I.12 Reconstitution of Solutions and Suspensions and Flow Rate Calculations

GOAL *To provide practice with calculations involving the reconstitution of dry powders for solution or suspension and calculation of flow rates for parenteral drugs given intravenously.*

OBJECTIVES

This chapter equips students to:

- Discuss the purpose of reconstituting drugs supplied as dry powder to prepare solutions or suspensions
- Calculate the concentration of the resulting solution or suspension given the volume of diluent used to reconstitute a dry powder
- Given the amount of diluent used to reconstitute a dry powder, the final volume of the resulting liquid, and the final concentration of the resulting liquid, determine the volume occupied by the dry powder and calculate the total amount of active drug in the resulting liquid
- Calculate the amount of diluent needed to reconstitute a dry powder to obtain a concentration of drug in the resulting liquid that is different from the concentration obtained by following the manufacturer's labeled reconstitution instructions
- Given a dosing guideline based on body weight or surface area, calculate the volume of diluent needed to reconstitute a dry powder so the resulting concentration is easily used to provide the dose required
- Calculate the volume of a reconstituted solution that should be added to an intravenous (IV) parenteral product to provide a specified dose for a patient
- Calculate the flow rate of an IV parenteral product needed to deliver a specified amount of drug per unit time

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Importance for Medical Math and Clinical Practice

Chapter 12 describes calculations and procedures for using a commercial drug dosage form to accommodate the need of a patient that may not have been anticipated by the drug's manufacturer. This kind of information is not often included in a drug product's official labelling. This chapter does not offer advice on substituting any particular generic version of a formulation for another version. See the Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/ [accessed October 1, 2017]) for details on this topic. Neither does this chapter address the issue of selecting biosimilars (see https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ [accessed October 1, 2017]). Also, Chapter 12 does not directly address all issues where a commercial product is incorporated into an extemporaneous formulation different from the manufacturer's original formulation. Specific references exist to guide compounding such as this. Extemporaneous compounding may be needed when a suitable dosage form of drug does not exist but a legitimate need for timely dosing does exist. For example, a child's life-threatening infection may require the use of a ground-up tablet or the contents of a capsule to be added to a suitable liquid vehicle. Compounding such as this must always consider determining expiration dating for the product and selecting quality assurance procedures to document the ingredients in the product. Again, specific references should be consulted for guidance. For compounded sterile

KEYWORDS

Admixture
Diluent
Dry powder for reconstitution
Flow rate
Parenteral product
Reconstitution
Solution
Suspension

products—as one example—*ASHP's Handbook on Injectable Drugs* is considered an authoritative source for compatibility and stability information.

Introduction

The manufacturer often supplies drug products intended for oral or parenteral use as dry powders. These may be sterile products in small vials if intended for parenteral route injection, or large amounts of powders in oversized containers if intended for oral use. Products for oral use usually have colors, flavors, and sweeteners in addition to other substances intended to preserve or chemically stabilize the resulting solution or suspension. Vials of sterile products for injection usually have relatively few added substances—often chemicals needed to maintain the pH, stability, or tonicity of the reconstituted solution.

The process for producing these drug products is known as *freeze-drying* (*lyophilization*). This method has been used since the mid-20th century when the need arose to ship urgently needed and chemically fragile drug products to military units stationed around the world. Blood products and penicillin were among the first produced by freeze-drying. A solution or suspension of the drug product is frozen and then held under vacuum to draw off moisture. This produces a dry powder that, in most cases, can be held at room temperature until it is reconstituted by adding moisture back in. Refrigeration may be needed after reconstitution to retard the drug's chemical degradation that would have occurred to the original drug solution or suspension in the absence of the freeze-drying process. The food industry adopted this process of preservation soon after its use was established for drug products—instant coffee being one of the first examples. There are usually four steps to the freeze-drying process: pretreatment, freezing, and two drying stages. The first of these, pretreatment, may produce a very concentrated drug solution or suspension. The goal is to pack a lot of drug activity into a small volume of powder.

Although there are many possible example problems to illustrate how a manufactured drug product in the form of a dry powder can be adapted for use under special circumstances or for special purposes, the best way for the student to begin the study of these uses is to review the product labeling to see what the usual instructions are for reconstituting the drug. Some good examples to start with are ampicillin, amoxicillin, cefazolin, and any other drug product for reconstitution that may be of interest you. Also, pay particular attention to the information sections dealing with reconstitution in a drug's package insert. For example, in addition to sections such as "How to Administer the Drug" and "How the Drug Is Supplied," notice whether a section on "How to Dilute the Reconstituted Drug" exists in addition to instructions for actually reconstituting the drug. Remembering that the original solution or suspension of drug may be highly concentrated before freezing and drying, the initial reconstitution of the drug may provide a highly concentrated form of drug suitable for one route of parenteral administration (e.g., intramuscular), but not dilute enough for a different parenteral route (e.g., IV).

The example problems in this chapter show some of the details for adapting a drug in dry-powder form to uses with concentrations other than the standard concentrations obtained following reconstitution according to the labeled instructions for the product. One piece of information that must be known is whether or not the amount of the dry