DISSOLUTION MECHANISM OF AMORPHOUS SOLID DISPERSIONS: IMPORTANCE OF CONGRUENT RELEASE FOR ENHANCED PERFORMANCE

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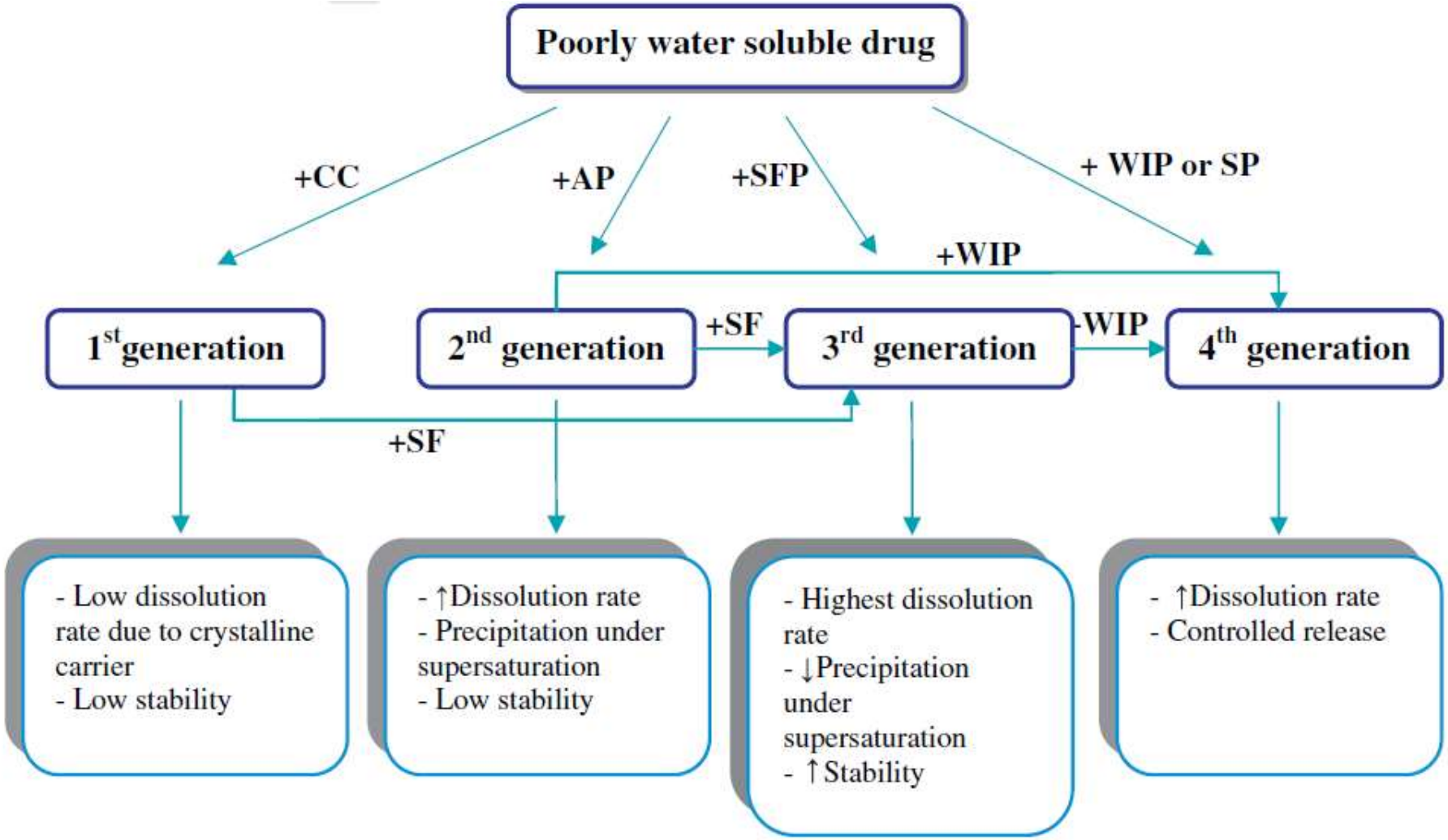


Composition and properties of four generations of solid dispersions. CC: crystalline carrier, AP: amorphous polymer, SFP: surfactant polymer, WIP: water insoluble polymer, SP: swellable polymer, SF: surfactant, ("): increase, (;): decrease.

Amorphous solid dispersions

ASDs are systems in which an active pharmaceutical ingredient (API) is embedded largely amorphously into a solid matrix, often consisting of polymers

ASDs are being employed frequently to improve bioavailability of poorly soluble molecules by enhancing the rate and extant of dissolution in drug product development process.

