Cobicistat on Silicon Dioxide a Drug Substance with a Sticky Beginning

FDA/M-CERSI CO-PROCESSED API WORKSHOP, 13 JULY 2022

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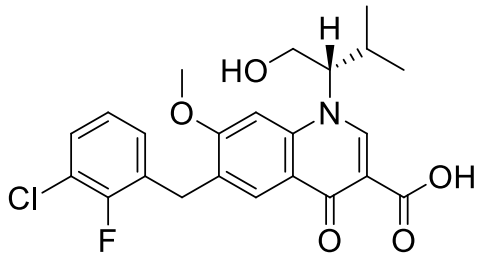
Discussion Outline

- Introduction and the need for cobicistat
- Cobicistat physical properties
  - Challenges with development of an amorphous foam
  - Efforts to identify a crystalline form
- Cobicistat on silicon dioxide

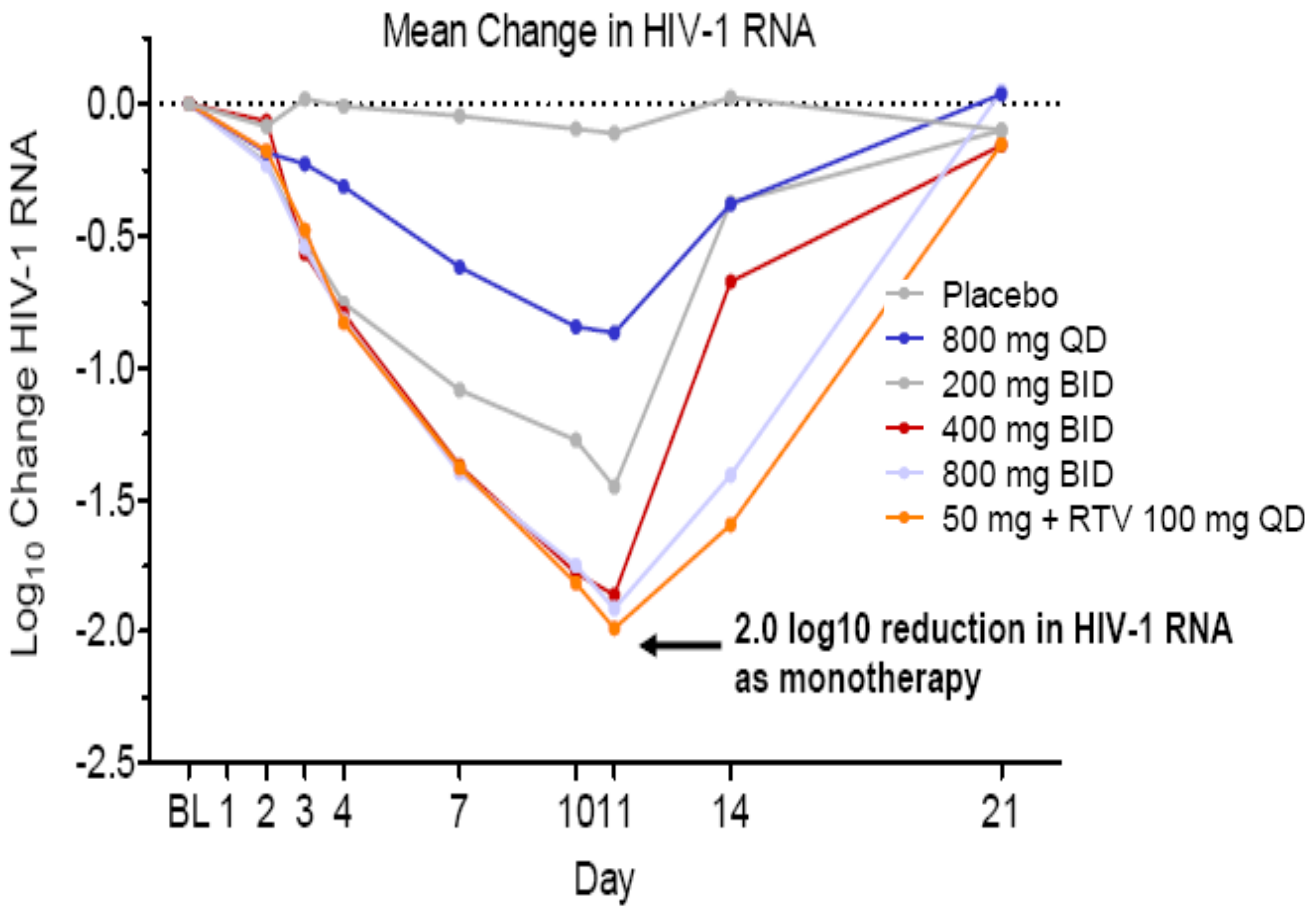
Single Tablet Regimen Strategy for HIV Treatment Required PK Enhancement for EVG

