Solubility enhancement of poorly soluble API using cellulose derivatives

28th April 2014
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Class up to improve drug solubility

- BCS: Biopharmaceutics Classification system*1

More than 60% of candidate drug

Absorption (Permeability)

Class IIa/IIb → Class I

Need to Improve

Class IV → Class III

Solubility

0.1mg/m

Formulation Change (hard technique)

Chemical Change (relatively easy)
Solid dispersion

Physical mixture

Solid dispersion

Drug (Crystal)  Drug (Molecule)  Carrier (Polymer)

Drug crystal amorphous (molecule)
Solubility Low High
Stability Stable Unstable (recrystallization)

- Drug & polymer miscibility
- Stable in the process
Approach to Improve drug solubility

Physical modifications
- Micronization
- Complexation (Surfactants, CyD, etc.)
- Polymorphs
- **Solid dispersion** (amorphous)

Chemical modification
- Soluble prodrugs
- Salts

Requirements of a good solid dispersion:
Superstation release profile (3hrs), high API content, Good stability.
Solid dispersion

➤ Approach to Improve Drug Solubility

- First paper
  Eutectic mixture
  (Sulfathiazole-Ascorbic acid, acetoamide, nicotineamide, urea…)
  Chiou and Riegelman, J. Pharm. Sci. 1969
  Solid dispersion
  (Griseofulvin-PEG6000)

- First commercial product
  - Sepamit
  Nifedipine Solid Solution by Kanebo since 1981

- Few products on the market: because of
  stability issues
  manufacturing issues
  other opportunities for delivery of insoluble compounds
Preparation of solid dispersions

- **Spray Dry**
  - Spray dryer
  - Powder

- **Spray Coating**
  - Fluidized bed
  - Core: lactose etc.

- **Co-precipitation**

- **Hot melt extrusion**

- **Drug**
  - Polymer
  - Solvent

- **Injection moulded tablets**

- **Capsule or Tablet**

- **Spray Coating**
  - Using poor solvent
  - Powder

- **Injection moulded tablets**
Preparation of Solid dispersion

• Solvent method
  – Spray drug-polymer solution
    • Co-soluble process
      – Miscible to solvent
• Hot Melt Extrusion
  – Heat and shear drug-polymer mixture
    • Co-melt process
      – Thermal misible
Particle morphology – Solid dispersion

Spray Drying

Spray Drying (lactose)

Melt Extrusion (milled)
Carrier substances for solid dispersion

- Polyvinylpyrrolidone
- Polyethylene glycols
- Cellulose derivatives
  - HPMC, HPC, HPMCP, HPMCAS…
- Polyacrylates
- Urea
- Sugar
Structure

- Enteric coating agent (cellulose derivatives)

HPMC → HPMCAS

: Methyl Hydroxypropyl

: Acetyl ... hydrophobic

: Succinoyl ... hydrophilic (anionic dissociation)
HPMCAS : Shin-Etsu AQOAT®

- Enteric coating agent
- Sustained release coating

Multi functional substituent
- hydrophobic
- H-bonding

Amorphous polymer chain network

CAS; 71138-97-1, listed in JPE, USP/NF

R= -H, -CH₃, -COCH₃,
- COCH₂CH₂COOH
- CH₂CH(OH)CH₃,
- CH₂CH(CH₃)OCOCH₃,
- CH₂CH(CH₃)OCOCH₂CH₂COOH
## Grades of HPMCAS pH dependent solubility

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<th>Acetyl (%)</th>
<th>Succinoyl (%)</th>
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<td>9</td>
<td>11</td>
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<tr>
<td>AS-HG/HF</td>
<td>12</td>
<td>7</td>
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G: Granular grade (HME and SDD)
F: Fine grade (Aqueous & dry coating)
Glass transition temperatures

<table>
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<tr>
<th>HPMC</th>
<th>AQOAT (HPMCAS)</th>
<th>HPMCP</th>
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<td><img src="image" alt="HPMC" /></td>
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<tr>
<td><img src="image" alt="AQOAT" /></td>
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<tr>
<td><img src="image" alt="HPMCP" /></td>
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</tr>
</tbody>
</table>

- **HPMC**
  - Tg: 165°C (P-606)

- **AQOAT (HPMCAS)**
  - Tg: 120°C (AS-L)
  - 130°C (AS-M)
  - 135°C (AS-H)

- **HPMCP**
  - Tg: 145°C (HP-55)
Screening study

Preparation

- API and polymer were dissolved in a mixed solvent (Ethanol:Dichloromethane = 1:1w/w) and then sprayed onto Teflon sheet and grounded.

