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Variables Affecting Reconstitution Time of Dry Powder for Injection

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The authors describe the factors affecting reconstitution time of dry powder for injection and classifies them as intrinsic and extrinsic parameters.

A number of drugs are unstable in an aqueous environment, even when exposed for a short duration, thus requiring packaging, storage, and shipping in a powder or lyophilized state to keep the product stable during its shelf life. Used for parenteral administration, these drugs are commonly known as powder for injection (PI), powder for reconstitution, dry powder injection, or powder for constitution. [USP 29–NF 24](#) describes more than 100 drugs available as dry powder for injection (1).

Typically, PI drugs are supplied in glass vials with rubber plugs and are mixed or reconstituted with a diluent (usually 5% dextrose solution, normal saline, bacteriostatic water, or sterile water for injection) before administration. An incompletely dissolved product can be hazardous to the patient, thereby making reconstitution a critical performance parameter for these products (1). *USP* defines the completeness of the reconstitution procedure as the state in which the solid dissolves completely; leaving no visible residue as undissolved matter or the constituted solution is not significantly less clear than an equal volume of the diluent or purified water present in a similar vessel and examined similarly (1). The International Conference on Harmonization ([ICH](#)) Q6A guideline on drug specifications recommends that "for dry products for injection, acceptance criteria for redispersibility or reconstitution time

should be provided and the procedure for resuspension or reconstitution (mechanical or manual) should be indicated. Time required to achieve resuspension or reconstitution by the indicated procedure should be clearly defined" (2).

Variability in the reconstitution time of a product from the same or different manufacturers can seriously affect patient safety. The mention of a specific reconstitution time in the product literature or label could ensure a reproducible performance of the product in terms of complete reconstitution. Few *USP* monographs of PIs specify the reconstitution time. For example, the monograph for amifostine sulfate, an anticancer drug, specifies the reconstitution time in 0.9% w/v sodium chloride solution to be not more than 45 s (3). Few PI products available in the market mention the time required for their reconstitution either on the label or in the literature supplied with the product. For instance, haemosolvate factor VIII, a glycoprotein necessary for blood clotting and hemostasis, specifies the reconstitution time to be not greater than 30 min. The long reconstitution time required for this product is because reconstitution must be carried out by gentle swirling to avoid foaming and gel formation in the product (4). However, for some drugs such as decitabine hydrochloride, a prolonged reconstitution time might be detrimental to drug stability (5). Therefore, special inputs from formulation scientists are required to optimize the reconstitution time during the development of these dosage forms.

Keeping in mind the importance of reconstitution, the knowledge of parameters affecting reconstitution time is critical for product development, quality control, and overall product performance. This article analyzes these parameters by classifying them as extrinsic or intrinsic and examines how they contribute to the variability of reconstitution time of PI drugs (see Figure 1).



Figure 1

Intrinsic parameters affecting reconstitution time

Intrinsic parameters are inherent to an active pharmaceutical ingredient (API) or a formulation and include the molecular-, particle-, and bulk-level solid-state properties of the API. Any

added excipients also influence the inherent reconstitution properties of the product.

Particle-size distribution. Powder dissolution is a kinetic phenomenon that depends primarily on the surface area exposed to the solvent, which in turn is a function of particle size. Particle size, therefore, influences reconstitution time. Coarser particles lower the dissolution rate because of their lower specific surface area in accordance with the Noyes Whitney equation (6). Conversely, very fine particles agglomerate because they are more cohesive (7) and therefore show longer wetting time, resulting in prolonged reconstitution (8). Therefore, particle size must be optimized and controlled to obtain short and reproducible reconstitution times. Particle shape and size affect the closeness of the powder packing, which in turn affects the penetration of water into interstitial spaces of the powder bed (9). Water penetration promotes wetting of each particle that is required before dissolution. Small particle size and symmetrical shape enhance close packing of particles, thus preventing the required penetration of water. Larger particles are usually more irregular in shape and therefore provide more space in the interstices for wetting.

Porosity. The porosity of dry powder may have a significant effect on its reconstitution. Haeger et al. showed that an increase in porosity of the lyophilized cake by decreasing the concentration of the fill solution before lyophilization yielded a fluffy, low-bulk density lyophilized parenteral formulation with the desired characteristic of rapid reconstitution time (10). Several methods for determining the porosity of powder by means of mercury intrusion porosimetry (11–14), nitrogen gas adsorption (14, 15), and X-ray tomography (16) have been reported.

Solid-state form. A drug can exist in crystalline, solvate, or amorphous form. Polymorphism, the existence of several crystalline forms of a single compound, affects dissolution properties of the drug (17). Different pseudopolymorphic forms also have different dissolution rates. For example, acyclovir exists as a hydrate and as an anhydrate, with each form having significantly different dissolution rates (18).

The amorphous form of a drug has higher kinetic solubility compared with the crystalline form as a result of its inherent high-energy state. Amorphization is, therefore, used to enhance a drug's dissolution properties in PI formulations.

Bornstein et al. reported that the reconstitution time of the freeze-dried amorphous form of cefazolin sodium was decreased by 50% when compared with its crystalline form (19).

