Amorphous Solid Dispersion (ASD) Products and Potential Alternative BE Approaches

Girish Nihalani, MS
Associate Director, Formulation Development,
Hikma Pharmaceuticals USA Inc.

(GDUFA Workshop - June 3-4, 2025)

[Note: The contents of this presentation and ideas/thoughts expressed are author's own or from literature and are not on behalf of his present or previous employer/s]

Disclaimer

This presentation reflects the views of the author and should not be construed to represent his present or past employer's views or practices.

Contents

- **Introduction:** What are ASD, Why/Benefits, Methods of preparation
- **ASD :** Mechanism, Considerations in development, Formulation Factors
- **Approved Drug products** (using ASD) (w.r.t. Polymer Type, Mfg. Process).
- **HME :** A tool for ASD, process variables affecting ASD
- **ASD in context to M13A guidance**
- **Alternate BE Approaches** (to waive Fed BE for IR (ASD))
- **Research Gap / Challenges**

Amorphous Solid Dispersions (ASD)

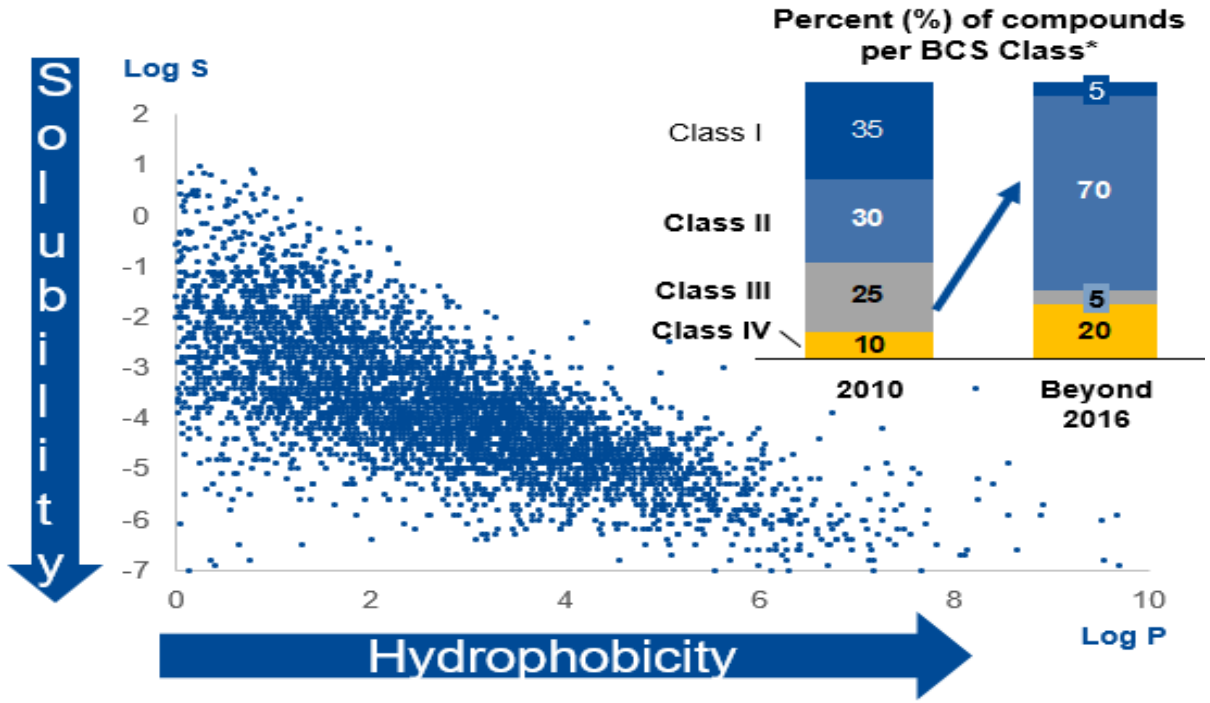
ASD : Solid-state formulations where the active pharmaceutical ingredient (API) is dispersed at a molecular level within a polymer carrier in an amorphous form.

Why / Benefits :