Polymers

- Hypromellose acetate succinate (HPMCAS: Shin-Etsu AEOAT® AS-MF, Shin-Etsu Chem.)
- Hypromellose phthalate (HPMCP: HP-55, Shin-Etsu Chem.)
- Hypromellose (HPMC: Pharmacoat® 606, Shin-Etsu Chem.)
- Polyvinylpyrrolidone (PVP: Kollidon® K30, Sigma)
Screening study (solvent method)

<table>
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<tr>
<th></th>
<th>Nifedipine</th>
<th>Griseofulvin</th>
<th>Dipyridamole</th>
<th>Carbamazepine</th>
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<tr>
<td><strong>Mw:</strong></td>
<td>346</td>
<td>352</td>
<td>504</td>
<td>236</td>
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<td><strong>Water solubility:</strong></td>
<td>0.0063mg/mL</td>
<td>0.0096mg/mL</td>
<td>0.004mg/mL</td>
<td>0.224mg/mL</td>
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<tr>
<td><strong>Solubility at pH6.8:</strong></td>
<td>0.0060mg/mL</td>
<td>0.0084mg/mL</td>
<td>0.0037mg/mL</td>
<td>0.163mg/mL</td>
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<tr>
<td><strong>Solubility at pH1.2:</strong></td>
<td>0.0061mg/mL</td>
<td>0.0011mg/mL</td>
<td>&gt;2.5mg/mL</td>
<td>0.192mg/mL</td>
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<tr>
<td><strong>Abbreviation</strong></td>
<td>NP</td>
<td>GRF</td>
<td>DIP</td>
<td>CBZ</td>
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Screening study (solvent method)

Dissolution test (pH6.8)

HPMCAS solid dispersion improved drug dissolution
Screening study (solvent method)

Inhibition effect of recrystallization of dissolved NP (pH 6.8), NP:carrier 1:1

Graph showing the dissolution of NP in different carriers over time.
Screening study (solvent method)

Stability (Storage condition: 50 °C in the closed bottle)

<table>
<thead>
<tr>
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<th>Assay by HPLC (%)</th>
<th>Dissolution of NP at 10min. (pH6.8) (mg/L_50mg/L)</th>
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<tr>
<td></td>
<td>initial</td>
<td>18 months</td>
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<td>NP</td>
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<td>HPMCP</td>
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<tr>
<td>PVP</td>
<td>93.2</td>
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</table>
Screening study (solvent method)

Hygroscopicity

Equilibrium moisture content (%) vs. Relative humidity (%)

- PVP
- HPMC
- HPMCP
- HPMCAS
Large scale spray drying

Formulation:
HPMCAS-LG: Felodipine 3:1 Solvent, Acetone

Preparation solution:
Felodipine was dissolved in acetone and the HPMCAS was added slowly and mixed for one hour.

Equipment:
GEA Niro 12.5CC pilot plant
Equipped with 4 pneumatic hammers, HEPA filters & Cyclone to collect the primary powder fraction.
Including the controlled room
<table>
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<tr>
<th>Test Number</th>
<th>Trial Temp(0C)</th>
<th>Nozzle Inlet</th>
<th>Nozzle Outlet</th>
<th>Solid content (%)</th>
<th>Pressure (bar)</th>
<th>Feed Rate (kg/hr)</th>
<th>Particle Size D50 (um)</th>
<th>LOD (%)</th>
<th>Quantity (kg)</th>
<th>Lose (%)</th>
<th>Tap (%)</th>
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## Post Drying

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<th>Test Number</th>
<th>Particle Size D50 (µm)</th>
<th>LOD (%)</th>
<th>Quantity (kg)</th>
<th>Mesh size (µm)</th>
<th>Temperature (°C)</th>
<th>Air flow</th>
<th>Time (min)</th>
<th>LOD after (%)</th>
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<td>37</td>
<td>30</td>
<td>1.41</td>
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</table>
X-ray diffraction

Intensity (cps) vs. 2θ (°) for different samples:
- felodipine crystal
- No.1
- No.2
- No.4
- No.6
- No.10
Summary

- Particle size has a large effect on your release profile and need to take are that when scaling up to production.
- With the larger particle size the flow improves therefore can avoid granulation step.
- Post drying is essential to remove the residual solvents.
- Increasing our solid content to 12.4% gave the best results which results to shorter processing times and good yield.
Screening study (solvent method)

XRD solid dispersion (API: carrier = 1:2)

NP

GRF* (GRF:carrier 1:4)

Amorphous solid dispersion
Operation window for melt extrusion

HPMCAS shows the wider operation window among cellulose derivatives.
Thermodynamic properties of HPMCAS

