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Formulation

RTU DRUG PRODUCTS

The Keys to RTU Parenterals

There are a number of challenges when it comes to ready-to-use products | BY PAULA YOUNGBERG WEBB, MS, AND RAO CHILAMKURTI, PHD

Editor's Note: This is the first in a three-part series on ready-to-use parenteral products. Part two will appear in our October/November issue.

Many parenteral drug products are administered as intravenous (IV) infusions in multiple-patient care settings, from hospitals to alternate care facilities. The drug product, typically packaged in a vial or ampoule, is added to an IV solution such as normal saline or 5% dextrose prior to intravenous infusion. Several drugs for IV infusion, premixed in an intravenous diluent, are also commercially available. These products are referred to as ready-to-use (RTU) products or “premix” drug solutions. Examples of commercially available RTU drug products are listed in Table 1 (see p. 41).

There are a number of key factors in the development of RTU parenteral products. In addition to container selection and optimization of formulation for drug stability, other key considerations include analytical method development, manufacturing process development and tech transfer, and stability testing programs for registration batches.

All About RTUs

Like most IV infusion solutions, RTU drug products for IV infusion are packaged in flexible plastic containers; however, some drugs that adsorb to plastic materials, such as nitroglycerin, may be packaged in glass containers. Flexible plastic containers offer several advantages over glass infusion bottles with respect to safety, handling, storage, and so on. Solution volumes of RTU drug products for IV infusion typically range from 50 mL to 1 L.

Depending on the stability of a drug, these products may be terminally sterilized, aseptically filled, or aseptically filled and frozen. These frozen products are distributed and stored in a frozen state and thawed prior to use. They are given a long-term

shelf life in a frozen state and a thawed shelf life at room or refrigerated temperature. Figure 1 (see below) depicts various types of parenteral RTU products based on type of container and manufacturing process.

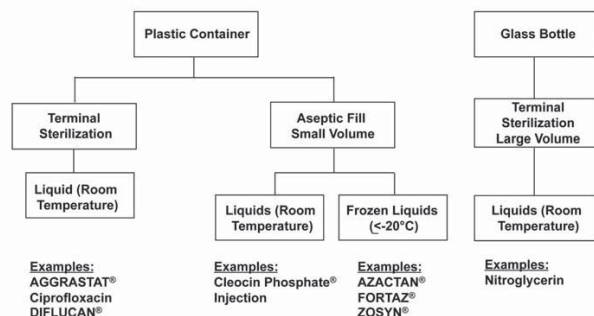
Parenteral RTU products for IV infusion offer many benefits compared to admixed IV drugs. One of the primary benefits is elimination of complex procedures required for traditional IV admixture and compounding, saving both time and labor. The use of RTU drug products in hospitals allows the pharmacist to allocate more time to clinical and other activities. These products also help to improve compliance with patient safety guidelines and reduce the risk of medication errors, medication contamination, and needle stick infections. Additionally, they help pharmacists to comply with stringent Joint Commission on the Accreditation of Healthcare Organizations and U.S. Pharmacopeia 797 guidelines.

The formulations of liquid RTU products are optimized for stability in the chosen IV diluent, which results in a longer shelf life than the “beyond use date” for compounded solutions. The formulation of frozen RTU products is also optimized for long-term stability during frozen storage and short-term stability after thawing. Due to formulation optimization, the thawed shelf lives of frozen RTU products are often longer than the “beyond use date” of compounded solutions. The longer thawed shelf lives allow the pharmacist to recycle the unused product (products not administered to any patient) for use at a later time. The RTU drug products are generally iso-osmotic due to the ability of the manufacturer to adjust the concentration of the tonicity agent, such as dextrose.