- Improve solubility
- Enhance dissolution rate
- Increase bioavailability

} BCS Class II / IV drugs

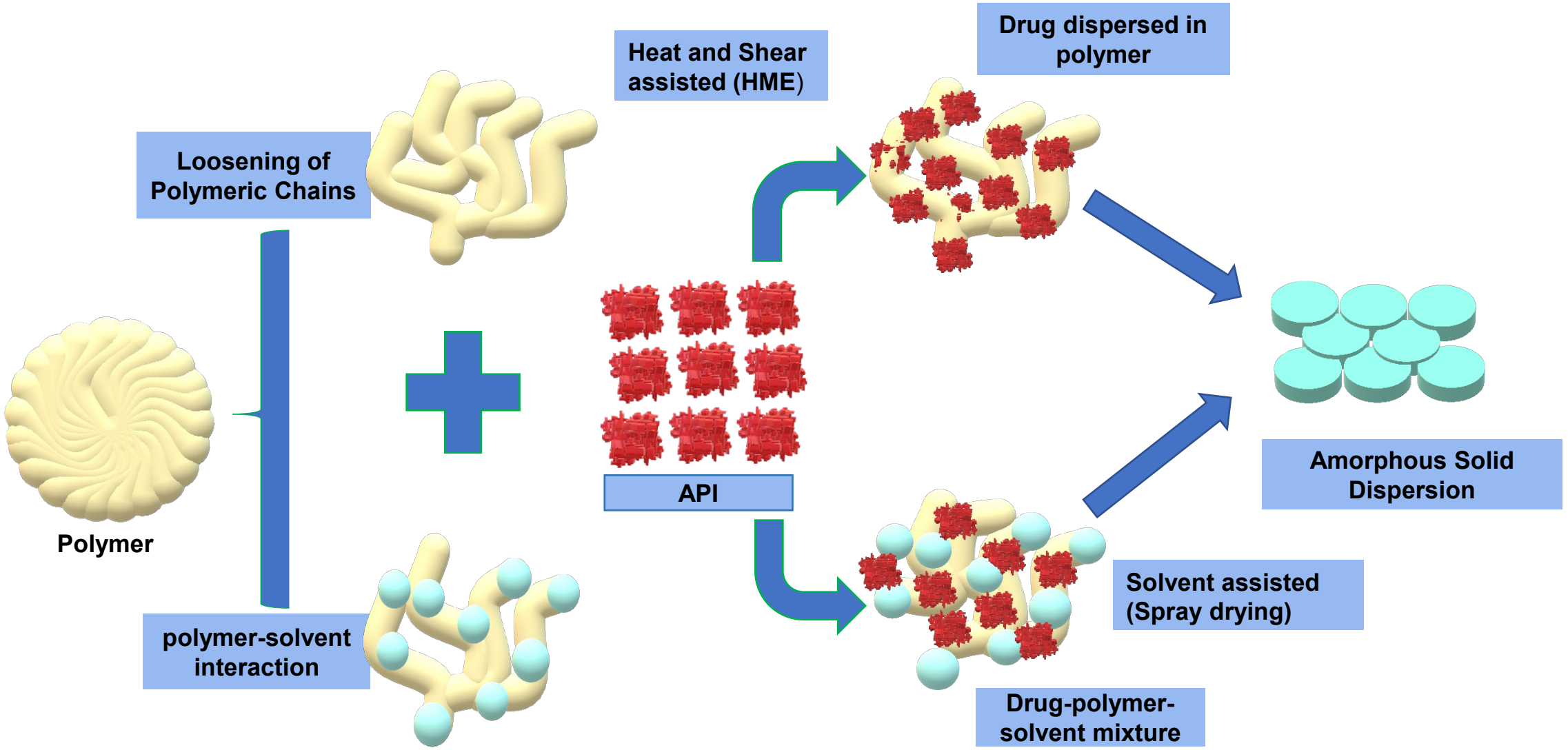
- Potential for reduced food effect
- 505 (b)2 application
- Paragraph IV certification
- Life Cycle management of a drug product



Preparation methods:

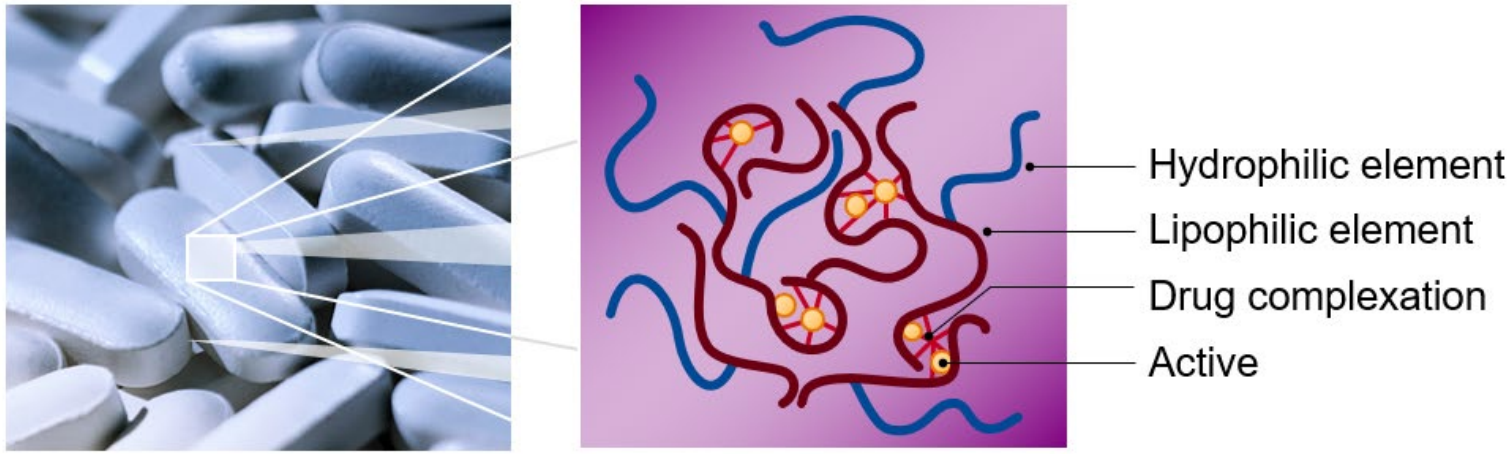
- Solvent evaporation . Lyophilization
- Melting . Co-precipitation
- **Spray drying** . Super critical Fluid technology
- **Hot Melt Extrusion** . Drug-Polymer Layering

Amorphous Solid Dispersions



Amorphous Solid Dispersions

- **To obtain a single amorphous drug–polymer phase, a certain degree of solid solubility, miscibility and kinetic stabilization is required.**
  - **Solid Solubility** - refers to the thermodynamic solubility of one solid into the other
  - **Miscibility** - refers to the miscibility of two amorphous compounds in their super-cooled liquid state
  - **Kinetic Stabilization** - refers to immobilizing supersaturated drug concentrations into a highly viscous matrix and hence preventing phase separation and crystallization.
- The presence of **functional groups** that are either donors or acceptors for **hydrogen bonds** is an additional benefit. specific interactions increase the solid solubility of the drug into its carrier and play an important role in inhibiting phase separation and crystallization of a drug from a **glass solution**."



