Evaluation of Acid Base Super-Solubilization Principle on Telmisartan to Lower Hot Melt Extrusion Temperature

By

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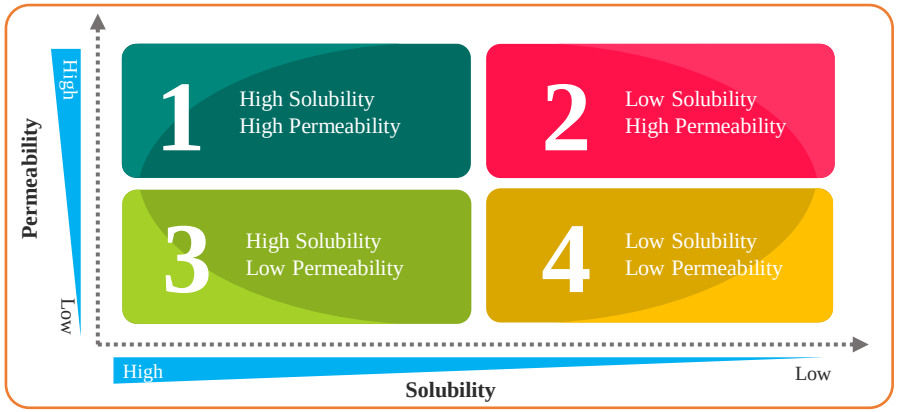
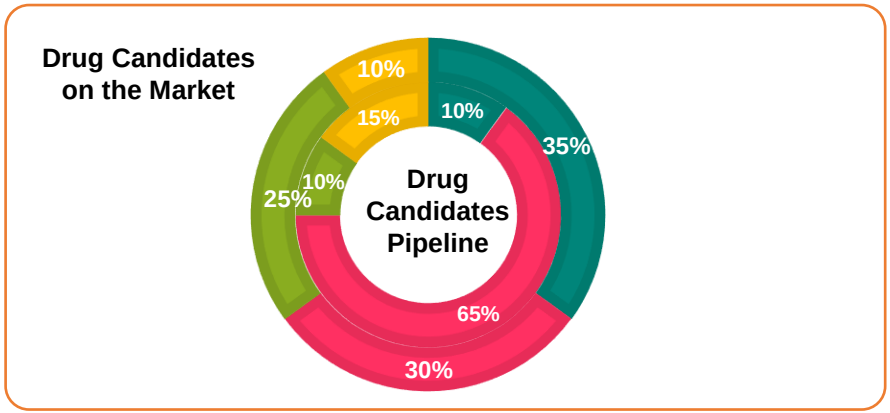
NEXT-GENERATION DELIVERY INNOVATIONS

