Treatment of Non-Active Components in Co-Processed API:

Do Excipients Obscure GMP DS Method Ability to Detect Chemical/Phase Purity?

FDA/M-CERSI Co-Processed API Workshop

Frank Bernardoni

Analytical R&D, Merck & Co., Inc.

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Biography and Contact Information

Principal Scientist within the Small Molecule Analytical R&D department at MRL, Merck & Co., Inc., Rahway, NJ, USA.

B.S. from King's College (Wilkes-Barre, PA) and Ph.D. from Seton Hall University (South Orange, NJ) through Merck Ph.D. program.

Worked to develop many commercialized drug substance [illegible]otably, Januvia, Marizev, Prevymis, Recarbrio, Vericiguat, and Lagevrio over a 19-year career at Merck.

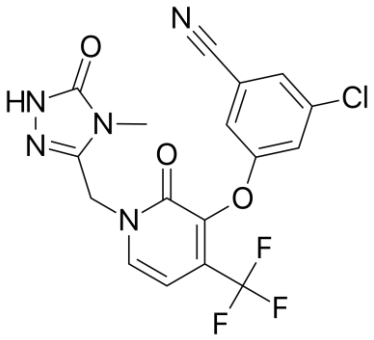
Key member of the Merck Mutagenic Impurities Council and Scientific Supervisor within Analytical R&D.

Led a team of >10 drug substance analytical chemists on the development of molnupiravir (Lagevrio), an antiviral for the treatment of COVID-19.

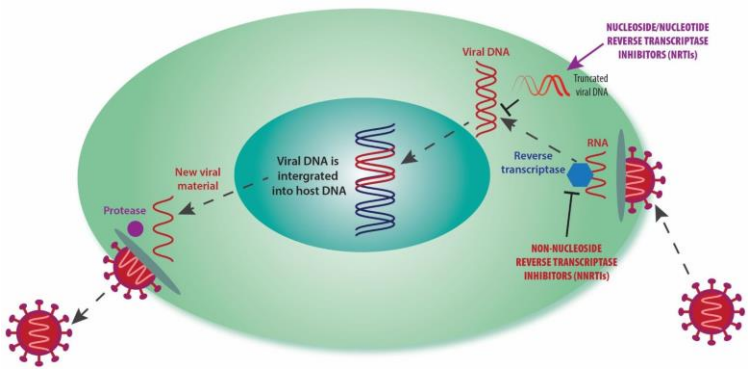
frank_bernardoni@merck.com

Compound A

Background: Compound A is a novel HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed for treatment of HIV-1 infection. Compound A has high antiviral potency in vitro and PK properties that support once-weekly dosing.



Pifeltro™ (Doravarine; shown above), is an example of an approved NNRTI for HIV



Reverse Transcriptase Inhibitor Mechanism
Image Courtesy of BioVision Inc.

As Compound A is **BSC Class 2** (low solubility, high permeability), it is spray dried with a polymer to create an amorphous solid dispersion (ASD) to increase solubility and maximize bioavailability.

Compound A DS (Free Base)
HPMCAS-LG
Acetone
→ Spray Dry
N2 (Atomization Gas)
→ 30% DS / 70% HPMCAS-LG
Drug Product Intermediate
→ Blend w/ Excipients
Dry Granulation
Compression
→ Compound A Tablets

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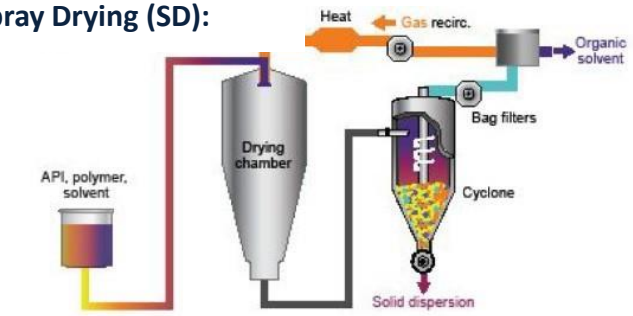
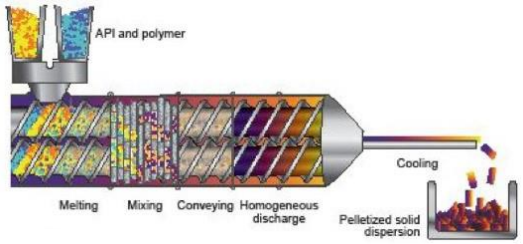
Amorphous Solid Dispersions: SD, HME, and cPAD

