Product Development Issues of Powders for Injection

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Powders for injection (PIs) are a popular parenteral dosage form for drugs that cannot be marketed as ready-to-use injectables because of their instability in an aqueous environment. PIs are relatively simple with respect to formulation and process development. However, their performance and stability is critically affected by a number of parameters. This article traces the preformulation, formulation, pack selection, and process scale-up issues to be considered for the development of stable and efficacious PIs.

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Powders for injection (PIs) constitute an important category of dosage forms for active molecules. Because of their instability in the aqueous environment, PIs cannot be marketed as ready-to-use injectables (1). Instead, they are marketed as dry powders to be reconstituted with a suitable vehicle just before administration. The final form after reconstitution may be either a solution or a suspension (2). Typical molecules in this category include β-lactam antibiotics, cephalosporins, and acyclovir. A few ready-to-use infusion products are marketed as frozen solutions in plastic bags for these molecules. However, the low temperature required for their shipment and storage makes these products an unviable option, especially in countries in which a cold chain from manufacturing to the point of consumption is difficult to establish.

Depending on their formulation strategy, PIs can be categorized into any of the classes shown in Figure 1. Two strategies can be adopted for the formulation and manufacture of PIs (see Figure 2). The first strategy of lyophilizing (freeze-drying) the primary pack allows the formulation of drugs that are thermolabile or unstable in aqueous solution. However, lyophilization normally yields an amorphous or partially amorphous product, which leads to solid-state instability (3). A more-stable crystalline stage can be obtained by crystallization in aseptic conditions, and it can be maintained by directly filling the sterile dry-powder drug into presterilized vials (see Figure 2, Strategy 2). The dry-filling process also is much more cost effective because it requires less infrastructure as well as a reduced amount of energy and a shorter amount of time to produce a batch (4). These reasons have made dry-filled PIs a popular dosage form. A PI formulation may consist of drug only or drug plus excipient. Table I lists a few examples of formulations containing functional excipients.

The dry-powder fill approach involves depositing a drug (plus excipient) into individual vials using suitable filling equipment. The entire process does not involve the addition of an excipient or processing step except when two drugs or a drug and an excipient are mixed. Complexities resulting from the presence of an excipient (e.g., interactions with the active molecule and product performance) are absent in PIs containing only the active drug. Formulations containing a drug and excipients also are relatively simple in terms of number and variety of excipients. For this reason, formulation development scientists tend to underestimate the development process of PIs. This is where the

Table I: Examples of formulations containing functional excipients.

Product Name	Trade Name (Manufacturer)	Excipient Present (Category)
Aztreonam for injection	Azactam for injection (Dura)	Arginine (solubilizer)
Cefepime for injection	Maxipime (Dura)	L-arginine (buffering agent)
Ceftazidime for injection (L-arginine formulation)	Ceptaz (Glaxo Wellcome Inc.)	L-arginine (solubilizer)
Ceftazidime for injection	Fortaz (Glaxo Wellcome Inc.) Tazicef (SmithKline Beecham)	Sodium carbonate (solubilizer)
Cephalothin for injection	Keflin (Eli Lilly)	Sodium bicarbonate (buffer)
Imipenem and Cilastatin for injection	Primaxin IV (Merck)	Sodium bicarbonate (buffer)
Penicillin G potassium for injection	Pfizerpen (Pfizer)	Sodium citrate/citric acid (buffers)

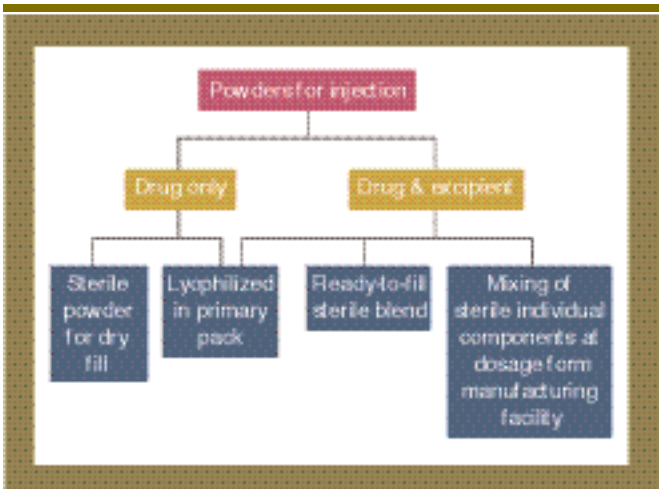

Figure 1: Classification of powders for injection.

danger lies. Scientists must understand the nuances and microbehaviors that are critical for product performance, and the development activity should be based on sound scientific principles. This article explains how a sound understanding of the preformulation, formulation, pack selection, and process scale-up parameters can ensure the development of a stable PI product.