Background-Solubility



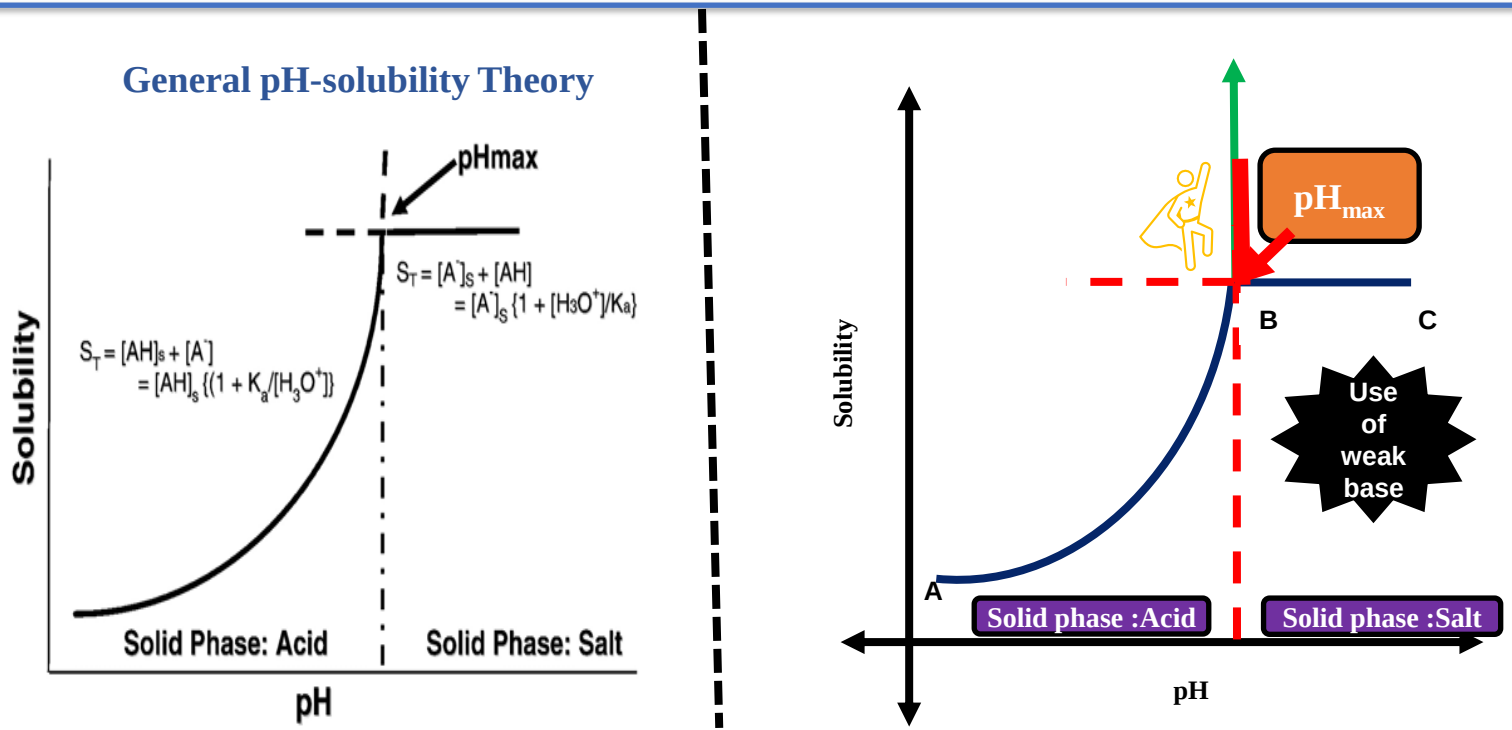


Solubility Enhancement

- ASD
- Solvent Composition
  - CoSolvent
  - pH
- Drug Carrier Systems
  - Cyclodextrins LDDS
  - Micelles Nanoparticles
- Miscellaneous
- Particle Size Reduction
- Chemical Modification
  - Prodrug
  - Salt

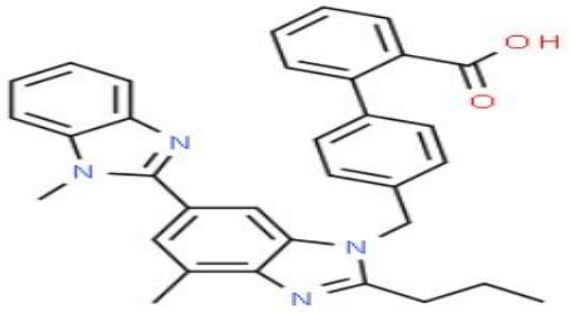
Hanada et al., Enhanced Dissolution of a Porous Carrier-Containing Ternary Amorphous Solid Dispersion System Prepared by a Hot Melt Method, J Pharm Sci. 2018; 107: 362-371

Acid-Base Super Solubilization Principle for Acidic Drugs



Singh, S., Parikh, T., Sandhu, H.K., Shah, N.H., Malick, A.W., Singhal, D., Serajuddin, A.T.M., 2013. Supersolubilization and amorphization of a model basic drug, haloperidol, by interaction with weak acids. Pharm Res 30, 1561–1573. https://doi.org/10.1007/s11095-013-0994-7

Telmisartan-Properties



Telmisartan

M.W-514.6
pKa -3.5, 4.1 & 6
M.P- 261-263 °C
Aq. Solubility ~0.1 µg/mL

Advantages

- Anti Hypertensive Drug- Angiotensin-II type 1 (AT1) receptor blocker
- Improved insulin sensitivity, mitochondrial activity & better endothelial function.
- Tmax-1-2 hrs.
- Long Half life-24hrs.(99% albumin bound)

Disadvantages

- Bioavailability 42%
- Most hydrophobic of all ARBs
- Very low solubility with dissolution rate limited absorption.
- BCS Class II drug
- pH dependent Solubility

Project Outline

Development of Rapid Release Acidic Drug

- Improve **Solubility**
- Prepare Stable ASD at **Low Processing Temperature.**
- **Enhance Dissolution Rate**

How ?

