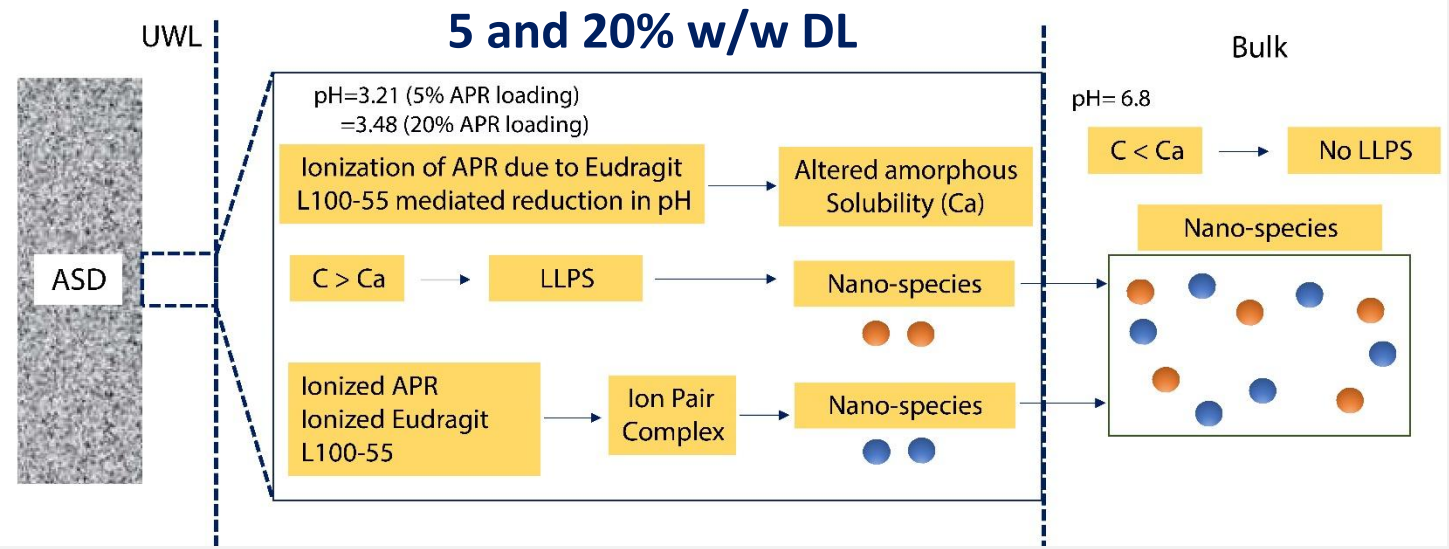


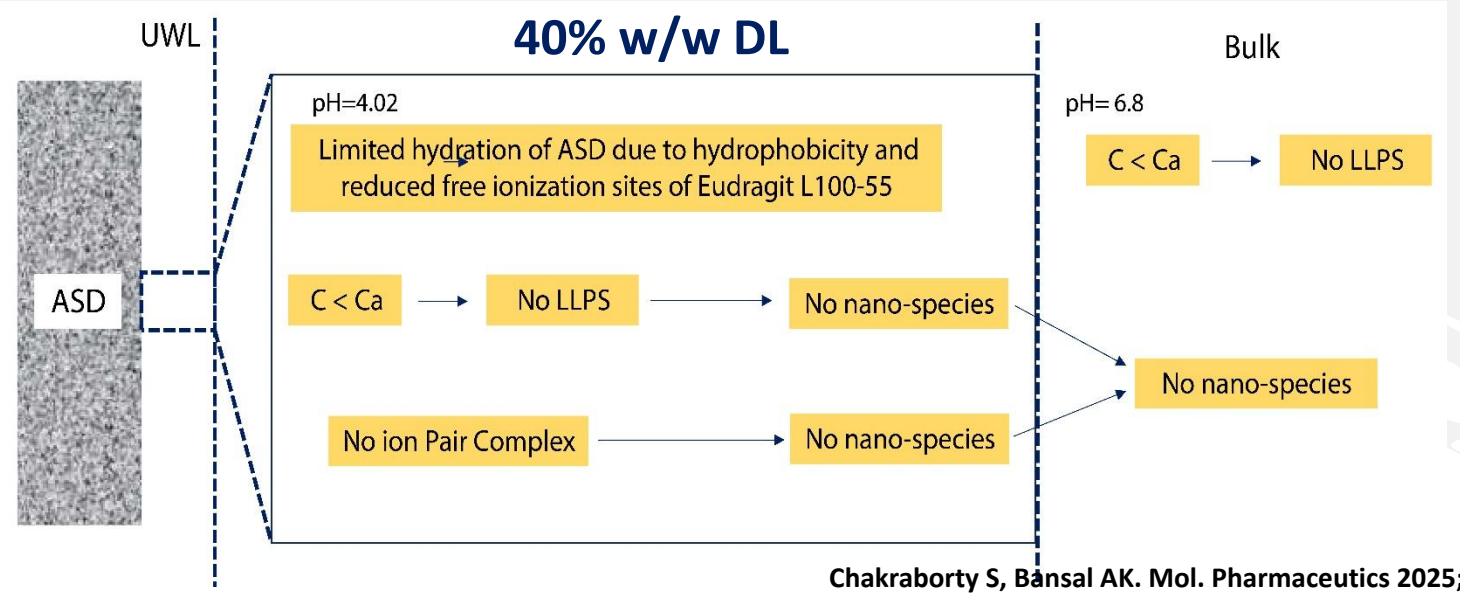


- At microenvironment pH anionic and cationic species of Eudragit L100-55 and APR, respectively interacted in UWL through ion-pair complexation.
- Ion-pair complexation led to nano-precipitation which was a parallel route of nano-species generation.

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

Effect of Microenvironmental pH and Drug Loading of ASD on Origin of Nanospecies formation from APR-Eudragit L100-55 ASDs





5 and 20% w/w DL

- Deprotonation of methacrylic acid in Eudragit L100-55 altered microenvironment pH of UWL.
- pH-dependent change in amorphous solubility
- Congruent release of drug and polymer enabled solubility>amorphous solubility leading to LLPS
- Additionally, oppositely charged of drug and polymer species contributed to ion pair complexation

40% w/w DL

- Absence of LLPS in UWL due to limited hydration of polymer and restricted release of drug.

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025; https://doi.org/10.1021/acs.molpharmaceut.5c00152

Key Takeaways

Mechanism of Generation/Absence of Nano-species

PVPVA	Eudragit L100-55
Mechanism of nanospecies generation at 5 and 20% drug loading	
AAPS in solid phase of dissolving ASD compact	LLPS in UWL Ion-pair complexation
Underlying reason for 'Mechanistic Switch'	
• Incongruent release • Dominance of P-W interaction over D-P interaction	• Congruent release • Dominance of D-P interaction over P-W interaction
Mechanism of Absence of nanospecies at 40% w/w DL	
• High spatial density and coalescence of phase separated APR domains. • Reduced hydration due to higher hydrophobicity.	• Higher hydrophobicity of ASD. • Availability of limited number of ionizable sites, thus limiting hydration. • Ion-pair complexation absent due to low percentage of MS II microspecies of APR.

Chakraborty S, Bansal AK. Mol. Pharmaceutics 2025

Contributors

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Chandigarh: The City Beautiful

NIPER-S.A.S. NAGAR

NIPER-S.A.S. Nagar was the first national-level institute in pharmaceutical sciences in India and was declared as an " Institute of National Importance " under the Act of Parliament on 26th June 1998.

Department of Pharmaceutics

The department of Pharmaceutics is one of the oldest departments of the Institute. It is equipped with state-of-the-art facilities to undertake research in drug development and delivery.

