Salt Screening and Selection: New Challenges and Considerations in the Modern Pharmaceutical R&D Paradigm

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Presentation Outline

• Introduction

• Theoretical Considerations
  • pH-solubility profiles, pKa and salt formation
  • Prediction of salt solubility
  • Solubility product and in situ salt screening
  • Solubility/dissolution rate of salts
  • Dissolution of salts in the GI fluids
  • Salts and other solubilization techniques
  • Effect of salts on chemical stability

• Practical Considerations
  • Dosage form considerations
  • Toxicity considerations
  • Salt and form selection strategies
  • Impact of salt on intellectual property (IP) and life cycle management (LCM)
  • Automation and high throughout

• Case Studies

• Summary
Introduction
Modern R&D Paradigm

- Combinatorial chemistry and high-throughput screening result in many more hits and more development candidates.

- Properties of NCEs become less favorable for development:
  - >40% compounds belong to class II and IV (FDA biopharmaceutical classification system)

- Gap between Research and Development is disappearing:
  - Profiling of pharmaceutical properties of drug candidates becomes a routine practice

- Success rate has not improved.

- Competition is intensifying:
  - Faster to market and protection of intellectual properties are becoming a necessity
New Challenges for Development Scientists: how do these challenges affect salt screening and selection?

- Consideration of pharmaceutical properties in drug design - developability assessment: Need to consider the impact of salts on developability
- Shorter development timeline: Need to select the right salt the first time
- Increased need for special drug delivery systems: Need to evaluate the impact of salts on the solubility and stability in these systems
Impact of Salts

- Impact on pharmaceutical properties required for a successful dosage form:
  - bioavailability
  - stability (both chemical and physical)
  - manufacturability

- Impact on physicochemical properties of the drug substance:
  - Solubility
  - Dissolution rate
  - hygroscopicity
  - Chemical stability
  - Crystal form
  - Mechanical properties
“Changing the salt, changing the drug”
Theoretical Considerations
pH-Solubility Profile

Ref: Serajuddin & Pudipeddi, in Handbook of Pharmaceutical Salts, IUPAC, 2002
The Role of pKa

- For stable salt formation to be complete, ionization must be effectively complete such that a single ionization state is form.

- 2 pH units difference between the pKas of the base and the acid typically necessary

- With counter ions that correspond to volatile acids or bases, the pKa requirement may be different, e.g.
  - pKa 1.8 - 2.2 (triazole antifungal agents of the α-styrylcarbinol)
  - Crystalline HCl salt (pKa -6.1): 12% loss of chloride after 6 hrs at 60°C
  - Crystalline mesylate salt (pKa -1.2): stable after 3 weeks storage at 60°C
Prediction of Salt Solubility

• Contributing factors to salt solubility:
  – solvation energy/heat of solvation
  – crystallinity/heat of fusion

• Solubility of salts are still largely unpredictable except for some general trends

• Most of the empirical methods requires melting point that is difficult to obtain without making the actual salt
Solubility Product and In Situ Salt Screening

• If free base is added to a certain concentration of acid, with the acid concentration high enough to ensure the pH of the solution is lower than pHmax, the base will form the corresponding salt with the acid.

• The solubility product (Ksp) and the solubility of the salt formed in situ can be calculated.

• Multiple counter-ions, added in predetermined amounts so as not to exceed the Ksp of any salt, can provide significantly higher solubility than single counter-ion.

Solubility and Dissolution Rate of Salts

- It is only at a pH value less than pHmax that the solubility of the salt can be determined.
- Saturated solution in the presence of buffer species: salt conversion may occur.
- Effect of solubility and microenvironment pH on dissolution rate: self-buffering effect.
Solubility and Dissolution Rate of Salts

- Intrinsic dissolution rate of bupivacaine and its HCl salt as a function of the pH of the dissolution medium

Ref: Pudipeddi et. al, in Handbook of Pharmaceutical Salts, IUPAC, 2002,
Dissolution Process of the Salt of Basic Drugs

- Dissolved Drug
  - Precipitate as HCl salt (crystalline or amorphous)
  - Dissolve or convert to free base and dissolve

