Disclaimers

- The views expressed in this presentation are my own, and should not be interpreted taken as the official view of any organization with which I am associated.
- In the interests of time, this presentation will only consider oral drug delivery.
  - Some of the approaches presented may apply to other routes of administration; however there may also be other approaches that will work for other routes of administration.
- This will be a very brief overview to show what techniques are available.
**Presentation Outline**

- **Introduction**
  - Poorly soluble drugs
  - Absorption from the gastrointestinal tract
  - Dissolution models
- **Formulation approaches for poorly soluble compounds**
  - Solubility-based methods
  - Surface area-based methods
  - Lipid-based systems
- **Potential impact for excipient manufacturers**
- **Summary**

**Poorly soluble drugs**

- Depending on the therapeutic area as many as 80% of new drugs are classified as poorly soluble.
- Poorly soluble is defined in the Biopharmaceutical Classification System (BCS) as not being soluble in \( \leq 250 \text{ mL} \) of aqueous media over the range pH1 – pH7.5.
- From my personal experience, poorly soluble means that it is soluble at \(<1 \text{ mg/mL}\) in dilute HCl.
  - There are differences between solubilities of \(>500 \text{ mcg/mL}\) and \(<10 \text{ mcg/mL}\) with respect to the types of formulation approach we can use.
- **Issues for clinical and commercial formulations.**
- **Issues for preclinical safety formulations.**
Biopharmaceutical Classification System

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<th>Solubility</th>
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<td>Low</td>
<td>High</td>
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<td>High</td>
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Absorption from the gastrointestinal tract

- **Passive diffusion**
  - Paracellular
  - Transcellular
- **Carrier mediated**
  - Facilitated diffusion
  - Active transport
- **Efflux**

1 – Transcellular
2 – Paracellular
3 – Carrier mediated
4 – Transcytosis
5 – Efflux
Dissolution models

Noyes-Whitney
\[
\frac{dQ}{dt} = k (C_s - C_b)
\]

Nernst-Brunner
\[
\frac{dQ}{dt} = DA \frac{(C_s - C_b)}{h}
\]

Where \(dQ/dt\) = dissolution rate  
\(k\) = mass transfer coefficient  
\(C_s\) = solubility  
\(C_b\) = bulk solution concentration  
\(D\) = diffusion coefficient  
\(A\) = solid surface area  
\(h\) = diffusion layer thickness

Thus we have three possible ways to influence the dissolution:  
• Solubility  
• Surface area  
• Diffusion layer thickness  

[Within the confines of the gastrointestinal tract, we do not have much control over diffusion layer thickness.]

When we talk about solubility, it can be either equilibrium solubility, or dissolution rate, or both.

Increasing the rate of dissolution may lead to supersaturation. The extent of supersaturation (concentration and time) are both important.

Dissolution models (contd.)

Ostwald-Freundlich-Kelvin
\[
\ln \left( \frac{S}{S_0} \right) = \frac{2\gamma}{rRT} = \frac{2M\gamma}{\rho rRT}
\]

Where  
\(S\) = drug solubility at temperature \(T\)  
\(S_0\) = equilibrium solubility \((r = \infty)\)  
\(r\) = particle radius  
\(M\) = molecular wt. of solute  
\(\nu\) = molar volume  
\(\gamma\) = interfacial surface tension  
\(\rho\) = true density of solute

From this equation we see that dissolution increases as the particle radius decreases.

This effect only really becomes apparent below 1 – 2 μm, and especially below 200 nm, i.e. in the ‘nano’ range.
Formulation methods - Solubility

• We are trying to increase the concentration gradient across the diffusion layer:
  – Alternative salt forms
  – Metastable crystalline polymorphic forms
  – Co-crystals
  – Complex formation
  – Co-solvents
  – Solubilization by surfactants
  – Amorphous forms

Alternative salt forms

• There are many different potential salts from both weak acids and weak bases.
• Can enhance solubility, and thus dissolution and bioavailability.
• Increase in bioavailability may be 1.5 – 2.5 fold.
  – Not really suitable for very insoluble drugs, i.e. $S_0 << 1\text{mg/mL}$.