Advantage :

- 10–1000 x solubility enhancement for BCS II/IV drugs.
- Kinetic stabilization of the amorphous state

Modeling and comparison of dissolution profiles of four generations of solid dispersions in supersaturated conditions

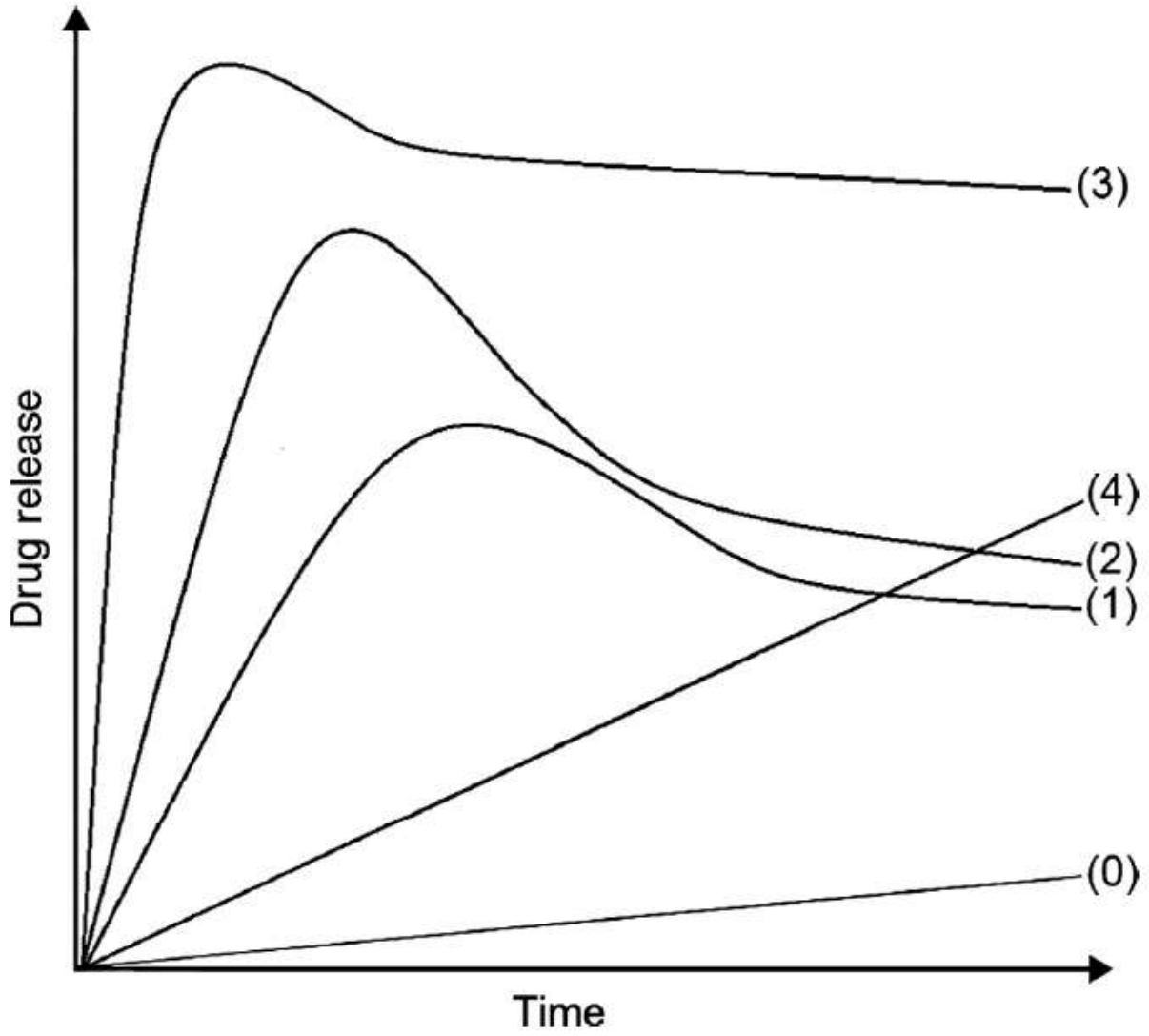
(0) pure API,

(1) the first generation solid dispersions which show improvement in dissolution rate compared to the pure API,

(2) the second generation solid dispersions which have improved dissolution profile compared to the first generation thanks to their faster dissolution rate,