- Salt of a basic drug

- Stomach (pH 1-3)
- Small Intestine (pH 5-7)

- Dissolve Drug
  - Remain in solution
  - Precipitate as free base (crystalline or amorphous)
  - Dissolve or convert to free base and dissolve

- Enteric Coating
Dissolution Process of the Salt of Acidic Drugs

- Basic salt of an acidic drug
- Microenvironment of diffusion layer (pH 5-6)
- Stomach (pH 1-3)
- Dissolved Drug
- Precipitate as free acid (crystalline or amorphous)
- Small Intestine (pH 5-7)
- Empty to small intestine and redissolve at higher pH
- Empty to small intestine for absorption
Salts and Other Solubilization Techniques

- Effect of salts on complexation
- Effect of salts on solubilization by surfactants
- Solubility of salts in non-aqueous solvents
- Effect of salts on amorphous/solid dispersion
Effect of Solvent Composition on the Solubility of Salts

• The addition of a cosolvent to an aqueous salt solution would be expected to reduce the solubility of the drug due to reduction in the dielectric constant of the medium with a corresponding reduction in the solvation of the ions.

• Crystalline hydrate formation may increase solubility of certain salts in cosolvents.
  – For example, Sodium Sulfathiazole solubility almost double in 50% PG

• Conversion of salts of weak bases to their free forms may not be as readily in cosolvents compared to in water.
• Solubility of 2,2-Diphenyl-4-(2’-piperidyl)-1,3-dioxolane

Effect of salts on amorphous/solid dispersion

- Effect on physical stability
  - \( T_g \)
- Effect on chemical stability
  - Microenvironment pH
  - Counter ions
Effect of Salts on Chemical Stability

- **Stability often affected by the hygroscopicity and micro-environmental pH of the salt form:**
  - Salts of mineral acids are polar, leading to hygroscopicity, low micro-environmental pH: not good for compounds readily hydrolyzed.

- **Stability often influenced by the hydrophobicity of the salt-forming acid:**
  - The formation of salts with low water solubility is a means of increasing the chemical stability of a drug that is sensitive to heat and moisture
  - e.g. Xilobam: acyl sulfonate salt more stable than sulphate salt

- **Different salts have different melting points and may have different thermal stability**
Potential Disadvantages of Salts

- Common ion effect for compounds with poor solubility as a HCl salt
- Poor chemical stability in gastric fluid
- Poor solid state stability at the micro-environment pH of the salt
- Precipitation of free acid/base form on the solid surface can reduce the dissolution rate of salts
- Formation of gel layer on the surface can inhibit de-aggregation and hence dissolution
  - e.g. Warfarin Sodium
Practical Considerations
Dosage Form Considerations

- IV vs. oral formulations
- Solution vs. suspension
  - Tetracyclines:
    - HCl: soluble and stable used as solution
    - Ca salt: less soluble and tasteless, used for suspension
- High dose vs. low dose
  - Dissolution may be the limiting factor for the high dose but may not be for the low dose
- IR vs. MR
  - Drug must be sufficient soluble over the wide range of physiological pH in a MR dosage form
- Direct compression vs. wet granulation
- Excipient incompatibility
- Considerations for Potential Combination Formulations
Considerations for Potential Combination Formulations

- **Effect on chemical stability**
  - Effect on microenvironment pH
  - Moisture migration
  - Chemical incompatibility
  - e.g. Propoxyphene HCl + Aspirin: not stable, but propoxyphene napsylate: stable

- **Effect on solubility/dissolution rate**
  - Salt conversion, forming of insoluble salt
Toxicity Considerations

- **Intrinsic Toxicity**
  - e.g. Lithium cations at high doses could cause irreversible damage to the kidney
  - e.g. Maleic acid has been reported to cause renal tubular lesions in the dog (Provadoline maleate)

- **Local Irritancy**
  - e.g. Alprenolol HCl (highly water soluble) has an irritant effect on the oesophagus whereas alprenplol benzoate has no irritant effect - related to the difference in solubility of the salts
  - Effect on GI tract leading to ulceration and bleeding: e.g. nitrate

