FDA-MCERSI Workshop on Drug Dissolution in Oral Drug Absorption

Supersaturation via Acid-Base Interaction

Abu T. M. Serajuddin, Ph.D.

St. John's University, Queens, New York

E-mail: serajuda@stjohns.edu; Phone: 718-990-7822

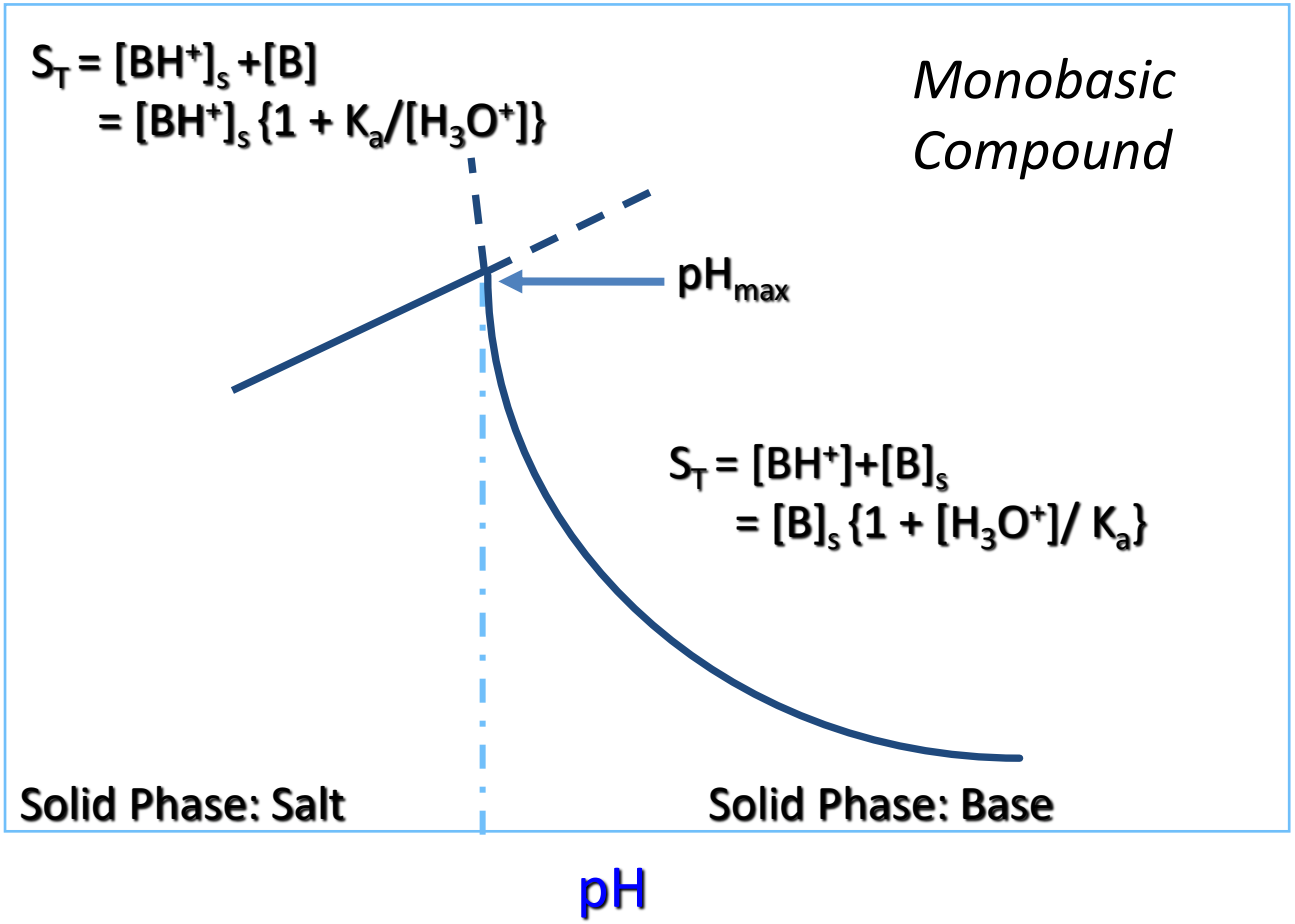
st. john's UNIVERSITY

Objectives:

- Describe Acid-Base Supersolubilization (ABS) Principle, with examples:
  - Haloperidol
  - Cinnarizine
  - Itraconazole
  - Flurbiprofen
- Application of ABS principle in dosage form development
- Drug dissolution

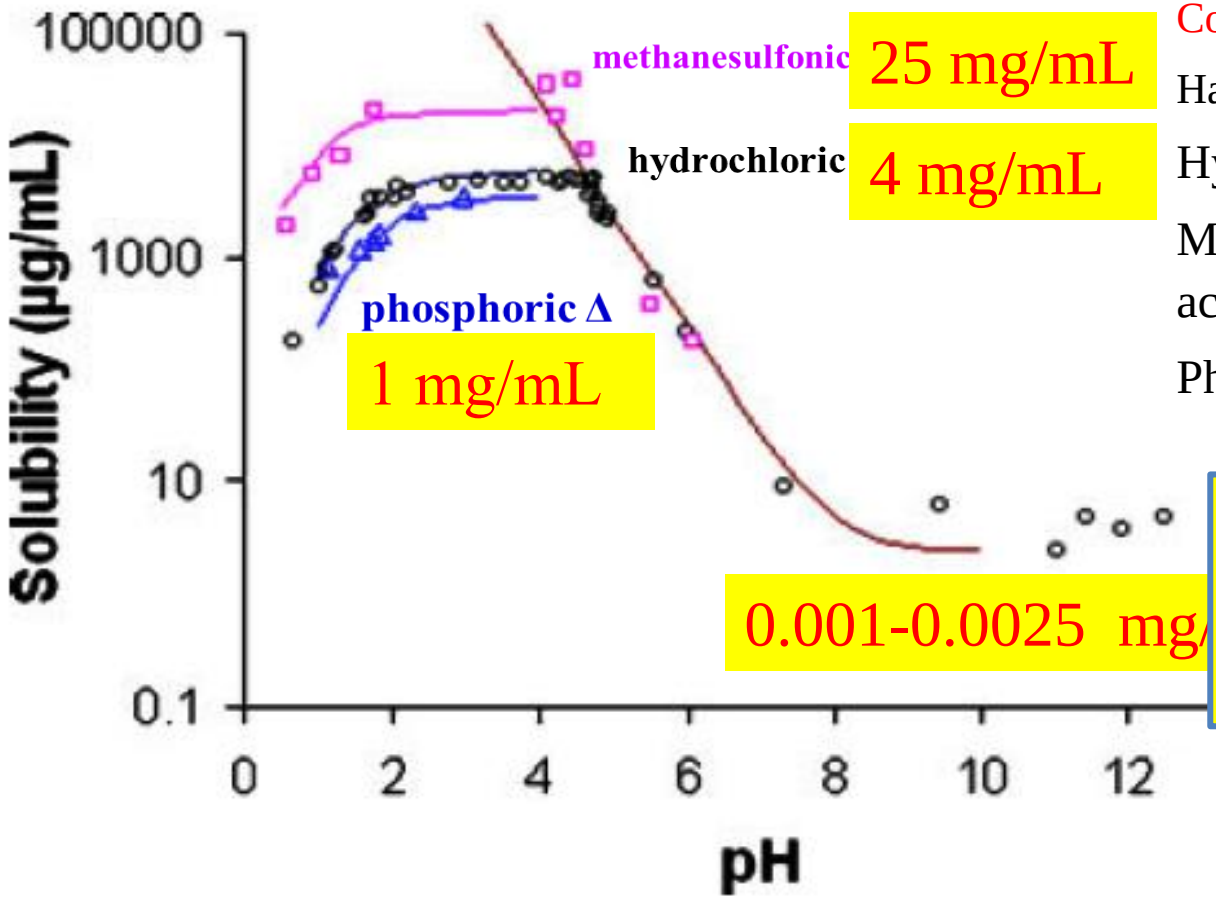
Effect of pH and pK_a on Solubility

General pH vs. Solubility Considerations



Ref: Kramer & Flynn, *J. Pharm. Sci.*, 61, 1896-1904,1972.

pH vs. Solubility Profiles of Haloperidol

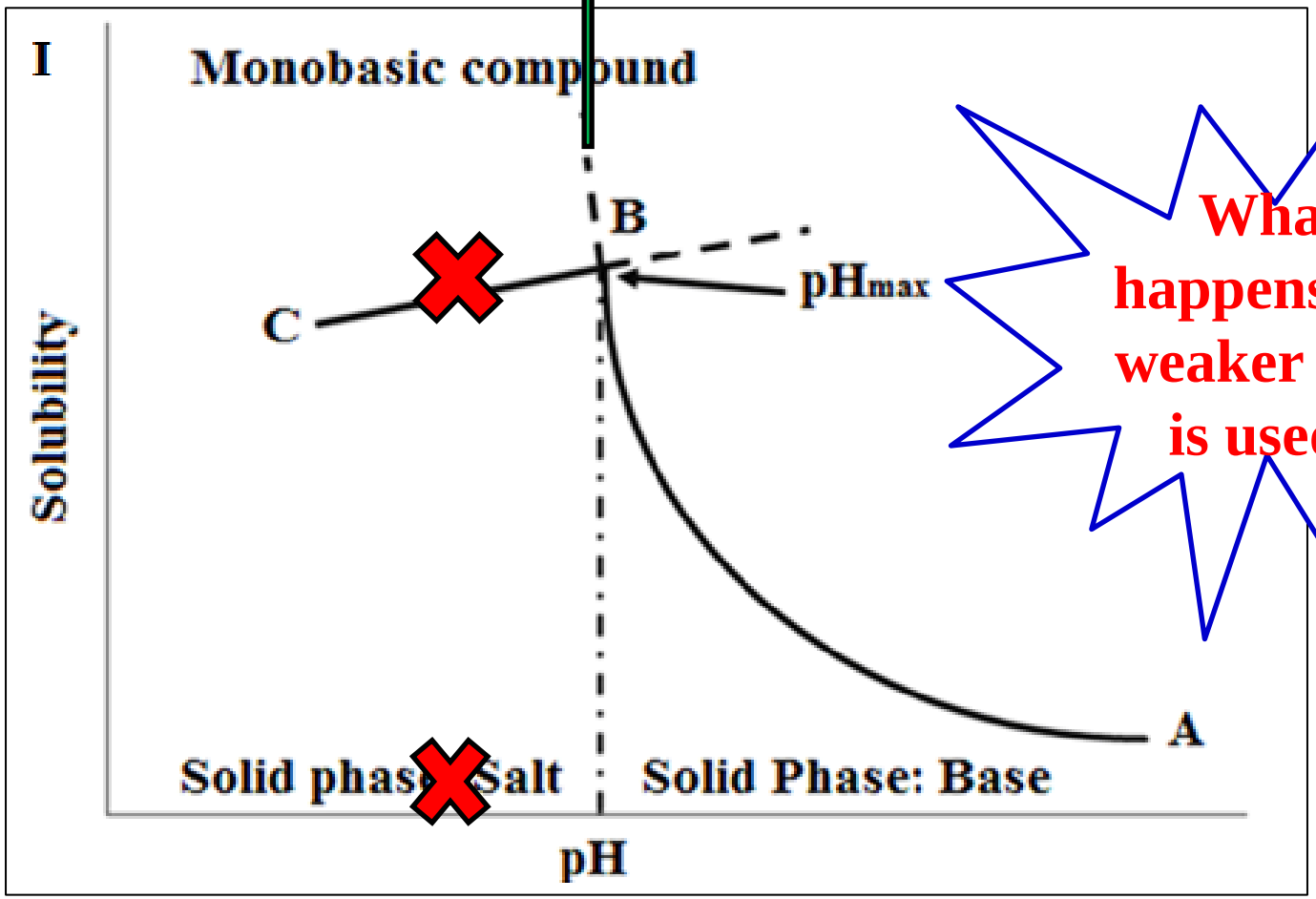


Counter-ion/drug	pKa
Haloperidol	8.6
Hydrochloric acid	-6.1
Mehanesulfonic acid	-1.2
Phosphoric acid	1.97, 6.82

