Overcoming Excipient Risks and Challenges for Parenteral Formulations

ATTRIBUTES OF EXCIPIENTS FOR HIGH-RISK FORMULATIONS

Excipients play an important role in parenteral formulations, which are high-risk given their route of administration. They protect, support, and enhance stability and bioavailability, modulate release of the API, and can enhance effectiveness of the drug.

As with any dosage form, excipient selection for parenteral applications should be based on the specific, targeted, and expected function. Critical material attributes (CMA) of the excipient must be considered as this may have a direct impact on the critical quality attributes (CQA) of the drug product. It is especially important that excipients be inert with low bioburden and low endotoxin for parenteral dosage forms as even trace amounts of impurities can interact with the active pharmaceutical ingredient (API) or other excipients. This ensures that API levels in the final formulation are not impacted, the API remains stable, and generation of reaction products with potential health hazards is prevented. Endotoxin and bioburden level control is also important to avoid any impact on the formulation and formulation stability and to reduce any direct risk to the patient.

Excipients should be unaffected by the sterilization or manufacturing process and be manufactured according to appropriate GMP, such as International Pharmaceutical Excipient Council and Pharmaceutical Quality Group Good Manufacturing Practices (IPEC-PQG GMP).

Several **excipient** categories are routinely used in parenteral applications including:

- Preservatives
- Buffers
- Tonicity adjusters
- Stabilizers
- Viscosity modifiers
- Antioxidants
- Solubilizers

DEVELOPMENT CHALLENGES FOR HIGH-RISK FORMULATIONS

There are many development challenges for parenteral formulations including:

- **Particulate matter**
- **Microbial purity**

- **No interaction with API**
- **Solubility enhancement**
- **Trace amount of impurities**
- **Stability**
- **Process optimization**

Each of these challenges is described in greater detail below.

Particulate Matter

Of the sterile injectable drugs recalled by the United States Food and Drug Administration (FDA) between 2008 and 2012, 22% were due to the presence of visible particles.[1] Root causes range from the API and excipients, to water, equipment, container closures, and crystallization of the drug itself.

Several strategies can be employed to mitigate the risk of particulate matter from excipients including manufacturing according to IPEC-PQG GMP guidelines in an environment that ensures low bioburden and appropriate use of quality control procedures. Paper-free packaging should be used to eliminate the possibility of particulate matter resulting from the paper.

In the case where particulate matter is unavoidable in an excipient, details should be provided by the supplier in the form of a technically unavoidable particle profile (TUPP).

Microbial Purity

Bioburden and endotoxin limits are defined for high-risk applications. Since excipients can introduce bioburden and endotoxin contaminations to the process and product, excipient suppliers must control the levels of impurities and provide the relevant information on the levels to the drug manufacturer. Our **Emprove® Expert portfolio** offers a range of excipients intended specifically for high-risk applications and feature low specified bioburden and endotoxin levels. The information is readily available in the relevant product specifications and Emprove® Dossier.

While they are not allowed in large-volume parenterals such as infusions or restricted in use for single-dose injections, a range of preservatives can be included in small-volume multi-dose containers to ensure sterility. Common preservatives are effective in a range of different pH values as shown in Figure 1.

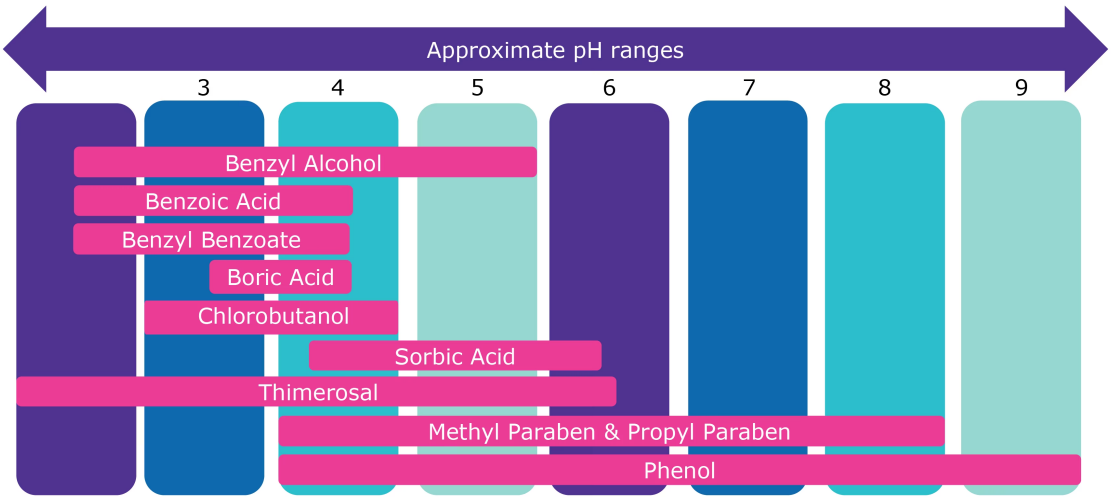

Figure 1. Approximate pH ranges of preservatives for multi-use formulations.