- **Toxic Reaction Products**
  - e.g. methyl and ethyl formate esters associated formic acid
  - e.g. mesylate esters associated with methanesulfonic acid
Toxicity Considerations

• Risks and Assessment of not Commonly Used Counter Ions
  – Such salts must be regarded as new chemical entities with all the consequences
  – Case by case situation
  – Difficulty in determining the causes of toxicity
    • safety of other salts of the same active entity may be necessary
Salt and Form Selection Strategies

• **Balancing Various Factors:**
  - Bioavailability: clinically relevant doses vs. tox coverage
  - Process consideration/manufacturability
  - Chemical stability/excipient compatibility
  - Other physicochemical and mechanical properties such as hygroscopicity, morphology, and compressibility
  - IP considerations

• **Salt Selection vs. Form Selection**
  - An integrated process
Salt Selection Decision Tree: Approach I

Figure 1: An SSCI Salt Selection Decision Tree

Salt Selection Decision Tree – Approach II

Tier 1
- Crystallinity (visual, microscopy)
- Crystallization from different solvents
- Aqueous solubility including microscopic examination of suspended solid

Tier 2
- Evaluation of crystalline form (powder X-ray diffraction, hot-stage microscopy)
  - Thermal properties (DSC, TG)
  - Hygroscopicity

Tier 3
- Humidity/temperature-dependent changes in crystal form (powder X-ray, DSC, TG, VT-XRD, etc.)

Tier 4
- Bioavailability (optional)
  - Stress stability
  - Scale-up considerations

Final Form

### Salt Selection Decision Tree – Approach III

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Crystal Form Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>rank order of salt solubility via in situ salt screening</td>
<td>if the unionized form is amorphous or mixture of multiple forms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Vitro Testing/In Silico Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>dilution (of the most soluble salt solution) into SGF and SIF &amp; intrinsic dissolution of the the unionized form, G+ simulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bioavailability in animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>solution of most soluble salt, oral (and ID if HCl salt insoluble to evaluate the need for enteric coating) vs. suspension of the unionized form</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solid State Properties of Top 2-3 Salts</th>
</tr>
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<tbody>
<tr>
<td>crystallinity, stability, polymorphism, ability to scale-up, processability and IDR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bioavailability conformation (if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suspension/capsule of the solid (projected clinical dose and tox dose)</td>
</tr>
</tbody>
</table>

### Final Salt Candidate

Timing of Salt and Crystal Form Screening and Selection

- **Option I:**
  - Complete salt and crystal form screening and select the best salt and crystal form for development prior to the GLP toxicity study
  - Additional screening around POC for IP protection
Timing of Salt and Crystal Form Screening and Selection

• Option II:
  - Complete salt screening but only limited crystal screening and select the best salt and crystal form for development prior to the GLP toxicity study
  - Carry out additional polymorph screening (or sometimes salt screening) to finalize the form selection and the definition of all characteristics of the drug substance prior to Phase IIa clinical studies
Timing of Salt and Crystal Form Screening and Selection

- Option III:
  - Select the best salt and crystalline form based on discovery chemistry/biology work and delay all salt and crystal form screening until POC
Balancing Investment, Risks and Return

- **Risk assessment:**
  - Indication, market need, development challenges, is the salt related issue on the critical pass?

- **Investment:**
  - Assuming one out of ten drugs make it to the market, how much will it cost to do all the salt and crystal form screenings?

- **Return:**
  - Product sale potential: every day counts
Impact of Salt on IP and Life Cycle Management

- Salts (and polymorphs) are important tools for product life cycle management
  - to expand the product time
    - Magnesium salt of resolved omeprazole
      - Nexium
    - to circumvent patents leading to branded generics
      - Paroxetine mesylate vs paroxetine HCl
      - Amlodipine maleate vs amlodipine besylate
- Laws governing intellectual property and their interpretation vary by countries
- Different countries view salt in somewhat ways
How can Salt and Polymorph Patents Provide Additional Patent Protection?