• May also increase stability of the API
  – e.g. amlodipine maleate $\rightarrow$ amlodipine besylate
Metastable polymorphs

- Inherently unstable.
  - They will tend to revert to the most stable (least soluble form)
  - Some are sufficiently stable to be viable.
  - Moisture may be an issue for stability.
- Increase in bioavailability may be 1.5 – 2.5 fold.
  - Not really suitable for very insoluble drugs, i.e. $S_0 << 1\text{mg/mL}$.

Co-crystals

- These are not salts; it is not necessarily an ionic association.
- There may be hydrophilic (hydrogen bonding) and hydrophobic interactions.
- Each API will be different, and what may work with one molecule will not work with another closely related molecule.
- Can provide a 2 – 4 fold increase in bioavailability.
- Stability can be an issue.
  - Sometimes other components can be added to stabilize the co-crystals.
Complex formation

- Complexes based on shielding of the hydrophobic portions of the molecule:
  - e.g. cyclodextrin complexation
- The complex must release the drug molecule in the gastrointestinal tract for the drug to be absorbed.

Co-solvents

- Water miscible co-solvents
- The final formulation may be a solution, partial solution/suspension, and either liquid or solid.
- Solid solutions may be preferred since they are likely to be more stable to moisture.
  - Liquid co-solvent solutions can crystallize on storage in e.g. soft gelatin capsules due to moisture uptake from the capsule shell.
- A partial solution/suspension can give extended release in vivo.
- Examples include:
  - Gris-PEG®: Griseofulvin in PEG 400/PEG 8000
  - Aprical®: Nifedipine in PEG 300/PEG 6000
Solubilization by surfactants

- Surfactants have the ability to form micelles in aqueous media.
- The drug molecule is able to be solubilized in the hydrophobic inner core of the micelle.
- There may be problems with the amount of surfactant required (e.g. laxative effects).
- The micelles must release the drug molecule for it to be absorbed.

Amorphous forms

- Amorphous forms of drug molecules are high energy forms.
- Since there is no crystal lattice structure (no long range order), the energy barrier to dissolution is much reduced.
- Inherently unstable, and will tend to revert to the most stable (least soluble form)
- Amorphous forms most often need to be stabilized
  - Solid solutions
  - Polymer dispersions
- Can give up to a 10 – 15 fold increase in bioavailability.
- Methods of manufacture include:
  - Spray drying
  - Hot-melt extrusion
  - Conversion to the amorphous form can also be achieved by milling (e.g. ball milling)
Formulation methods – Surface area

• An increase in specific surface of the bulk active drug (API), can aid dissolution:
  – Milling
  – Micronization
  – Nanomilling
  – Nanocrystals
• The lower the equilibrium solubility of the drug, the smaller the particle size needed to get adequate drug dissolution, and thus absorption.

Milling methods

• Milling is the breaking down large particles to smaller particles. At the same time the total surface area is increased.
• There are several milling methods, but they can be grouped as either wet or dry methods.
• For particle size reduction beyond what can be achieved air-jet milling (micronization), wet milling is necessary.
Dry milling

- There are several different types or dry milling equipment. The most common in the pharmaceutical industry are:
  - Comminuting mills (e.g. Fitzmill, Comill, etc.)
  - Pin mills (either with one rotary head or contra-rotating heads)
  - Fluid energy mills
- The more energy we put into the milling operation, the finer the resulting particles.
- However, there is a lower limit for dry milling since powder particles become more cohesive the smaller they get.
- Using dry milling methods we can get down to a median particle size of ca. 1 – 10 μm (e.g. using fluid energy milling), depending on the material being milled.