NO SALT FORMED WITH WEAKER ACIDS

pH-solubility profile of haloperidol at 37 °C determined by using **methanesulfonic □, hydrochloric ○,** and **phosphoric Δ** acids to adjust pH

Acid-Base Supersolubilization Theory



What happens if a weaker acid is used?

$$S_T, \text{base}(\text{pH} > \text{pH}_{\text{max}}) = [\text{B}]_s + [\text{BH}^+] = [\text{B}]_s \left(1 + \frac{\text{H}_3\text{O}^+}{K_a}\right)$$

st. john's UNIVERSITY

Supersolubilization by Acid-base Interaction: Haloperidol Example

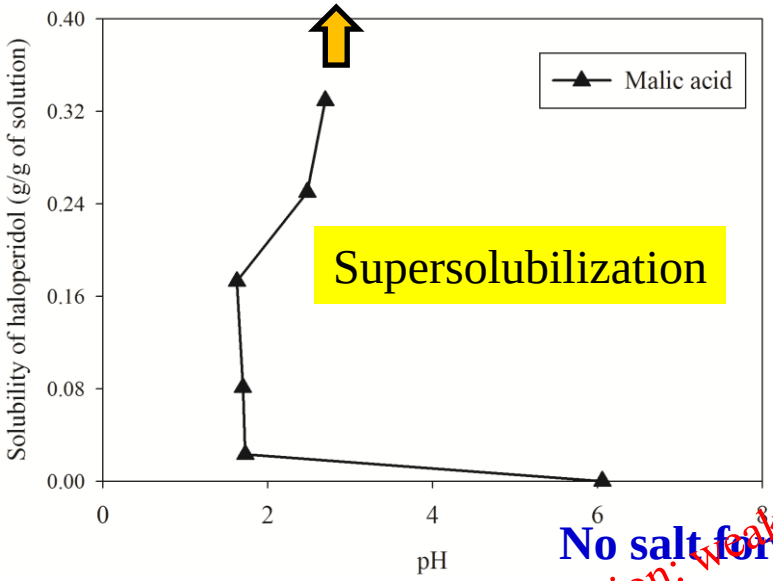
Singh et al., Supersolubilization and amorphization of a model basic drug, haloperidol, by interaction with weak acids, Pharm Res (2013) 30:1561-1573

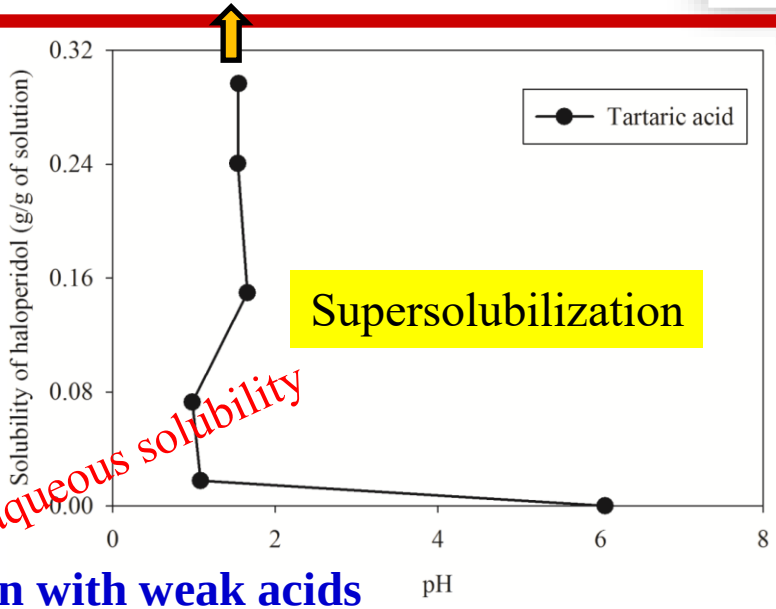
Materials

Name	Solubility in water (25 °C)	pKa	Molecular weight (g/mole)
Haloperidol	1 - 2.5 µg/ml	8.60	375.87
Citric acid monohydrate	1.65 g/g	2.91, 4.34, 5.68	210.14
Malic acid	1.25 g/g	3.25, 4.68	134.09
Tartaric acid	1.40 g/g	2.79, 3.90	150.09

References:
Avdeef A, 2012 (book)
Li et al., J Pharm Sci 2005;94:2224-2231
Singh et al., Pharm Res 2013;30:1561-1573

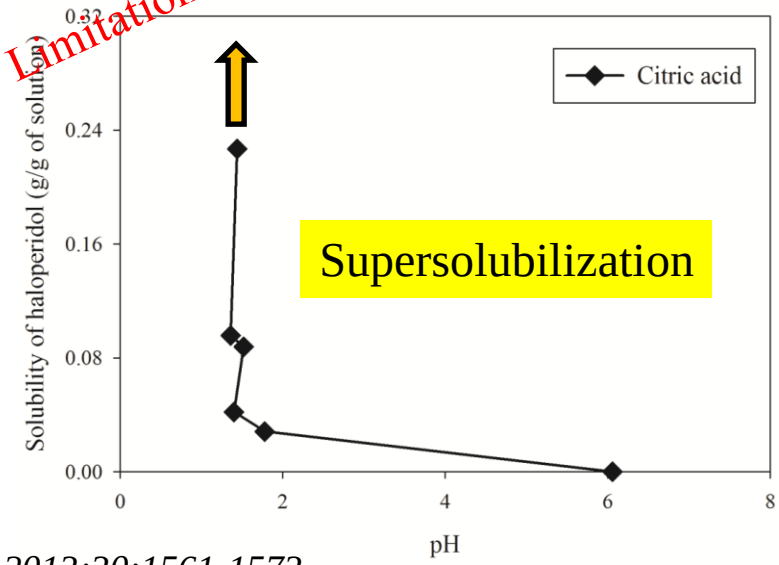
Supersolubilization of Haloperidol by Weak Acids





Limitation: weak acid aqueous solubility

No salt formation with weak acids

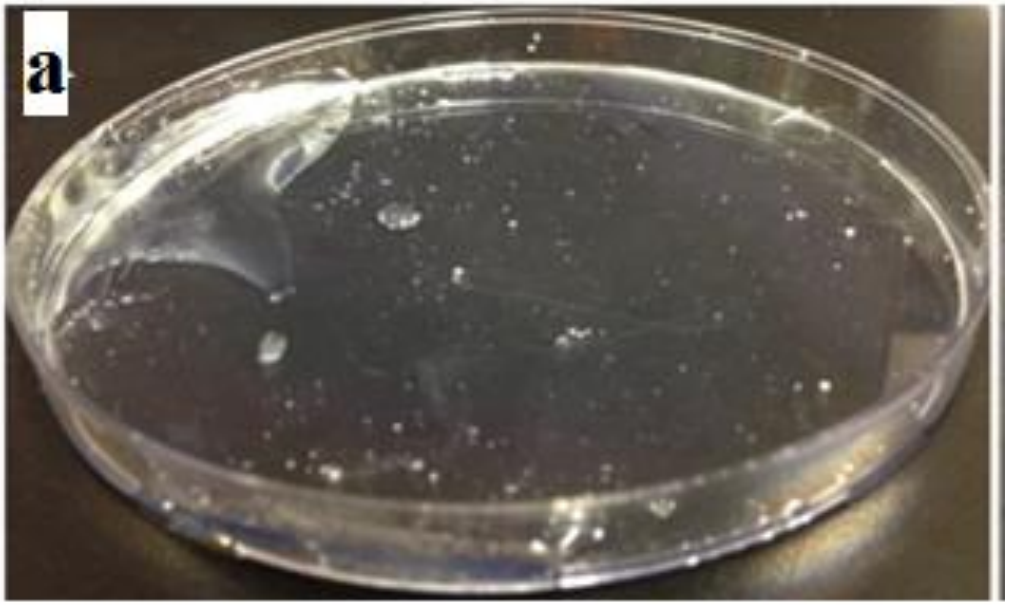


300,000-500,000 times higher solubility as compared to intrinsic solubility (2.5 µg/ml)

Solubility of haloperidol HCl salt at pH 2 is 4 mg/ml

Reference: Singh et al., Pharm Res 2013;30:1561-1573

Issues with Conversion to Amorphous Solid Dispersions (Dry Materials)