Feasibility of utilizing ABS Principle

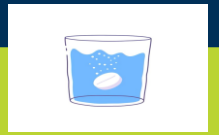
- pH Solubility Study as a function of meglumine

Evaluate Drug to Base Molar Ratio

- Preparation of Dry Solids.
- Characterization of Dry Solids by DSC and PXRD.
- Hot Stage Microscopy

ASD Preparation by HME

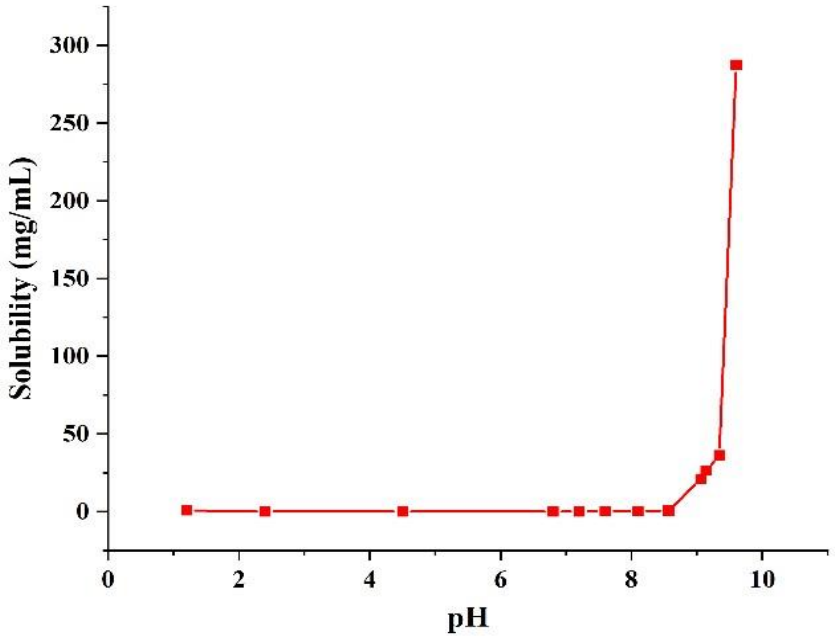
- Rheological Screening as pre-requisite for HME
- Hot Melt Extrusion of formulations.



Dissolution Rate Evaluation of Melt Extrudates

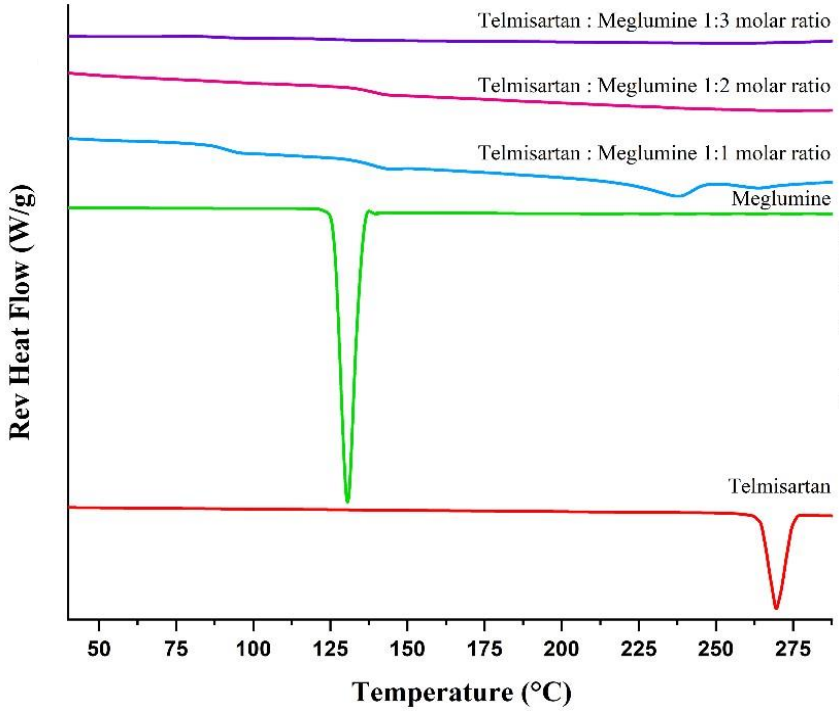
- Dissolution rate of extrudates of 1:2 MR and 1:3 MR

