Regulatory Perspectives Surrounding Non-traditional Uses of Excipients

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Symposium
Excipients as Atypical Actives in Nutraceuticals and Pharmaceuticals: Applications and Development Considerations

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Excipients

- Historically, excipients are considered *inert substances* that can be used mainly as diluents, binders, fillers, lubricants, etc. to assist in drug product manufacturing and performance.

- It is common practice to use the term ‘excipient’ and ‘inactive ingredient’ interchangeably to reference the components in the drug product, other than the active pharmaceutical ingredient (API).

- Code of Federal Regulations (CFR) Title 21, 210.3(b)(8) – an inactive ingredient is any component of a drug product other than the active ingredient.

- 21 CFR 314.94(a)(9)(ii) – inactive ingredients do not affect the relative safety or efficacy of the drug product.
Over the years, with the advancement in pharmaceutical science and technology, a broad range of excipients have become available that may possess several functions.

In addition to the capability of facilitating manufacture and performance of drug products, many excipients are added to achieve different purposes in a formulation, for example, increasing solubility of the drug, enhancing drug bioavailability, and controlling rate of drug release from the formulation, and so forth.

Not all excipients are *inert* substances!
Pharmaceutical Excipients

USP Definition

“All substances, other than the active drug or product, that have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support or enhance stability, *bioavailability*, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.”
Qualification of Excipients

◆ Excipients must be suitable for their intended use.
   Consider -
   ❖ Dosage form
   ❖ Route of administration
   ❖ Patient population
   ❖ Level of exposure
   ❖ Duration of exposure
   See FDA Inactive Ingredient Guide (IIG) or Database (IID)
   http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

◆ From a quality perspective, compliance with USP/NF specifications is generally sufficient to qualify an excipient. However, full CMC information is necessary for a non-compendial excipient from a different supplier and/or used in a different product.

◆ Safety information should be provided for new/novel excipients.
Safety of Excipients

- In general, compendial excipients are considered safe based on their history of use.

- If an excipient has been used in an approved drug product for a particular dosage form and route of administration, it is considered safe for use in similar drug products.

- An excipient that has been used in a marketed drug product given by a route of administration may be considered ‘new’ when administered by another route of administration. The level of concern will depend on the extent of direct exposure to the body.

- Consult review on safety data/information is generally requested for an ANDA (generic drug application) where a novel/new excipient is identified, or a known excipient is existing in IID with a different indication, route of administration, and/or duration of exposure.
Novel or New Excipients

◆ Safety data/information (animal pharm/tox or first-in-human studies) may be needed for a new or novel excipient.


◆ General Principles

❖ Perform risk-benefit assessment
❖ Establish permissible and safe limits
“Active” Excipients

◆ Most excipients included in drug products may not have direct pharmacological action, but a number of excipients can interact with the drug, other excipients, or physiological factors and thus affect drug solubility, permeability, dissolution, absorption and bioavailability.

◆ With the remarkable advances in science and technology, certain commonly used excipients that were thought to be ‘inactive’ in the past have recently been found to be ‘active’ and affect drug absorption and bioavailability.
An “atypical active” is currently used to denote an excipient that is being used as an “active ingredient” in a formulation. This is commonly seen as a single ingredient and/or used in OTC products, e.g., mineral oil (as a lubricant) and ethanol (as a hand sanitizer).

In many cases, the therapeutic activity of an “atypical active” may be derived from its own physical effect (not strictly pharmacological action).

The purpose of this presentation will be focused on excipients that may become ‘active’ due to -

- Physicochemical interactions with drugs or other excipients
- Interactions with biological processes *in vivo*
Physicochemical Interactions

- Complex formation between drugs and excipients has long been used to alter drug solubility, stability, dissolution or bioavailability. Example: cyclodextrin and acyclovir.

- Co-processing of drugs and excipients are utilized to improve drug solubility and/or dissolution rate. Example: lipid-based formulations for hydrophobic drugs.

- Most physical or chemical interactions in solid dosage forms take place between a drug and an excipient. However, an excipient-excipient interaction has been used to design a sustained-release theophylline formulation. The interaction between sodium alginate and calcium gluconate forms a cross-linked matrix that modulates the release of theophylline from the formulation.

Unintended Interactions

- Certain commonly used excipients have been reported to give rise to inadvertent or unwanted effects through a physical or chemical interaction with the drug.

Examples:

- Lactose with drugs containing amino group(s)
- Magnesium stearate and aspirin
- Eudragit® polymers with drugs bearing carboxylic moiety(ies)
- Povidone with haloperidol, ketoprofen and indomethacin, etc.