Sandrien Janssens and Guy Van den Mooter, Review: physical chemistry of solid dispersions, JPP 2009, 61: 1571–1586, DOI 10.1211/jpp/61.12.0001

Courtesy of BASF

ASD – Considerations in Development

- Manufacturing Process Selection
- Drug Load
- Polymer Selection : Drug Polymer miscibility
- Selection of Surfactant / other excipients
- Stability considerations
- QTPP
- In-vitro In-vivo correlation
- BE (Clinical Study) design

ASD – Formulation and Excipient Parameters

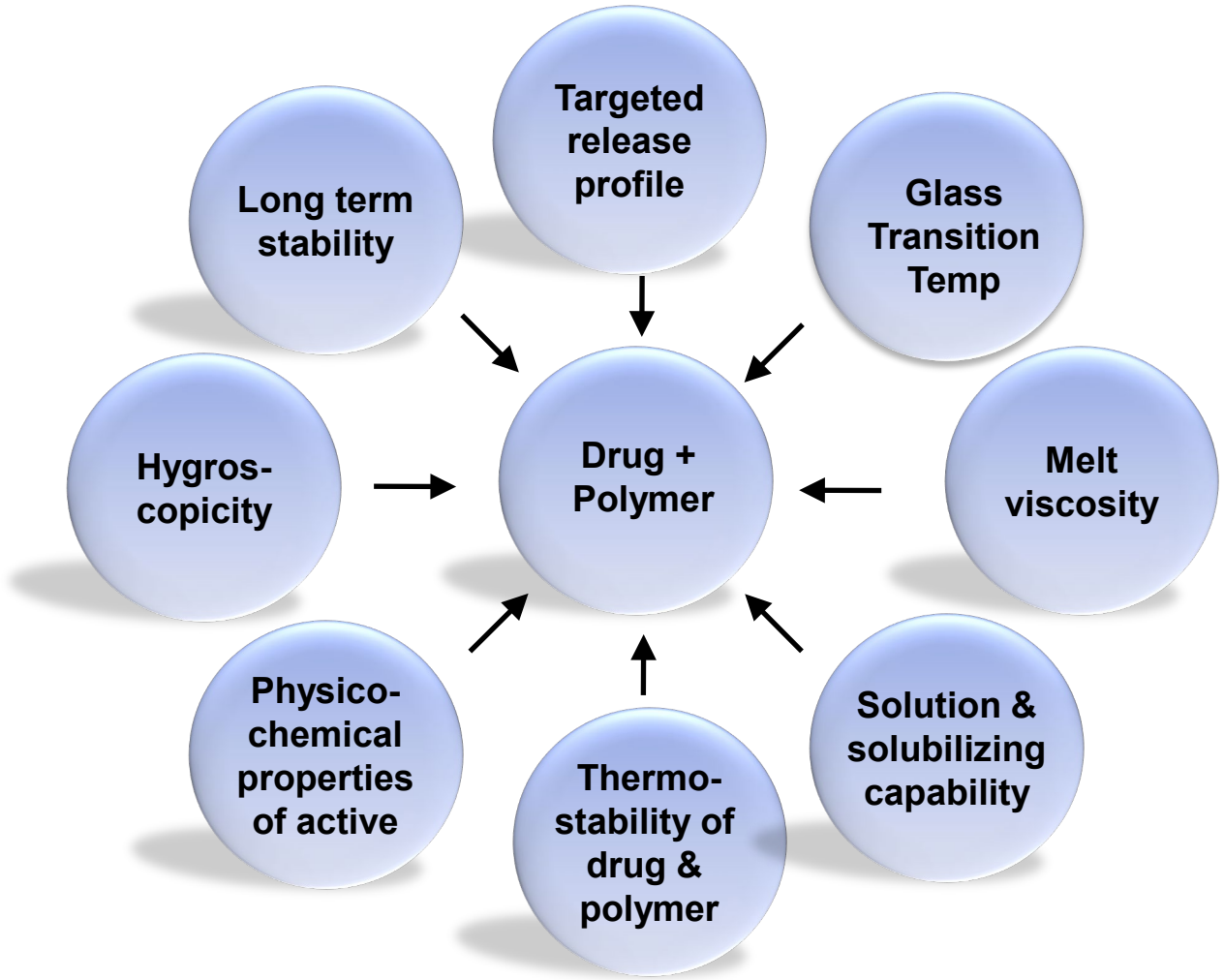
Active + Polymer → Choose the appropriate polymer

+

Plasticizer → For improved processability, To lower tg.

+

Solubilizer → For improved drug content / dissolution, prevention of crystallization in gastric and intestinal fluid