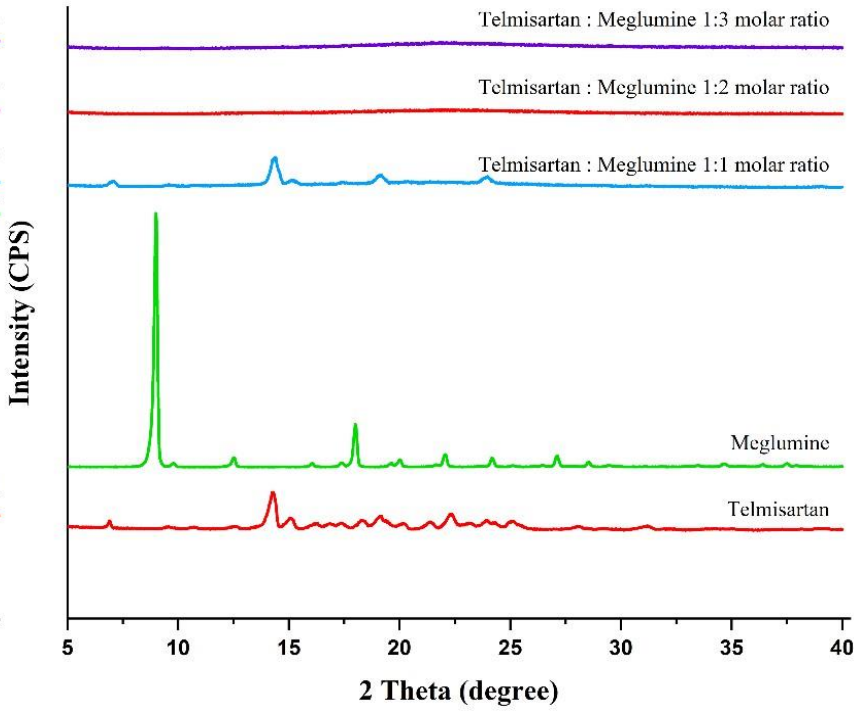
ABS Feasibility Evaluation-pH Solubility Study



pH	Solubility (mg/mL)
1.2	0.84
2.4	0.09
4.5	0.06
6.8	0.067
7.2	0.144
7.6	0.3
8.1	0.48
8.57	0.6
9.06	21.2
9.14	26.4
9.34	36.4
9.6	287.5

