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for chemical biology and early drug discovery

FASS Ultrafast Light Scattering vs. UPLC for Solubility and Aggregation Profiling of Drug Candidates

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The Aggregation Problem in Drug Discovery

Colloidal aggregation, the self-association of small molecules into nanoscale particles, is a leading cause of false positives in biochemical assays and a significant source of wasted resources in early drug discovery. It often goes undetected: UPLC-based solubility assays are slow, consume ~10–100 µg of compound per datapoint, and cannot detect aggregation before gross precipitation occurs.

FASS addresses this gap with Ultrafast Light Scattering (ULS), combining two non-destructive complementary optical methods on the same sample using a femtosecond pulsed laser: Second Harmonic Scattering (SHS) to detect nanoscale assemblies at the earliest stages of aggregation, and Linear Light Scattering (LLS) for particle sizing as aggregates grow; in a 384-well plate, in under 15 minutes, with ~100× less compound than UPLC.

Here we benchmark FASS against UPLC and nephelometry across a structurally diverse compound set to assess concordance, identify where the platform provides additional insights, and define practical applications for physicochemical profiling in drug discovery.

FASS Technology: Key Performance

<15 min
384 well plate

<1µM
Sensitivity

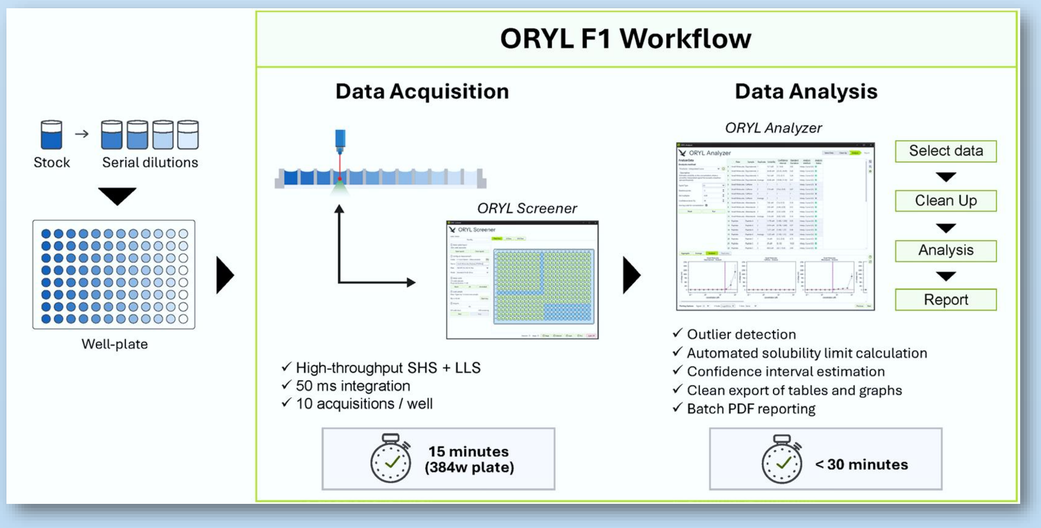


200 fs
Laser pulses

100×
Less compound vs UPLC

Materials and Methods

Parameter	UPLC	FASS (ORYL F1)
Format	96-well filter plate	384-well COC plate
Compound vol.	~36 µL DMSO stock a 10 mM	~3 µL DMSO stock at 10 mM
Detection	UV chromatogram	SHS + LLS (optical)
Throughput	20 injections á 3 min per compound	<15 min / 384 wells, 10 compounds
Conc. range	1 µM – 100 µM	<1 µM – 1 mM
Solvent use	105 mL / compound	4 mL / compound
Buffer / medium	PBS pH 7.4 (filtered, sterile)	
Compound set	n = 32; drug-like compounds / known aggregators / structurally diverse	



OBJECTIVES

- ✓ Benchmark FASS against UPLC for solubility ranking and aggregation detection
- ✓ Establish UPLC solubility reference values for a diverse compound set
- ✓ Identify compound classes where FASS provides improved or orthogonal insight