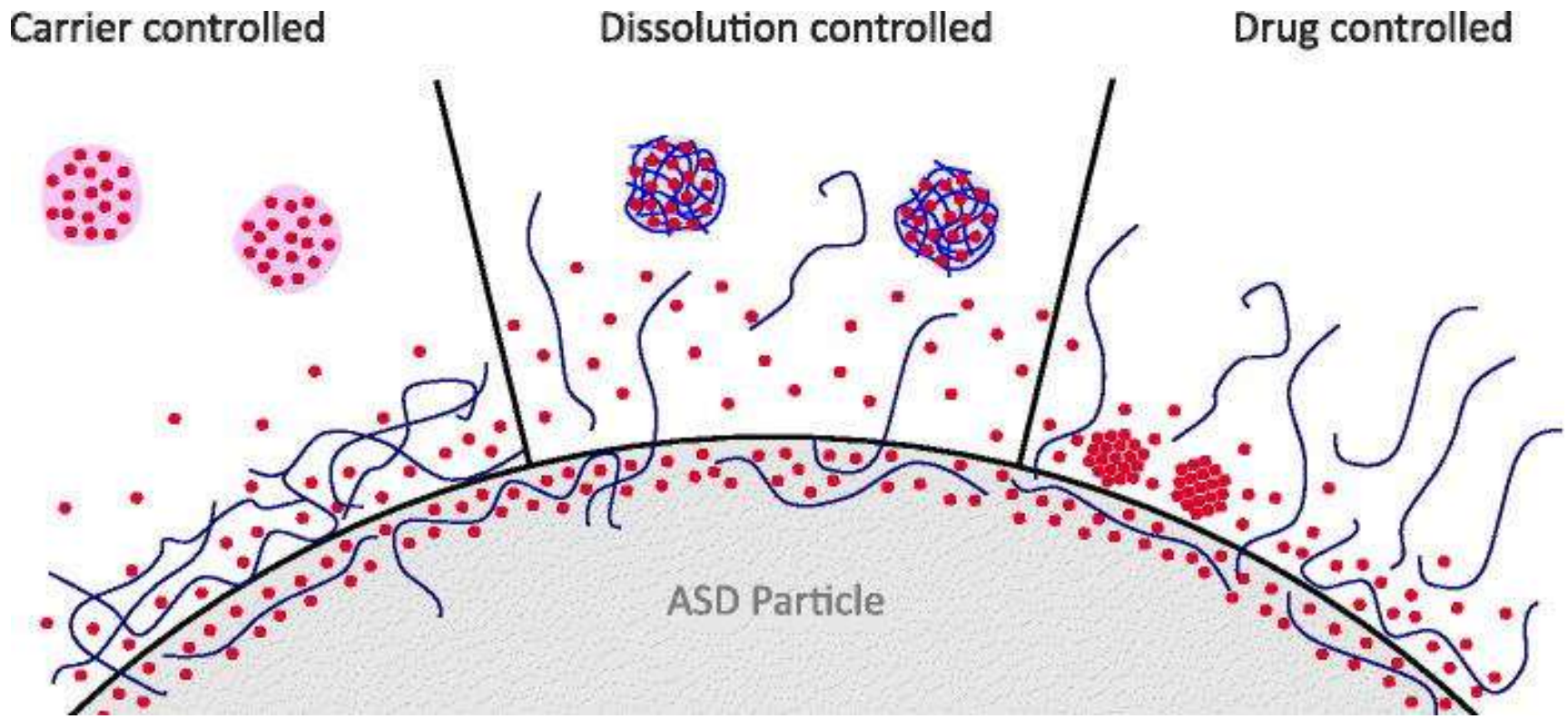
(3) the third generation solid dispersions which have improved dissolution profile compared to second generation thanks to their faster dissolution rate and lower precipitation rate and extend in supersaturated state,

(4) the fourth generation solid dispersion swhich have improved dissolution profile in a controlled or zero-order manner.



Challenges:

- Physical instability (crystallization).
- Non-congruent release → precipitation



Congruent Release

Synchronized release of drug and polymer

Mechanism:

- Polymer swells, forming a gel layer that controls drug diffusion.
- Drug-polymer interactions (H-bonding, hydrophobic) prevent phase separation

Consequences of Non-Congruent Release:

- Burst release → supersaturation → precipitation

Liquid-Liquid Phase Separation (LLPS)

Formation of drug-rich (amorphous or oily) and polymer-rich phases during dissolution

Impact on Performance:

Positive: LLPS droplets can sustain supersaturation

Negative: Uncontrolled LLPS → nucleation → crystallization.