- Target product profile for Gilead's HIV treatment required QD dosing of elvitegravir (EVG)



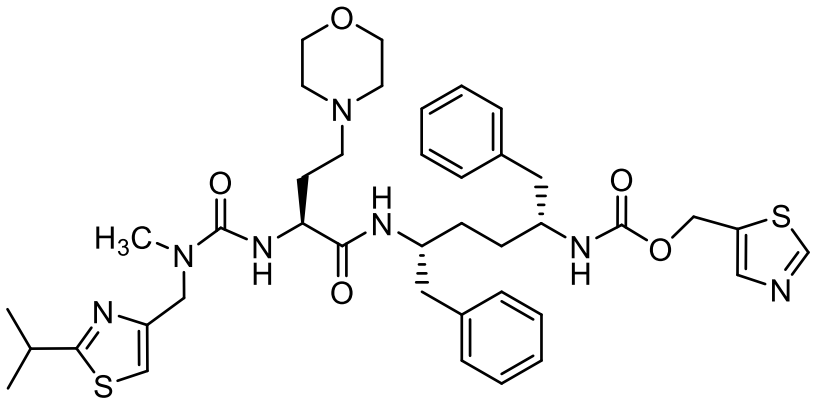
elvitegravir

- EVG is metabolized by cytochrome P450 CYP3A
- Co-administering ritonavir results in a 20-fold increase in systemic EVG exposure (AUC_{tau})
- Viral load reduction is enhanced for EVG monotherapy with ritonavir boosting



Cobicistat (Tybost): A Potent CYP3A Inhibitor

- Novel pharmacokinetic enhancer
- Potent, selective and mechanism based human cytochrome P-450 3A (CYP3A) enzymes inhibitor
- Does not demonstrate HIV protease activity
- Improves the PK of drugs metabolized by CYP3A