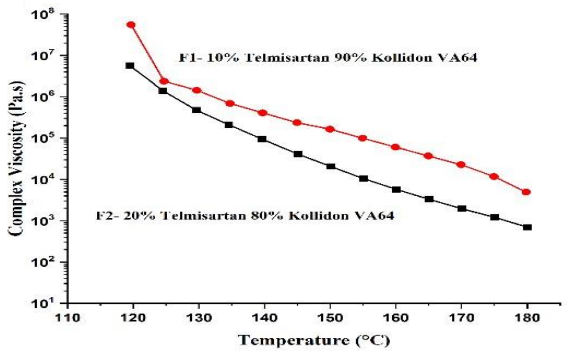
Dry Solid Characterization

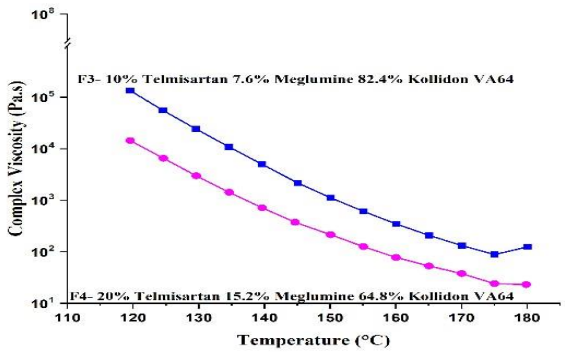


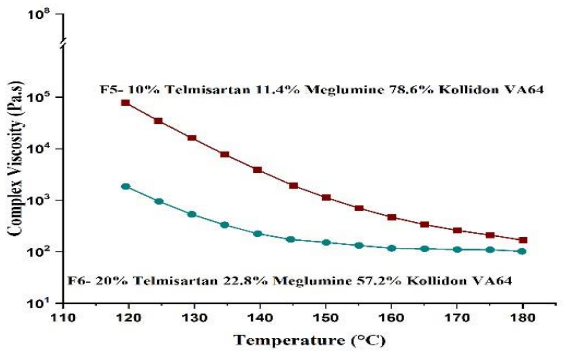


Melt Viscosity Evaluation & ASD Preparation

Formulation Number	Polymers used	Drug conc. (%w/w)	Meglumine conc (%w/w)	Polymer conc. (%w/w)	Extrusion Temperature (°C)	Drug: Meglumine Molar Ratio
F1	Kollidon® VA 64	10	-	90		
F2	Kollidon® VA 64	20	-	80	Could not be extruded as strands	
F3	Kollidon® VA 64	10	7.6	82.4	130	1:2
F4	Kollidon® VA 64	20	15.2	64.8	120	1:2
F5	Kollidon® VA 64	10	11.4	78.6	130	1:3
F6	Kollidon® VA 64	20	22.8	57.2	120	1:3