Dissolution Testing

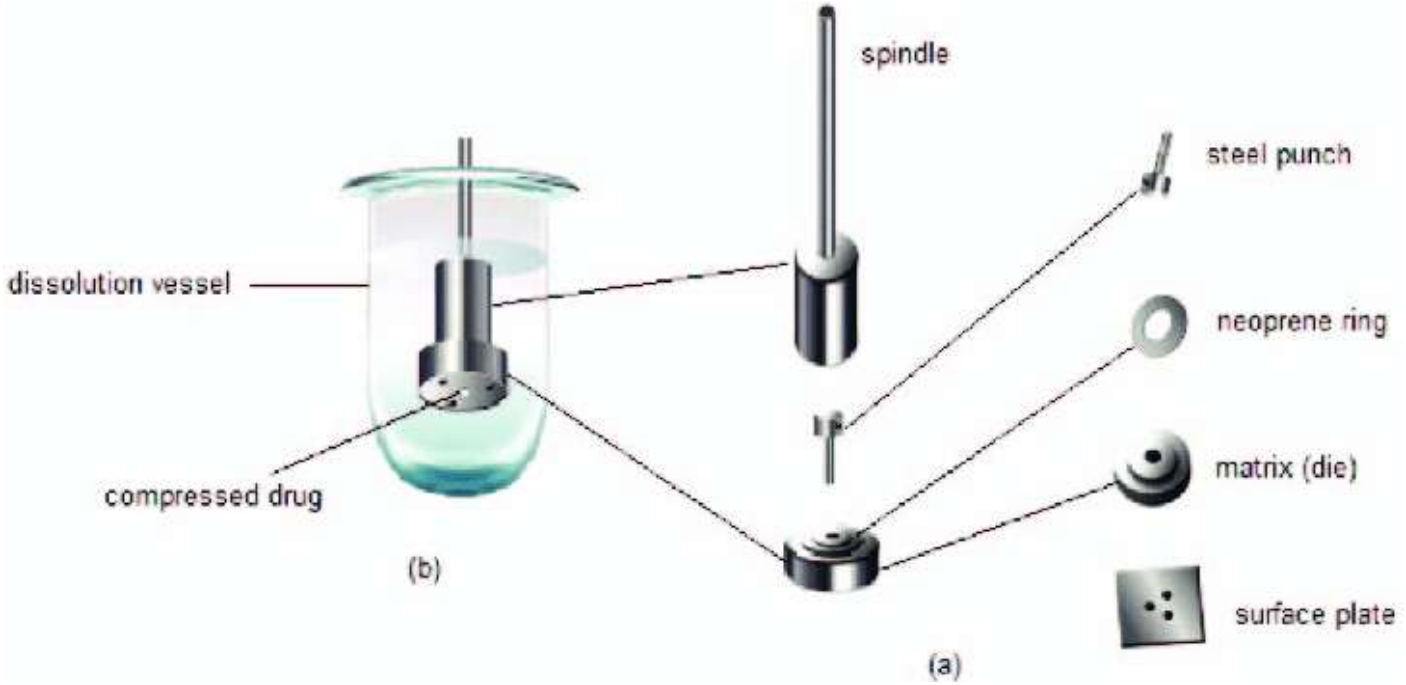
Most dissolution tests use sink conditions (simulating rapid absorption), But non-sink conditions better mimic scenarios like: Poor permeability (e.g., P-gp substrates), High-dose drugs (saturation in GI fluids).

Surface-Normalized Dissolution (Intrinsic Dissolution Rate, IDR)

Definition: Dissolution rate per unit surface area (mg/cm²/min).

Why Normalize?

- Removes particle size effects.
- Focuses on solid-state properties (crystallinity, polymorphism).



Why Study IDR Under Non-Sink?

- Reveals true solubility-limited dissolution.
- Predicts behavior in vivo (e.g., gastric fluids with limited volume).
- Helps identify risks (e.g., precipitation, form conversion).