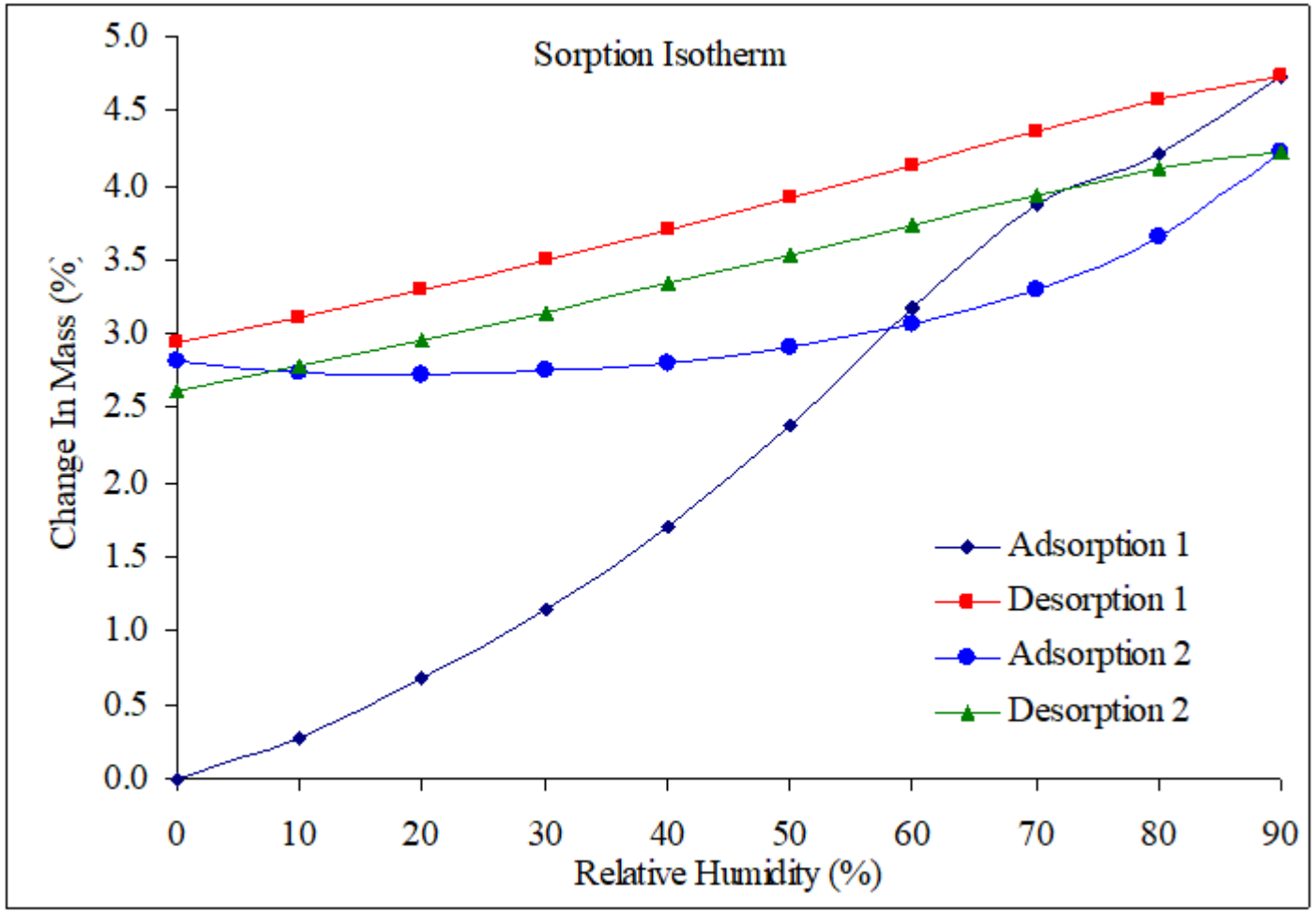


Cobicistat Physical Properties

- Cobicistat is an amorphous solid
- Has no defined melting point with a low glass transition temperature of 35 °C
- Exhibits high solubility in a range of solvents and acidic aqueous media
- Three pKa values at 1.8 (thiazole), 2.5 (alkylthiazole) and 6.4 (morpholino)

Amorphous Cobicistat is not a Physically Stable Solid

- Cobicistat is hygroscopic based on dynamic vapor sorption studies
- Glass transition temperature is lowered at 60% RH and physical change occurs at room temperature



Amorphous Cobicistat is an Intractable Solid

- Low glass transition temperature results in moisture and temperature induced phase transition from a solid foam into a viscous liquid
- Isolation and handling a solid foam or viscous liquid are not scalable
- Analytical challenges with sample preparation
- Challenges with solvent retention and homogeneity

No Crystalline Forms of Cobicistat Found

- Internal R&D and four separate CROs evaluated overlapping experimental space and proprietary techniques without identifying a crystalline form
- Extensive salt and co-crystal screening performed in high-throughput and batch modes (thousands of solvent mixtures, salts, and cocrystal combinations)
- Vapor diffusion, polymer heteronucleation, mechanochemical techniques were also evaluated

Amorphous Cobicistat Salts Exhibit Similar Physical Properties

- All salts formed were amorphous hygroscopic solids with glass transition temperatures from 17 to 90 °C
- Enabled formulations of various cobicistat salts through spray drying with polymers (HPMCs, PVP, VA, and combinations) were also evaluated but none had a sufficiently high glass transition temperature

Cobicistat in Ethanol: A Potential Solution

- Cobicistat in ethanol was incorporated in the drug product formulation during the wet granulation process
- Silicon dioxide was included as an excipient for its effective adsorptive properties
- Supported Phase 1/2 clinical development activities

Ethanol results in headaches:

- Chemical stability of cobicistat in ethanol is limited
- Analytical challenges with volatile solutions
- Shipping, handling, and storage restrictions for flammable solvents
- Limited drug product manufacturing capacity for flammable substances