Spray Drying (SD):



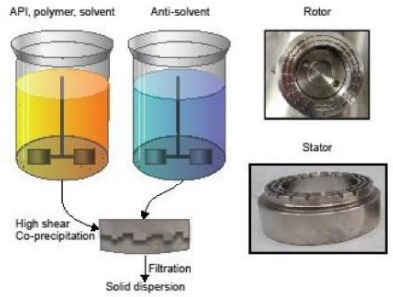
- Performed at temperatures below melting point of the DS or polymer
- Requires specialized equipment with large footprints and appreciable capital cost
- Requires sufficient DS and polymer solubility in suitable low boiling solvents

Hot Melt Extrusion (HME):



- Low cost
- High Throughput
- Limited to APIs and polymers that are thermally stable above melt temperatures

Co-Precipitated Amorphous Dispersion (cPAD):



- Allows for the use of both low and high meting DS with a more expansive set of solvent / antisolvent pairs.
- Mixing can be easily modelled, controlled, and reproduced between facilities
- Mode of isolation (filtration or thin film evaporation) affords precise tuning of bulk powder properties
- Can be executed in simple equipment common to DS facilities

Image and content courtesy of N Strotman and L Schenck (Merck)[1]

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cPAD as a Drug Substance

Internal (Merck): Discussions with cross functional partners suggests that DS designation is the optimal path forward for early phase development.

- Enables a more streamlined manufacturing process.
- Enables more flexibility for downstream DP manufacturing.
- Existing GMP systems and process capabilities can readily support deploying cPAD as DS.

External (Regulatory): Several approved products are known to contain a DS mixture to help stabilize the DS in a matrix.

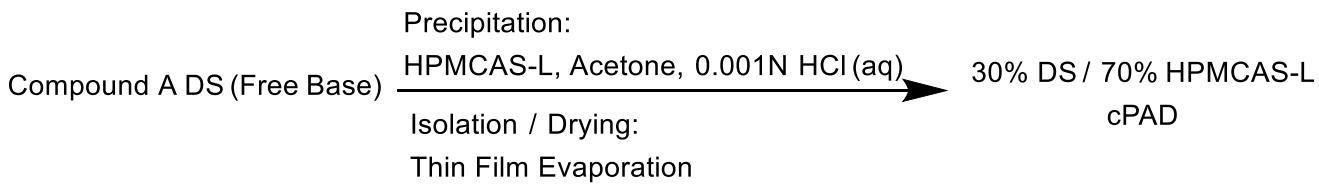
- Zelboraf® (Genentech / Roche) via precipitation with HPMCAS[2].
- Tybost® (Gilead) via precipitation with silica dioxide[3].
- However, since approval of these two compounds, EMA has issued a Q&A on the designation of API mixtures for marketing applications[4] – **essentially an API mix is considered the first step in the manufacture of a finished product.**

Compound A cPAD Process

Compound A cPAD: DS and HPMCAS dissolved in acetone and precipitated in water using a high-shear mixer; dried via thin film evaporation.