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Solid State Pharmaceutics
Department of Pharmaceutics
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The Solid State Pharmaceutics lab, works with a mission statement ' *developing science-based industrially viable pharmaceutical technologies* '

Solid State Pharmaceutics Research Group, NIPER-S.A.S. NAGAR

Thank You!

Any questions?

You can find me at:
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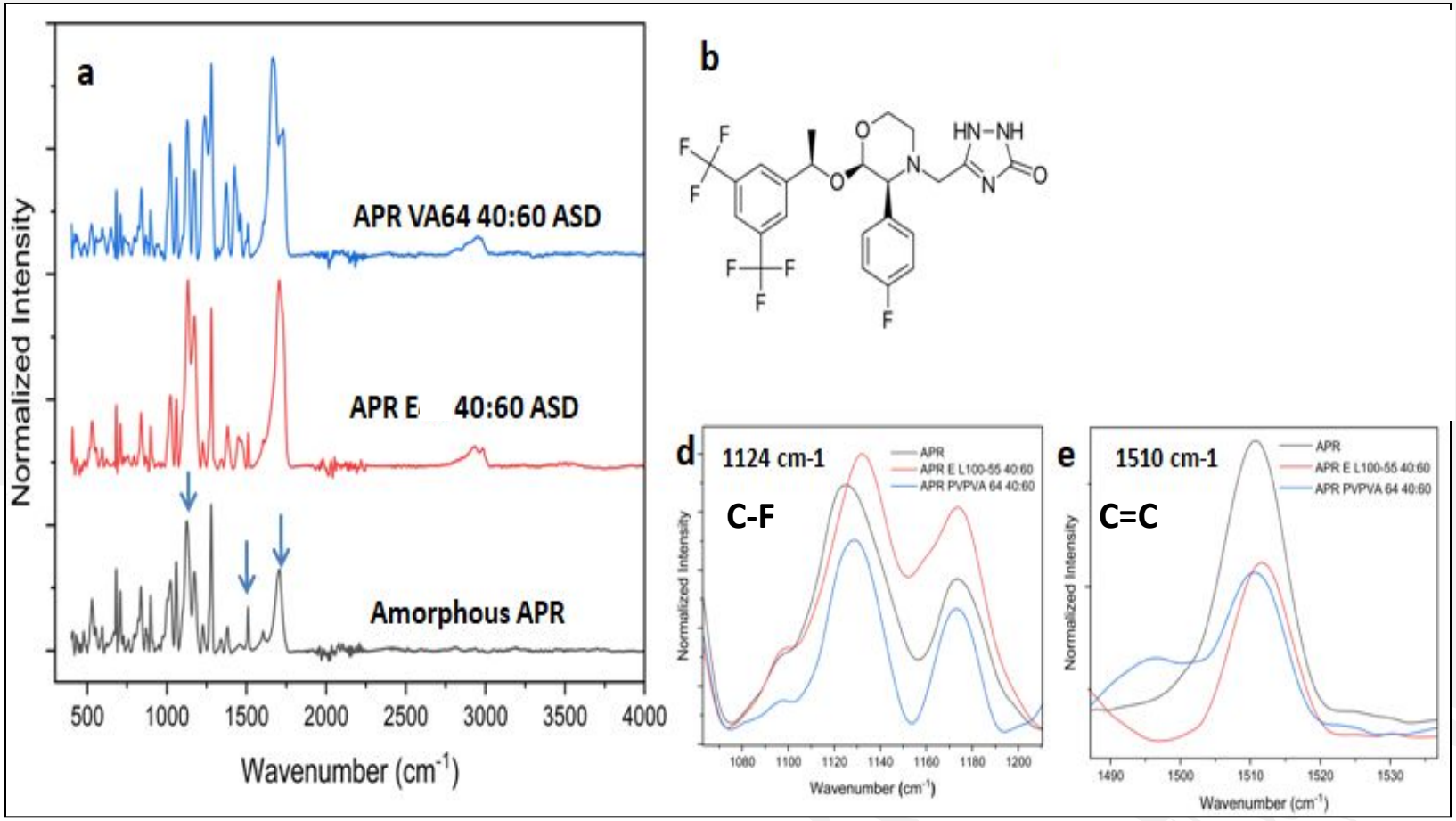
Reserved Slides