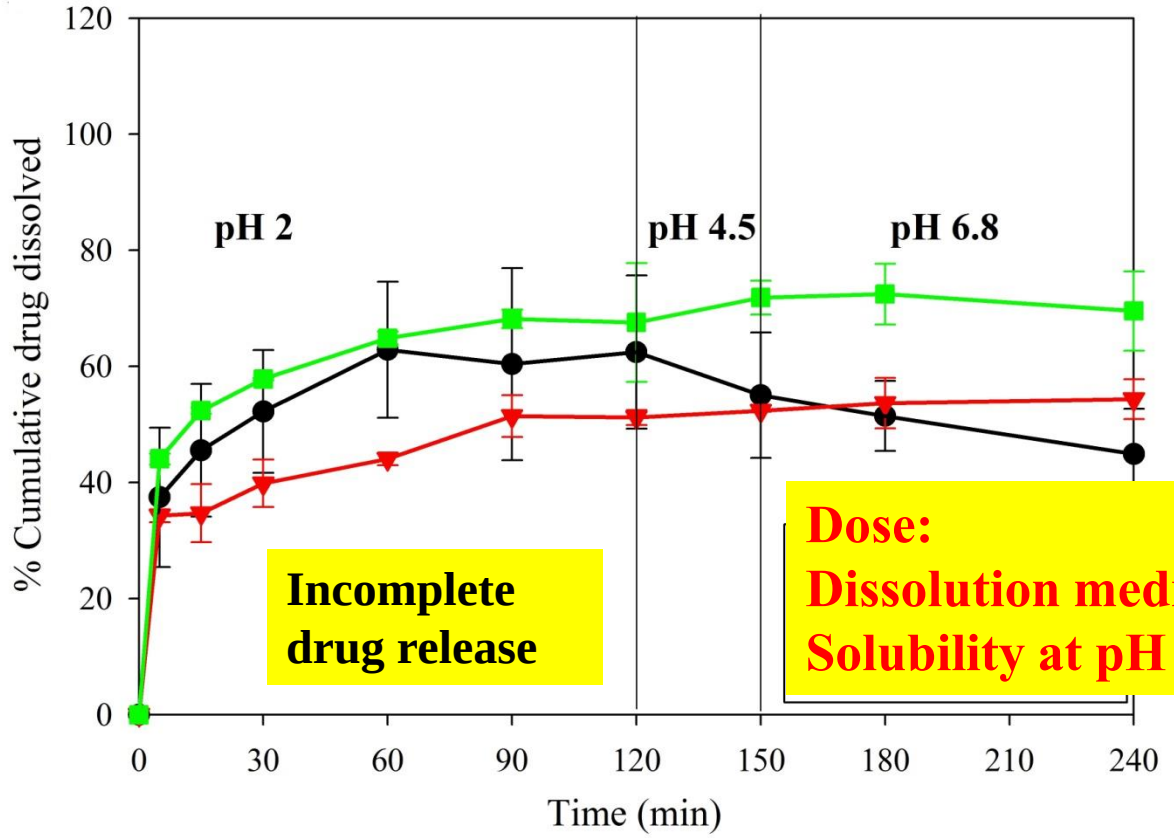


Haloperidol-malic acid (0.81:1 w/w, molar ratio 0.29:1) solid dispersion

- Amorphous solid dispersions formed; sticky and gummy in nature
- Difficult to process them into tablets or powder filled capsules
- Incomplete drug release

Multi-step Dissolution of Amorphous Solid Dispersions

0.15 g haloperidol present in each formulation



Dissolution parameters

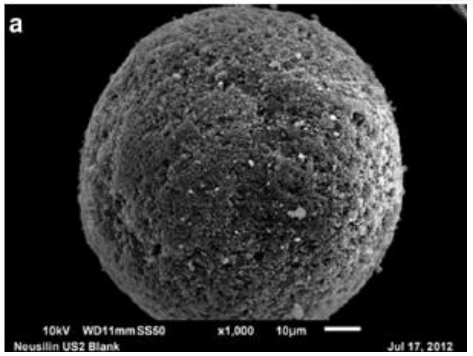
- USP Apparatus II
- 50 RPM, 37ºC
- 250 ml media
- 00 size hard gelatin capsules

Dose: 150 mg
Dissolution medium: 250 mL
Solubility at pH 6.8: 2 to 3 µg/mL

Reference : Singh et al., Pharm Res 2013;30:1561-1573

Enhance Processability of Haloperidol-weak acid Solid Dispersions

Neusilin® US2



- High surface area (~300 m^2/ g)
- Amorphous microporous granules
- High liquid loading capacity
- Widely explored for loading of liquid microemulsion preconcentrates

Haloperidol-weak acid solution in water

Neusilin® US2

Blending

Vacuum drying for 24 h

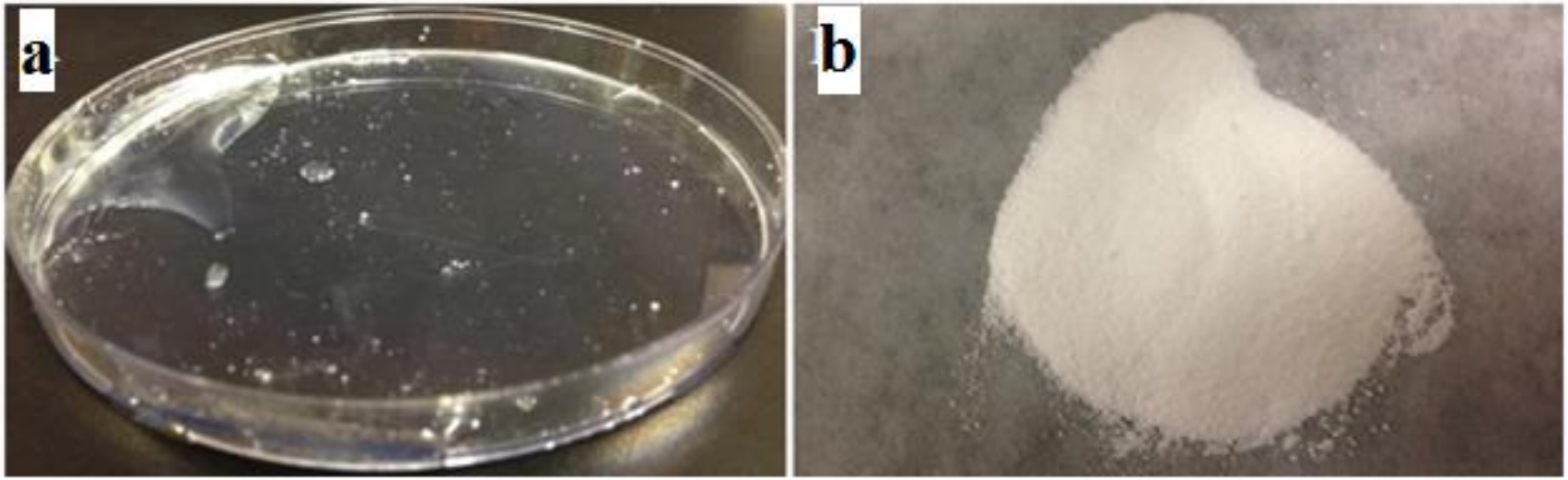
Optimized ratio: (Haloperidol-weak acid) to Neusilin® US2 is 1.5:1 w/w

References:
Fuji Chemical Industry Co. http://www.neusilin.com/product/general_properties.php.
Gumaste et al., Pharm Res 2013a;30:3170-3185
Gumaste et al., Pharm Res 2013b;30:3186-3199

Solid Dispersions After Loading onto Neusilin® US2

ST. JOHN'S UNIVERSITY

Haloperidol-Malic acid (0.81:1 w/w)