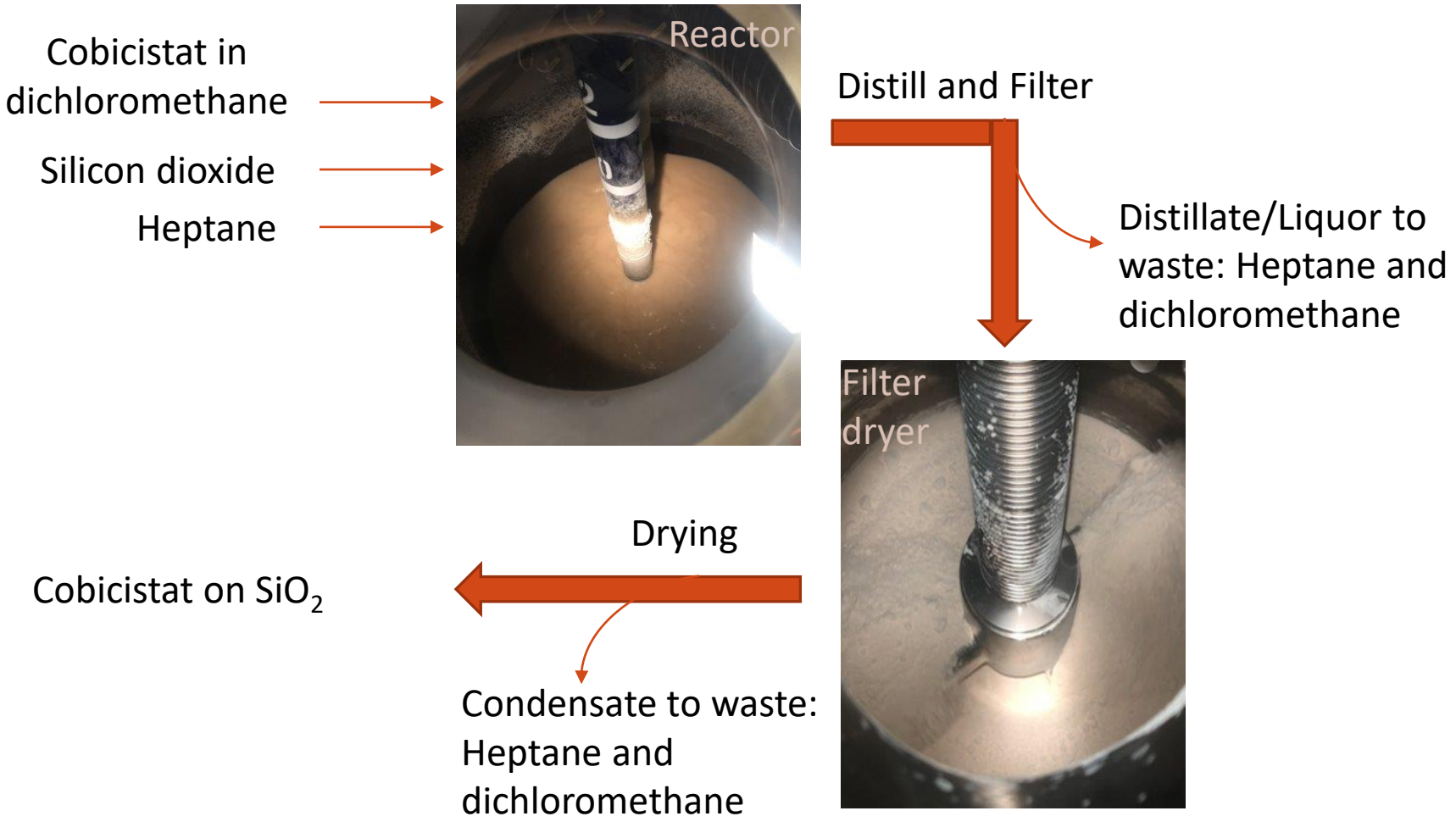
Silicon Dioxide: the ideal solid

- High pore volume of approximately 2.6 mL/g, which imparts effective adsorptive properties, without losing its physical and flow characteristics
- Common additive in food products
- Flow agent used in drug products
- Cost effective

Possible to harness SiO_2 physical properties by including into the API Step?