Preformulation studies

Preformulation research involves pharmaceutical and analytical investigations that both precede and support formulation development efforts for all dosage forms (5). The general subject of preformulation research has been discussed in detail in the literature (6–8), and preformulation studies specific to parenteral medication also have been described (5). The following section discusses preformulation issues specific to PIs.

One of the major factors controlling performance of a powder dosage form like PIs is the solid-state pharmaceutics of the drug powder. It acts at three levels: molecular, particle, and bulk.

The molecular level is characterized by the crystal lattice arrangements of the molecules and how they affect properties such as aqueous solubility, dissolution kinetics, hygroscopicity, and chemical stability. A drug can exist in amorphous or crystalline form. *Polymorphism* is the existence of several crystalline forms of a compound, and it has serious implications on physicochemical properties and product stability (9,10). Ashizawa et al. studied various solid forms of an investigational 3 betaine–type cephalosporin, E1040, with respect to chemical stability (11). Three forms were studied: freeze-dried anhydrous amorphous form, crystalline form, and sodium chloride–additive freeze-dried amorphous form. They found that only the latter two forms were chemically stable during thermal stress.

Particle and bulk properties primarily control derived powder properties such as flow. At the particle level, the forces are influenced by several fundamental physicochemical properties, including particle density, particle-size distribution, particle morphology (i.e., shape, habit, surface texture), and surface composition (e.g., absorbed moisture) (12). These characteristics have an important effect on powder bulk properties. Flow is the most important bulk property that influences the filling of PIs into primary packaging containers. It is a function of the principal adhesive forces between particles (e.g., Van der Waals forces and electrostatic forces) (13).

The particle size of the drug can affect the PI formulation by modifying the dissolution rate and time required for reconstitution and by influencing the syringeability of the suspension. Particle size also affects the level of pain at the site of injection with suspensions.

The particle-size distribution should be controlled at the sterile bulk drug manufacturing facility. Attempts to modify particle-size distribution by milling and sieving could seriously affect sterility and levels of particulate matter. Therefore, pharmaceutical preformulation scientists should establish the specifications for particle-size distribution that must be met by the bulk drug manufacturer.

Optical or scanning electron microscopy provides useful information about particle-surface morphology and individual particle-surface characteristics that affect particle-flow characteristics. Heterogeneity of morphological forms could indicate the existence of hydrates, solvates, or polymorphic forms, which could significantly alter physicochemical properties (9,10). In the case of PIs, these factors could seriously affect the reconstitution time and product stability.

A high degree of hygroscopicity in the drug greatly influences a spectrum of parameters in PIs. Apart from a deleterious effect on product stability, it can affect flow properties. Classification of drugs into hygroscopicity classes such as nonhygroscopic, slightly hygroscopic, moderately hygroscopic, and very hygroscopic helps one decide the environmental conditions needed

Table II: Preformulation studies carried out on APIs.

Preformulation Study	Affected Properties	Evaluation Technique
Crystalline form, crystalline versus amorphous polymorphism	Aqueous solubility, dissolution characteristics (reconstitution time), chemical stability, hygroscopicity	X-ray diffraction, DSC, IR spectroscopy, polarized light microscopy, hot-stage microscopy
Particle characteristics, particle size, crystal habit, particle shape	Flow properties	Optical microscopy, SEM
Particle-size distribution	Flow properties during filling operations in auger-filling machines. Solutions: reconstitution time, blend uniformity. Suspensions: syringeability and pain at the injection site	Sieve analysis with particle-sizing equipment
Bulk density and compactibility	Flow properties and compact formation in vacuum-based rotary filling machines	Angle of repose, Carr index, Hausner ratio
Water content	Chemical stability during storage, flow properties	Karl Fischer apparatus, ERH meter
Hygroscopicity	Stability, environmental conditions for processing	Gravimetric method

during processing and filling operations (5). For example, sodium cefazolin can exist in a number of hydrated forms. Evaluation of the water content of the hydrate forms of sodium cefazolin as a function of relative humidity (RH) reveals sesquihydrate as the most stable structure (14). A hygroscopicity profile of a generic product that is different from that of the innovator product indicates the presence of a different polymorph, solvate, or hydrate, a condition that should be carefully monitored to ensure product equivalency to the innovator.