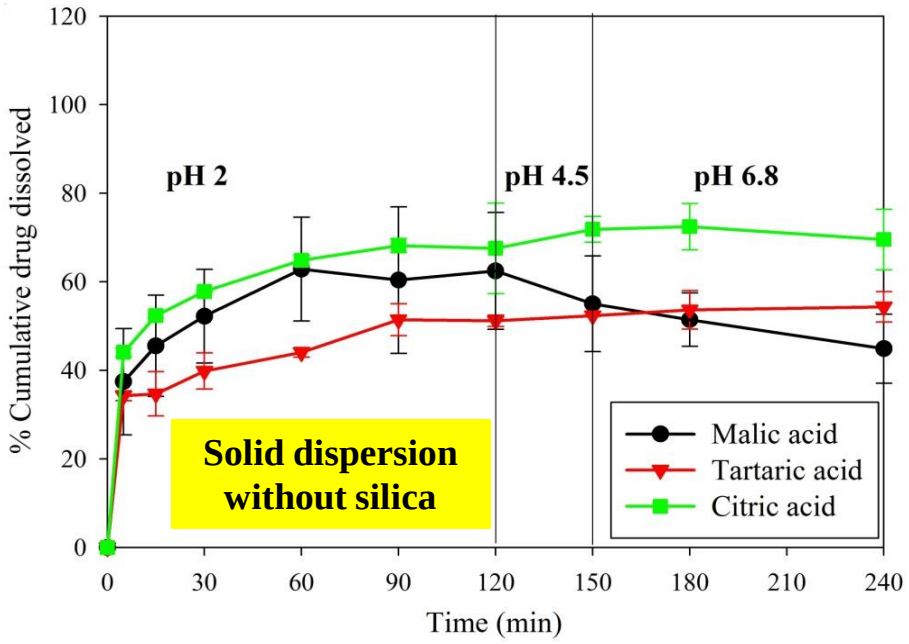


Solid dispersion without Neusilin® US2

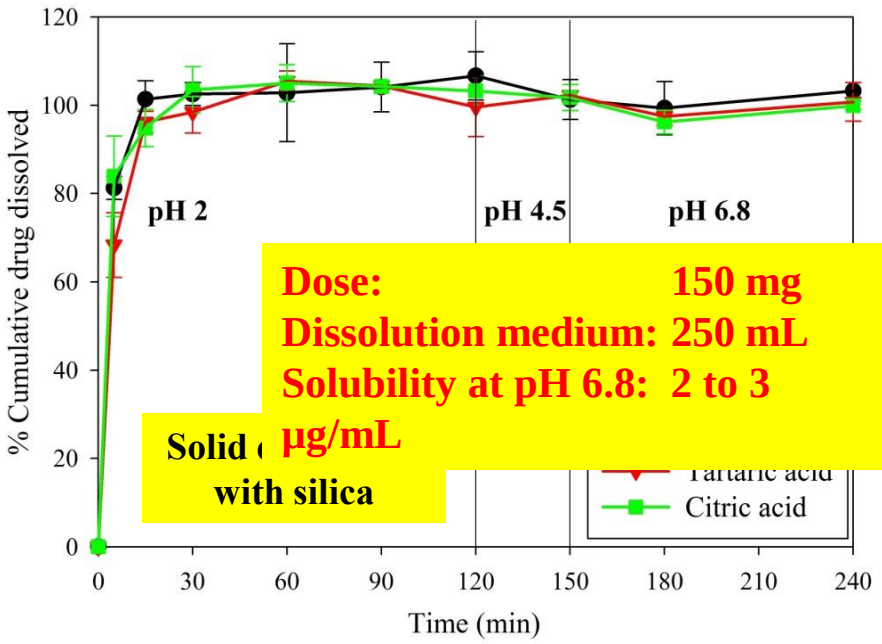
Solid dispersion with Neusilin® US2

Solid dispersions loaded onto Neusilin® US2 were free-flowing, amorphous powders

Complete Drug Release from Solid Dispersion with Silica



Incomplete drug release from capsules



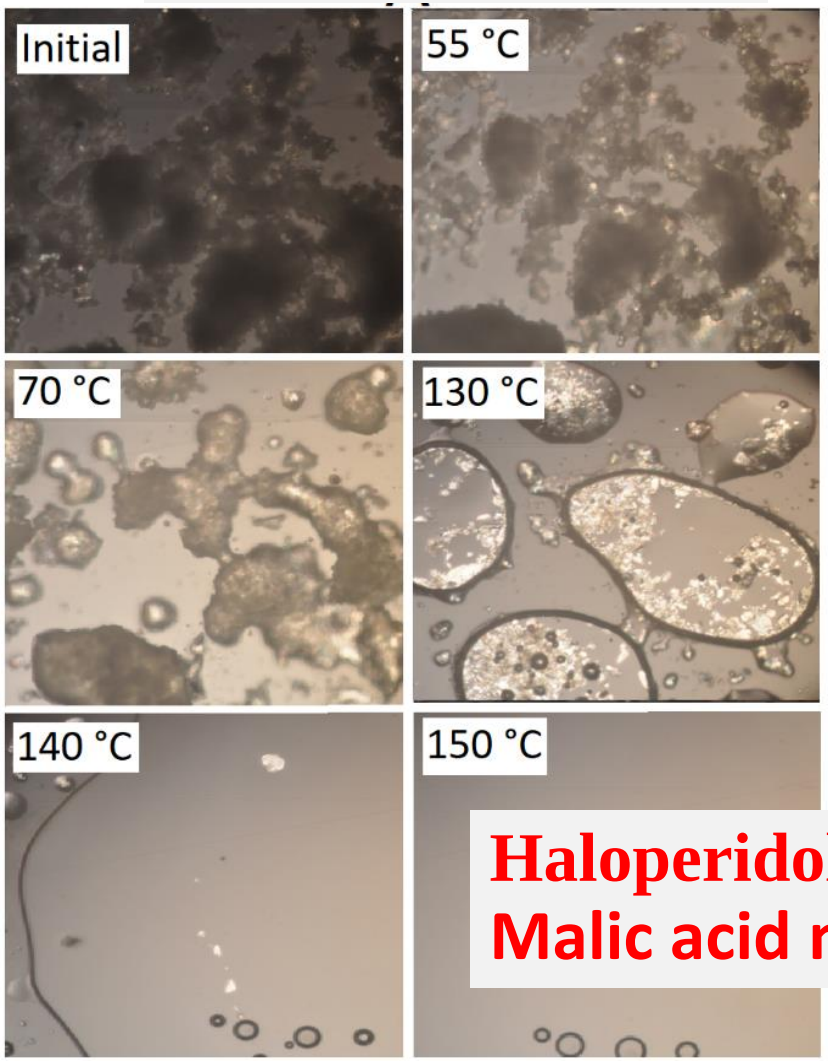
Complete drug release from tablets

Reference: Shah A, Serajuddin ATM., Int J Pharm 2015;484:172-180

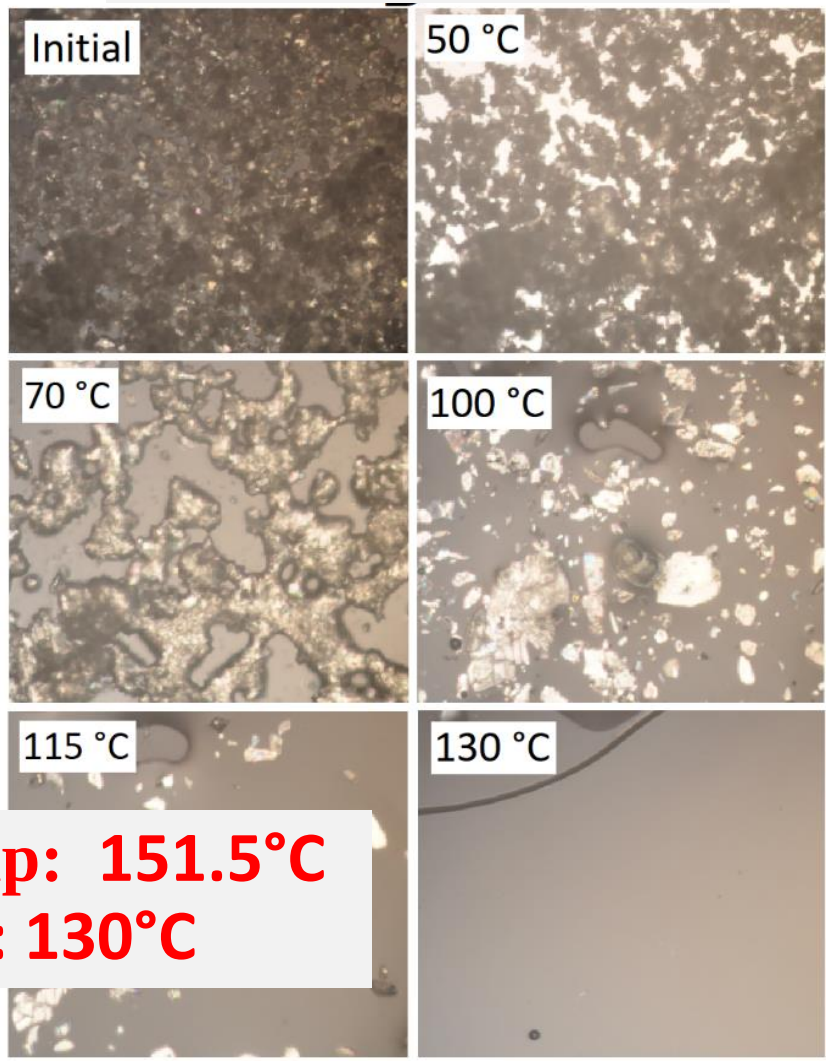
Acid-Base Interaction in Absence of Water (Haloperidol:Malic Acid Mixture)

ST. JOHN'S UNIVERSITY

1:1 molar ratio

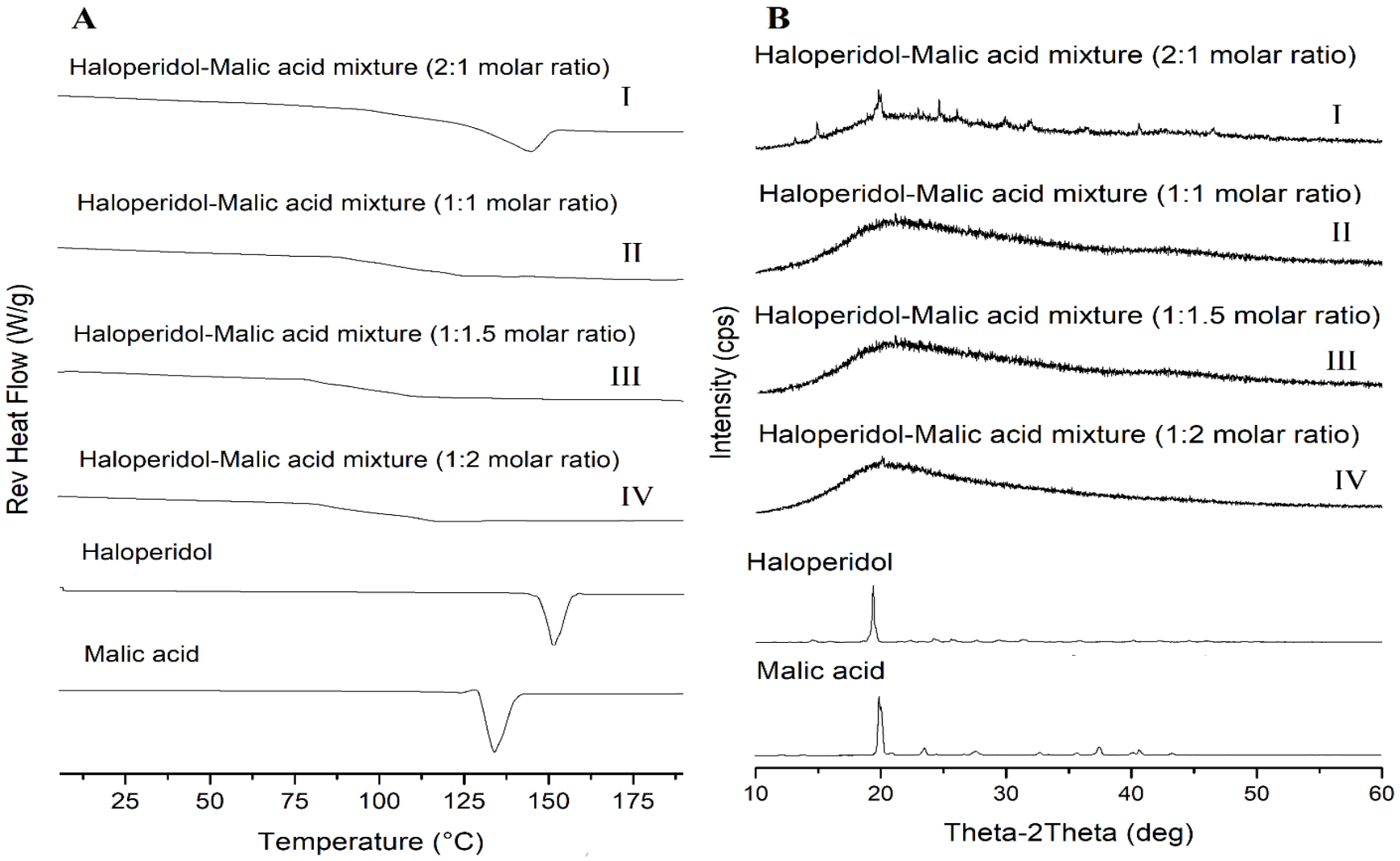


1:2 molar ratio



Haloperidol mp: 151.5°C
Malic acid mp: 130°C

High Miscibility in Solid State (Malic Acid Example



Melt Extrusion and FDM 3D Printing (Malic Acid Example)