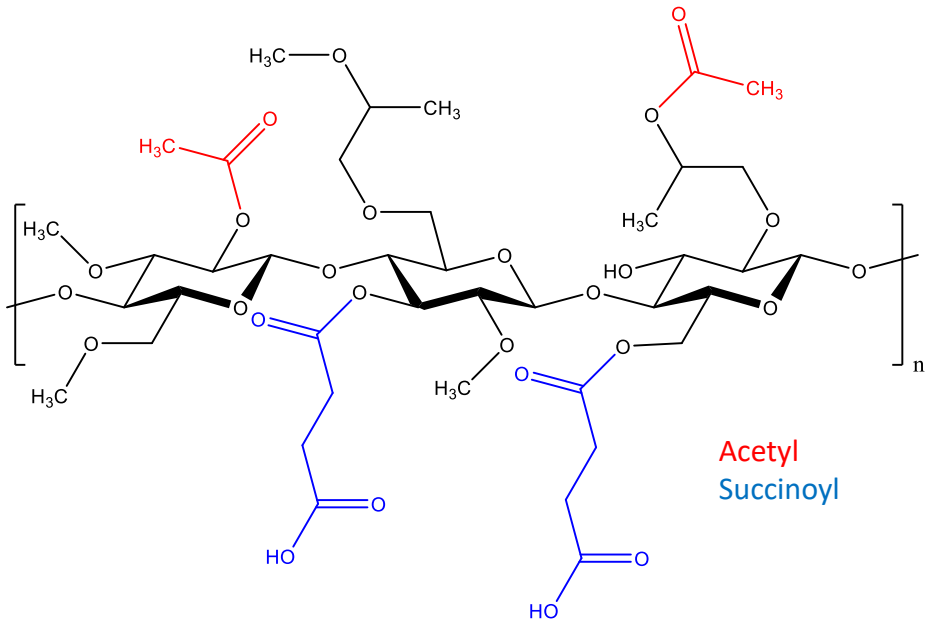
Comparison of SDI and cPAD Process

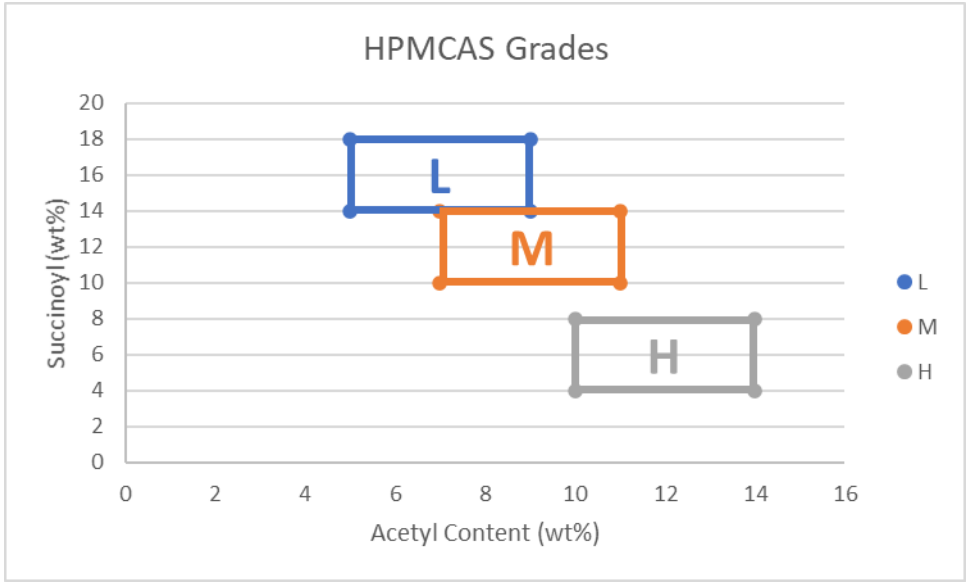
	SDI Process	cPAD Process
Polymer	HPMCAS-L	HPMCAS-L
Solvent System	Acetone	Acetone and Water
Drug Load	30%	30%
Classification	Drug Product Intermediate	Drug Substance



What is HPMCAS?

HPMCAS: Hydroxypropylmethylcellulose acetate succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethylcellulose with a MW of ~10-500 kDa.