- DSC and TGA measurement

- Glass Transition temperatures were appeared in cellulose derivatives (HPMC & HPMCAS)
- Thermal plasticity (HPMC & HPMCAS)
- Similar thermal decomposition temperature
HME- Feasibility studies

**Labo Scale**
- Apparatus: MiniLab (Haarke Thermo)
- Sample: 5g (Drug-polymer[1:2] mixture)
- Condition: 170° C, 20rpm[screw]
- Milled after extrusion

**Formulation:**
NP/AQOAT (AS-L,M,H) 1/2
NP/KollidoneVA64* 1/2 & 1/6

*: Kollidone VA64 (BASF; PVPVA copolymer)

**Evaluation**
- Drug crystallinity
- Improvement of drug dissolution
Improvement of Drug Dissolution

NP Dissolution in pH 6.8

Improvement (sustained high drug release): HPMCAS > Kollidone VA64
Design of experiments- optimum process parameters

Formulation:
Shin-Etsu Aqoat HPMCAS-MG: Ibuprofen 2:1

Pharma 11 Thermo Scientific, Germany

<table>
<thead>
<tr>
<th></th>
<th>Torque (%)</th>
<th>Speed(rpm)</th>
<th>Feeder(kg/hr)</th>
<th>Pressure(bar)</th>
<th>Melt Temperature (Degrees)</th>
<th>Initial</th>
<th>Zone 2</th>
<th>Zone 3</th>
<th>Zone 4</th>
<th>Zone 5</th>
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</table>
Extrudates

During processing the measured extruder torque was 25%.

Our general recommendation is to use extrusion temperature for HPMCAS is 150°C but in the presence of 33% ibuprofen it could be readily processed at 100°C.

This suggests that ibuprofen acted as a plasticiser and allowed processing at a reduced temperature.
Injection moulding & Results

Mini Jet (Thermo Scientific, UK) 120°C of the injection piston and 30°C of the mould
Pressure: 400 bar over 5 seconds and post pressure: 300 bar 2 sec
## Hotmelt Extrusion
(Pure HPMCAS, Haake MiniLab)

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<tr>
<th>grade</th>
<th>lot</th>
<th>viscosity</th>
<th>Loss on Drying</th>
<th>Substituent (%)</th>
<th>free acid (%)</th>
<th>Total acid (%)</th>
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<td>23.1</td>
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<td>9.3</td>
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<td>1.2</td>
<td>23.0</td>
<td>7.2</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**Cleavage of Succinic Groups**
Stability for Melt Extrusion

Discussion:

- Cleavage of Succinoyl Groups → Free acid increase (dissolution pH shifts to higher)
- Color Change (more yellowish)
- Slight Reduction in Molecular weight at 200°C → Possibility of interaction between API and free acid
### Storage stability (NP solid dispersion)

#### NP content of solid dispersion

<table>
<thead>
<tr>
<th>Assay by HPLC (%)</th>
<th>Initial</th>
<th>40°C, 75%RH</th>
<th>50°C, closed bottle</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AQOAT</td>
<td>95.6</td>
<td>98.0</td>
<td>96.9</td>
</tr>
<tr>
<td>HPMC</td>
<td>100</td>
<td>96.8</td>
<td>98.7</td>
</tr>
<tr>
<td>HPMCP</td>
<td>93.1</td>
<td>93.8</td>
<td>93.1</td>
</tr>
<tr>
<td>PVP</td>
<td>93.2</td>
<td>93.3</td>
<td>88.4</td>
</tr>
<tr>
<td>Eudragit L</td>
<td>94.8</td>
<td>96.2</td>
<td>94.8</td>
</tr>
</tbody>
</table>

In most cases, drug content remain the same level. (Stable)
Storage stability (NP solid dispersion)

Equilibrium moisture content (25°C)

- **PVP** is highly hygroscopic. → absorb moisture → recrystallize
- HPMC is lower hygroscopic.
- HPMCP
- HPMCAS

A diagram showing the equilibrium moisture content (%) against relative humidity (%) for various HMCs. The moisture content increases as the relative humidity increases, with PVP showing the highest absorbance.
AQQAT-NP solid dispersion pellet

Core beads: Nonpareil® -101
Spray solution: 9% AS-M/NP (2:1) solution*
*Solvent: CH$_2$Cl$_2$/EtOH, MeOH, Acetone
Layering amount: 10% NP rotary fluidized bed granulator

- CH$_2$Cl$_2$·Ethanol
- Methanol
- Aceton

Dissolution amount of NP (μg/mL)

Time (min)

NP only
Conclusion

- AQOAT could be useful as carrier of solid dispersion.

Benefit:
- Amorphous SD with small carrier ratio
- Great improvement of drug dissolution (enteric)
- Inhibition of recrystallization
- Good stability
HME Cleaner

The cleaner consist of Hypromellose and water soluble plasticizer which is commonly used in pharmaceutical applications.