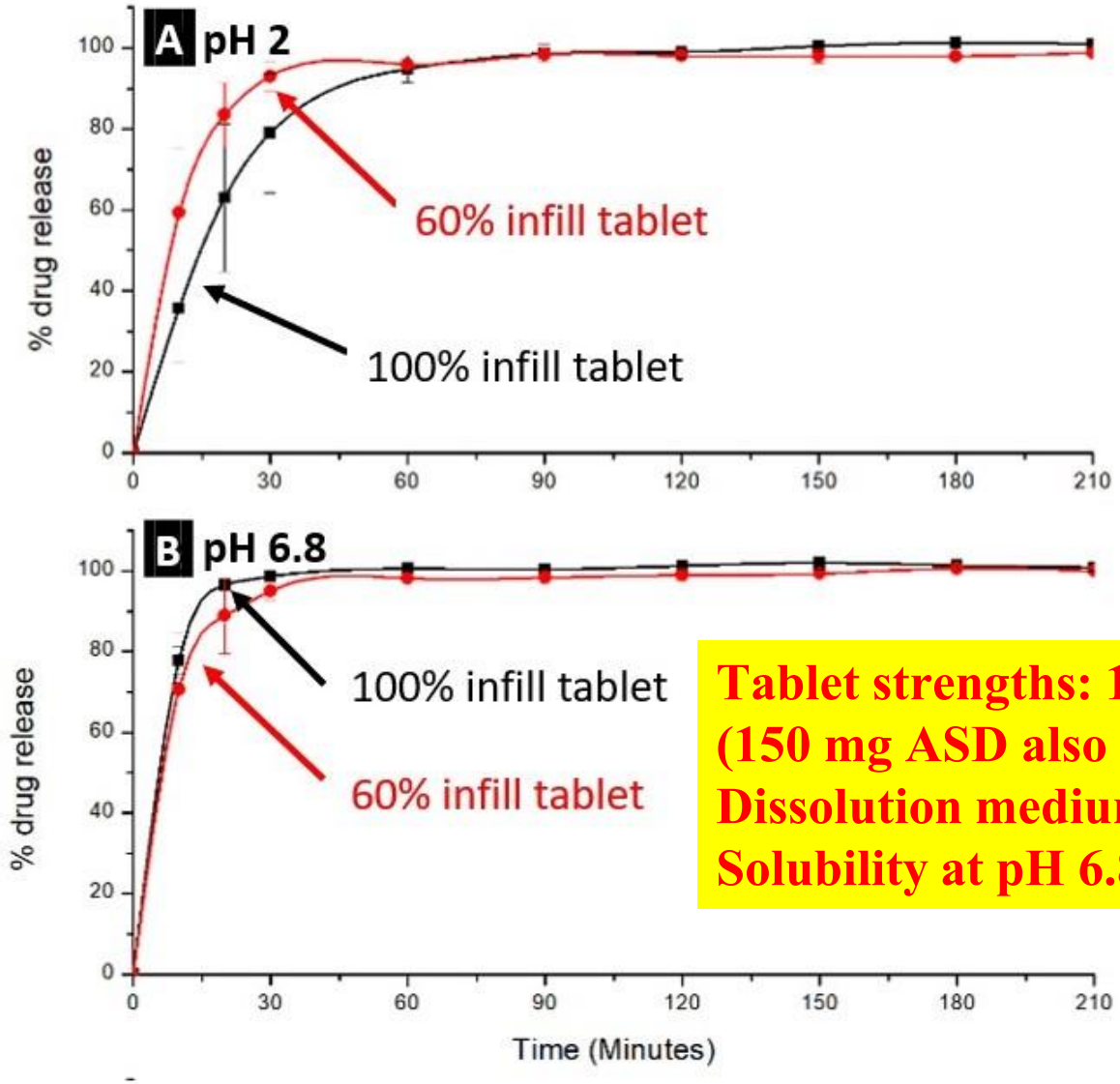
- Limited Drug-Polymer Miscibility (20% and less)
- High Drug Load by Acid-Base Interaction
- Lower Temperature Extrusion for ASDs
- Low Temperature 3D Printing Possible

Kollidon® VA64 (%w/w)				3D Printing (°C)
100				Too brittle
90				Too brittle
80	20	-	150	Too brittle
79.6	15	5.4	120	125
59.3	30	10.7	120	100
45.7	40	14.3	120	Too brittle
32.2	50	17.8	120	Too brittle
74.3	15	10.7	120	125
48.6	30	21.4	100	100
31.5	40	28.5	120	Too soft
14.3	50	35.7	120	Too soft

Rapid and Complete Drug Release from FDM 3D-printed Tablet

ST. JOHN'S UNIVERSITY

15% Haloperidol + 10.5% Glutaric Acid + 74.5% Kollidon VA64



Tablet strengths: 12 & 48 mg
(150 mg ASD also used separately)
Dissolution medium: 250 mL
Solubility at pH 6.8: 2 to 3 µg/mL

Haloperidol Supersolubilization

A novel organic solvent-free approach

Solubility of haloperidol using weak acids: >300 mg/g of solution

Can be converted to amorphous solid dispersion

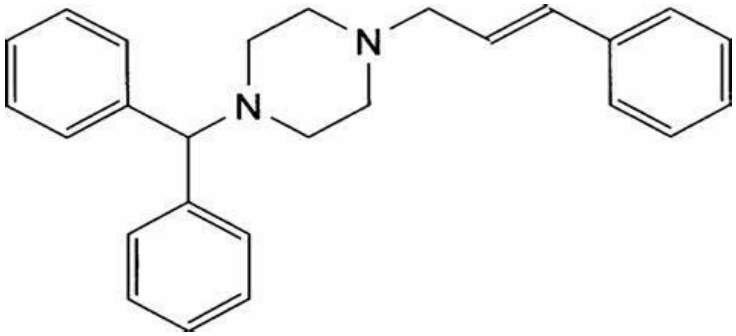
Weak acids act as carrier and pH modifier to increase drug dissolution rate

st. john's UNIVERSITY

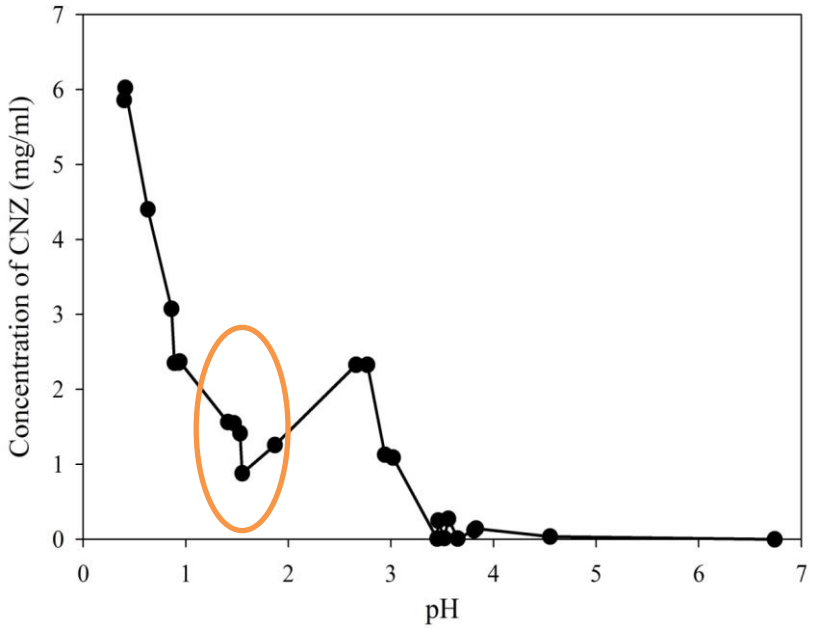
Super-solubilization by Acid-base Interaction:

Cinnarizine Example

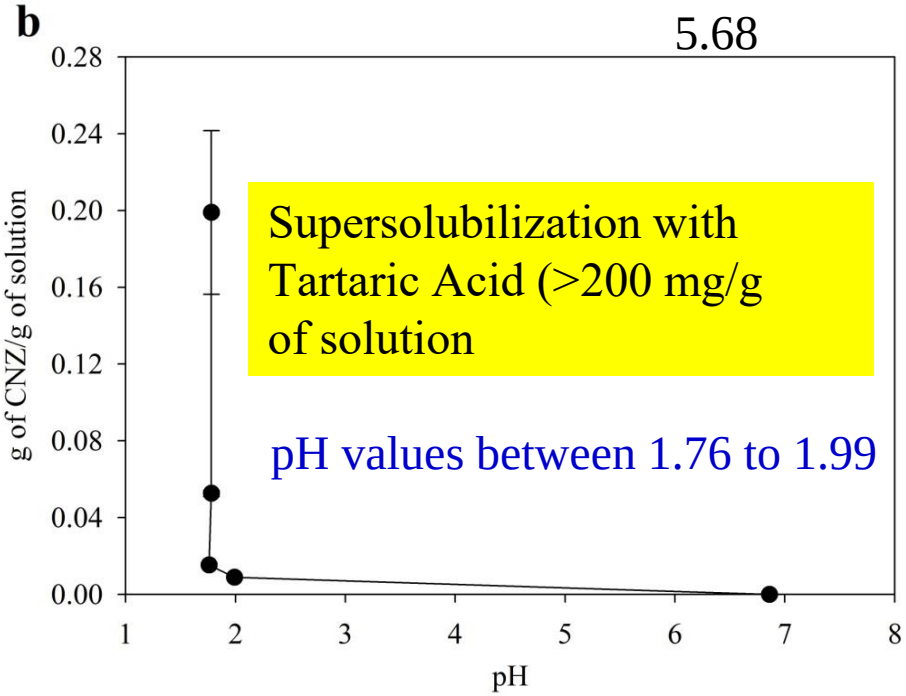
Cinnarizine pH-Solubility Profiles



Counter-ion/drug	pKa
Cinnarizine	2.55, 7.69
Malic acid	3.25, 4.68
Tartaric acid	2.79, 3.90
Citric acid	2.91, 4.34, 5.68