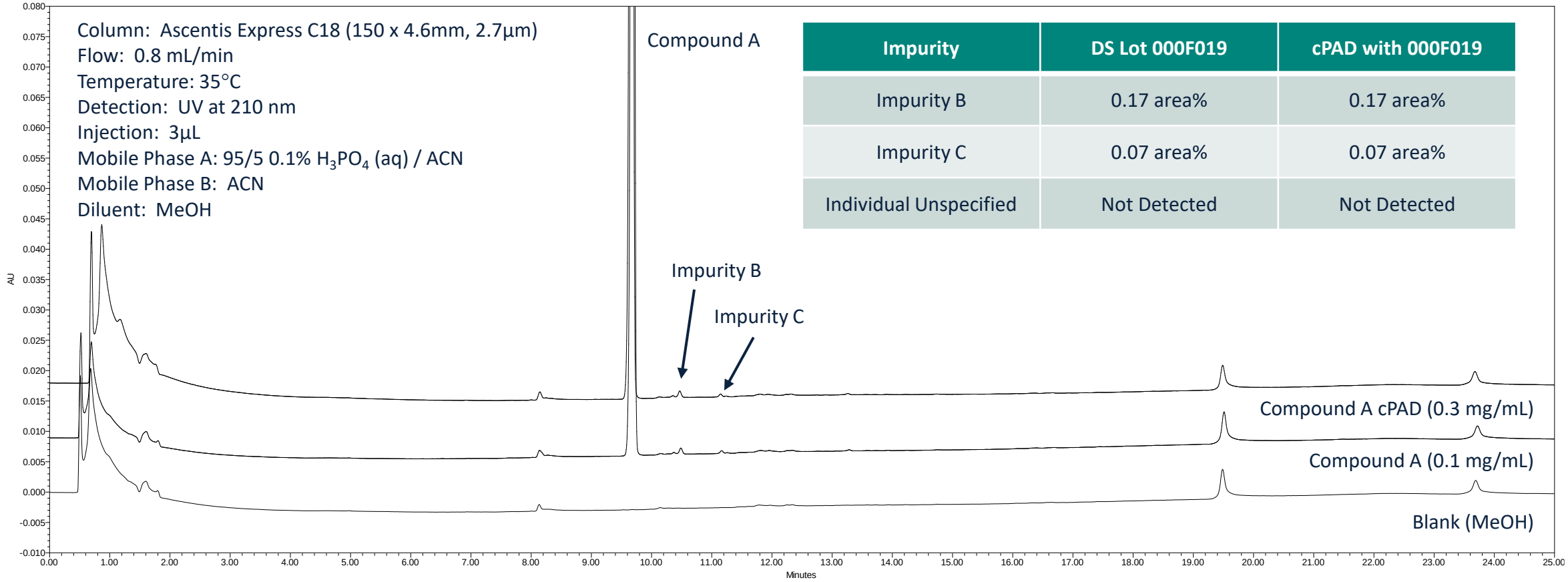




Analysis: Often characterized using size exclusion chromatography with light scattering or charged aerosol detection. Limited conjugation may make this compound **UV agnostic**.

Assay and Impurities by HPLC

Column: Ascentis Express C18 (150 x 4.6mm, 2.7µm)
Flow: 0.8 mL/min
Temperature: 35°C
Detection: UV at 210 nm
Injection: 3µL
Mobile Phase A: 95/5 0.1% H_3PO_4 (aq) / ACN
Mobile Phase B: ACN
Diluent: MeOH