Evonik's Aeroperl® 300 Pharma

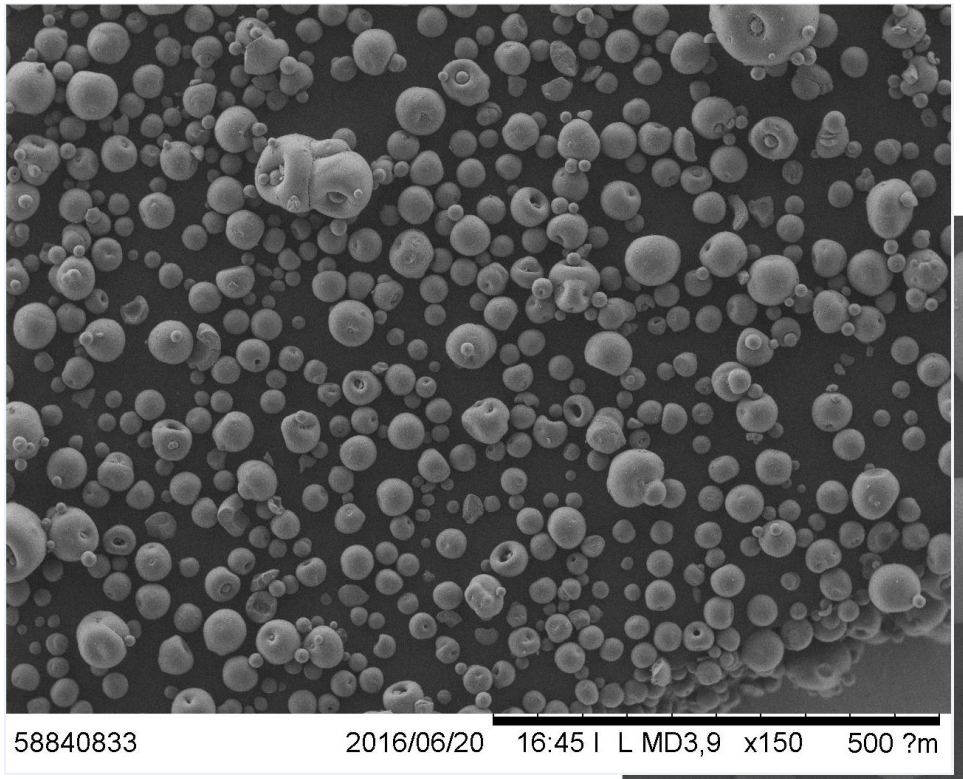
Loading Cobicistat onto Silicon Dioxide

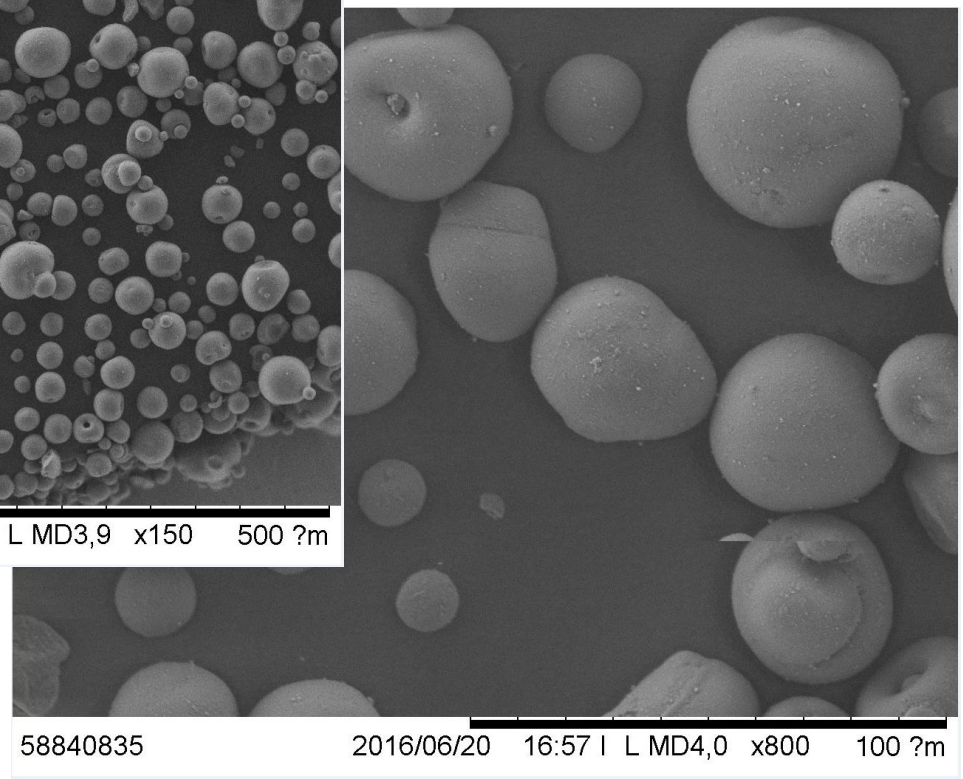


- Cobicistat on silica isolation process is comparable to routine API crystallization and isolation processes
- Uses common equipment and operating procedures present in API manufacturing facilities