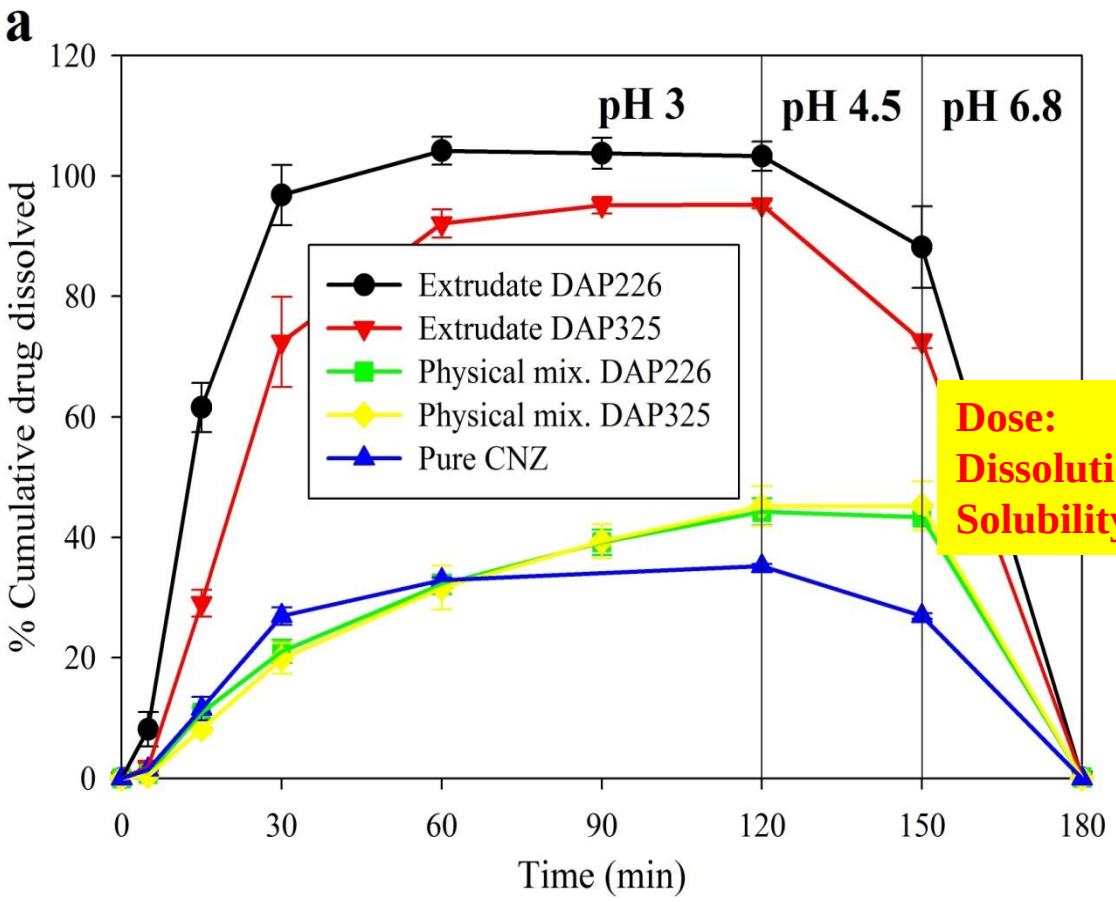


Maximum solubility with HCl at pH 1 to 2 is 1-2 mg/ml



Maximum solubility achieved at pH 1 to 2 is 240 mg/g with tartaric acid

Step Dissolution of Cinnarizine ASD with Malic Acid and Polymer Prepared by HME



Ternary Solid Dispersions Prepared

Drug (D): Cinnarizine
Weak acid (A): Malic acid
Polymer (P): Kollidon 30

Dose: 150 mg
Dissolution medium: 250 mL
Solubility at pH 6.8: <1 µg/mL

…all formulation

Dissolution parameters

- USP Apparatus II
- 50 RPM, 37ºC
- 250 ml media

Extrudates (solid dispersions) achieved ~*3* and *2* times higher dissolution as compared to pure CNZ and physical mixtures, respectively

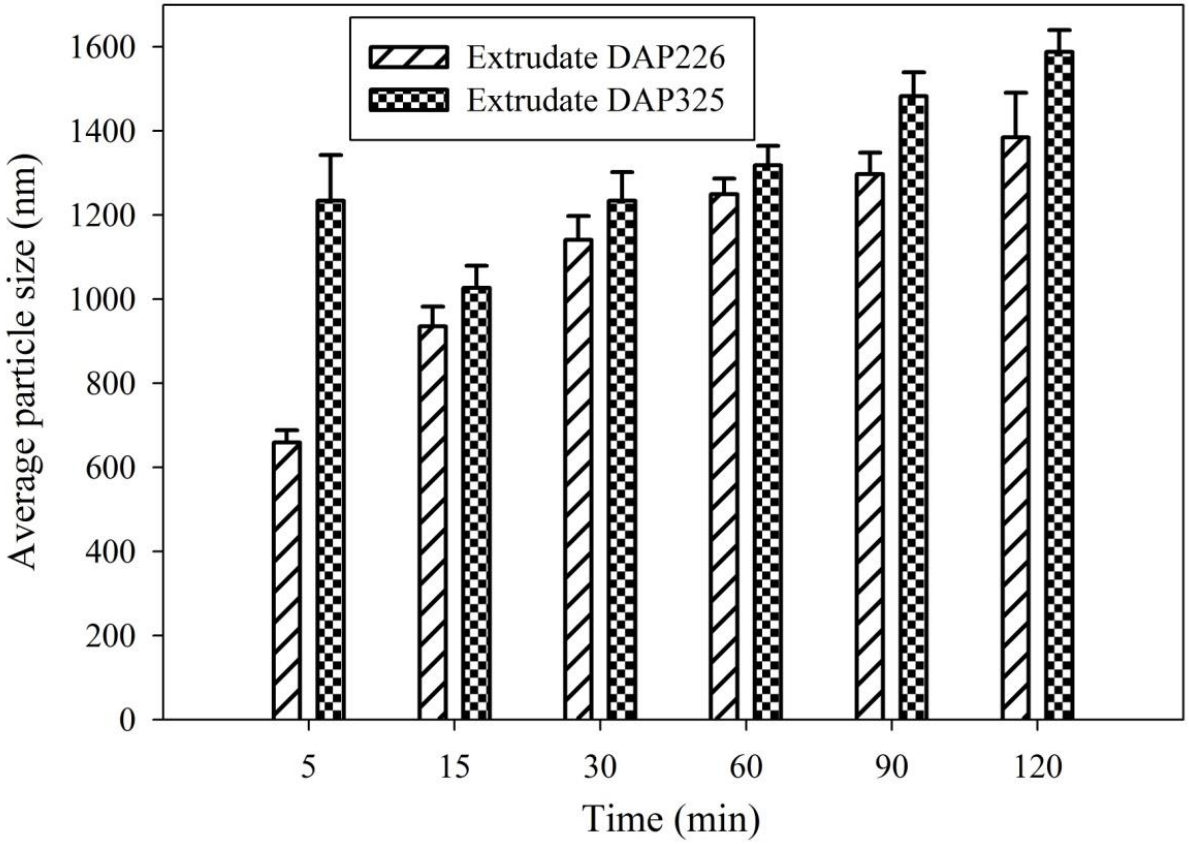
In situ Nanoparticles in pH 6.8 Media

ST. JOHN'S UNIVERSITY

Ternary Solid Dispersions

Cinnarizine/Malic acid/Kollidon 30 (2:2:6 and 3:2:5 w/w)

Cinnarizine is insoluble in pH 6.8 buffer (<0.5 µg/ml)



In-situ Nanoparticles Formed

20% drug load vs 30% drug load

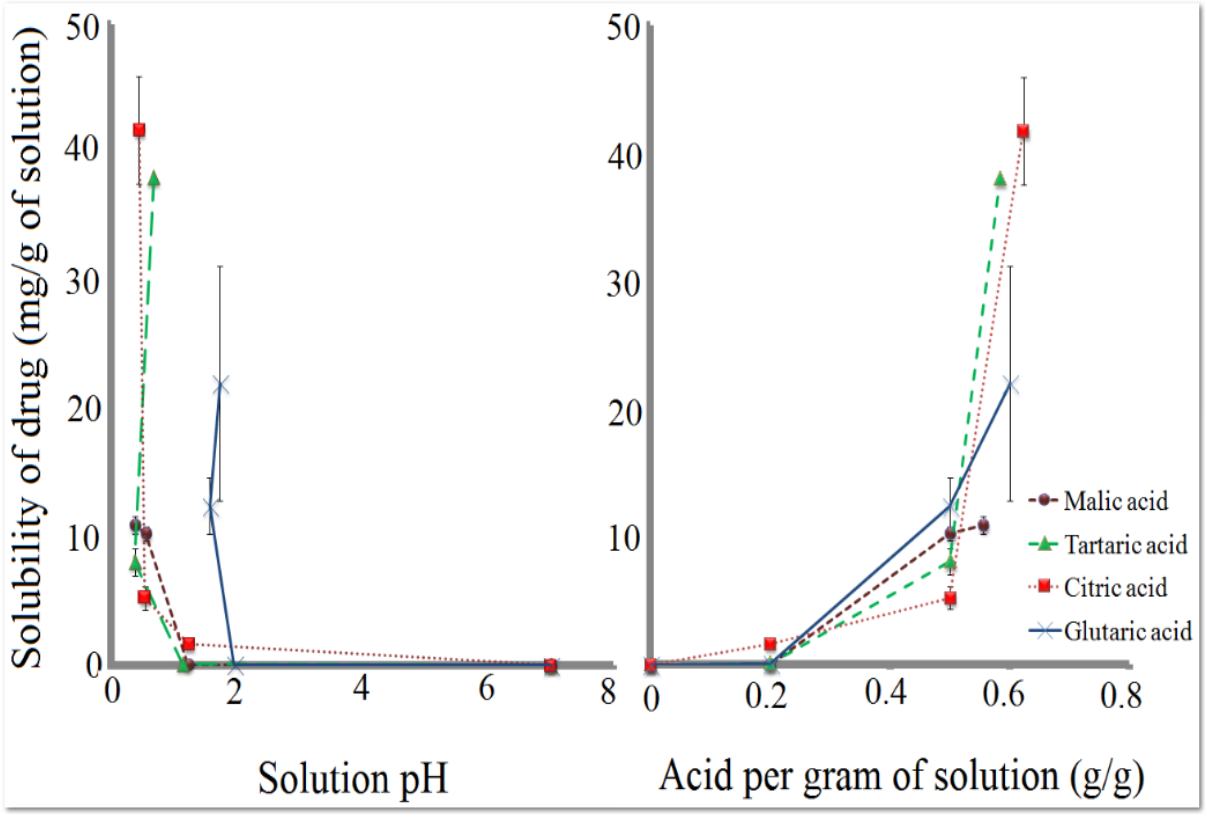
st. john's UNIVERSITY

Super-solubilization by Acid-base Interaction:

Itraconazole Example

Supersolubilization of Itraconazole

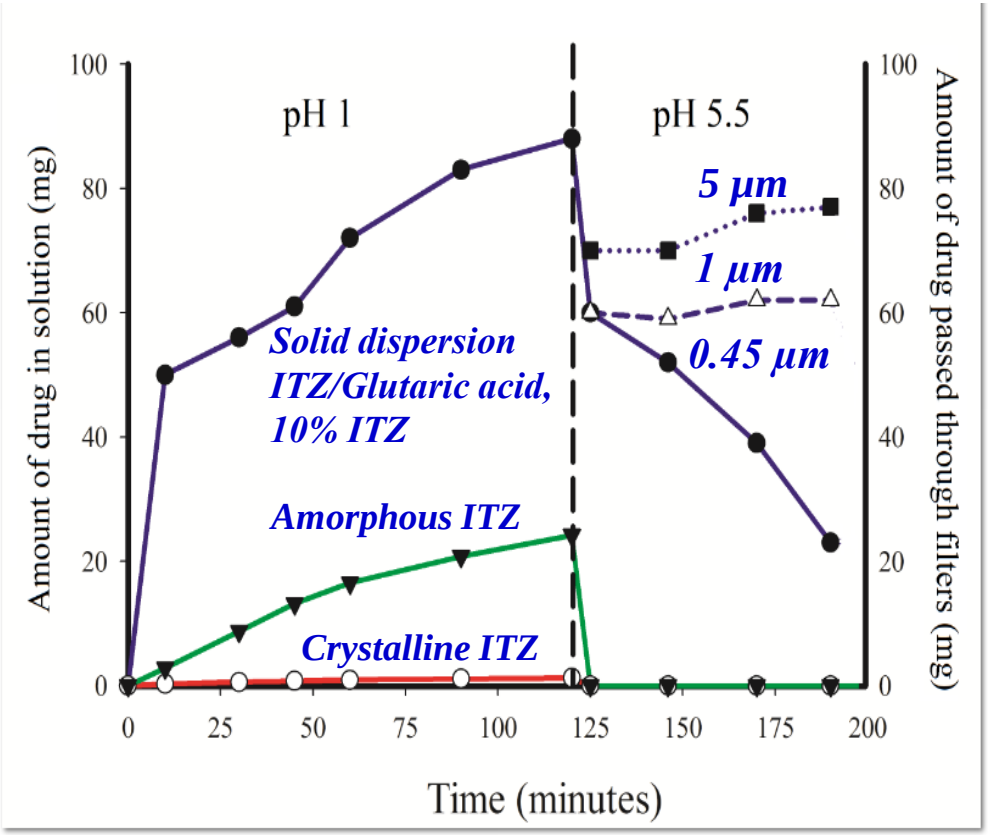
Itraconazole is one of the lowest water-soluble drugs in the market:
Aqueous solubility of itraconazole is ~4 ng/ml
At pH 1, the solubility increases to ~4 µg/ml



pKa values
Itraconazole 3.7
Citric acid 2.91, 4.24, 5.68
Malic acid 3.25, 4.68
Tartaric acid 2.79, 3.90
Glutaric acid 4.4, 5.4