FASS vs. UPLC vs. Nephelometry

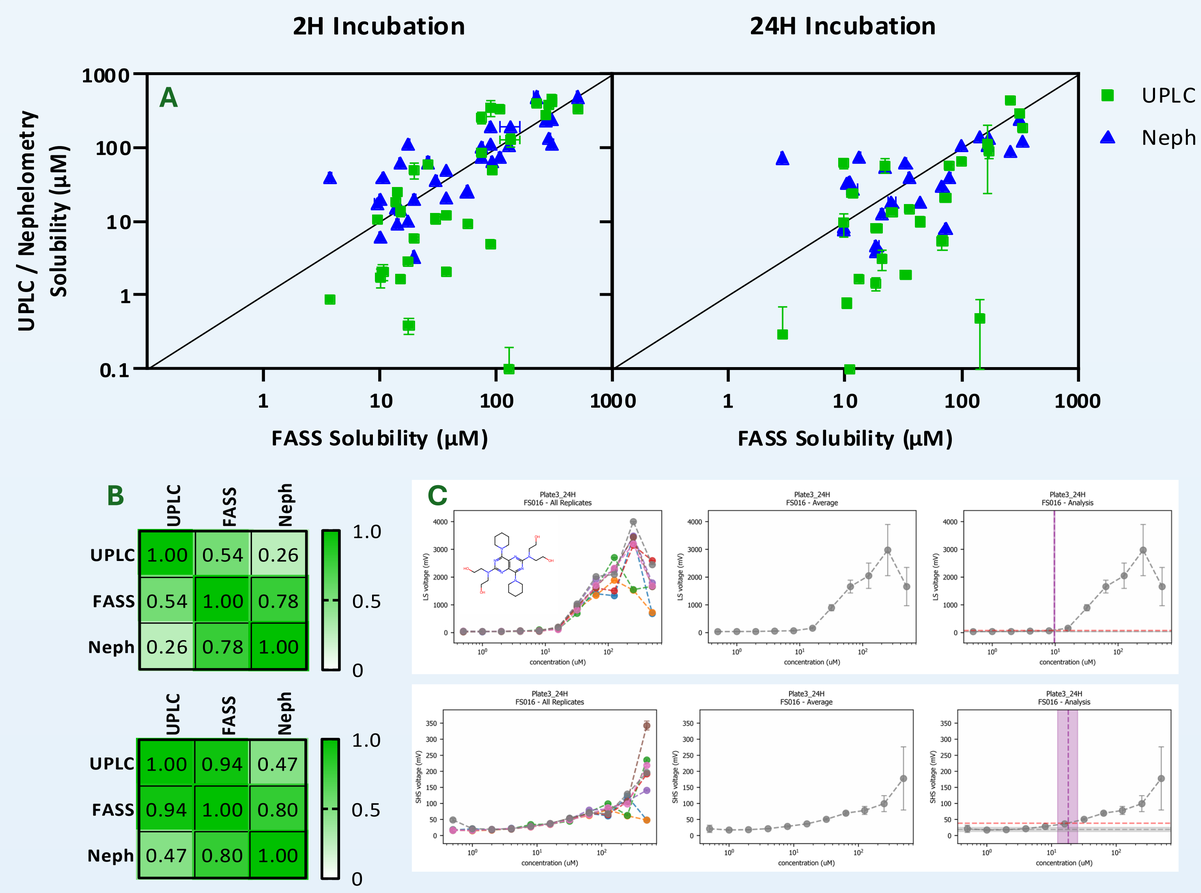


Figure 1: Solubility determination of 32 compounds with FASS, UPLC-UV and Nephelometry. (A) Scatterplot at 2h incubation and 24h incubation in PBS, pH 7.4 (1% v/v DMSO). (B) Pierson correlation factors at 2h (above) and 24h (below). (C) Typical FASS spectra obtained for dipyridamole at 24h in Linear Light Scattering and Second Harmonic Scattering.

ORYL F1 Platform open for user projects

- Diverse hydrophobic small molecules (stilbenoids, drug-like compounds for screening)
- New modalities (library of PROTACs, molecular glues and chemogenomic compounds)
- Gross aggregation and well-defined self assembling structures (lignins, peptides)
- Screening of drugs with excipients or at various pH's to inform pre-formulation phase

Conclusions

🔬 FASS detects aggregation onset at the µM scale even for compounds difficult to assess with UPLC, like PROTACs, molecular glues, and chemogenomic substances.

⚡ A 384-well plate is profiled in <15 minutes with ~100× less compound than UPLC, enabling routine aggregation screening of full compound libraries to flag aggregation-prone substances.

✅ UPLC and FASS are complementary rather than competing: UPLC provides absolute solubility values (note: compound loss possible due to filtration step); FASS provides rapid, sensitive aggregation onset detection in complex mixtures.

🌱 Integration of FASS into early discovery workflows substantially reduces compound consumption, cost, and environmental footprint of physicochemical profiling.

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