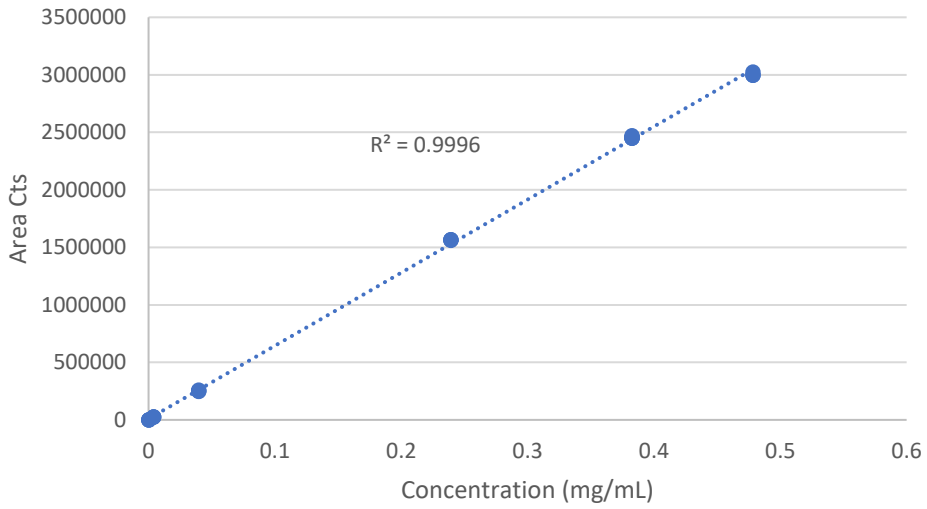


Impurity	DS Lot 000F019	cPAD with 000F019
Impurity B	0.17 area%	0.17 area%
Impurity C	0.07 area%	0.07 area%
Individual Unspecified	Not Detected	Not Detected

Assay and Impurities by HPLC (Method Validation)

cPAD Method Validation: Assay and impurities method was appropriately validated for clinical use with the only change being an adjustment in sample prep for the cPAD material. Linearity, Precision, LOD/LOQ, and Robustness was assessed.

Compound A cPAD Linearity



Linearity was assessed from 0.0002 mg/mL to 0.48 mg/mL, which is **0.05% to 120%** of the target prep (0.4 mg/mL)

Injection Precision and Method Precision (Repeatability)

Compound A cPAD	Compound A Area	Impurity B Area	Impurity C Area
100% Solution (0.4 mg/mL)	2452175.868	8250.722	2036.517
	2449218.703	8224.983	2046.150
	2451226.354	8254.802	2043.919
	2458395.612	8256.434	2039.051
	2469127.367	8321.609	2076.004
	2452202.580	8267.421	2030.277
%RSD	0.3%	0.4%	0.8%

Compound A cPAD	Compound A	Impurity A	Impurity B	Impurity C
Prep A	30.4 wt%	0.11 A%	0.33 A%	0.08 A%
	31.3 wt%	0.11 A%	0.33 A%	0.08 A%
Prep B	31.4 wt%	0.11 A%	0.33 A%	0.08 A%
	31.4 wt%	0.11 A%	0.33 A%	0.08 A%
%RSD	1.5%	2.0%	0.1%	0.4%

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Assay and Impurities by HPLC (Method Validation)

cPAD Method Validation: Assay and impurities method was appropriately validated for clinical use with the only change being an adjustment in sample prep for the cPAD material. Linearity, Precision, LOD/LOQ, and Robustness was assessed.

LOD / LOQ

Compound A cPAD	Area Counts	S/N
LOD (0.02%)	658 659 643	18:1 16:1 13:1
LOQ (0.05%)	1378 1353 1378	27:1 39:1 27:1

Solution Stability (Ambient)

Analyte	Compound A	Impurity A	Impurity B	Impurity C
Initial	31.1 wt%	0.11 area%	0.33 area%	0.08 area%
1 Day	31.4 wt%	<LOQ (0.04 area%)	0.34 area%	0.08 area%
3 Days	31.4 wt%	<LOQ (0.04 area%)	0.34 area%	0.08 area%

Solution Stability (5°C)

Analyte	Compound A	Impurity A	Impurity B	Impurity C
Initial	31.1 wt%	0.11 area%	0.33 area%	0.08 area%
1 Day	31.2 wt%	0.06 area%	0.33 area%	0.08 area%
3 Days	31.0 wt%	<LOQ (0.03 area%)	0.34 area%	0.08 area%