Degree of crystallinity. The degree of crystallinity, which is the percentage of crystalline form of any compound in the amorphous matrix, can markedly affect dissolution properties. Analytical techniques used to determine the degree of crystallinity include powder X ray diffractometry (20), near infrared spectroscopy (21), Raman spectrometry (22), solid-state nuclear magnetic resonance (23), dynamic vapor sorption (24), and thermoanalytical techniques such as isothermal microcalorimetry (24–26), differential scanning calorimetry (27), modulated temperature differential scanning calorimetry (28), and solution calorimetry (29). Reliability of the results may improve if several techniques are used in parallel (30).

Powder wettability. Wetting is the primary step in the reconstitution process that is followed by the submergence, dispersion, and dissolution of the particle (31). Wettability, is a measure of the ability of a bulk powder to imbibe the liquid under the influence of capillary forces, and it depends on variables such as particle size, density, porosity, surface charge, surface area, and surface activity (32). Although, several techniques are available to determine the wettability of a powder, it is difficult to accurately assess powder wettability because of the complexity of this phenomenon in powder systems.

Wettability is largely reflected by the contact angle between the powder surface and the penetrating diluent (32). The commonly used contact angle measurement on solid surfaces is influenced not only by the physicochemical properties of the powder, but also by factors such as surface roughness, chemical heterogeneity, sorption layers, molecular orientation, swelling, and partial dissolution of the solid in the liquid (33). Consequently, there is no universal test to measure the wettability of powders and each powder–liquid pair must be examined on a case-by-case basis to select the most appropriate method (33).

Methods to determine wettability of powders have been classified according to the size of the sample and the mechanism of wetting as shown in Figure 2 (33). Details of each method can be found in the cited literature (9, 34–45).

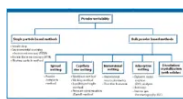


Figure 2

Formulation factors. The inherently low aqueous solubility of an API in formulation may contribute to incomplete reconstitution. Several formulation interventions are used in such instances, including the use of cosolvents, cyclodextrin complexation, lipidic systems, and amorphization by freeze drying. A rapid dissolution of anidulafungin, an antifungal compound, was observed with 5–30% w/v ethanolic solution used as a diluent (46). The reconstitution behavior of melphalan, an anticancer drug, was improved by using cyclodextrins ((SBE)7m- β -CD or HP- β -CD) solution as the reconstitution diluent (47).

Freeze drying is an important technique to formulate PI because it enhances the solubility and stability of the final product (48). High moisture content in the end product adversely affects not only the stability but also the reconstitution properties. Excipients used during freeze drying also have an impact on reconstitution time. Use of (SBE)7m- β -CD as a freeze-drying excipient in melphalan formulation improved the formulation's reconstitution behavior (47). The chemically modified cyclodextrins such as 2-hydroxypropyl- β -cyclodextrin (HP β CD), 2-hydroxypropyl- γ -cyclodextrin (HP γ CD) and γ -cyclodextrin (γ CD) enhanced the rate of dissolution of prototype lyophilized formulations of doxorubicin. It has been reported that HP γ CD, present in five-fold excess relative to doxorubicin, decreased the reconstitution time from 26 min to less than 9 min (49). Using organic-aqueous mixtures instead of only aqueous solution during freeze-drying generates amorphous cakes with a large surface area, resulting in enhanced reconstitutability. Freeze drying of sucrose and lactose solutions from a *tert*-butanol and water mixture demonstrated rapid reconstitution, which was attributed to higher cake porosity (48, 50).

Degradation products. The presence of excess moisture in the formulation can sometimes accelerate chemical and physical degradation, which results in the formation of less-soluble degradation products that slow the reconstitution process. A lyophilized bovine serum albumin formulation when stored at elevated temperature (37 °C) and high relative humidity exhibited a loss of solubility that was attributed to protein aggregation occurring in the wet solid. Similar observations

were made for recombinant human albumin, insulin, and tetanus toxoid (51). In such cases, special attention should be given to the choice of rubber plugs because it is the most potential source of ingress of moisture to the product (50).

Foaming. Foaming during reconstitution is a serious problem for biopharmaceutical drugs because it may lead to protein denaturation and a consequent loss in their activity. This situation necessitates determination of the protein activity that is lost as a result of shaking, which may further assist in setting specifications for reconstitution time. Kanavage et al. reported that the usual reconstitution time for lyophilized antivenom preparations by gentle swirling is approximately 45 min. Minimal changes observed in activity of the antivenom formulation, even with severe intentional foaming, obviated the need for any special reconstitution specifications (52). Apart from product stability, foaming also causes problems during administration, requiring it to be dissipated before use. In case of lyophilized palivizumab (Synagis, MedImmune), a rapid spurt of water into the vial may cause immediate and prolonged foaming that will require up to 2 h to dissipate (53).