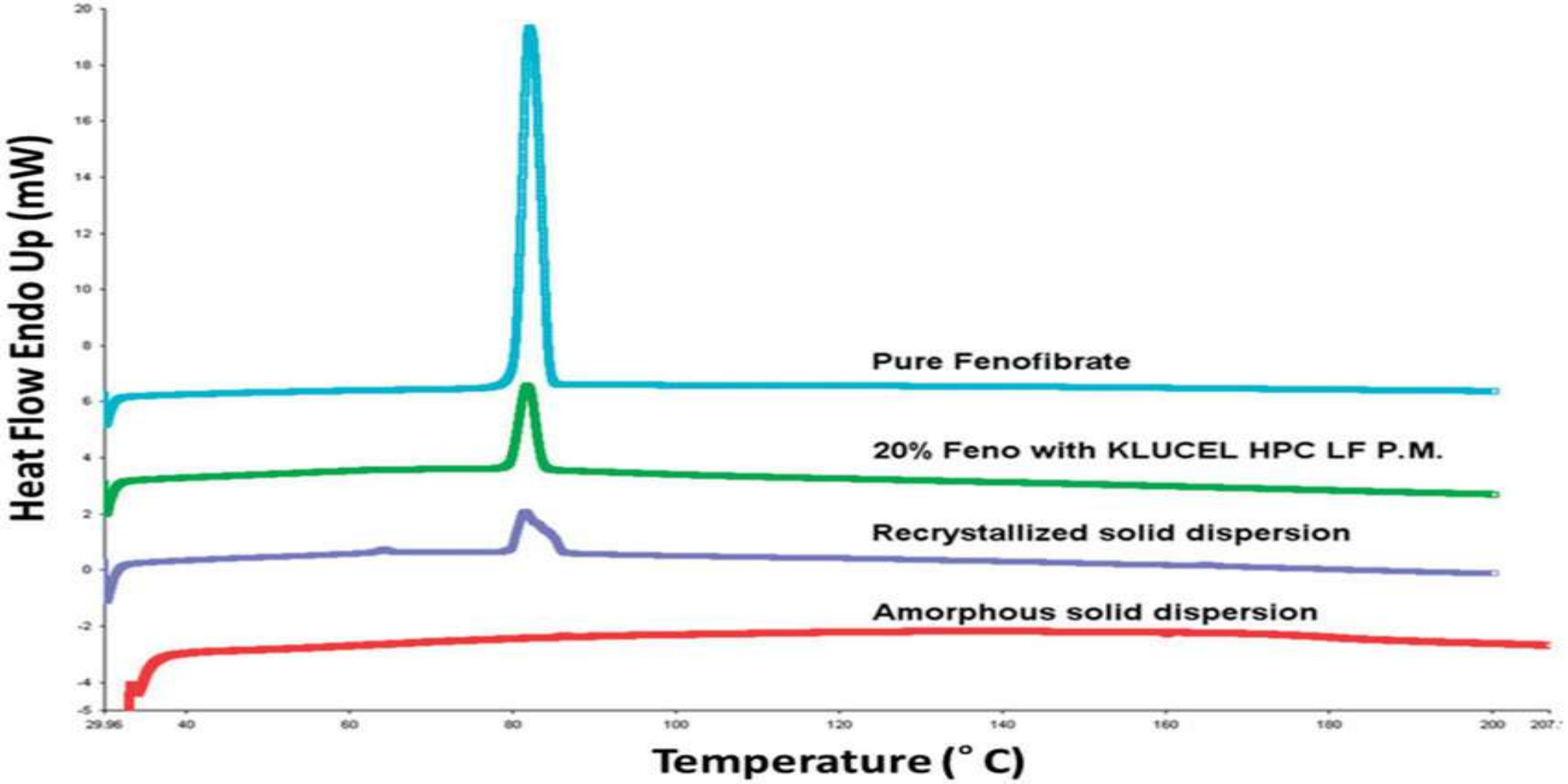
Under sink conditions, dissolution is dominated by the large concentration gradient, masking properties like:

- True solubility limitations.
- Surface area effects (e.g., particle size impact).
- Solid-form transitions (e.g., amorphous vs. crystalline).

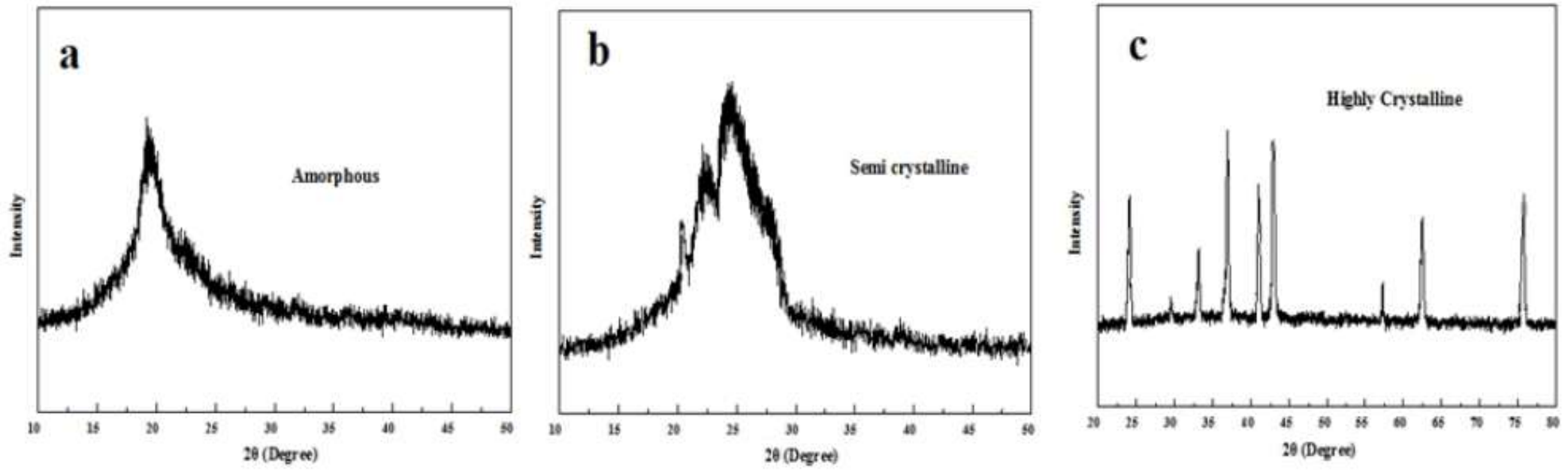
ASD maintains its supersaturation in the gastrointestinal (GI) tract which is the reason for the improvement of bioavailability.
When supersaturation is controlled, the absorption of a compound can be increased to be more than that of a saturated solution condition. Furthermore, among different crystalline forms solubility can be eliminated as they are converted to the amorphous form.