‘Mechanistic Switch’ Between PVPVA and Eudragit L100-55-based ASDs

Apart from micro-environmental pH and polymer hydrophobicity……..

Drug-Polymer Interaction Study



The C=O of APR can not form H-bond with PVPVA 64, but can form with –OH group of Eudragit L100-55

The C-F of APR can form halogen bond with both polymers, but can form hydrogen bond with only Eudragit L100-55.
APR-PVPVA 64 ASD: 1124-1128 cm-1
APR-EL100-55 ASD: 1124-1132 cm -1

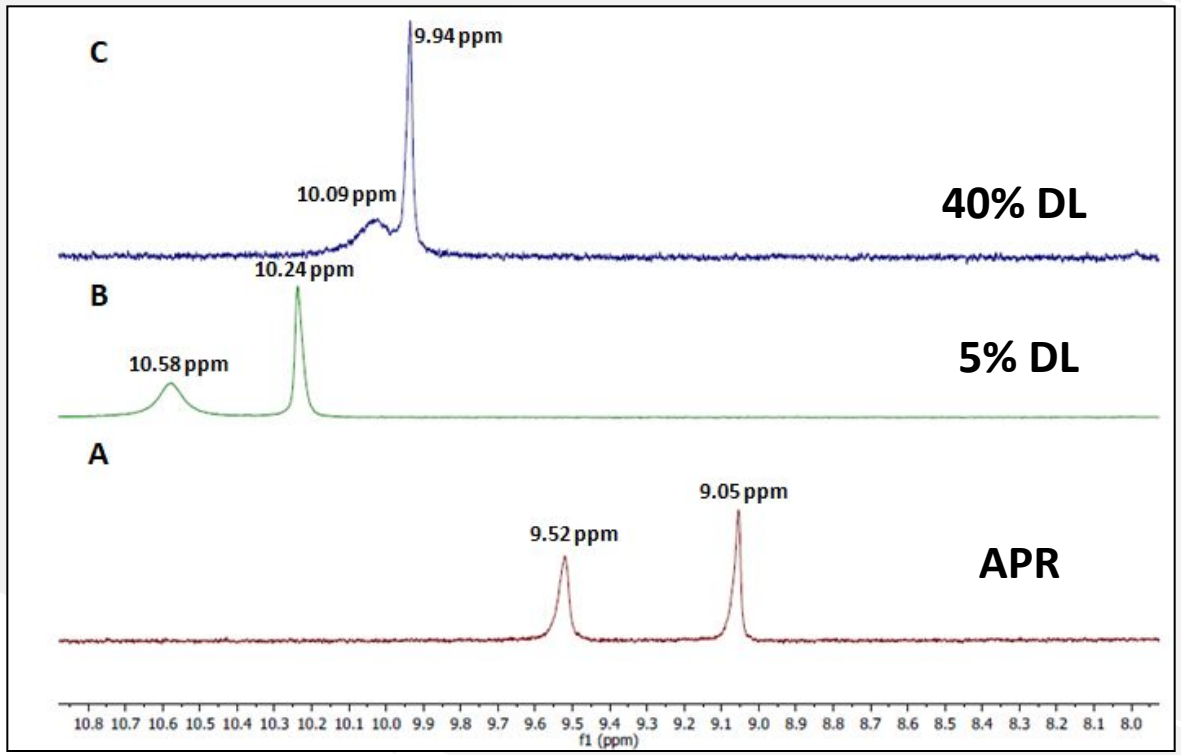
C=C stretching band of APR
APR-PVPVA 64 ASD: No Shift
APR-EL100-55 ASD: 1510 cm^{-1} to 1512 cm^{-1}
Involvement in non-specific hydrophobic interaction

The extent of interaction with APR was higher for Eudragit L100-55, as compared to PVPVA 64.