Compound A DS Methods and Specifications

Test	Acceptance Criteria	Method
Description	White to Off-White Powder	Visual
Identification	Consistent with Reference	IR
Assay	97.0 to 103.0% (dry basis)	HPLC
Related Compounds Impurity A Impurity B Impurity C Individual Unspecified Total	 Max 1.00 area% Max 1.00 area% Max 1.00 area% Max 0.15 area% Max 3.00 area%	HPLC
Residual Solvents Acetone Acetonitrile	 Max 1.00 wt% Max 0.50 wt%	GC
Moisture	Report Results	KF
Elemental Impurities	Complies with ICH Q3D, USP <232>	USP <233>

No change to description and ID via IR;
cPAD mixture can be assessed directly using ATR

Assay and impurities can utilize the same method with the only adjustment being sample concentration to account for ~30% drug load.

Current method is selective for acetone, but method involves direct injection, and HPMCAS may result in interference.

Coulometric KF vessel solvent is methanol, which provides adequate solubility of cPAD and USP <233> generally involves sample digestion, and so no immediate impact from HPMCAS

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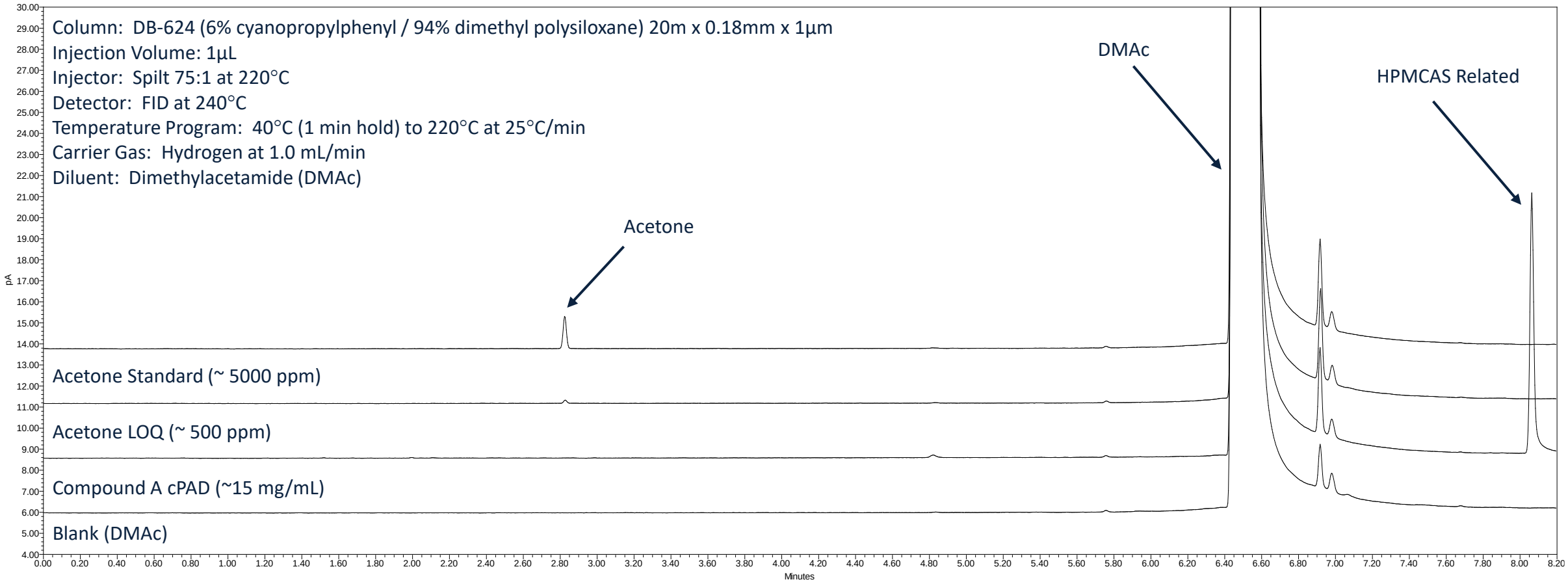
Residual Acetone via GC-FID