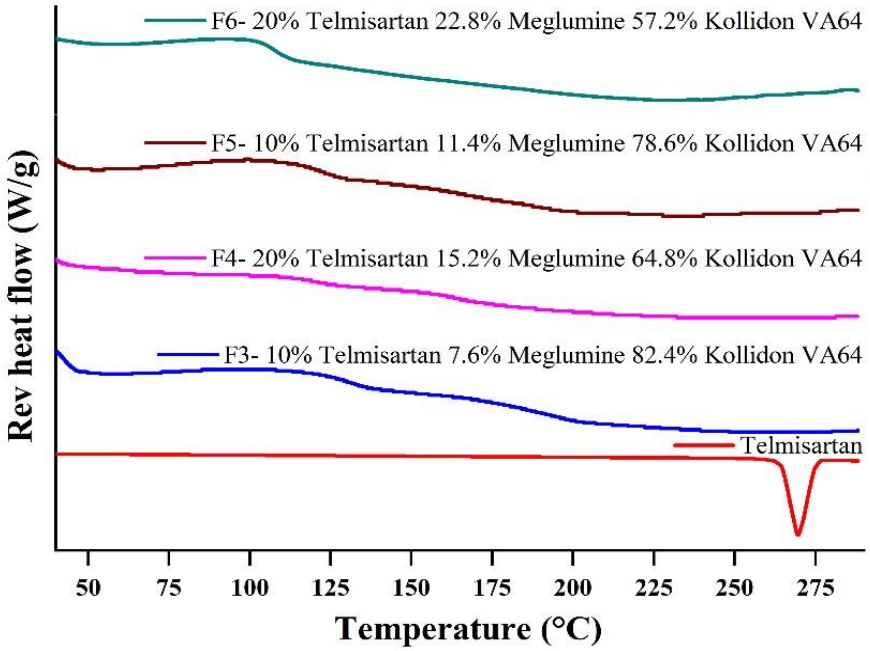


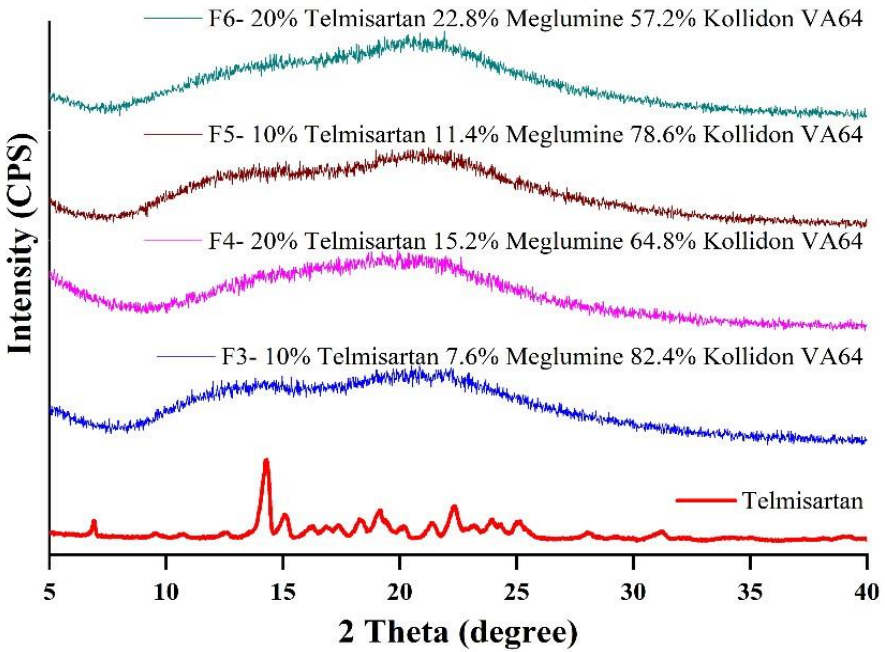




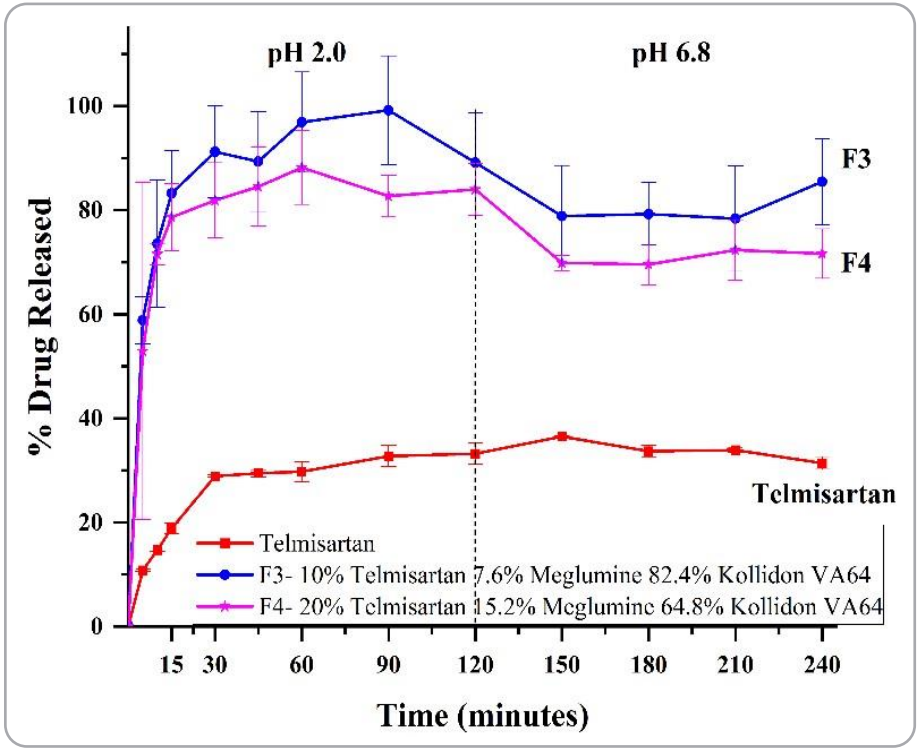
Ideal viscosity is 1,000-10,000 Pa.s

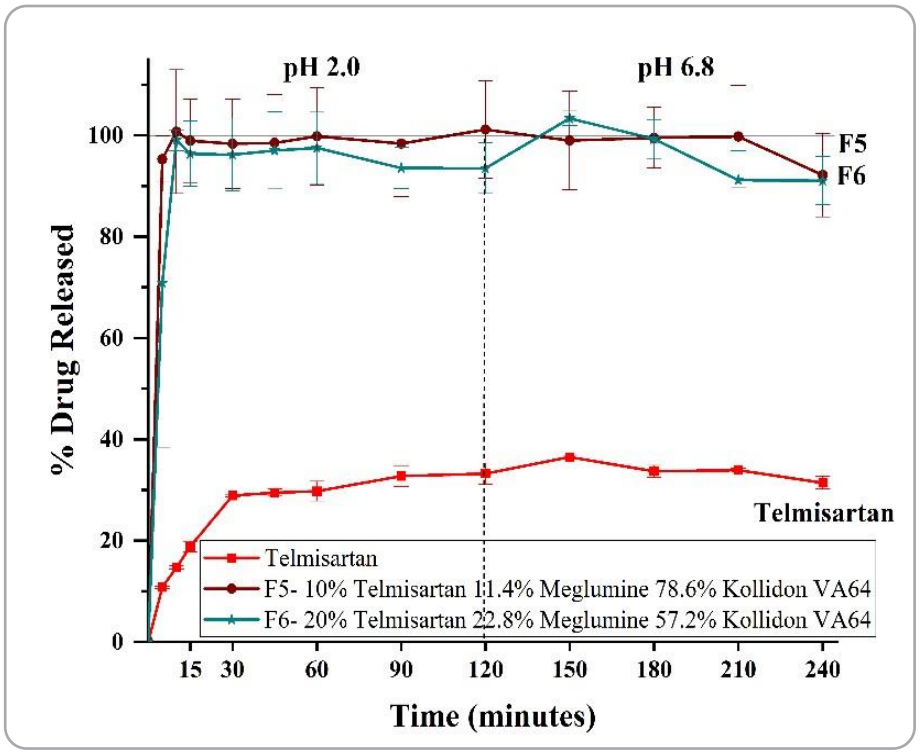