Characterization of physicochemical properties

1. Differential Scanning Calorimetry (DSC)



2. Powder X-ray diffraction (PXRD)

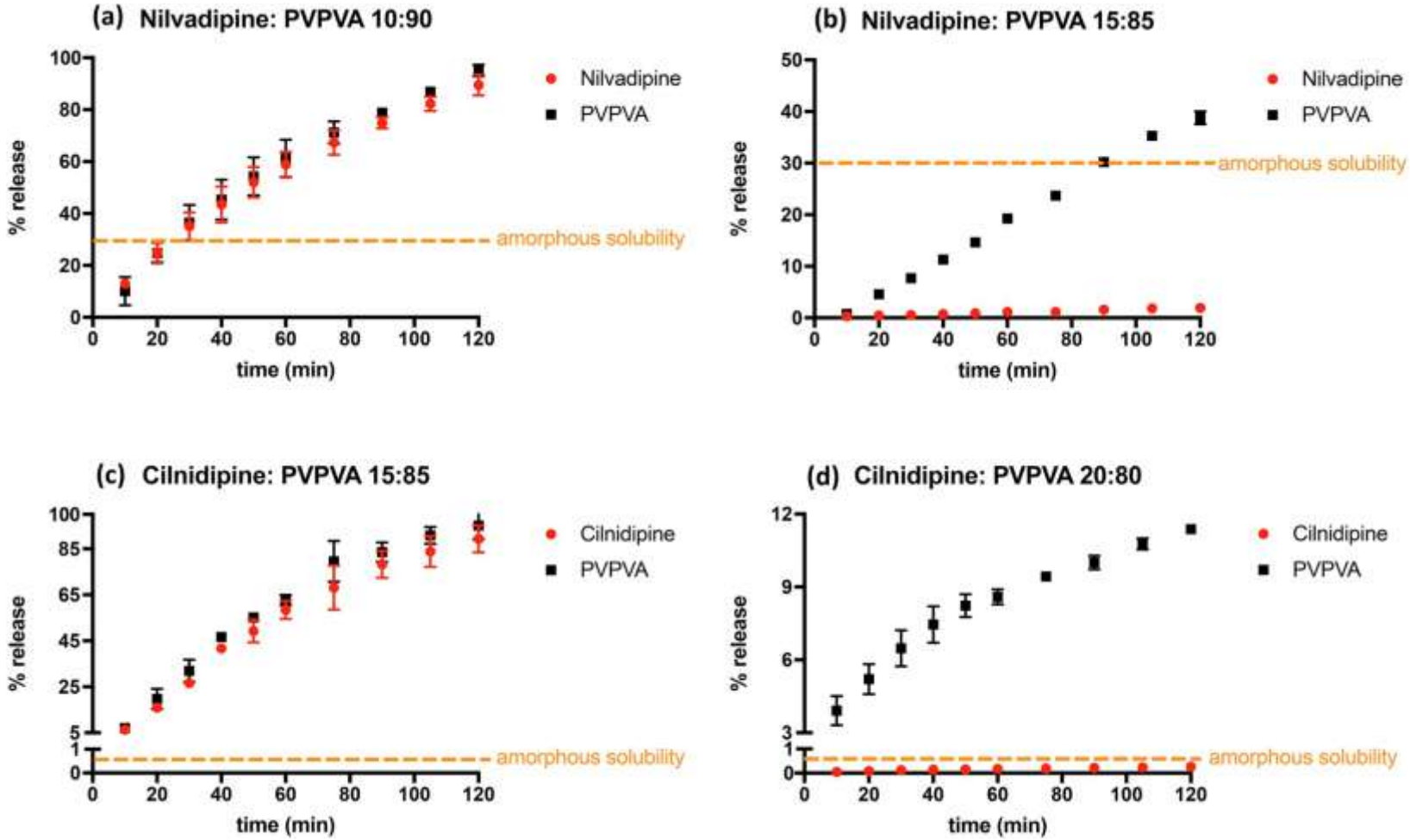


P-XRD profiles of (a) amorphous (b) semi crystalline and (c) highly crystalline systems.