ASD: Factors making it complex

Complexity : Composition / Mfg. Process / Equipment

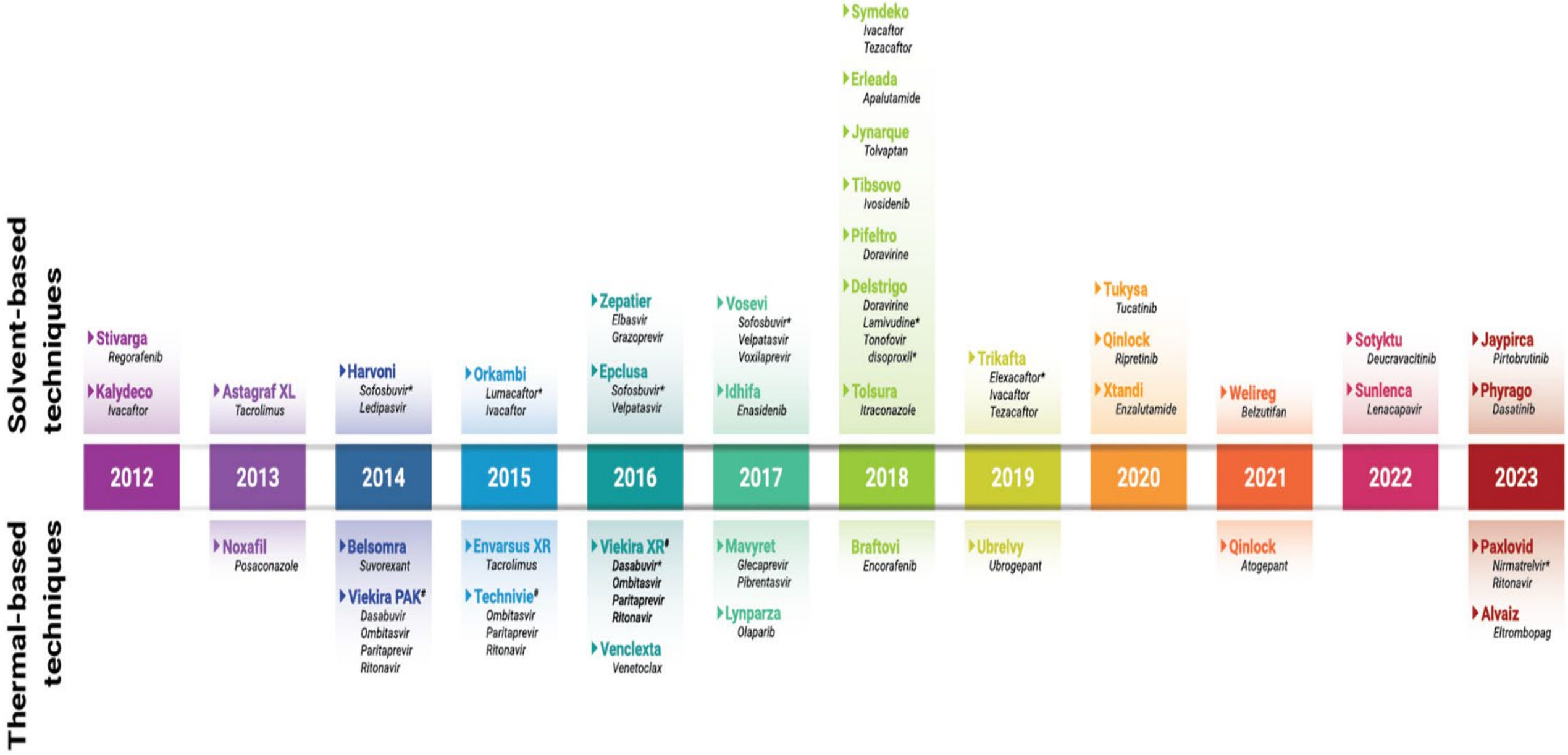
- Polymer/Carrier Characteristics : Compatibility, chemistry, Tg, Processibility / Cleanability
- Polymer type & quantity (it's effect on dissolution rate) and need for additional ingredients in the system
- Drug substance characteristics: Melting point , Solubility in polymer (as a function of temperature), hygroscopicity (corelated to recrystallization).
- Manufacturing Process Parameters : Product Temperature, rate of spray drying/extrusion, Uniformity of dry mix.
- Manufacturing Equipment : Design , processing of intermediate
- Processing challenges (such as milling of hot melt extrudes subject to heat during milling)
- Solvent system

All of above factors influence amount / rate of drug solubility/dissolution and hence bioavailability

Challenges :

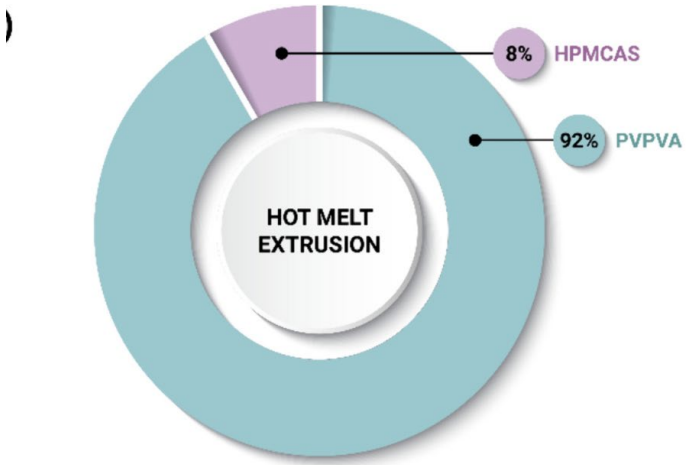
- Stability (w.r.t. PK performance throughout shelf life) / Recrystallization
- Characterization (XRD / DSC)
- Quantification of amorphous form (Sensitivity of method)
- Drug-Polymer Interaction

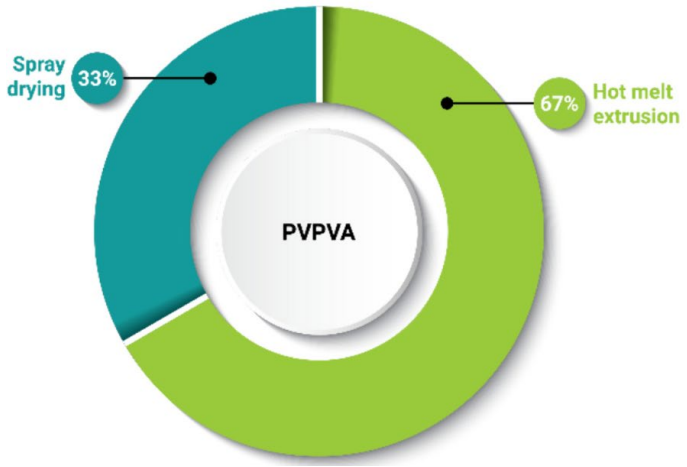
Approved Drug Products (using ASD)