Impact on Product Quality

- Unwanted physicochemical interactions between a drug and an excipient in the dosage form or during manufacturing process may affect quality and stability of the drug product.

- Cases have been seen during the review of drug applications in FDA where lactose interacts with the drug having an amino group and forms an adduct (i.e., impurity) in the drug product.

- The level of adduct/impurity formed in the product may vary greatly with the grade, quality and quantity of lactose, as well as the manufacturing process.

- Controls for the plausible impurities formed by such drug-excipient interactions are necessary.
Effects on Biological Process

Many excipients can interact with biological environment or physiological factors, and influence drug bioavailability through a variety of mechanisms.

- Change in solubility or permeability of the drug
- Modulation of pH in gastrointestinal (GI) fluid
- Alteration of dissolution rate \textit{in vivo}
- Influence on GI motility and transit time
- Inhibition of metabolizing enzymes and/or transporters
- Other mechanisms

Effect on GI Motility

Some excipients are known to be osmotically active in the GI tract, which can enhance GI motility and accelerate intestinal transit, thereby shortening absorption time of the drug in the intestine and reducing its bioavailability.

Examples of excipients may include:
- Non-absorbable sugar alcohols (sorbitol, mannitol, xylitol)
- Polyethylene glycols (PEG 400, PEG 4000)
- Sodium acid pyrophosphate
- Lipid excipients
Sorbitol and Ranitidine

Mannitol & PEG 400

Osmotically Active Excipients

- Effects of these excipients on GI motility/transit time are related to the characteristics (such as intestinal permeability) of a drug.

- While 5 gm of sorbitol was shown to decrease the absorption of ranitidine (a low permeability drug) by 45%, 10 gm of sorbitol had minimal effect on the bioavailability of theophylline (a high permeability drug).


- Similarly, in the FDA contract study, 5 gm of sorbitol decreased the bioavailability of ranitidine by 45%, but the same amount of sorbitol only reduced metoprolol absorption by 7%. Metoprolol is a drug with high permeability.

Interplay with Physiological Factors

- Apart from drug permeability, whether change in GI transit time will affect drug bioavailability may also vary with the amount of excipient, mechanism and site of drug absorption, and perhaps other factors (e.g., metabolism, efflux and/or degradation) of the drug in vivo.

- Studies in men on PEG 400 (excipient) with ranitidine (drug)
  - Study I, PEG 400 from 1 to 5 gm
    Drug bioavailability ↓ as excipient amount ↑
  - Study II, PEG 400 from 0.5 to 1.5 gm
    Drug bioavailability ↑ as excipient amount ↑

- The observed difference these study results has been attributed, in part, to the potential interplay between the osmotic effect of PEG and its modulation of intestinal permeability via inhibition of P-gp efflux.

Surfactants and polymers are most common excipients that have been reported to inhibit drug metabolizing enzymes and efflux transporters *in vitro* or *in vivo*. **Examples:**

<table>
<thead>
<tr>
<th>Enzymes/Transporters</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP 3A</strong></td>
<td>Cremophor, PEG-400, Oleic acid, Tween-80, Tween-20, Pluronic block copolymers</td>
</tr>
<tr>
<td><strong>UGT 2B7</strong></td>
<td>PEG-400, Tween-20, Tween-80</td>
</tr>
<tr>
<td><strong>P-gp or MRP</strong></td>
<td>Cremophor EL, RH40, PEG-300, PEG-400, Tween-20, Tween-80, Triton X-100, Vitamin E-TPGS, sodium caprate, solutol HS-15, Pluronic block copolymers</td>
</tr>
</tbody>
</table>

Lipid Excipients

- Lipid excipients are commonly used to enhance the solubility and bioavailability of poorly water-soluble drugs.

- Unlike traditional excipients, lipid excipients are able to solubilize hydrophobic drugs within the dosage form matrix.

- However, as with dietary lipids, lipid excipients can be digested and dispersed \textit{in vivo}. They can also be transported by lipoproteins that are involved in the intrinsic lipid pathway through the vascular and extravascular body fluids to the cells.

- Different types of lipid excipients can have a significant impact on the transport process and clearance kinetics of lipid-based formulations.

- For example, cholesterol-poor liposome vesicles were cleared more readily than cholesterol-rich vesicles. While cholesterol-poor vesicles were predominantly localized in the liver, incorporation of cholesterol increased liposomal uptake by both spleen and bone marrow.

Many hydrophobic drugs are primarily metabolized by CYP3A enzymes. Several of these drugs are also substrates and/or inhibitors of P-gp. The potential interaction between lipid excipients and these enzymes/transporters further complicates drug absorption.