3. Fourier Transformed Infrared spectroscopy (FTIR)

4. Polarized Light Microscopy (POM)

Surface normalized dissolution rates of drugs, polymer and ASD tablets



Dynamic Light Scattering (DLS)

To confirm the presence or absence of colloidal species upon dissolution

Size of amorphous nano-droplets from ASD powder dissolution (mean ± SD, n = 3).

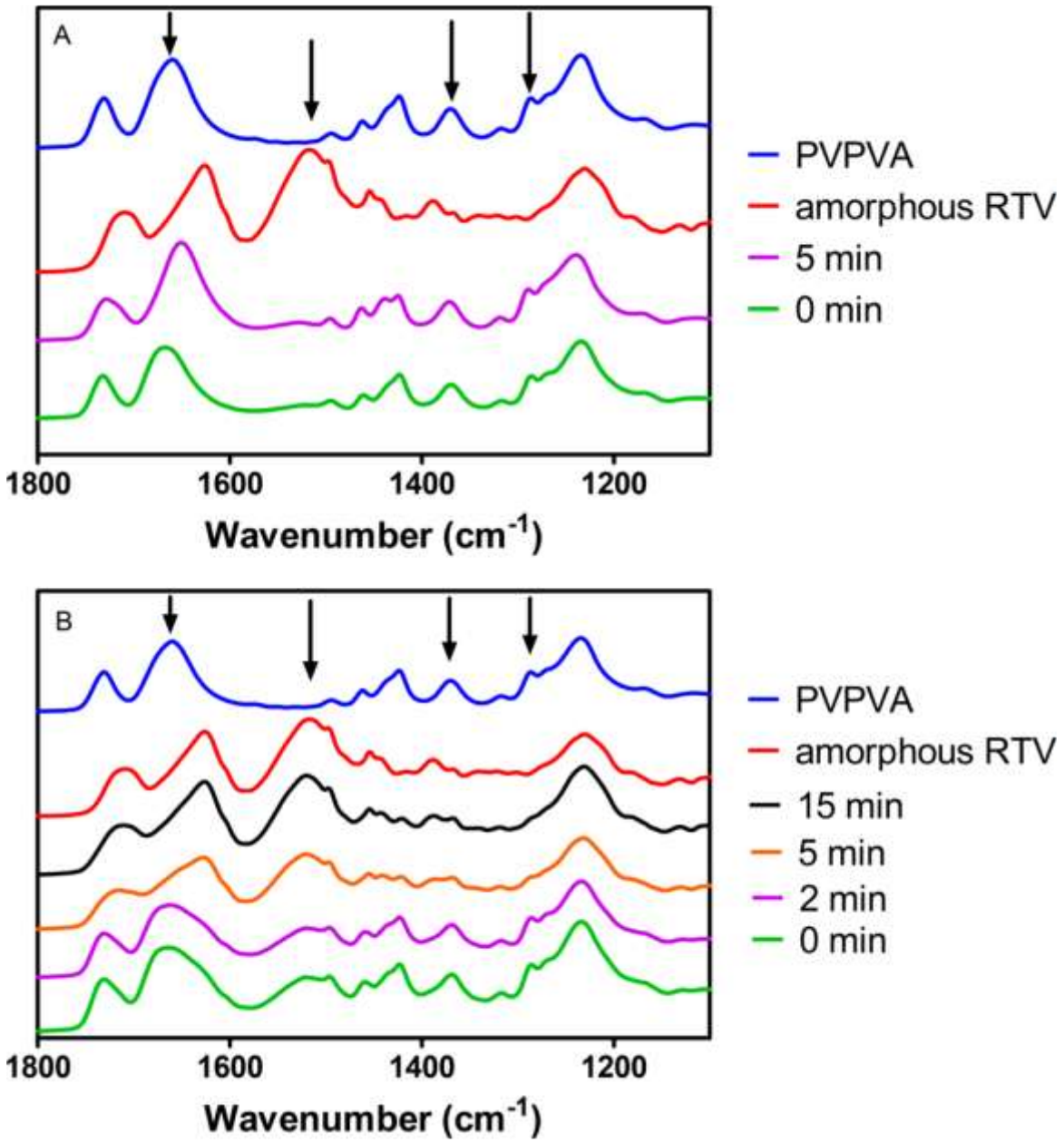
Drug: Polymer weight ratio	Diameter (nm)	
	Nil: PVPVA	Cil: PVPVA
05:95	237 ± 8	255 ± 1
10:90	246 ± 3	300 ± 2
15:85	None[a]	366 ± 7
20:80	None[a]	None[a]
25:75	N/A	None[a]

N/A- not applicable (drug loading not performed).