<table>
<thead>
<tr>
<th>Compound Claimed</th>
<th>Product Lunch</th>
<th>Patent expired</th>
<th>Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>2001</td>
<td>2010</td>
<td>2015</td>
</tr>
</tbody>
</table>

**Original API**

- **Polymorphs/Salts Claimed**: 1998
- **PTR**: Patent Term Restoration = half of the investigational period + all of the FDA review period

Ref: Lucas J and Burgess P., PharmVOICE, Feb., 2004
How can Salt and Polymorph Patents Provide Additional Patent Protection?

- **Importance of Timing**
  - After the core NCE patent but before anyone else has an opportunity to do the same screen
  - Too early?
    - maleate salt of amlodipine as part of the core NCE patent
  - Too late?
    - Paroxetine mesylate (an alternative salt for Paxil) filed by Synthon
    - Topiramate: sodium trihydrate patent by Transform

Ref: Lucas J. and Burgess P., PharmVOICE, Feb., 2004
Automated and High Throughput Salt Screening

- Automation of manual steps and enhancement in data handling ability:
  - enable screening of more counter ions and solvents for crystallization
  - not a solution for all
  - Still require intellectual input and critical analysis
- What about time for crystallization and combination of various methods?
- Analytical methods consideration
- Drug substance requirement: quantity and purity
An Example of Automated Approach to Salt Screening

- Automated salt formation set-up on the Biomek 2000 workbench

Case Studies
Case Study #1: RPR111423

- **Strategy:**
  - Preliminary screen using counter-ion and solvent matrix to identify crystalline salts
  - Characterize crystalline salts to compare to freebase

- **Results:**
  - Two salts found crystalline: HCl and mesylate
  - Solubility enhanced: 25.7 and 131.4 mg/mL, respectively at 25ºC
  - Both salt forms with polymorphs: 4-6 forms
  - Both salts convert to free base readily in water and intestinal fluids

- **Salt Selection Decision:**
  - Free base is selected for further development

Case Study #1: RPR111423

• Key Learning and Comments:
  – Identifying what properties to modify by a salt prior to any salt screening can save time and resources: a salt may not always be needed
  – In vitro dissolution and in silico simulation would indicate that there is no need for a salt from PK point of view in this case
  – A PK study in animal comparing a solution formulation to a suspension of the micronized free base at the projected clinical dose maybe useful to help decide if a salt is needed and to establish some IVIVC
  – If the projected dose is much higher for this compound, a salt would provide advantages
Case Study #2: RPR127963 – Salt for both Oral and Injection Dosage Form

Background:

− Indication: Cardiovascular diseases
− Projected Doses: 250 mg solid, up to 50 mg/mL for Injection
− Free Base:
  • Weak base with a pKa at 4.10
  • Intrinsic solubility: not reported
  • Permeability: not reported
  • Multiple interconvertible hydrates
  • Anhydride form with low MP (\(\sim 119-123^\circ\text{C}\))

Case Study #2: RPR127963 – Salt for both Oral and Injection Dosage Form

- **Salt Screening and Characterization:**
  - Comprehensive evaluation of possible salts:
    - Five crystalline salts identified: HCl, mesylate, citrate, tartrate, sulfate
    - Citrate and tartrate salts dropped due to their poor solubility
      - 0.83 (pH 2.49) and 0.89 (pH 2.56) mg/mL in water, respectively
    - Tartrate salt is also hygroscopic
    - HCl salt dropped due to low solubility, polymorphs, hydrates
    - Mesylate and sulfate:
      - high MP
      - excellent aqueous solubility: 108 (pH 1.76) and ~50 (pH 1.32) mg/mL in water, respectively
      - Non-hygroscopic
      - No evidence of polymorphs

Case Study #2: RPR127963 – Salt for both Oral and Injection Dosage Form

• Salt Screening and Characterization:
  – Further characterization on the two lead salts:
    • solubility in non-aqueous solvents:
      • Sulfate salt has greater solubility in cosolvents
    • Powder flow properties
    • IDR

• Salt Selection Decision: Sulfate salt for further development with mesylate as the backup
Case Study #2: RPR127963 – Salt for both Oral and Injection Dosage Form