Reference: Parikh and Serajuddin et al., Pharm. Res. 2016; 33: 1456-1471

Step-Dissolution at pH 1 and 5: Itraconazole/Glutaric Acid Solid Dispersions



All tablet formulations 100 mg ITZ, 20% Kollidon CL

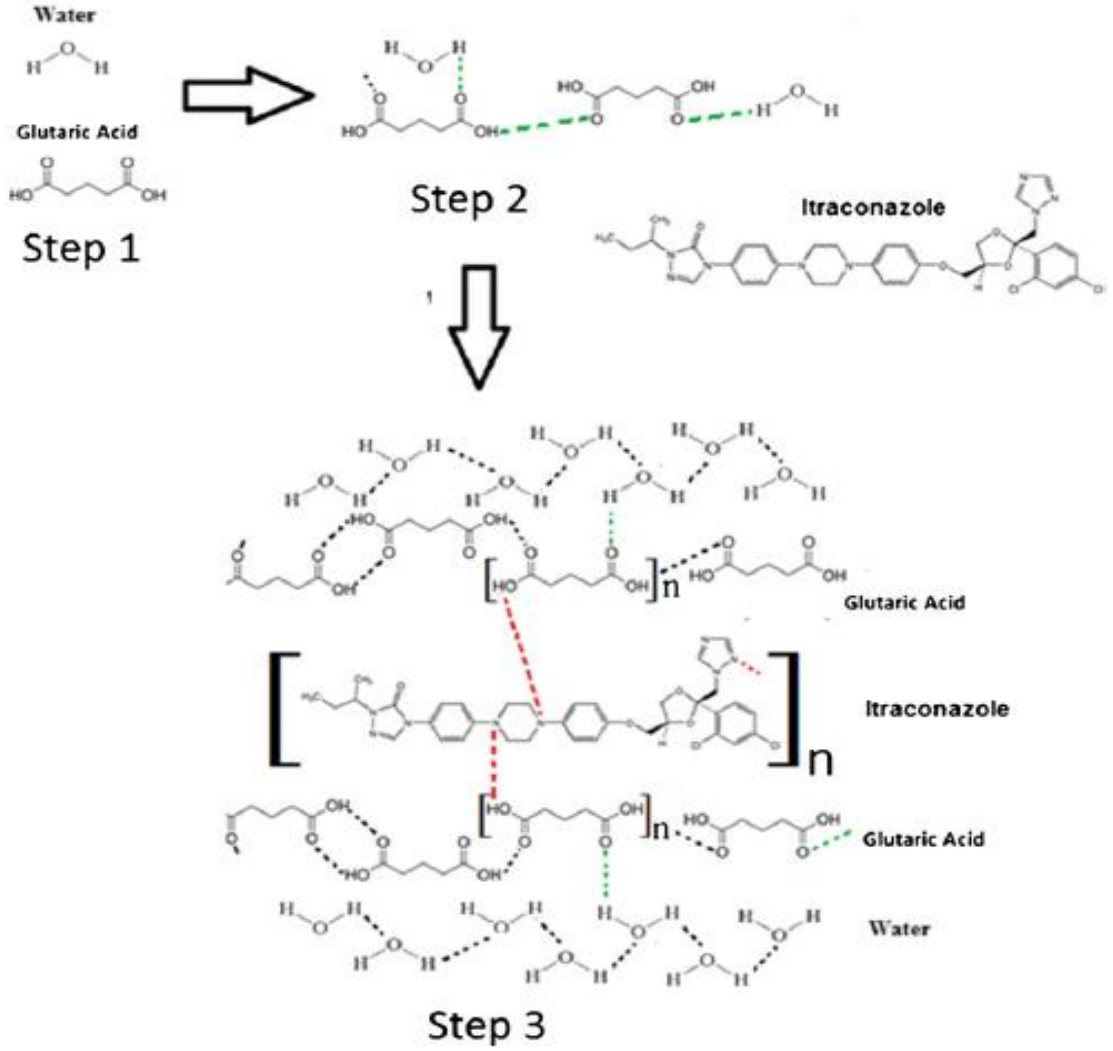
Dose: 100 mg
USP II Apparatus
250 mL
75 rpm

Different filters were used at pH 5.5 to determine particle size

Aqueous solubility of itraconazole is ~4 ng/ml
At pH 1, the solubility is~4 µg/ml

Reference: Parikh and Serajuddin et al., Pharm. Res. 2016; 33: 1456-1471

Proposed Mechanism of Interaction Between Itraconazole and Glutaric Acid



Possible H-bond Interactions between N atom of ITZ and -OH of the carboxyl group in glutaric acid

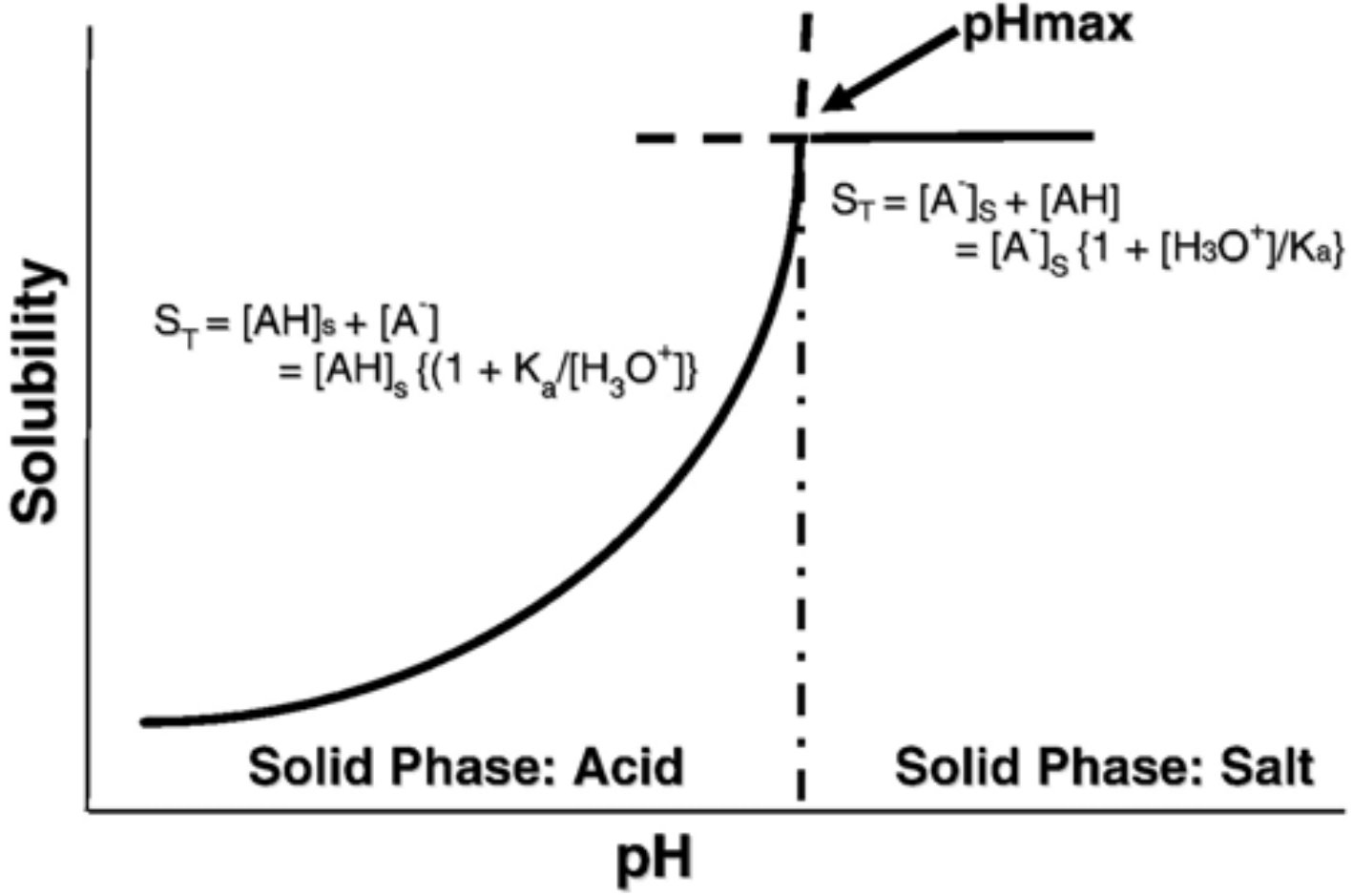
Reference: Parikh and Serajuddin et al., Pharm. Res. 2016; 33: 1456-1471

st. john's UNIVERSITY

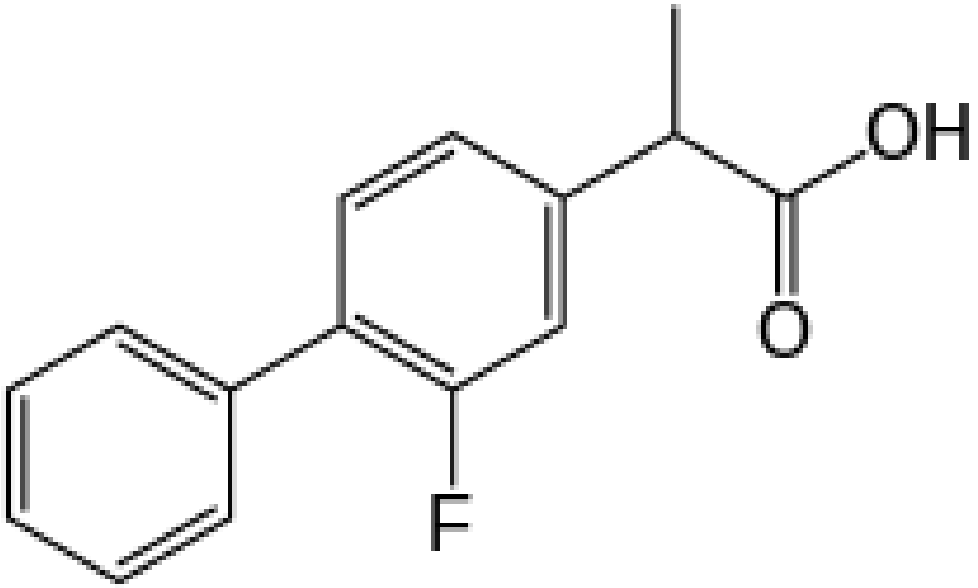
Super-solubilization by Acid-base Interaction:

Flurbiprofen (Acidic Drug)

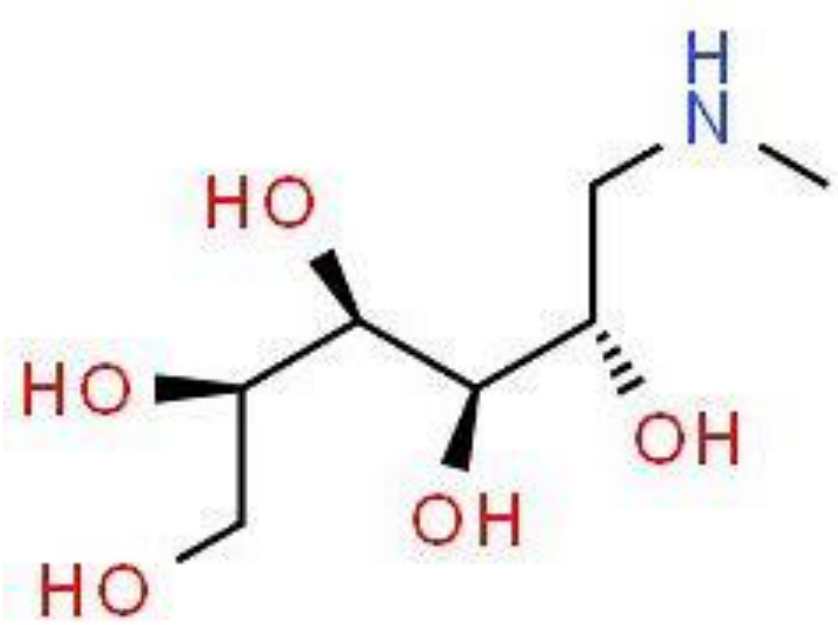
pH vs Solubility Relationship of Acidic Drug



Acid-Base Combination



Flurbiprofen (MW: 244.26; pKa: 4.2; m. p.: 117◦C)



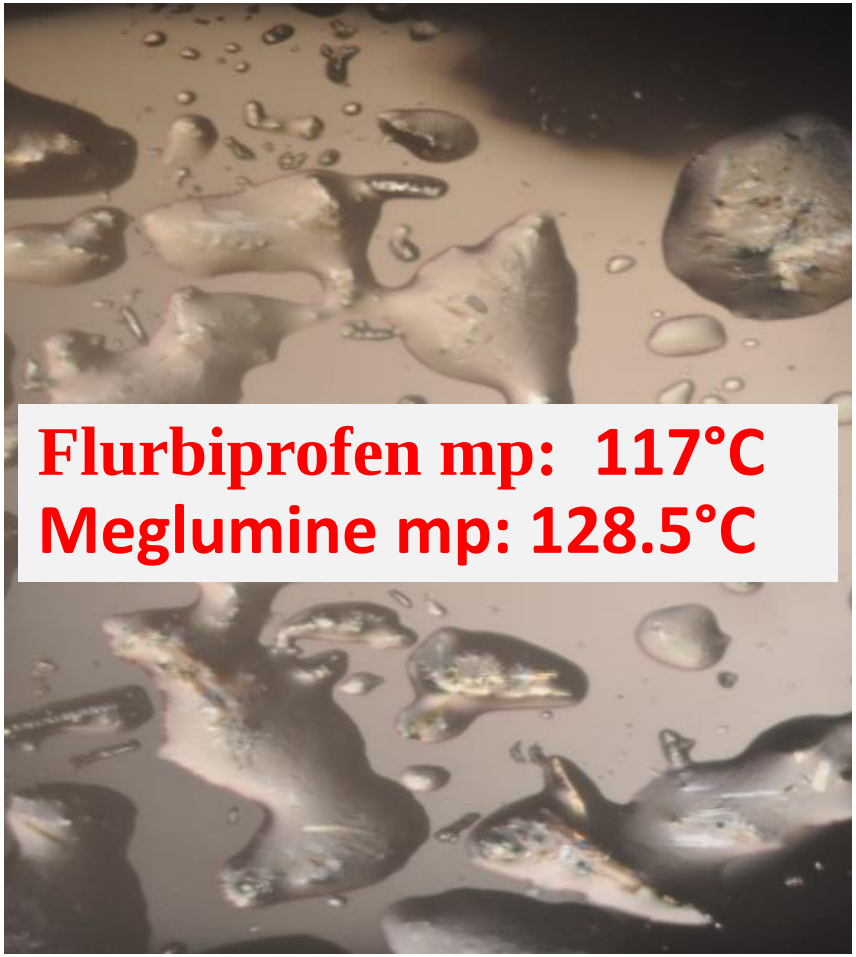
Meglumine (MW: 195.2; pKa: 9.6; m. p: 128.5 ◦C)

Supersolubilization of Flurbiprofen by Meglumine

Buffer solution	Conc (mg/mL)
Water	0.011
1.2 HCl	0.009
2.0 HCl	0.009
4.5 Acetate Buffer	0.013
5.5 Acetate Buffer	0.019
6.8 Phosphate Buffer	0.215
7.2 Phosphate Buffer	0.283

Meglumine (mg)	Water (mg)	Flurbiprofen Solubility (mg/g of solution)	pH
25	1000	20.5	6.32
50	1000	58.7	6.32
100	1000	115	6.3
200	1000	187	6.27
400	1000	357	6.24

Supersolubilization of Flurbiprofen by Meglumine (Potential for Melt Extrusion

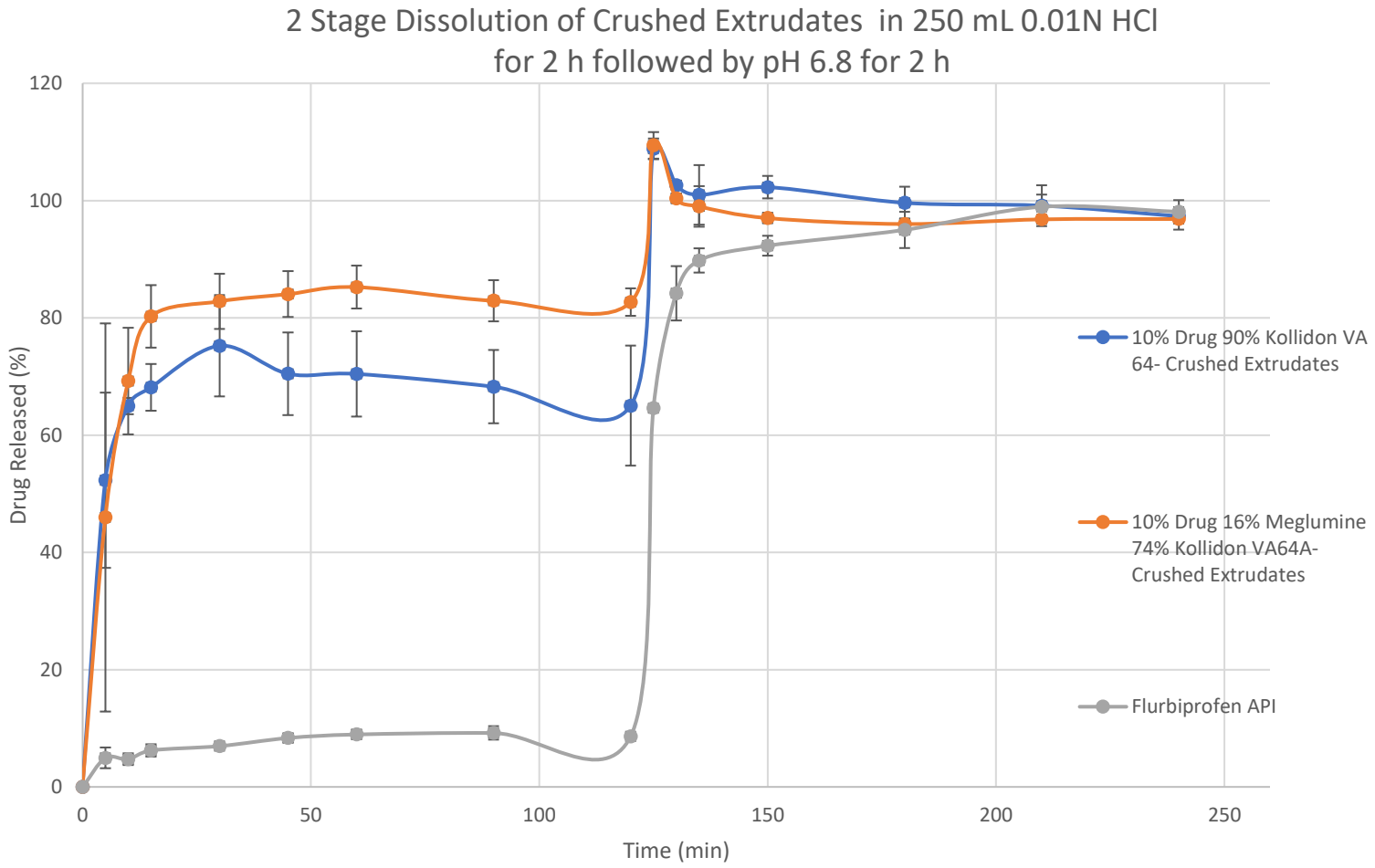


Hot State Microscopy at 70º, Flurbiprofen:Meglumine, 1:2 molar ratio

- Low temperature melt extrusion
- High drug loading
- High dissolution rate

FEASIBLE

Dissolution at Flurbiprofen ASD pH 2 and pH 6.8



Summary

- Supersolubilization of poorly water-soluble weakly acidic and basic drugs was achieved by using non-salt forming acids and bases
- Viscous /gummy solid dispersions can be converted to solid powders by loading onto porous silica carriers or by hot melt extrusion with polymers
- Acid-base interaction makes extruded filaments printable
- Provides rapidly dissolving amorphous solid dispersions (ASD)
- High drug loading can be achieved
- Supersaturation of dissolution media occurred and/or in situ nanoparticles formed
- The acid-base interaction is apparently non-ionic in nature

Thank You!