<table>
<thead>
<tr>
<th>CYP 3A Substrate</th>
<th>P-gp Substrate</th>
<th>P-gp Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td></td>
<td>x</td>
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<tr>
<td>Carbamezpine</td>
<td></td>
<td></td>
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<tr>
<td>Cyclosporine</td>
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<tr>
<td>Indinavir</td>
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<tr>
<td>Itraconazole</td>
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</tr>
<tr>
<td>Ketoconazole</td>
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<td></td>
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<tr>
<td>Lanzoprazole</td>
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<td>Lovastatin</td>
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<tr>
<td>Ritonavir</td>
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<td>Saquinavir</td>
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<tr>
<td>Sirolimus</td>
<td></td>
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<tr>
<td>Tacrolimus</td>
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</tr>
</tbody>
</table>

Lipid-based Formulations

- Use of lipid excipients for formulations is inevitably complicated and has presented challenges for pharmaceutical industry and regulatory scientists.

- Complex interactions can occur between lipid excipients, surfactant(s), incorporated drug and GI environment for a lipid-based formulation administered orally.

- To ensure product quality and performance, special attention should be given to the unique characteristics of lipid excipients and dosage forms. Selection of lipid excipients should also consider -
  - Compatibility with active ingredients and capsules
  - Physical and chemical stability
  - Consistency in quality/performance throughout shelf life
  - Safety of new/novel excipients
Evaluation of Bioequivalence

◆ A regulatory concern for ‘active’ excipients lies in the determination of relative bioavailability and bioequivalence.

◆ Two products with the same drug substance in the same dosage form may not be bioequivalent if one product contains an ‘active’ excipient and the other does not.

◆ The question of whether two products in comparison are bioequivalent or have similar bioavailability may also arise if both products have the same ‘active’ excipient (but different amounts) in their formulations.

◆ Example – Sorbitol vs. Sucrose
Sorbitol vs. Sucrose

5 gm of sorbitol or sucrose (N=20)

Sorbitol Effect: Dose-Dependent

# Sorbitol Study

## 90% Confidence Intervals vs Tx4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GeoMean</th>
<th>% Ref</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax</strong></td>
<td>(ng/mL)</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Tx 1</td>
<td>244</td>
<td>47.9</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>Tx 2</td>
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<td>70.3</td>
<td>63</td>
<td>78</td>
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<tr>
<td>Tx 3</td>
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<td>92.7</td>
<td>83</td>
<td>104</td>
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<tr>
<td>Tx 4</td>
<td>509</td>
<td>*</td>
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</tr>
<tr>
<td><strong>AUClast</strong></td>
<td>(ng*hr/mL)</td>
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<td>Tx 3</td>
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<td>84</td>
<td>101</td>
</tr>
<tr>
<td>Tx 4</td>
<td>2553</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>AUC inf</strong></td>
<td>(ng*hr/mL)</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Tx 4</td>
<td>2685</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Another regulatory concern for ‘active’ excipients may be related to the development and quality of generic drug products.

As an example, use of lactose in formulations for APIs that have amino group(s) may lead to the formation of an impurity in the drug product.

Scenario 1 – innovator has lactose in the formulation (RLD)
- A generic sponsor may include lactose in its formulation with or without knowing the impact of this ‘active’ excipient on the product quality.
- Control of the impurity can be made by establishing the impurity limit comparable to (or tighter than) that of RLD, close to the expiration date.

Scenario 2 – generic product has lactose, but RLD does not.
- In this case, qualifying the impurity for generic product based on testing with the innovator product is impossible, and thus safety data/information is needed for approval of the generic product.
Applying Quality by Design (QbD) principle for the development and selection of excipients in a formulation is essential.

The QbD approach encourages
- Understanding variation of excipient properties as they relate to product quality attributes
- Building robustness and flexibility into manufacturing process to mitigate variability
- Establishing appropriate specifications to ensure product quality

References – ICH Quality Guidelines related to QbD principle
- Q8, Q9, Q10 and Q11
Conclusions

- The importance of recognizing the presence of an ‘active’ excipient in a formulation cannot be overemphasized during drug development for both generic and innovator companies.

- It is conceivable that the presence of an ‘active’ excipient may have a significant influence on the product quality, stability, bioavailability, bioequivalence, and consequently, safety and efficacy.

- Mechanistic understanding of interactions between an ‘active’ excipient with drug, other excipients or biological environment will help to ensure product quality and performance.

- The QbD approach facilitates better understanding of the properties of an ‘active’ excipient and fosters the optimal use of the excipient in a formulation.
Thank You!