

GRAPHICAL ABSTRACT

### THE CHALLENGE

**Poor aqueous solubility + rapid systemic clearance**

- Limited oral bioavailability
- Reduced colorectal exposure
- Need for sustained localized delivery

**Free DAPA shows inadequate GI retention**

### OUR STRATEGY

DAPA + PVA + SA

Sonication / Nanoprecipitation

Polymer chains wrap DAPA → Nanoparticle formation → Gravity-induced nanogel mass (sedimentation)

Size	Encapsulation Efficiency (EE)	Zeta Potential
90.40 ± 20.90 nm	88.37 ± 0.04%	-33.22 ± 0.22 mV

pH-responsive hydrogel | Sustained oral delivery | Targeted colorectal exposure

### NANO GEL DESIGN & OUTCOME

Hydration layer, PVA/SA polymer shell, DAPA (core), Crosslinked SA network

Mucus interaction

Prolonged GI residence, Controlled release, Improved absorption, Enhanced HCT-116 activity

- 1.8-fold solubility enhancement
- Sustained release in GI conditions
- ↓ KRAS / IL-6 / TNF-α / TGF-β
- Improved oral exposure in vivo

**In vitro & in vivo evidence**

Nanoscale particle (~90 nm), Gel formation in gastric fluid

### OPTIMIZATION & SOLUBILITY TESTING

Optimized nanoparticle preparation P2 Solubility

- Particle size: 90.40 ± 20.90 nm
- PDI: 0.32 ± 0.03
- Zeta potential: -33.22 ± 0.22 mV
- Encapsulation efficiency: 88.37 ± 0.04%

Group	0.1 N HCl Solubility	pH 6.8 Solubility
DAPA raw	1.05 ± 0.02	1.20 ± 0.02
DAPA-PVA-SA-NPs	1.90 ± 0.04	2.03 ± 0.04

### CONTROLLED RELEASE & GELATION

Formulation	IDR mg/min	MDT1.2 h	MDT6.8 h
F1	5.09±0.03	4.16±0.11	3.22±0.03
F2	2.91±0.05	6.31±0.33	4.32±0.01
F3	6.87±0.02	3.21±0.22	2.44±0.05

### IN SITU GEL CHARACTERIZATION

#	Weight g	Volume mL	Strength g	Durability min
F1	1.45±0.10	10.30±0.25	12.50±0.20	85
F2	1.50±0.12	9.00±0.30	25.00±0.15	≥120
F3	1.40±0.11	9.50±0.20	18.00±0.18	95

F2 showed the strongest, most compact, and most durable gravity-induced hydrogel mass.

### IN VIVO ABSORPTION

Parameter	Free DAPA	DAPA nanogel
Cmax	300±2.11 ng/mL	200±4.03 ng/mL
Tmax	4±0.11 h	6±0.12 h
AUC <sub>0-∞</sub>	3235.33±1.50	3472.35±1.60
T <sub>1/2</sub>	6±0.03 h	12±0.11 h
Ka	0.23±0.04 1/h	0.17±0.05 1/h
Relative F	1.00±0.02	1.07±0.04

### PXRD and TEM CHARACTERIZATIONS

PXRD DAPA crystalline peaks were attenuated/disappeared after nanoencapsulation, supporting amorphous transformation

### ONCOGENIC & INFLAMMATORY MARKERS (HCT-116)

IC50 values: DAPA-PVA-SA-NPs 12.47±0.68 µg/mL (~30.5 µM), blank PVA-SA NPs 16.61±0.91 µg/mL, free DAPA 19.12±1.23 µg/mL (~46.8 µM).

Compared with free DAPA, DAPA-PVA-SA-NPs reduced:

- KRAS: 45.20±2.50 → 15.80±1.40 pg/mL
- TGF-β: 52.70±3.00 → 17.20±1.60 pg/mL
- IL-6: 44.90±2.40 → 15.60±1.30 pg/mL
- TNF-α: 50.30±2.60 → 17.90±1.20 pg/mL

TEM confirmed nanoscale polymeric morphology