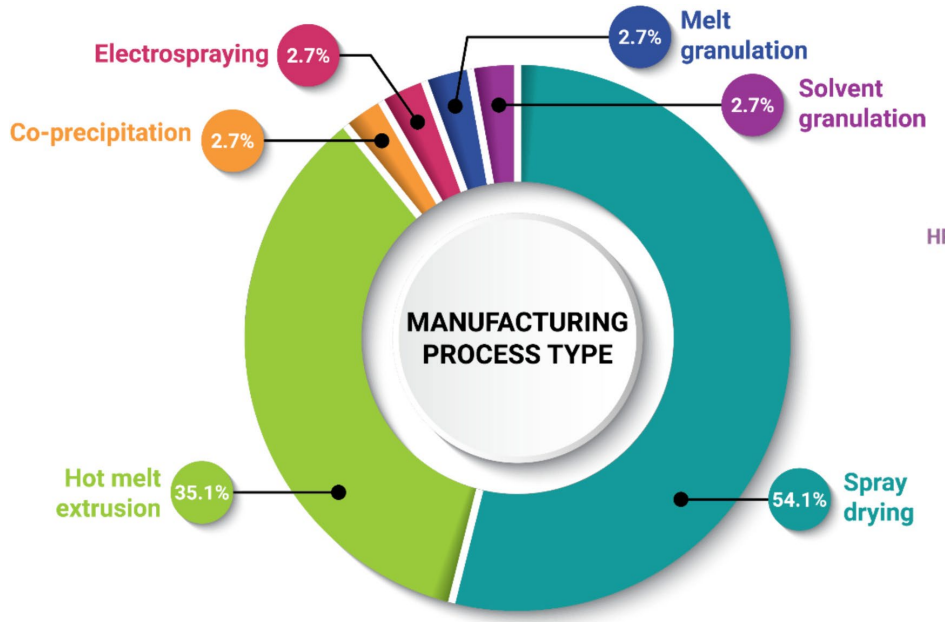


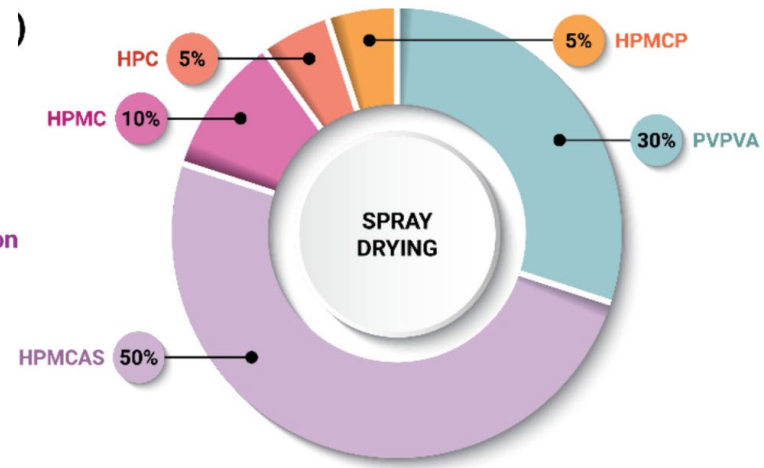
Dana E. Moseson, Trong Bien Tran, Bharathi Karunakaran, Rohan Ambardekar, Tze Ning Hiew, Trends in amorphous solid dispersion drug products approved by the U.S. Food and Drug Administration between 2012 and 2023, International Journal of Pharmaceutics: X, Volume 7, 2024, 100259. Source: https://www.sciencedirect.com/science/article/pii/S2590156724000318

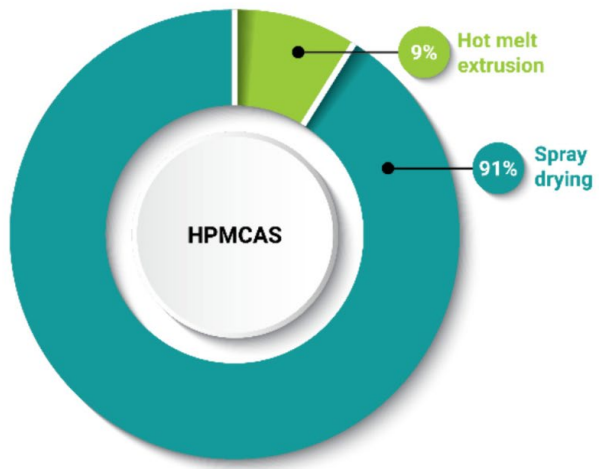
Approved Drug Products (ASD): Polymer Type, MFG. Process