Solubility and dissolution rate are of primary importance for PIs that must yield a clear solution upon reconstitution. Solubility and pH-solubility determinations provide useful information for formulation development (5). The preformulation data may indicate whether one must improve the solubility of the drug. The addition of buffering agents (such as sodium carbonate) to control the pH or solubilizers (such as L-arginine) is the most commonly followed approach (see Table I) for improving the solubility of a drug in PI dosage forms. Table II summarizes the preformulation studies to be carried out on the active pharmaceutical ingredient.

Prototype formulation development

Dry-mixing step. Mixing the sterile drug with an excipient adds a degree of complexity to the formulation process in terms of verifying uniformity of blend, and it introduces the possibility of demixing during bulk-drug shipment and formulation processing. Particle parameters such as differences in bulk densities of drug and excipient, particle morphology, and flow properties are of critical importance. For optimal mixing, the bulk densities of the bulk drug and excipient should be similar, and the particles should exhibit a smooth spherical surface. However, the latter also increases the chance of demixing in the postmixing and prefilling steps. All these parameters need cautious optimization to ensure a uniform product.

The following strategies are adopted during bulk-drug and dosage form manufacturing to prevent the segregation of constituents having varying particle sizes:

- bulk-drug manufacturing: vacuum packing of API–excipient blend to prevent relative particle movement and segregation during shipment and storage
- dosage form manufacturing: optimization of mixing in terms of mixer speed and mixing time.

Stability of the reconstituted solution or suspension. The stability of a PI includes two aspects: the stability of the powder and the stability of the reconstituted suspension or solution. To evolve meaningful postreconstitution utility times, stability data after reconstitution should be generated using all the probable reconstitution solvents at various temperature conditions. The reconstituted solutions must be assessed for both physical and chemical stability (15,16). Color absorbance sometimes can be used as a quantification tool during early product-stability studies (17). The effect of any other medicinal product that is likely to be coadministered also should be assessed (18–20). These stability studies should be carried out at the extremes and median value of product pH. Simulation studies in the presence of materials likely to come in contact with the reconstituted injection (e.g., plastic syringes and intravenous tubings) also should be conducted to assess their effect on product stability.

The following parameters must be evaluated during the course of accelerated and real-time stability studies:

- assay and related substances (dry powder and reconstituted suspension)
- water content
- discoloration (color absorbance value)
- pH of the reconstituted solution
- pH of the reconstituted product
- reconstitution time
- clarity of the reconstituted solution (particulate matter)
- sterility
- bacterial endotoxins.

Selection of the rubber closures. Important factors to consider when selecting rubber closures for PIs are the physical and chemical compatibility with the formulation, water vapor permeability, oxygen permeability, and leachables (21).

Commercially available rubber plugs are broadly categorized

Figure 2: Two strategies for the formulation and manufacture of PIs.

as butyl or halobutyl. However, rubber closures that are classified in the same chemical category but come from various vendors can have subtle differences in gas and moisture-vapor transmission. Gas transmission affects the retention of postfilling purged inert gas, and moisture-vapor transmission affects the ingress of environmental moisture into the pack. Both parameters have serious implications on product stability. The migration of volatile components into the headspace of vials sealed with rubber closures is a potential source of haze formation in reconstituted solutions of PIs. Gas chromatography–mass spectrometry techniques have been used to characterize these volatiles in butyl and halobutyl rubber plugs and have identified components such as saturated hydrocarbons, unchlorinated and chlorinated olefins, alkylbenzenes, and low molecular weight polydimethylsiloxanes (22).