**How to use the cleaner:**
After your actual extrusion of solid dispersion using HPMCAS, set your extruder (mixing zones) at higher than 160°C (depending on scale size). HME Cleaner will be stuck in the barrels when it is below 160°C. In cases of extrusion at higher temperature, like 200°C, keep the temperature for the first extrusion with HME Cleaner until complete substitution is done. Then set the lower temperature (170°C) for additional cleaning extrusion. (HME Cleaner starts to decompose over 200°C)

Samples are available in 4kg bags
Examples of HME Cleaner

The cleaner consist of Hypromellose and water soluble plasticizer which is commonly used in pharmaceutical applications.

- Temperature profile of Pharmalab (Thermo Scientific, UK)
  L/D: 10/40, Screw=18mm, Screw speed: 50-150rpm, Die: 2mm·d,

<table>
<thead>
<tr>
<th>Zone No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Die</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>20</td>
<td>50</td>
<td>70</td>
<td>90</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
</tr>
</tbody>
</table>

- After cleaning: Pharma lab (Thermo Scientific)

There was only little amount of residual polymer around the screws. After screws were removed, there were films of cleaning agent in the melting and kneading zone, which can be easily peeled off.
“Microprecipitated Bulk Powder” (MBP) Method

Vemurafenib
(For Melanoma)

<table>
<thead>
<tr>
<th>Solubility</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Aqueous</td>
<td>&lt; 0.1 mg/mL</td>
</tr>
<tr>
<td>Organic Solvents (mg/mL)</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>MeOH</td>
<td>4.57</td>
</tr>
<tr>
<td>AcCN</td>
<td>1.40</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>1.95</td>
</tr>
<tr>
<td>Acetone</td>
<td>&lt; 6</td>
</tr>
</tbody>
</table>

m.p. 272.1°C

Shah et al. J. Pharm. Sci. 102 (3), 2013
Coprecipitation Process for Preparation of MBP

HPMCAS, HPMCP, Eudragit L 100-55

Vemurafenib

Ionic polymer

Crystalline API

Drug + polymer
dissolve in solvent

Cold dilute acid / base

Solvent removal
Aqueous wash

Drying

Shah et al. J. Pharm. Sci. 102 (3), 2013
Dissolution Profiles of Vemurafenib

USP Apparatus 2 (b) with 0.09% HTAB

Shah et al. J. Pharm. Sci. 102 (3), 2013
Quality by Design (HPMCAS)

Factors that may affect to performance

Substitution level: Acetyl / Succinoyl
Methoxy / Hydroxypropoxy

Viscosity: (Molecular weight)

Impurities: Free acetic acid
Free succinic acid
Residual salt (sodium acetate)
Moisture
Factors that may affect to performance

Acetyl / Succinoyl
- Affect to API dissolution.
- May affect to stability of API
- Subject to hydrolysis
- Recommended to set up a range

Methoxy / Hydroxypropoxy
- May affect to API dissolution

Viscosity (Molecular weight)
- May affect to API dissolution
Effect of Succinoyl / Acetyl Groups

*The original solubility of Nifedipine is 12 mg/L

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>AS-LG</th>
<th>AS-MG</th>
<th>AS-HG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Succinoyl, %</td>
<td>18.1</td>
<td>15.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Acetyl, %</td>
<td>5.7</td>
<td>7.9</td>
<td>8.4</td>
</tr>
</tbody>
</table>
Impurities within HPMCAS

- Acetic acid / Succinic acid
- Sodium acetate
- Moisture

- May affect stability of API.
- Gradually increases during storage.
  (Except sodium acetate)

Shin-Etsu is open to communicate customers to discuss QbD strategy such as Extreme samples, Variability Data, and Custom Specifications.
Recent approval of solid dispersion using Shin-Etsu AQOAT (HPMCAS)

<table>
<thead>
<tr>
<th>Approved on</th>
<th>Mft</th>
<th>Brand</th>
<th>API</th>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>May, 2011</td>
<td>Vertex</td>
<td>INCIVEK</td>
<td>Telaprevir</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Aug, 2011</td>
<td>Roche</td>
<td>ZELBORAF</td>
<td>Vemuratenib</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Jan, 2012</td>
<td>Vertex</td>
<td>KALYDECO</td>
<td>Ivacaftor</td>
<td>Systic Fibrosis</td>
</tr>
<tr>
<td>Nov, 2013</td>
<td>Merck</td>
<td>NOXAFIL TAB</td>
<td>Posaconazole</td>
<td>Immune deficiency</td>
</tr>
</tbody>
</table>