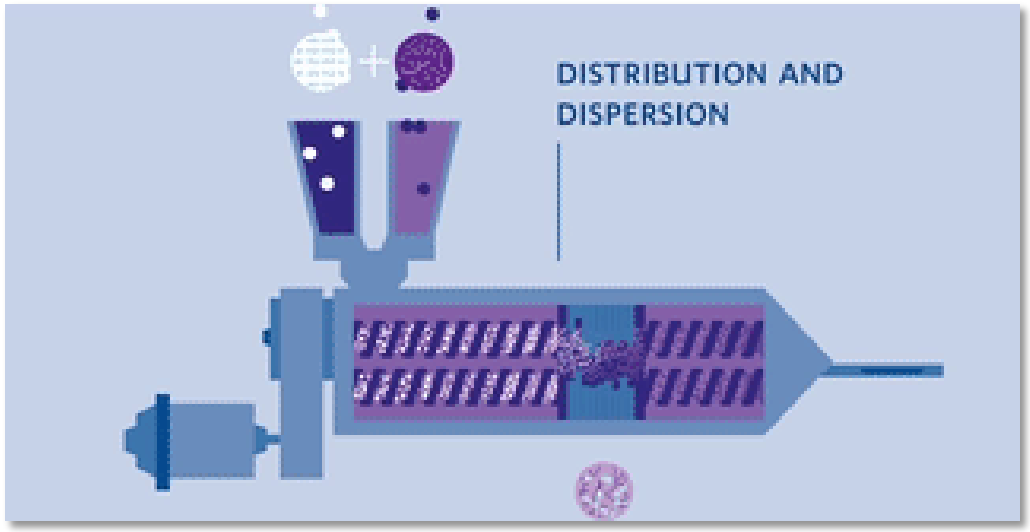


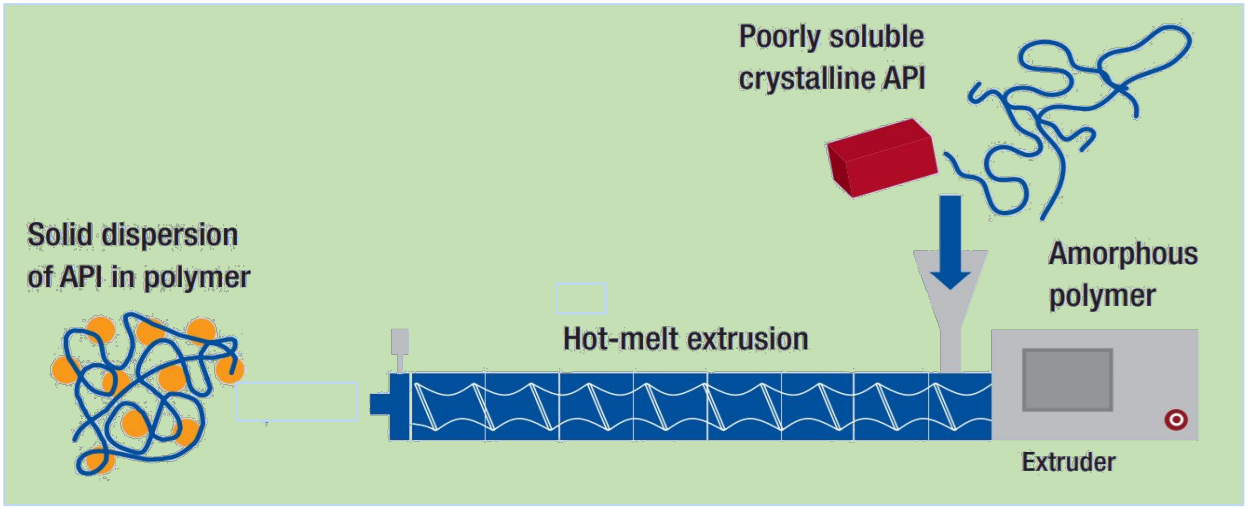




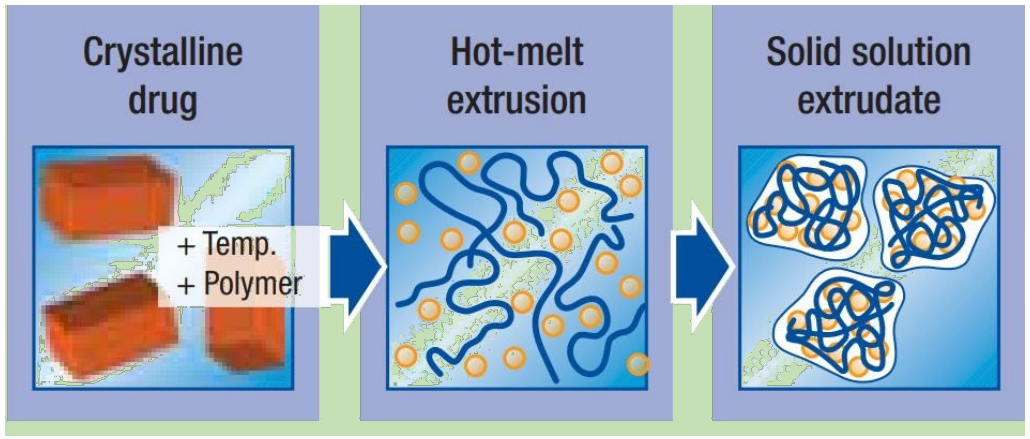
Source / Courtesy: https://www.sciencedirect.com/science/article/pii/S2590156724000318 / https://doi.org/10.1016/j.ijpx.2024.100259