Compound A Characterization (DS versus cPAD)

Test	Drug Substance Acceptance Criteria	cPAD Acceptance Criteria
Description	White to Off-White Powder	White to Off-White Powder
Identification	Consistent with Reference	Consistent with Reference
Assay	97.0 to 103.0% (dry basis)	90-100% of label claim (dry basis)
Related Compounds		
Impurity A	Max 1.00 area%	Max 1.00 area%
Impurity B	Max 1.00 area%	Max 1.00 area%
Impurity C	Max 1.00 area%	Max 1.00 area%
Individual Unspecified	Max 0.15 area%	Max 1.00 area%
Total	Max 3.00 area%	Max 5.00 area%
Residual Solvents		
Acetone	Max 1.00 wt%	Max 0.50 wt%
Acetonitrile	Max 0.50 wt%	N/A
Moisture	Report Results	Report Results
Elemental Impurities	Complies with ICH Q3D, USP <232>	Complies with ICH Q3D, USP <232>

Implies 27-33 wt% based on 30% target for Compound A cPAD

Individual unspecified and total impurity limits aligned with Merck drug product development intermediate specifications

Qualification threshold of 0.15% for DS (ICH Q3A) versus 0.2% for DP (ICH Q3B) based on 400 mg dose

Acetone limit tightened to align with process capabilities and ICH Q3C Option 1 for Class 3 solvent

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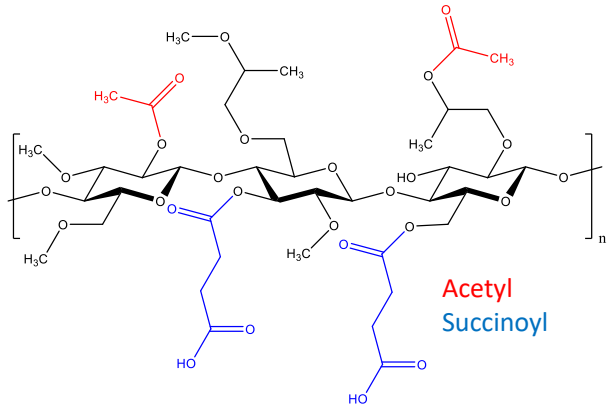
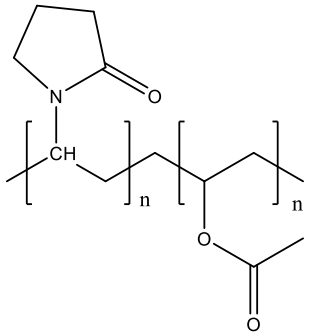
Typical Polymers for Co-Processed API

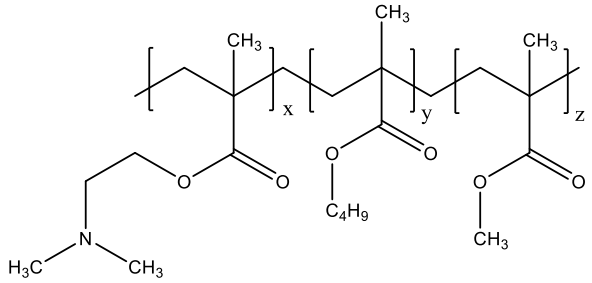
Although HPMCAS (Hydroxypropylmethylcellulose acetate succinate) is used extensively for co-processing of API, other polymers are generally screened:



HPMCAS



PVPVA



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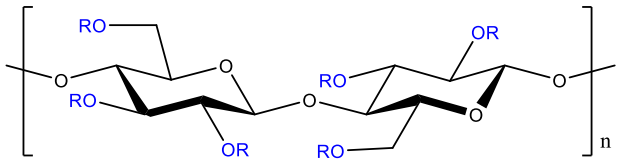
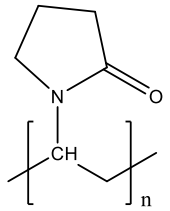
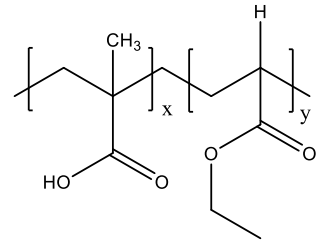