• Key Learning and Comments:
  − It is important to consider both oral and injection dose forms when selecting salt
  − In situ salt screening would help in this case to identify the poorly soluble salts without having to actually make the salts
  − In situ salt formation may be an option for liquid formulations
  − A PK study to compare salts would have been useful
  − Mesylate salt in ethanol may produce highly toxic esters
Case Study #3: L-649,923 – Salt to Improve Stability

- Key Issues:
  - The free acid form equilibrated rapidly with the less active cyclic \( \gamma \)-lactone in solution:

![Chemical Structure]

Case Study #3: L-649,923 – Salt to Improve Stability

- **Salt Selection Strategy:**
  - Four salts (sodium, ethylenediamine, calcium, and benzathine) studied for:
    - Solubility
    - Intrinsic dissolution rate
    - Crystallinity
    - Hygroscopicity
    - Thermal stability
    - Photosensitivity
    - Drug-excipient compatibility
Case Study #3: L-649,923 – Salt to Improve Stability

- **Salt Selection:**
  - Crystalline ethylenediamine salt dropped due to thermal instability (20% loss after 40C/2 weeks)
  - Amorphous sodium salt dropped due to its hygroscopicity (pick up ~18% water at 76% RH)
  - Crystalline benzathine salt dropped due to low solubility and poor PK
  - Amorphous calcium salt selected for further development
    - chemically stable
    - not very hygroscopic (~1.2% water)
    - stability further enhanced by increasing microenvironment pH
    - difficulty crystallizing the compound: two organic carboxylate anions of a racemate might be difficult to form the required constrained crystal lattice network during the nucleation process
Case Study #3: L-649,923 – Salt to Improve Stability

- Plasma concentration vs time profiles for the calcium and benzathine salts of L-649,923 in rat (n=4), 20 mg/kg, 1% Methocel suspension
Case Study #3: L-649,923 – Salt to Improve Stability

• Key Learning and Comments:
  – Microenvironment pH should be a key consideration for salt selection
  – Understand the degradation mechanism is the basis for selecting the right salt and developing a chemically stable solid dosage form:
    • For Moisture-induced degradation in acidic conditions
      • selecting a basic salt
      • minimize the amount of free acid in the drug substance
      • ensure basic microenvironment pH by adding alkalizing agent
      • avoid an aqueous granulating process
      • use excipients that have low water content
Case Study #4: Carbapenem 1 – Different Salt Form for API and Formulation

• Background:
  – **Indication:** Anti-methicillin-resistant *Staphylococcus aureus* antibiotic.
  – **Chloride salt selected for parenteral formulation, in part because of its high aqueous solubility:** > 270 mg/mL at 25ºC.
  – **Structure:**

Case Study #4: Carbapenem 1 – Different Salt Form for API and Formulation

• Challenge:
  – Lyophilized drug product (citrate buffer and sucrose) is stable with 0.2% residual moisture. However, the API is not stable.
  – The difference in stability is due to the large discrepancy in moisture level (both initial and over storage).
  – Elimination Products (A and C)
  – Hydrolysis Products (B and D)
Case Study #4: Carbapenem 1 – Different Salt Form for API and Formulation

**Strategy:**
- Selection of benzensulfonate salt which is a crystalline, nonhygroscopic, and stable at RT.
- Use a nanofiltration process to convert the benzensulfonate salt (storage entity) to the chloride salt (formulated drug product).

**Benefit:**
- combine the positive attribute of these two salts into a single scalable process that
  - reduces process cycle time
  - increases the flexibility in manufacturing schedule
  - improve overall product quality
Case Study #4: Carbapenem 1 – Different Salt Form for API and Formulation

• Key Learning and Comments:
  – API and drug product may not have to be in the same salt form
  – What are the regulatory challenges with this approach?
  – Is the free base stable in this case? Can in situ salt preparation be used for the parenteral formulation?
Summary

• Selecting a desirable salt for development is an critical step in ensuring successful and efficient development of a robust product.

• Salt screening and selection involve multiple functions and require a well planned decision process.

• Salt selection is not necessary 100% science. There is no one size fits all approach.

• The new development in automation and high throughput technology for salt and polymorph profiling will make it possible to discover more possible salts and forms with less drug substance and time.

• Salt screening and selection should be an integral part of life cycle management.
Key References

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