Solution-state 1D NMR Spectroscopy

1D- ^{1}H NMR

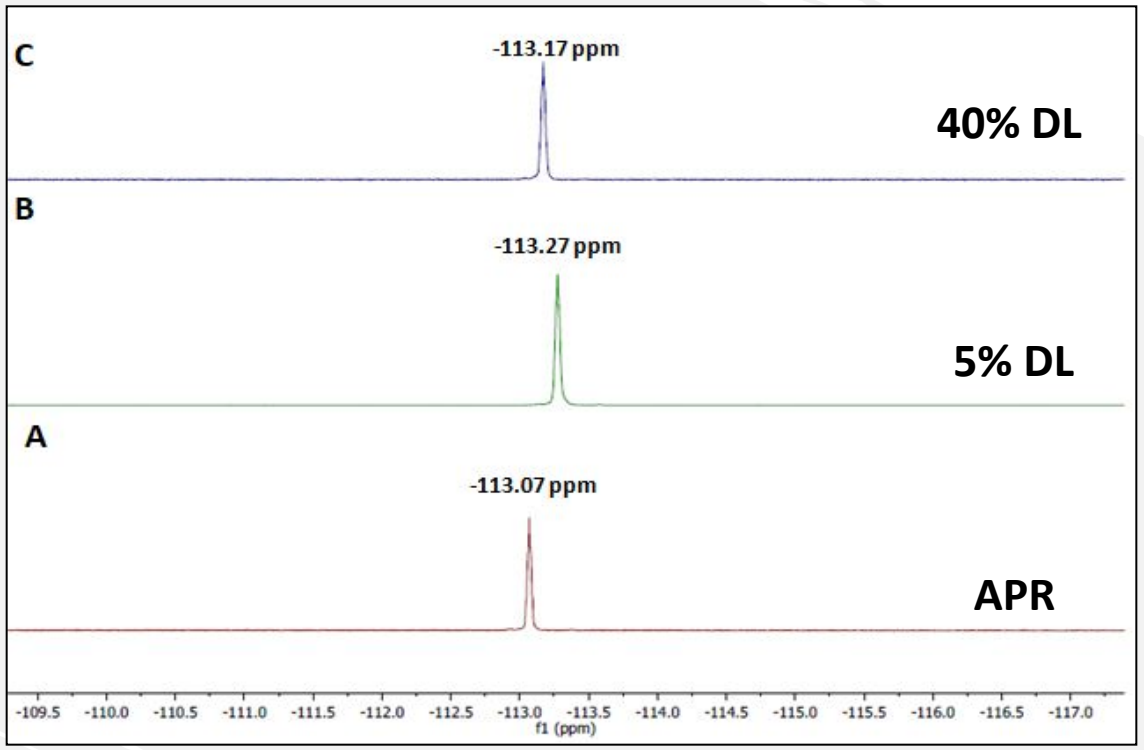
Protons of secondary amine of APR appeared as two distinct singlets at 9.05 and 9.52 ppm.



Downfield shift due to participation in hydrogen bonding

1D- ^{19} F NMR

Fluorine atom(s) of flurophenyl moiety appeared as singlet at -113.07 ppm .



Upfield shift due to participation in halogen bonding

Although both drug loadings have same nature of drug-polymer interaction(s), 5% w/w APR loaded ASD had more efficient drug-polymer interaction, due to availability of excess sites on the polymer. In contrast, 40% w/w drug loaded ASD exhibited less efficient drug-polymer interaction, due to higher drug loading in the ASD.