[a] No meaningful data could be obtained.

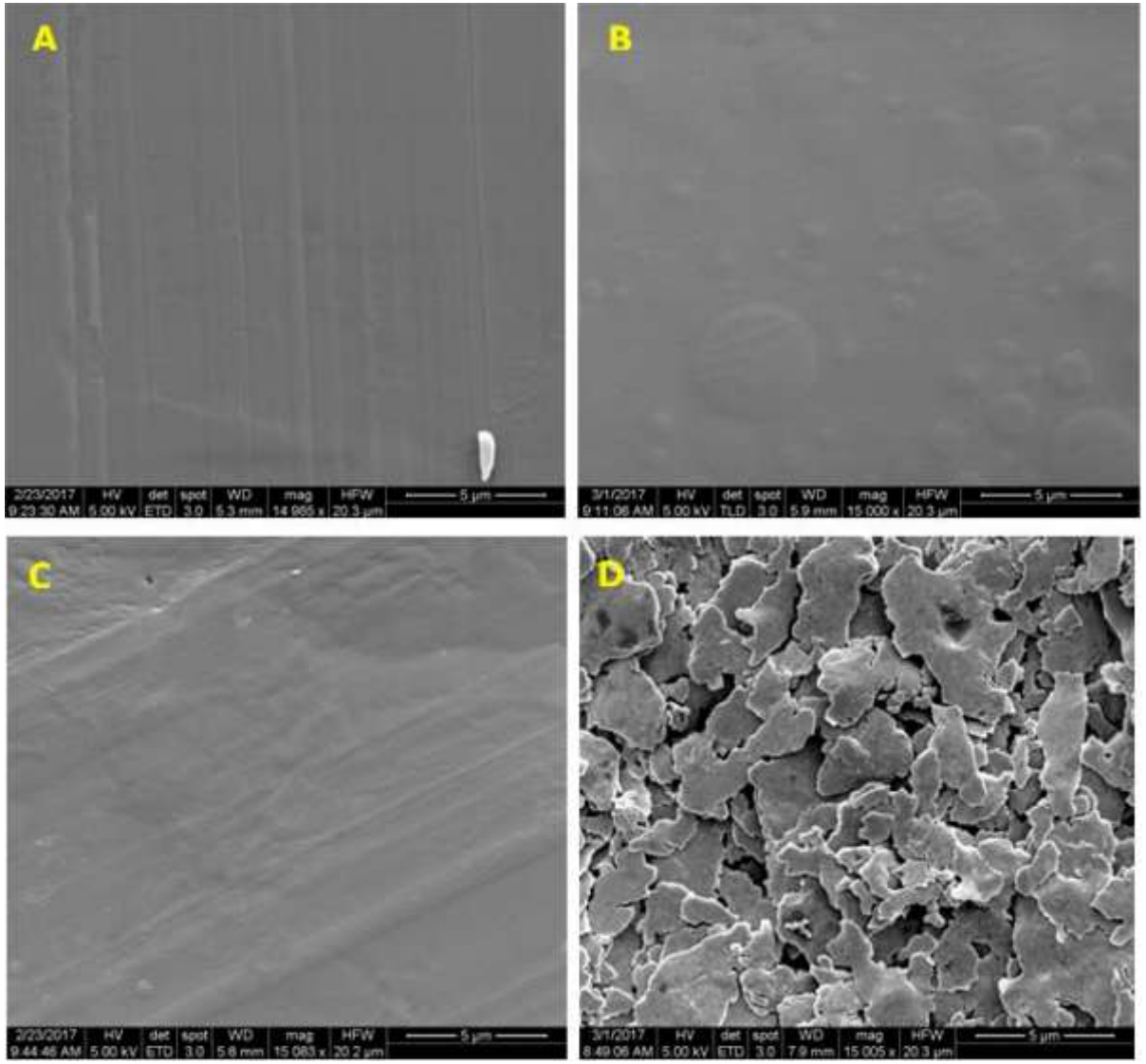
1. ATR-IR Spectroscopy

IR spectra of (A) 20 and (B) 50% DL ASD tablet surface acquired at different dissolution time points.



2.Scanning Electron Microscopy (SEM)

SEM images of ASD tablet surface. (A) 20% DL unexposed, (B) 20% DL 5 min after dissolution, (C) 50% DL unexposed, and (D) 50% DL 15 min after dissolution.



Thank You