PXRD and DSC-Characterization



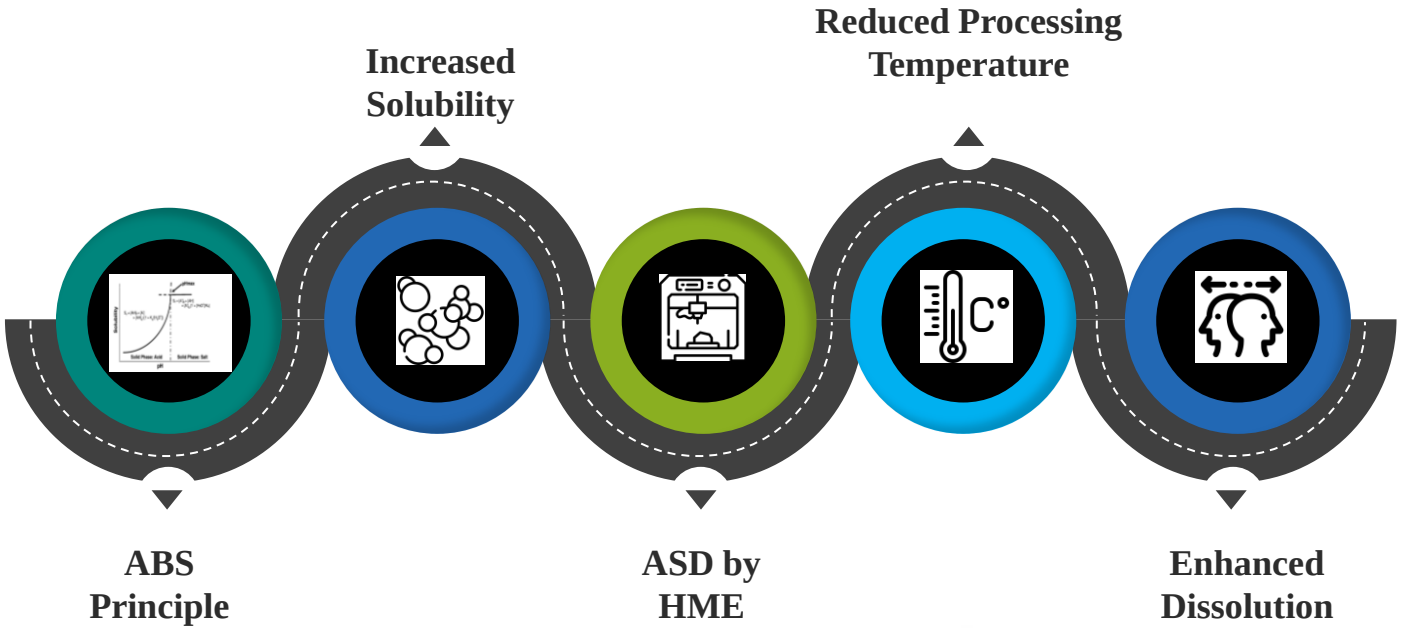


Drug Release Profile Evaluation





Conclusion


Increased Solubility
Reduced Processing Temperature
ABS Principle
ASD by HME
Enhanced Dissolution