Wet milling

- As the name implies, this is milling where the powder to be milled is suspended in a liquid.
- Wet milling methods include:
  - Ball milling
  - Bead milling
  - Colloid milling
  - Microfluidization
- Easier to handle very fine powders as a suspension:
  - Reduced dust.
  - Reduced agglomeration/crystallization e.g. through including crystallization and agglomeration inhibitors dissolved in the liquid.
- For every material and type of milling there is a particle size below which it will not be possible to obtain any further size reduction.
Nanocrystallization

- Refers to crystallization under conditions of very high shear to produce nano-sized crystals:
  - Drug and stabilizing polymer in solution, and an antisolvent are fed under high pressure into the crystallization chamber and caused to impinge directly.
  - The conditions of very high shear creates very nanocrystals, and the presence of the stabilizing polymer, which adsorbs onto the nanocrystal surface, prevents agglomeration and crystal growth.
  - Particle sizes <100 nm are claimed

What is the target particle size?

- It depends on the drug and its solubility:
  - Griseofulvin:
    - Aqueous solubility: 0.1 – 1 mg/mL
    - Critical particle size: <ca. 10 μm
  - Digoxin:
    - Aqueous solubility: ca. 0.01 – 0.02 mg/mL
    - Critical particle size: <5 μm
  - Investigational compound:
    - Aqueous solubility: <50 ng/mL
    - Critical particle size: <300 nm
Mesoporous particles

- Highly porous particles with nano-sized pores that are able to take up the drug from a solvent solution and then release it in the body after administration.
- Particles typically prepared from amorphous silica.
  - Other materials may be possible.
- The drug-laden particles can be further formulated for encapsulation or compressed into tablets.

Formulation methods – Lipid-based

- Lipid-based systems are alternatives to the non-lipid-based formulations; however, drug solubility and surface area still apply.
  - Self-emulsifying systems (SEDDS)
  - Self-microemulsifying systems (SMEDDS)
  - Lipid solutions
  - Solid lipid nanoparticles (SLNs)
SEDDS and SMEDDS

- Both types of formulations are combinations of the API with a mixture of oils and surfactants which emulsify on addition to an aqueous phase.
- The difference between the two types concerns the particle size of the discrete phase.
  - SEDDS have more coarse droplets and the emulsions are opaque when sufficiently concentrated.
  - SMEDDS have much finer droplets and the resulting microemulsion is clear/translucent, even when concentrated.

Sandimmun® vs. Neoral®

- Sandimmun® a SEDDS; Neoral® a SMEDDS
- Neoral® is less dependent on bile salts for absorption.
- Neoral® gives better, more linear, and less variable bioavailability.

Lipid solutions

- Can be used with some drugs. The lipid should be a liquid at body temperature.
- Natural fixed oils (vegetable oils) are preferred.
- Can be a useful formulation for short term preclinical safety studies.
- Has been used to administer oil-soluble vitamins.

Solid lipid nanoparticles

- Reports from the literature have shown improved bioavailability using this formulation approach.
- SLNs are prepared using high pressure homogenization techniques.
- Median particle sizes <300 nm have been reported.
Potential drawbacks for all methods

- Stability:
  - Physical,
  - Chemical.
- Drug loading:
  - Typically <50%
    - Potential problem for high-dose drugs.
  - Problems for safety studies:
    - Volume of material to be administered.
    - Dose of excipients may be too high.
      - High doses of surfactants is a problem.

Implications for excipients

- For poorly soluble compounds we need to focus on getting the drug into a form from which it can be absorbed.
  - This is in contrast to more soluble drugs where we were able to focus on what was needed to formulate the tablet or capsule.
  - Once we have the drug in a suitable form for absorption, we can then focus on what else is needed to produce the formulation to be administered to patients.
- We need better understanding of how to increase the drug loading of these formulations; particularly for preclinical safety studies.
- We need new excipients/excipient combinations capable of providing higher drug loadings and more stable formulations.
- Note: we will still need ‘conventional’ excipients to manufacture the final product.
Summary

- Very poorly water-soluble compounds are going to be a big part of the future for pharmaceutical formulation.
- There are methods available, and under development, that can provide a means to administer such drugs to patients and achieve a reasonable bioavailability.
- None of these methods are fully understood.
  - We need better understanding of how these methods work.
- We need better excipients/excipient combinations to provide more stable formulations with higher drug loadings.
- Preclinical safety studies will continue to present issues when working with very poorly soluble drugs.

Thank you!
Any questions?