Cobicistat on Silicon Dioxide

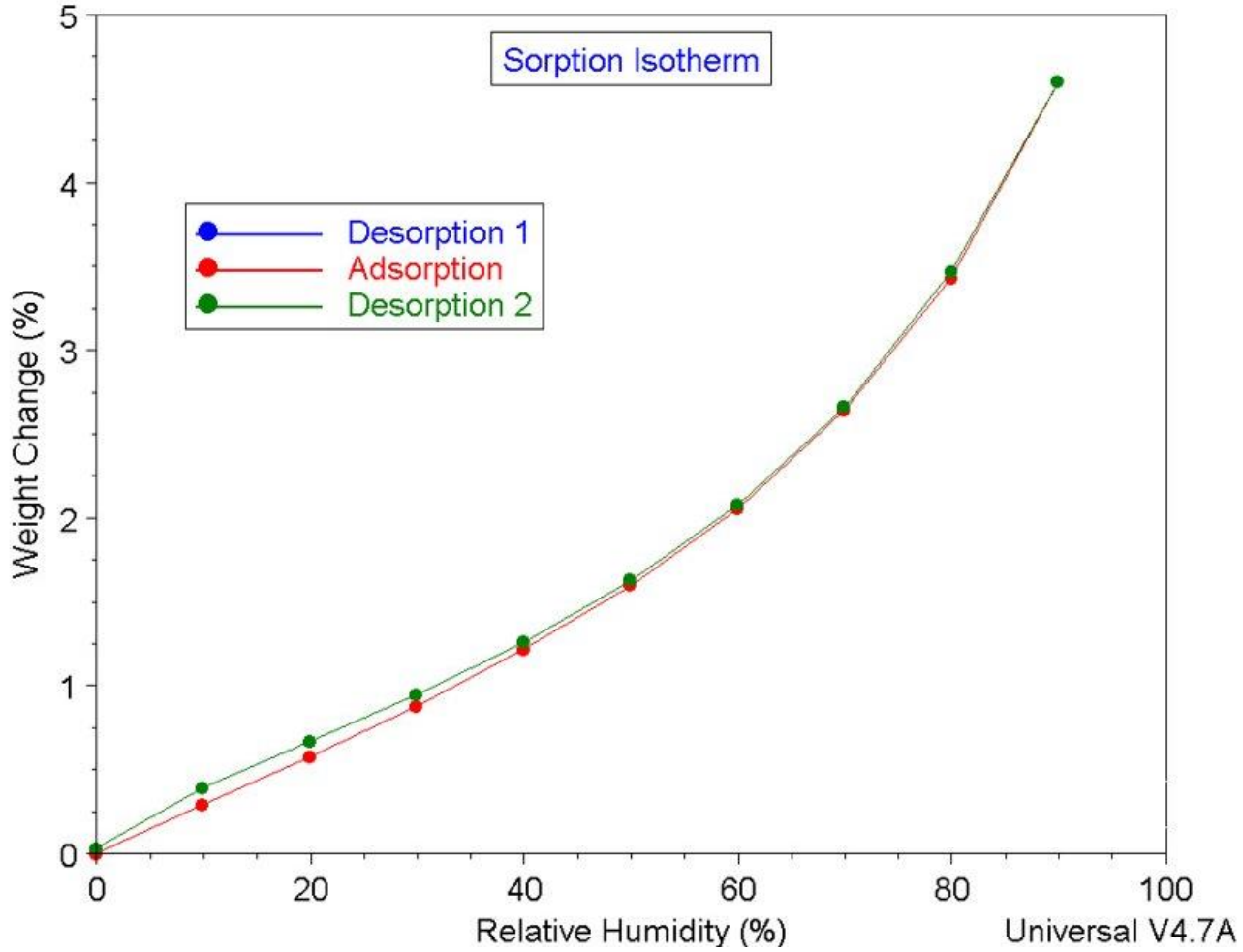
- Provides desired physical properties
- Enables API isolation, handling, transportation storage and formulation
- Implement as the Drug Substance step to support Phase 3 studies and commercial supplies