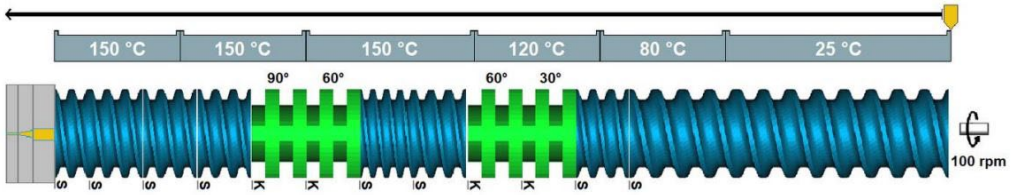
HME : As a tool to develop ASD

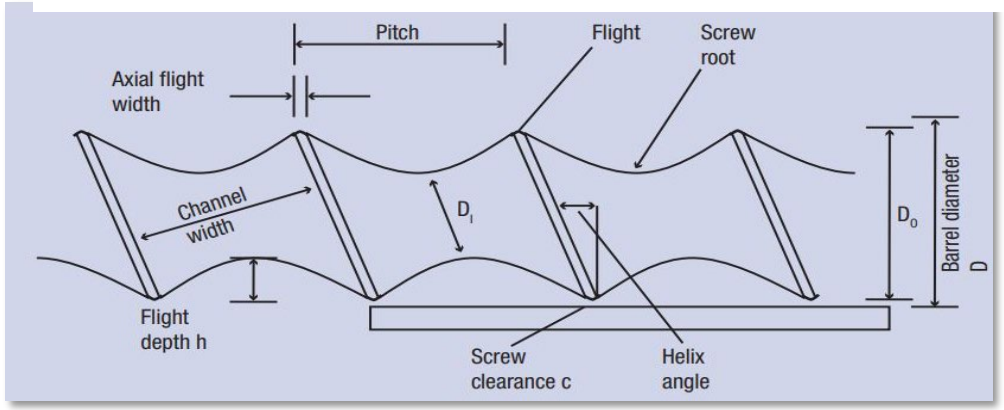


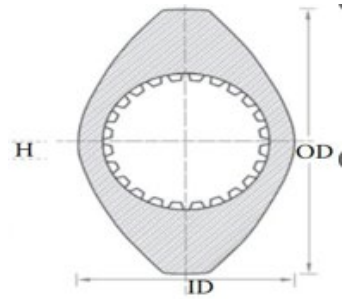


Down streaming Process

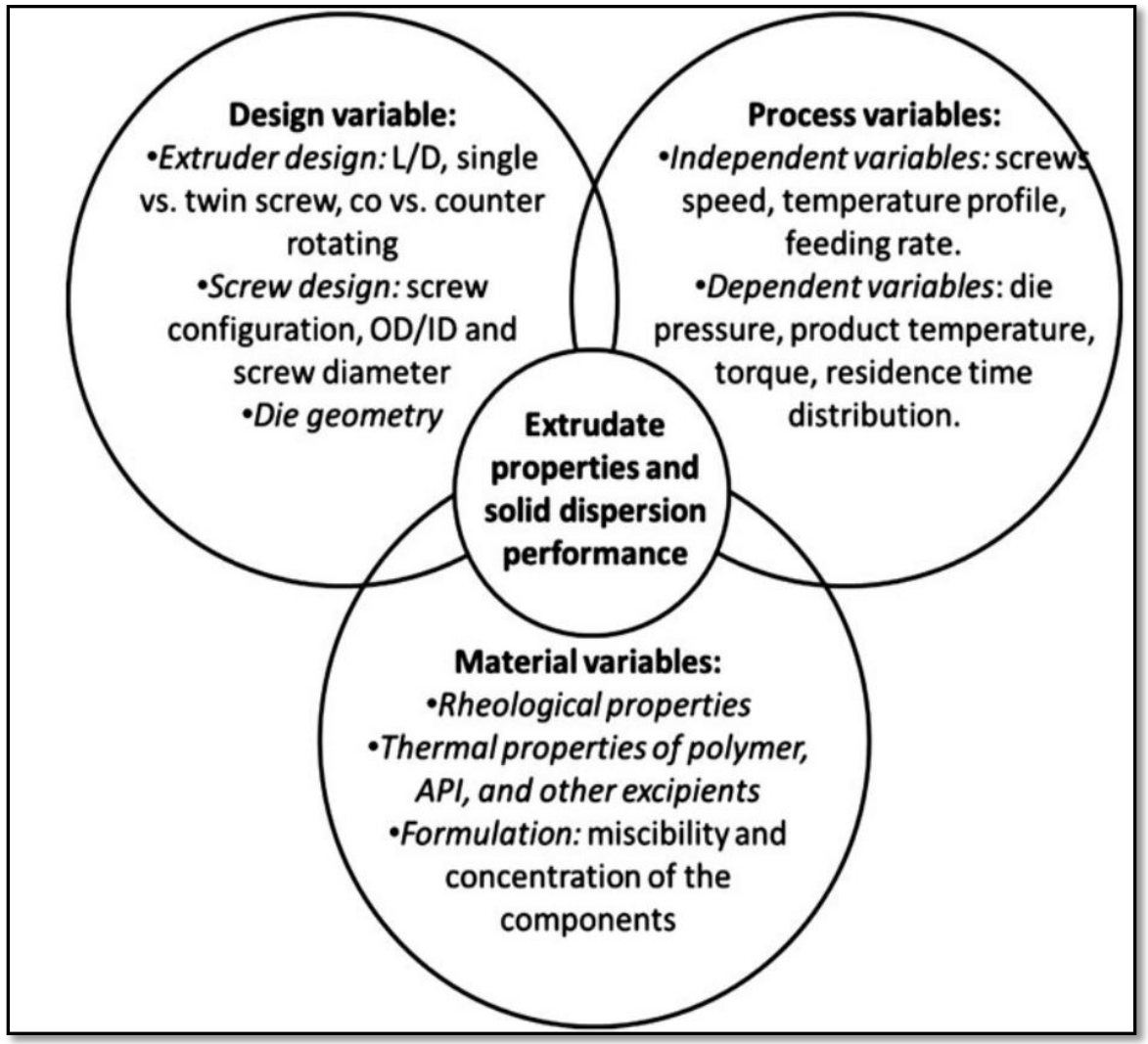


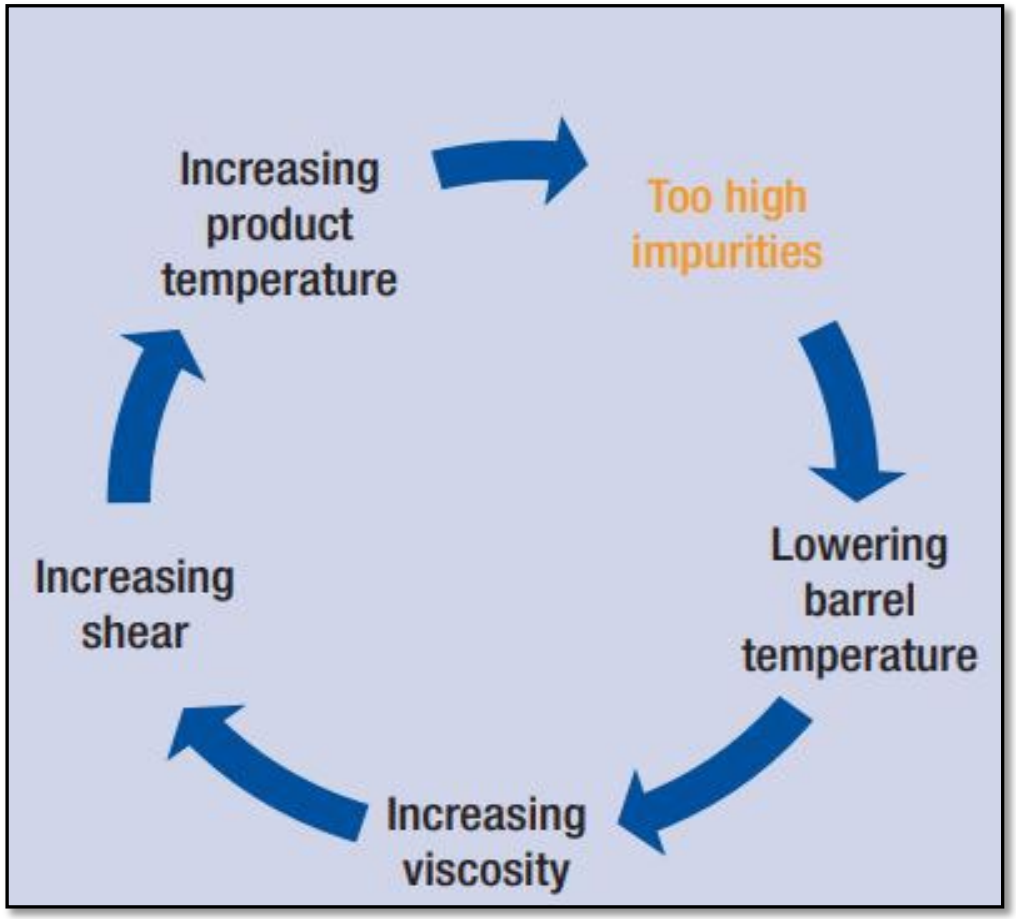




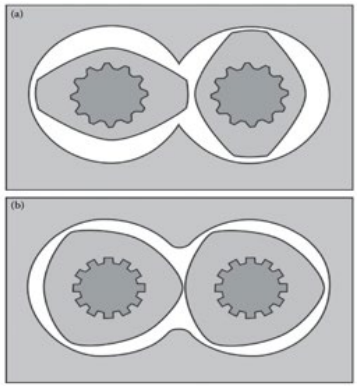


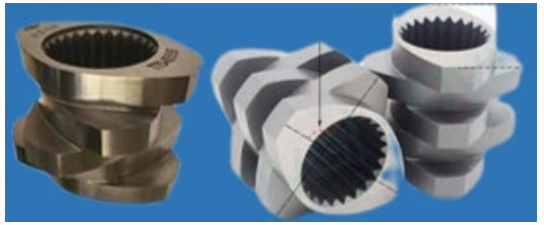
HME: Process Parameters





HME: Process Parameters





Process related:

- Screw Speed (RPM)
- Temperature profiling
- Screw design : Bilobal / Trilobal, angle of kneading elements
- L/D of extruder (related to Residence time),
- OD/ID of screw affects the free volume.
- Conveying element with proper pitch and LD/OD ratio
- Location of kneading elements
- Pressure build up near the die →indicates the degradation of product
- Lack of degassing → causes the formation of bubbles on extrudates.
- Feed rate

Excipient related

- Polymers for HME: Stability (as a function of temperature), tg (glass transition temperature), Hgroscopicity
- Polymers for HME: Presence of lipophilic groups for solubilization capacity (Ex: Soluplus and Co-Povidone)
- Plasticizers: act as precipitation inhibitors, wetting agents by reducing the surface tension.

  Examples: Vitamin E TPGS, Poloxamer 188, Poloxamer 407, L-HPC, Kolliphor RH 40, PEG 3350, PEG 1500

ASD in context to M13A

- Complex formulation / manufacturing methods (BCS Class II) : Solid dispersions, co-processed drug substances, microemulsion, nanotechnologies, lipid based formulations.
- Substantial variability in GI conditions limits the assessment of differences in performance of a high-risk product.

  Potential interaction between the performance enhancing characteristic(s) (formulation/mfg. technology) of the drug product and GI tract conditions.

  The ASD system vs non-ASD system could be more or less sensitive to food effects (based on composition/state)
- Deviations from the M13A guidance may be acceptable based on appropriate scientific justification. Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken.
- No in-vitro approach / model has provided reliable and accurate predictions, new methodologies are welcomed.

Reference M13A: Q&A

Potential Alternate BE Approaches

➢ Physiologically-based pharmacokinetic (PBPK) modeling (to assess food effects)

EX.: In-vitro lipid lipolysis model to assess food effect (Dose dependent, formulation/API form dependent).

Rivaroxaban (Xarleto 2.5/10/20 mg) , Itraconazole (Sporanox/Sempera/Tolsura) , Ritonavir (Norvir).

➢ Physiologically based biopharmaceutics modeling (PBBM)