No Interaction with API

Incompatibility of the excipient and API can lead to undesirable results as shown in Table 1. For example, if the API has a primary amine functional group and the excipient is a mono- or disaccharide, a Maillard reaction can take place resulting in a formulation color change.

Functional group	Incompatibilities	Possible Type of Reaction
Primary amine	Mono- and disaccharides	Maillard reaction
Ester, cyclic lactose	Basic components	Ring opening, ester-base, hydrolysis
Aldehyde	Amine, carbohydrates	Aldehyde-amine, Schiff base or glycosylamine formation
Carboxyl	Bases	Salt formation
Alcohol	Oxygen	Oxidation to aldehydes and ketones
Sulfhydryl	Oxygen	Dimerization

Phenol	Metals	Complexation

Table 1. Examples of API and excipient incompatibilities.

Another example is benzyl alcohol; the presence of a benzaldehyde impurity will interact with the benzyl alcohol as well as the API, leading to its degradation. This problem can be avoided by selecting a benzyl alcohol excipient with a lower level of benzaldehyde impurity when formulating an oxidation-prone API.

Solubility Enhancement

A number of excipients are available to enhance the solubility and stability of APIs in parenteral formulations including meglumine and hydroxypropyl-β-cyclodextrin.

Meglumine is a derivative of sorbitol in which the hydroxyl group in position 1 is replaced by a methylamino group. The pK_a value of meglumine is 9.52, its solubility in water is 1000 mg/mL and it can form counterions with the API. This organic base can be used as a pH, solubilizing, buffering, and stabilizing agent. It can also scavenge for formaldehyde which is an impurity generated during storage of many excipients including polyols, hydroxypropyl methylcellulose (HPMC), polysorbates, poloxamers, and polyethylene glycols (PEGs).[2]

Hydroxypropyl-β-cyclodextrin can also enhance API solubility and stability. Cyclodextrins are cyclic oligosaccharides derived from natural starch. The α-1,4-D-glucopyranoside units are arranged in the form of a hollow cone with a hydrophilic exterior and a hydrophobic cavity. Within this cavity, cyclodextrins can interact with hydrophobic, poorly water-soluble APIs forming an API-cyclodextrin inclusion complex. This “host-guest” interaction is reversible, and the API is easily released once administered to the body.

Trace Impurities

The presence of trace impurities can be a challenge during formulation of high-risk parenteral and ophthalmic products. The limits defined by the excipient manufacturer should be considered in relation to those set by the relevant pharmacopeia; in many cases, a lower level is advantageous for high-risk dosage forms.

For example, use of highly concentrated solutions of Tris (hydroxymethyl) aminomethane can lead to precipitation of polyoxymethylene (POM). To minimize this risk, our **Tris Emprove® Expert** has POM levels of ≤ 90 ppm.

Similarly, the level of reducing sugar in an excipient must be considered as this can lead to Maillard reactions with amine drugs leading to a reduction in drug potency and discoloration as described above. Our **Mannitol** and **Sorbitol Emprove® Expert** products have reducing sugar limits below the limits defined in Ph. Eur. and USP.

Stability

Stability of liposomal formulations, also in the high-risk category of parenterals, is essential, and trehalose is a commonly used excipient to deliver the desired particle size and polydisposability index (PDI) following lyophilization. Use of trehalose also minimizes the amount of residual moisture in the liposomes, further stabilizing their structure. Lipids are prone to hydrolysis and a higher level of moisture in the formulation can lead to generation lyso-lipids as an impurity which can lead to faster *in vivo* drug release.

Our high-quality grade of trehalose, **Trehalose Emprove® Expert**, is multicompendial with specified low levels of endotoxins and bioburden, making it ideal for high-risk applications.

Process Optimization

Compatibility of excipients with the manufacturing process must be considered so that the overall process can be optimized.

For example, many preservatives bind or are adsorbed to membrane filters which causes a loss of the desired amount of preservative in the final formulation. Figure 2 compares the concentration of benzalkonium chloride (BAK) following filtration of a 0.1% solution through different 0.2 mm sterilizing grade polyethersulfone (PES) or polyvinylidene difluoride (PVDF) membranes. The filter with the lowest BAK binding (Millipore Express® SHF) showed the lowest BAK loss in the final product. Other filters would require additional flush volume or cause loss of drug product.