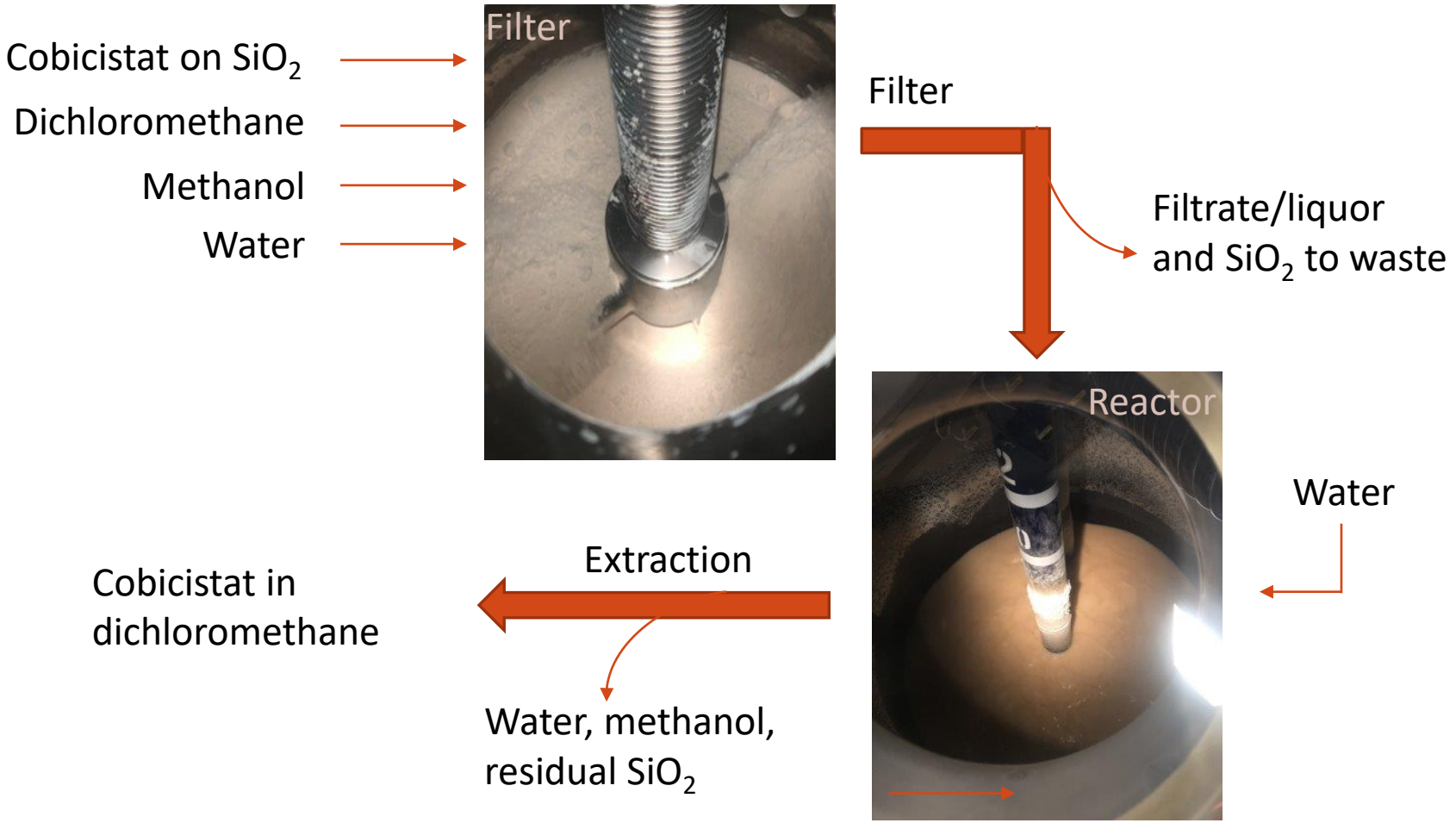


Cobicistat on SiO_2 is a Physically Stable Solid

- Cobicistat on silicon dioxide has low hygroscopicity, even lower than silicon dioxide alone
- Moisture uptake of cobicistat on silicon dioxide is reversible
- Physical properties of cobicistat on silicon dioxide remain unchanged after desorption



Unloading Cobicistat From Silicon Dioxide



- Solvents can be used to desorb cobicistat from silicon dioxide to provide intermediate COBI in dichloromethane
- Cobicistat unloading enables reprocessing or reworking to correct for potential non-conformances

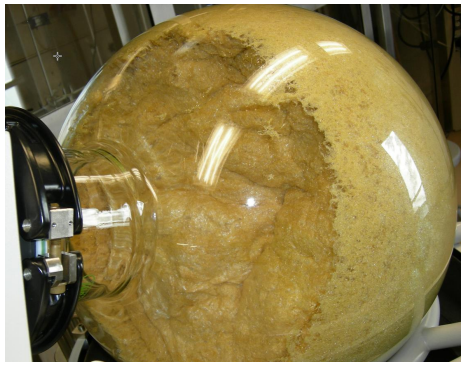
Analysis of Cobicistat on Silicon Dioxide

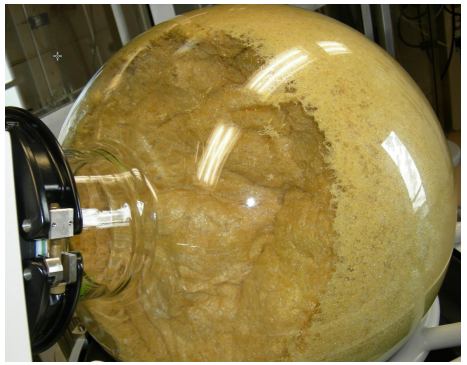
- Analysis of the following attributes are performed directly on the drug substance
  - Appearance
  - Residual solvents (GC-headspace)
  - Elemental impurities (compendial method)
  - Amorphous physical form (PXRD)

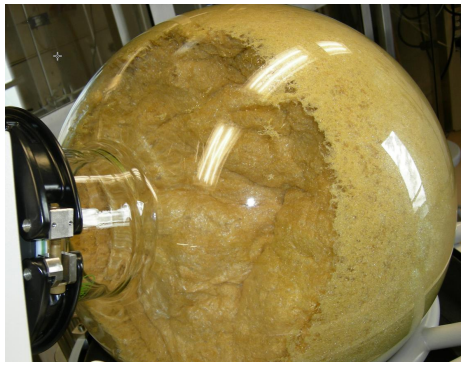
- Analysis of the remaining attributes are performed by unloading cobicistat from the silicon dioxide and measurements are made with the cobicistat containing solution
  - Identification of cobicistat by IR, UV
  - Purity and assay of cobicistat by LC-UV