- ❖ Consideration of formulation characteristics and gastrointestinal physiology.
- ❖ Extensive in-vitro characterization

EX.: Sempera® and Tolsura® (ITA in ASD)

- ▪ Solubility Studies of API and DP
- ▪ Single Stage Dissolution Tests, FaSSGF, FaSSIF, FaSSIF, FEDSGF
- ▪ Fasted state two-stage dissolution: FaSSGF (250 ml, pH 1.6) → FaSSIF (250 ml, pH 7.5) (Final pH 6.5)
- ▪ FEDGAS three-stage dissolution: FEDGASearly (pH 6), FEDGASmiddle (pH 4.5) and FEDGASlate stage (pH 3)

PBBM accurately predicted positive impact of food on the absorption of Sempera® and the negative food effect of Tolsura®.

➢ GI Tract Models, Compartmental PK Modeling

? A harmonized workflow to predict drug and formulation-food interactions for ASD containing BCS Class II drug is not available

R.P. Patel et al./Journal of Pharmaceutical Sciences,113(2024)2361–2373
https://doi.org/10.1016/j.ejps.2025.107047 (European Journal of Pharmaceutical Sciences 209 (2025) 107047)

Potential Alternate BE Approaches

OTHER Considerations (topic of discussion, case to case) :

- For BCS Class II : Consideration of API solubility **from API-polymer complex** or intermediate to demonstrate highly soluble (the BE waiver for one/Fed study to be based on solubility of API. if solubility of API in ASD is enhanced , it may (not necessarily) behave like BCS class I / III w.r.t. solubility)
- Dissolution in multi-media of drug product at proposed shelf life time (final time point).
- To demonstrate dissolution of ASD products in: physiological pH range to be comparable with RLD.
  Fed and Fast Media (FaSSIF and FeSSIF)
- Development of In-Vitro models/dissolution test during formulation development/pilot clinical batches.

In addition to / assuming :

- Mfg. process and stability (e.g. RT/24 months) does not change the API form and its solubility.
- RLD and proposed generic are qualitatively same and with same drug release mechanism.
- Discrimination of ASD product by intentionally mfg. formulations to contain 0%, 10%, 20% crystalline API.

Based on case to case, risk associated with molecule (risk vs benefit), therapeutics index of drug (MDD), justifications can be reviewed to support biowaiver.

Research Gaps / Challenges

- **Reliability** & Accuracy of prediction for in-vitro methods / models
- Lack of Pool of PK Data and its correlation to in-vitro tests
- Multiple factors affecting bioavailability (varies)

Additional Methods / Models are welcomed

Acknowledgements

Acknowledgements

- Chris Edlin, Ph.D., VP, Product Development, Hikma pharmaceuticals USA Inc.
- Assessment Teams
- BASF

Thank You !