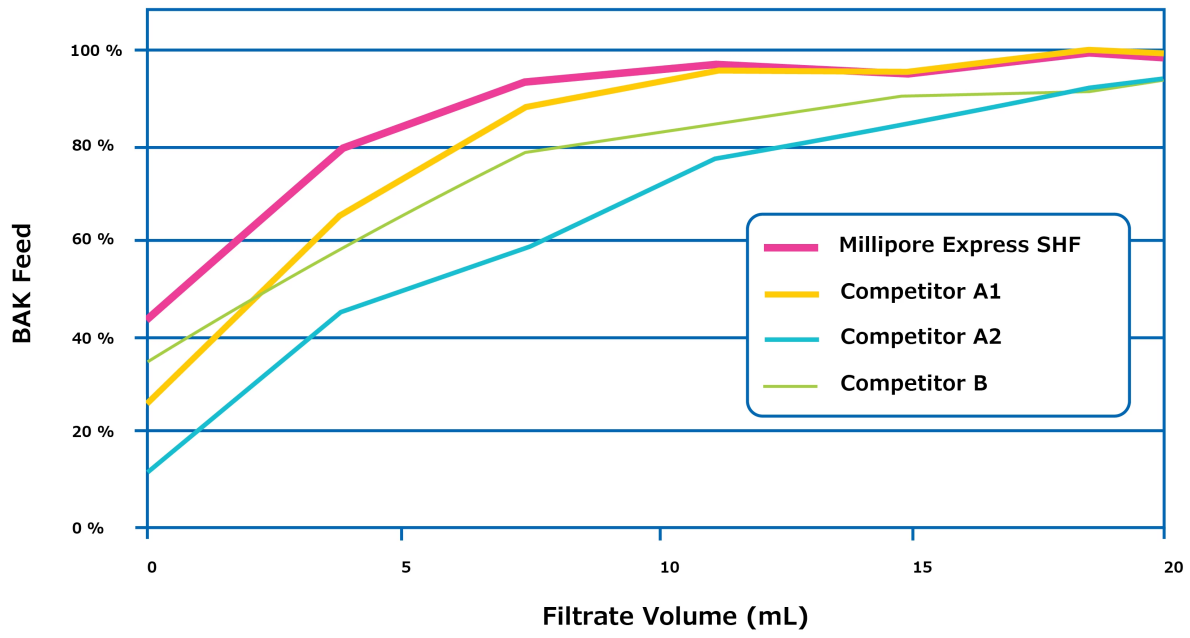

Figure 2. BAK concentration in filtrate of Millipore ® Express SHF and competitive PES filters.

REGULATORY REQUIREMENTS FOR EXCIPIENTS

Controlling the quality of excipients is important because they are a critical component of final drug formulations. GMP requirements for excipients are not defined by authorities in a prescriptive way. Therefore, the burden of assuring excipient quality falls on the drug manufacturer. Further complicating the excipient selection process is that for many manufacturers, the excipient application of their product is not the primary focus. Oftentimes, excipients were initially designed for use in other applications where quality requirements can be quite different from the biopharmaceutical industry.

It is therefore incumbent upon drug manufacturers to assure excipient quality requirements are met. Achieving this goal necessitates development of controlled processes and systems for ensuring that raw materials and suppliers meet expectations, which requires implementation by excipient manufacturers and their support by providing all necessary information to drug manufacturers.

REDUCE RISK WITH THE RIGHT EXCIPIENTS

A wide variety of excipients are available to address the challenges presented by high-risk formulations such as parenterals. Excipients can be used to solve problems related to solubility, stability, and viscosity, among others, and should be of the highest quality, have low bioburden and endotoxin levels, and interact with the API in a desirable manner.

Overcome Excipient Risks in Parenteral Formulations

For more detailed information on excipient selection for high-risk formulations:

- **Read the article** “**Assuring Excipient Quality for Parenteral Products**”
- **Watch the on-demand webinar “Excipients Selection for High-Risk Formulations**”

Related Products

Product No.	Description	SDS	Pricing
1.06187	**Meglumine** EMPROVE® EXPERT, Ph. Eur., ChP, JP, USP		**Expand**
1.42020	**Cyclodextrin HPB** EMPROVE® EXPERT, Ph. Eur., NF		**Expand**
1.08307	**Tris(hydroxymethyl)aminomethane** (Trometamol) high purity, EMPROVE® EXPERT, Ph. Eur., BP, ChP, JPC, USP, ACS		**Expand**

Product No.	Description	SDS	Pricing
1.37096	**D-Mannitol** EMPROVE® EXPERT, Ph. Eur., BP, ChP, JP, USP		Expand
1.11597	**Parteck® SI 400 LEX (Sorbitol)** EMPROVE® EXPERT, Ph. Eur., BP, NF, JP		Expand
1.02776	**Trehalose dihydrate** EMPROVE® EXPERT, Ph. Eur., ChP, NF, JP		Expand

View All Products Dedicated to Parenteral Applications

References

1. Steven L. FDA Office of manufacturing and Product Quality. 14 May 2013.

2. Fujita M, Ueda T, Handa T. 2009. Generation of Formaldehyde by Pharmaceutical Excipients and Its Absorption by Meglumine. *CHEMICAL & PHARMACEUTICAL BULLETIN.* 57(10):1096-1099. **https://doi.org/10.1248/cpb.57.1096**