Gel formation. Formation of a gelatinous mass (lump) during reconstitution is a major reason for a long reconstitution time. The gel layer that forms immediately after drug–diluent contact is highly viscous and sticky and adversely influences dissolution kinetics, thereby causing extreme difficulties in measuring reconstitution time (54). Farina et al. reported that two anthracyclines (antitumour drugs), doxorubicin (Adriamycin) and epirubicin (Pharmorubicin), marketed as lyophilized formulations showed a formation of a gel mass during reconstitution. A new formulation (i.e., rapid dissolution formula, RDF) containing parabens (hydroxybenzoate esters) as anti-aggregants manufactured by freeze drying was suggested to overcome the problem (55).

Extrinsic parameters affecting reconstitution time

Extrinsic parameters include variables related to the container of the product and the conditions used on the product in storage and during the reconstitution process.

Method of reconstitution. Reconstitution of ziprasidone (Geodon), an antipsychotic drug, was found to be quick and more effective when carried out by hand shaking rather than using a commercially available agitation machine (56). Stogniew made a comparison between shaking and hand

swirling for anidulafungin, an antifungal drug, and found that swirling generally resulted in longer reconstitution times, although with reduced foaming. With shaking, reconstitution times were shortened, but foaming was invariably observed (46).

Within a particular method, reconstitution time is further dependent on several variables, including shaking frequency, height of stroke, inclination of the shaking axis, and the dimensions of the mockups. Thiermann et al. studied the reconstitution of HI 6 dichloride, a broad-spectrum cholinesterase reactivator, and observed that horizontal shaking reduced the frequency required for reconstitution (57). Shaking intensities may vary significantly among patients, healthy subjects, doctors, and nurses resulting in differences in reconstitution time (57). Freeze-dried or lyophilized protein drugs need unique reconstitution procedures to avoid excessive stress that might lead to foaming. Foaming causes physical instability of proteins such as denaturation, surface adsorption, aggregation, and precipitation, which might evoke undesired immune response in a patient. It is, therefore, recommended to reconstitute these drugs by either rolling them between palms or swirling them despite higher reconstitution times observed with these methods (58).

Storage conditions and storage time. A change in reconstitution time may be observed during storage of a PI. Common reasons include cohesion, crystal growth, and/or moisture sorption, which promote lump formation. Cohesional forces increase with reduced distance between the particles and become prominent in the powder cake, which is usually a result of vibrations experienced by the product during transit or storage. Stresses during storage might induce crystal-form transformations and ultimately alter the reconstitution time (59).

Treatment of glass vial. Glass vials are sometimes coated internally with a silicone fluid to produce a hydrophobic surface. This operation is usually performed to avoid sticking or adherence of drug to the glass vial, thereby ensuring better reconstitutability (60). However, use of organic cosolvents as diluent must be avoided with siliconized glass vials or stoppers because organic cosolvents can solubilize or extract silicone oil from the package component. The extracted silicone oil can impede the wetting of the affected portions of the cake, resulting in incomplete reconstitution (48).

Headspace of glass vial. PIs are considered small-volume parenterals and therefore packaged mostly in glass vials of volumes not more than 100 mL. The amount of headspace available determines the volume available for agitation of the product. A decrease in reconstitution time of dry-fill cyclophosphamide was observed by increasing the headspace of glass vials, which obviated the need of an expensive freeze drying process for improving the reconstitution time (61).

Temperature of diluent. The temperature of the diluent influences the reconstitution time. A significant reduction in reconstitution time was observed using diluent prewarmed to 41 °C for dantrolene (62). Although a warmed diluent would speed up the reconstitution of almost any powdered substance, it might adversely affect the drug stability, which may necessitate the evaluation of the effect of temperature by conducting appropriate stability studies (62). Reconstitution of lyophilized amifostine powder (500 mg) with 2.9 mL sodium chloride solution or sterile water for injection at 20–25 °C resulted in complete dissolution within minutes. Reconstitution with smaller volumes (2.0 or 2.5 mL), although feasible, required more time and/or a warmer temperature (63). Dissolution of amifostine for subcutaneous injection was thus proved to be volume and temperature dependent (63). Mitchell et al. showed that dantrolene solubility increases linearly with increasing temperature between 20 and 40 °C (64). However, a temperature higher than 40 °C is not recommended because it could cause red blood cell lysis and local tissue burns (64, 65).

Conclusion

Reconstitution, a pharmaceutical prerequisite for powder for injection, has direct implications on patient safety, making it a critical parameter to evaluate powder for injection formulations. Numerous intrinsic and extrinsic parameters affect the time and reproducibility of reconstitution of powders. Identification and control of these parameters during product development and quality control can reduce batch-to-batch variability in reconstitution time and provide confidence among the end users, thereby making the powder for injection formulation an attractive and safe alternative for moisture-sensitive drugs. A short and reproducible reconstitution time will also save the precious time and labor of caregivers while dealing in emergency situations, ensuring a more effective critical care during compromised clinical situations.

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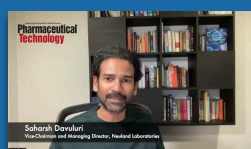
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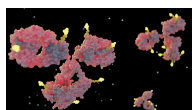
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Page 17

17/17
Sun Ex. 1032