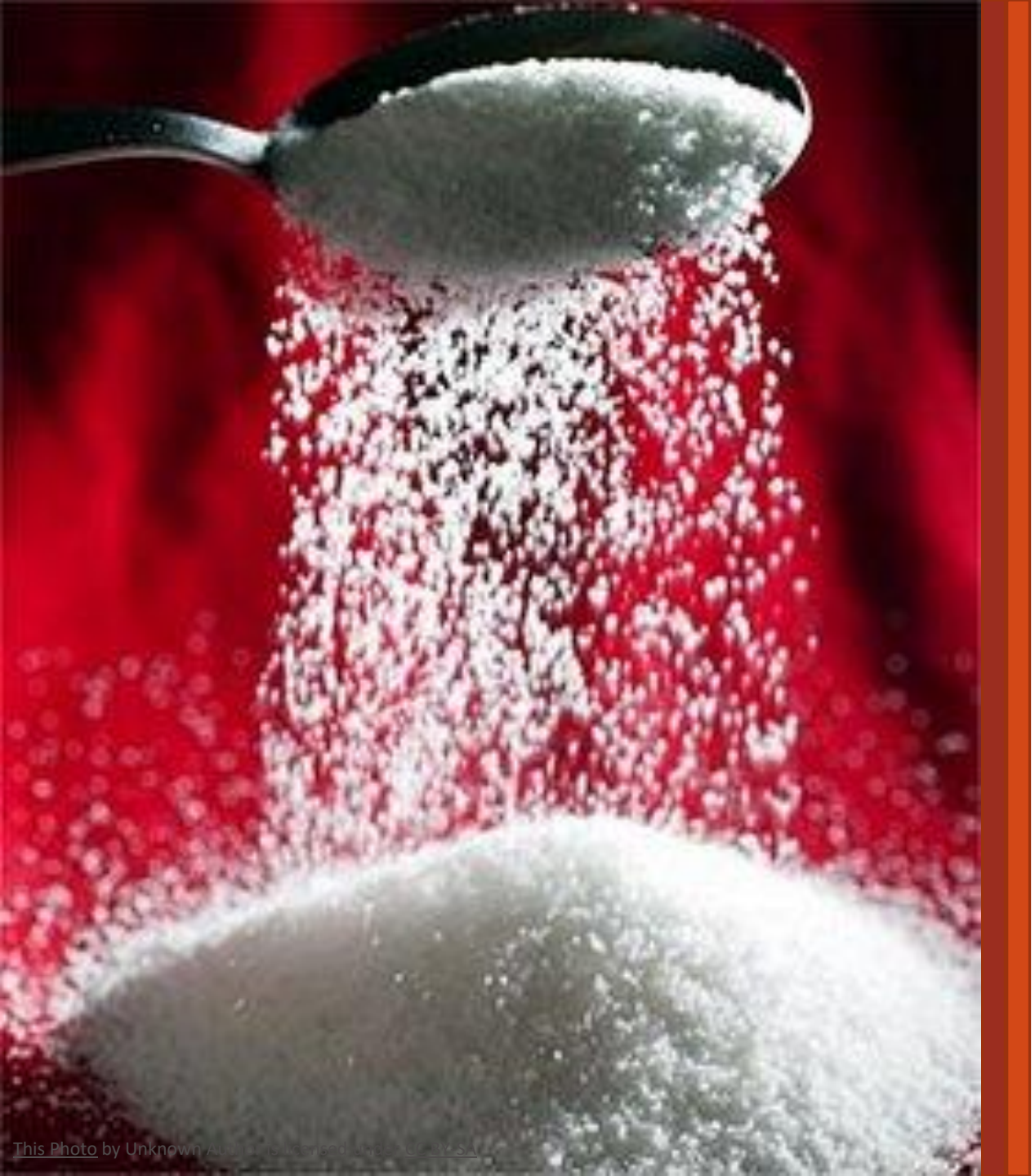
- Methods were developed and validated in a straightforward manner

Attribute	Ideal DS Solid 
Physical properties	Ideal
Stability	Ideal
Ease of Isolation and Handling	Ideal
Ease of Transportation	Ideal
Ease of Analysis	Ideal
Ease of Formulation	Ideal

Attribute	Amorphous COBI	Ideal DS Solid
		
Physical properties	Challenging	Ideal
Stability	Challenging	Ideal
Ease of Isolation and Handling	Challenging	Ideal
Ease of Transportation	Limited	Ideal
Ease of Analysis	Challenging	Ideal
Ease of Formulation	Challenging	Ideal

Attribute	Amorphous COBI	COBI Ethanol Solution	Ideal DS Solid
			
Physical properties	Challenging	Limited	Ideal
Stability	Challenging	Limited	Ideal
Ease of Isolation and Handling	Challenging	Limited	Ideal
Ease of Transportation	Limited	Limited	Ideal
Ease of Analysis	Challenging	Limited	Ideal
Ease of Formulation	Challenging	Challenging	Ideal

Attribute	Amorphous COBI	COBI Ethanol Solution	COBI on SiO_2	Ideal DS Solid
				
Physical properties	Challenging	Limited	Ideal	Ideal
Stability	Challenging	Limited	Ideal	Ideal
Ease of Isolation and Handling	Challenging	Limited	Ideal	Ideal
Ease of Transportation	Limited	Limited	Ideal	Ideal
Ease of Analysis	Challenging	Limited	Ideal	Ideal
Ease of Formulation	Challenging	Challenging	Ideal	Ideal



….a Solid Conclusion

- Amorphous cobicistat possesses a low T_g that prevents isolation and processing
- Amorphous cobicistat's intractable physical properties were managed by loading onto silicon dioxide
- The manufacturing process to form cobicistat on silicon dioxide is comparable to routine API crystallization and isolation processes
- Cobicistat on silicon dioxide possesses ideal physical properties for isolation, storage, shipment, and forward processing in drug product formulation activities