Rubber plugs should be finalized after stability studies are carefully performed while the product is in continuous contact with the rubber plug (inverted state). Product parameters such as drug assay, water content, and color absorbance should be evaluated during the stability studies.

Pack considerations. *USP* specifies that "containers, including the closures for dry-powder solids intended for parenteral use, do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling shipment, storage, sale, and use" (23). Theoretically speaking, PIs can be packed in Type III glass vials because only a remote possibility exists of leaching inorganic ions from the glass as a result of the inherently low moisture content of PIs. However, the final decision must be based on stability studies conducted on the dry powder and on the reconstituted product. Sensitivity of the product to pH fluctuations in either the dry-powder or reconstituted state calls for the use of USP Type I glass.

One must also give due consideration to the neck diameter of the glass vials being used. Glass vials generally are available in standard diameters of 13, 20, and 28 mm. Products that require postfill purging of inert gas for stability reasons will retain the inert gas for a longer period of time if the product is packed in vials with small neck diameters. A dual advantage is achieved as a result of an overall reduction of headspace and a reduction of rubber-plug surface area, which is a critical factor for decreasing the escape of inert gas introduced in the headspace. The reduced surface area of the rubber pack will decrease the rate of escape of the inert gas. However, one should take into account the surface-area requirements for fitting the devices for delivery of reconstituted product to a patient.

Effect of equilibrium relative humidity (ERH) during filling on product stability. Trial simulations of the filling process can be carried out by filling the product at various RH conditions. Changes observed in a product's water content (using a Karl Fischer technique or ERH meter) and other properties will help finalize the environmental conditions to be maintained during product processing. If the humidity is too high during filling, then the powder may become compacted and physicochemically unstable. Humidity conditions that are too low can create electrostatic charge, causing poor flow (24) and/or efflorescence from the drug powder.

Effect of postfilling inert gas purging in the overhead space. Because of the inherently unstable nature of drugs presented as PIs, all the parameters capable of altering stability should be carefully monitored. Postfill purging of the vial with an inert gas such as helium or nitrogen helps to improve chemical stability and prevents product discoloration as the result of aging. This lab-scale study is best performed using glass ampules because they provide a perfect, hermetically sealed pack. This type of container helps prevent the ingress of oxygen and, if required, helps retain the inert atmosphere. Studies performed on products contained in glass vials sealed with rubber closures provide unreliable results because of the variable gas-permeation rates of different rubber closures. However, comparing data from studies of oxygen-purged and inert gas–purged packs can generate conclusive results. Once the need for inert-gas purging has been established, various strategies to reduce the loss of inert gas during shelf life should be evaluated. These approaches include selecting the proper rubber closure (type and size) and optimizing vial headspace. The scale-up of the inert-gas purging process to production levels also requires careful consideration to ensure optimum and uniform purging in all packs. Two types of devices are used to complete this process: valve-controlled gas delivery using a dosing needle and a continuous blanket of inert gas in the postfilling, presealing zone. Both strategies require careful monitoring of parameters such as moisture content of the gas, filtration through 0.2-μm filters, and gas pressure to ensure uniformity of purging in all packs.

Helium and nitrogen are the most commonly used gases for purging. Though more costly than nitrogen, helium can be advantageous because it has a higher density than air and consequently is less likely to escape.

Postfilling vacuum treatment. Many PIs contain sodium carbonate or sodium bicarbonate as a solubilizer. Adding aqueous solvent at the time of reconstitution produces carbon dioxide gas. The pressure generated inside the vials ejects the plunger of the syringe used for withdrawing reconstituted solution. In extreme cases the plunger may be thrown out of the syringe,

Troubleshooting approach for problems related to particulate matter

Particulate matter detected in reconstituted solution.

Stage 1: Examine the API bulk for particulate matter. Particulate matter detected: remedial action at API manufacturing facility; change API source.

Stage 2: Cleanliness of primary packaging materials (glass vials and rubber plugs). Particulate matter detected: Validate the cleaning procedure; investigate particle shedding from inner metal surfaces of vial drying tunnel, dry-heat sterilizer, autoclave, and, if needed, initiate remedial actions.

Stage 3: Assessment of contribution of environmental factors. Initiate remedial actions if particle counts in air beyond specified limits.