R = H or CH_3 or $CH_2CH(OH)CH_3$

HPMC



PVP



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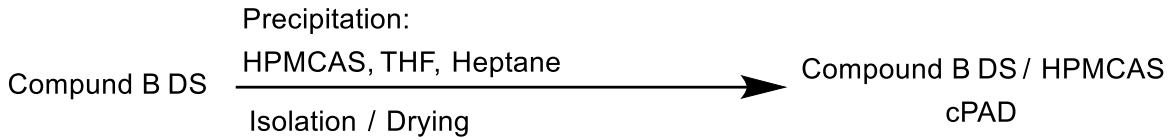
Additional Programs

Compound B: An investigational compound for monotherapy and used in combination with pembrolizumab (Keytruda®) for participants with advanced solid tumors who have not responded to conventional therapy.

Compound B SDI Process	
Polymer	HPMCAS-LG
Solvent System	Acetone / Water
Drug Load	40%
Classification	Drug Product Intermediate



Test	Drug Substance Acceptance Criteria	cPAD Acceptance Criteria
Description	White to Off-White Powder	White to Off-White Powder
Identification	Consistent with Reference	Consistent with Reference
Assay	97.0 to 103.0% (dry basis)	90-100% of label claim (dry basis)
Related Compounds Individual Unspecified Total	 Max 1.00 area% Max 3.00 area%	 Max 1.00 area% Max 5.00 area%
Chiral Purity Minor Enantiomer	 Max 1.00 area%	 Not Tested
Residual Solvents THF Acetonitrile Toluene	 Max 0.50 wt% Max 0.50 wt% Max 0.08 wt%	 THF: Max 0.50% Heptane: Max 0.50%
Moisture	Report Results	Report Results
Elemental Impurities	Complies with ICH Q3D, USP <232>	Complies with ICH Q3D, USP <232>

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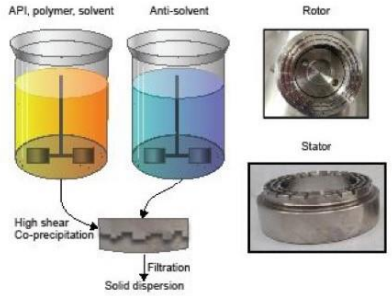
Conclusions

cPAD is an emerging technique with many advantages over traditional methods used to enhance solubility by forming a stabilized amorphous drug substance.

Analytical methods and specifications for release of a drug substance can be applied directly to it's cPAD counterpart with little to no modification.

Polymers generally used for spray drying can be used for cPAD; these polymers contain limited conjugation, and in many cases will not impact the underlying analytical method for the characterization of the drug substance.

Co-Precipitated Amorphous Dispersion (cPAD):



Compound A:

- No change to the appearance, identity, residual solvents, moisture, and elemental impurities analysis
- Only change was related to the sample prep for the assay and impurities method

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Thank you

Small Molecule Analytical Research and Development

Merck Co., Inc.

E-mail: frank_bernardoni@merck.com

Address: 126 E. Lincoln Ave., Rahway, NJ

Acknowledgements and References

Analytical R&D:

Amanda Mann

Stella Betancourt

Sarika Patel

Chemical Engineering R&D

Luke Schenck

Derek Frank

CMC Regulatory

Bob Orr

Llorente Bonaga

References:

1. N Strotman and L Schenck, *Org. Process Res. Dev.,* **2022**, 26, 10-13.
2. EMA Zelboraf Assessment Report (2011)
3. EMA Tybos Assessment Report (2013)
4. EMA Quality Working Party Q&A on API Mix (CHMP/CVMP/QWP/152772/2016)

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