Stage 4: Assessment of role of personnel, especially cleanroom dresses and rubber gloves. Initiate remedial action if particle shedding observed from dresses; validate cleaning process of rubber gloves to remove traces of lubricants such as starch and talc from glove surfaces.

Stage 5: Cleanliness of filling machine and particle shedding from moving parts coming in contact with the API bulk. Validate the cleaning process; replace packing used around agitation blade's rotating shaft with particle nonshedding packing.

Stage 6: Particle shedding from rubber plugs. Replace with compatible rubber plugs.

leading to spillage of reconstituted solution. This outcome can be avoided by providing postfilling vacuum treatment, which balances the pressure generated during solubilization.

Scale-up issues

Scaling up a PI formulation involves the following:

- Powder homogeneity requires critical evaluation if drug–drug or drug–excipient mixing is carried out at the formulation manufacturing facility. Depending on the formulation's composition, one should apply the requirements of weight variation or content uniformity mentioned under "Uniformity of Dosage Units" in *USP 24–NF 19* (25).
- Product sterility in PI dosage forms is governed by the validation and control of manufacturing operations (26). Another formulation/packing parameter that contributes to sterility is assessing the failure of rubber plugs to maintain a hermetic seal. To ensure a hermetic seal, part of the stability protocol should include pack-integrity studies performed during the stability studies of scale-up batches.

Control of particulate matter in PIs

It is widely recognized that the level of particulate matter in an injectable product, apart from the systemic hazards (27,28), is a measure of quality that directly reflects the success with which a manufacturer applies good quality control (29). Particulate matter consists of mobile, randomly sourced, extraneous substances other than gas bubbles. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, essentially should be free from particles that can be observed on visual inspection. Furthermore, the *USP* limits for subvisible particulate matter in the small-volume parenterals by light obscuration technique are not more than 6000 and 600 per container for particles $\geq$10 and 25 μm, respectively (30).

Particulate matter in dry-powder injectables remains a primary area of concern. Various investigative reports in the literature have addressed this important issue. Longe presented a comparative assessment of particulate contamination in parenteral products and classified them as: fibers >100 μm, 51–100 μm, 25–50 μm, and 10–24 μm. He concluded that particulate counts appear to correlate with the manufacturing process; bulk drugs were found to be highly contaminated, followed by lyophilized powders and stable solutions (31). Backhouse et al. found similar results in their investigation (32). Several reports specifically describe particulate contamination in PIs. Alexander and Veltman studied 12 antibiotic formulations from five South African sources using a light-blocking particle analyzer (33). Results were within *USP* XXI limits, but four formulations contained particles >50 μm, which likely were visible particles. Parkins and Taylor studied particulate matter content in 11 reconstituted PIs and found that all complied with *USP* limits (34). In other studies, researchers concluded that PI products made with a bulk-fill technique have a greater amount of particulate contamination than products processed by solvent extraction, lyophilization, or spray-dry methods (35,36).

Elemental analysis suggests that the majority of intrinsic particles result from leaching and dissolution of the surfaces of glass containers or coatings of rubber closures as well as from later stages of the drug manufacturing process, container filling, and closure (32). The problem of particulate matter in PIs assumes greater significance because no active approach such as filtration can be applied during the manufacturing stage. However, judicious application of preventive approaches can help achieve desired standards of particulate matter. The steps shown in the sidebar, "Troubleshooting approach for problems related to particulate matter," provide an approach to help in troubleshooting problems related to particulate matter. All possibilities should be carefully evaluated because many times, multiple factors might be contributing to the problem.

Summary

PIs are relatively simple formulations with regard to the number of excipients and the manufacturing process. Development of a successful formulation requires careful study of preformulation parameters, especially those related to solid-state pharmaceutics. By acting at the molecular, particle, and bulk levels, these parameters affect both the fundamental and derived properties of a bulk drug. In addition, contribution of packaging and process parameters to overall product stability must be carefully considered. Particulate matter in PIs is a common and troublesome issue. A stepwise approach giving due consideration to all contributing factors can help limit the particulate matter within specified limits. A multidimensional approach involving preformulation, formulation development, packaging development, process optimization, and environmental control will ensure the development of a stable PI formulation.

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