Formulation and Container Selection

Several factors, including clinical, formulation, container, and marketing, play a key role in selecting a parenteral drug to

Figure 1. Categories of Parenteral RTU Drug Solutions For IV Infusion



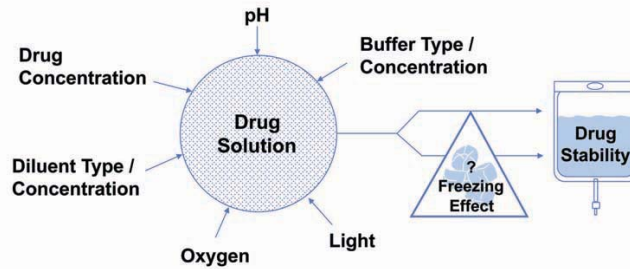
be developed as an RTU product. Because the RTU products typically deliver a unit dose, the dosing regimen for candidate drugs involves a fixed standard dose; the drugs are administered with an IV diluent such as sodium chloride injection, dextrose injection, or lactated ringers injection. The type of diluent selected often depends upon clinical considerations such as sodium or electrolyte levels and limitations on carbohydrate intake (such as dextrose for the diabetic patient population).

The solution volume of the product selected also depends upon the recommended rate of infusion for a specific drug. Injection site interactions such as pain or erythema, along with limitations on fluid intake, are also considerations in selecting the solution volume. In addition to these clinical considerations, the benefits of RTU drug products for infusion over the traditionally compounded drug admixtures play a major role in the decision to develop and market an IV drug for infusion as a RTU product.

Key considerations in selecting a container system for an intravenous RTU product include drug-container compatibility, protection of drug from external elements, safety profile, and functional performance. Adsorption of drug to plastic film or absorption, particularly during autoclave sterilization, must be considered as a part of compatibility. A pH change in solution due to leaching of plastic excipients is another important factor; pH change may result in increased drug degradation or drug precipitation. Leached extractables may also precipitate in solution in the presence of certain drugs or may cause the drug to precipitate.

The chosen container system should protect the drug from light and oxygen, if necessary, and should have low water vapor transmission to ensure minimum water loss. Water loss from flexible plastic containers may affect delivered volume and may also result in increased concentration of drug in the solution over time. The selected container system must also act as a barrier to microbial ingress. It must pass biological testing and toxicological evaluation. Finally, the container system must exhibit relevant functional performance with respect to integrity, delivery of dose, and rate of delivery.

Figure 2. Effect of Formulation Factors on Drug Stability



Formulation Development

The primary purpose of formulation development is to achieve the desired stability and shelf life of the final product through optimization of various factors affecting the stability of the drug in aqueous solutions. These factors, as depicted in Figure 2 (see above), include solution pH, buffer type and concentration if required, drug concentration, diluent type and concentration, oxygen, and light. For most drugs, stability in aqueous solutions is affected by pH. Therefore, a thorough understanding of the pH-rate profile is essential.

If the solution pH cannot be maintained within the optimal range, a buffer that is suitable for IV administration can be added. However, the type of buffer selected depends upon the formulation pH and the dissociation constants of the buffer to achieve the desired level of buffering capacity. The amount of buffer added must be optimized to ensure maintenance of pH and to minimize buffer catalysis. In addition, the amount/concentration of buffer must be acceptable from a toxicological perspective. In some instances, different concentrations of a drug may show different rates of degradation due to self-association.

The type of diluent that is added to the formulation—sodium chloride or dextrose, for example—may also play a role in the degradation of a drug. Addition of sodium chloride may result in increased ionic strength, which may alter the degradation rate or cause potential precipitation of drug. Stability of certain drugs can also be affected by the presence of carbohydrates like dextrose. Finally, oxygen and light may play a significant role in drug stability. These factors can be controlled by the use of an appropriate container system and/or the addition of antioxidants.

In general, due to phase changes that occur upon freezing of a drug solution, formulation development and optimization for drug stability for frozen products is more complicated than for those liquid formulations stored at room temperature. When a drug solution is frozen, water crystallizes as ice, and the remaining solution becomes concentrated. At the intended long-term storage temperature, for example -20°C , the drug (and some excipients) may precipitate from the solution or remain in a concentrated state. Depending on the temperature, it may also exist as a glassy state.

(Continued on p. 42)

Table 1. Examples of Commercially Available RTU Parenteral Products for IV Infusion

Liquid Products
<ul style="list-style-type: none"> AGGRASTAT (tirofiban hydrochloride injection premixed). INTRAVIA Plastic Container, 250mL Ciprofloxacin Injection, USP (In 5% Dextrose) for Intravenous Infusion in INTRAVIA Plastic container, 200 mL CLEOCIN PHOSPHATE IV Solution (clindamycin injection) in 5% Dextrose, GALAXY Plastic Container, 50mL DIFLUCAN (fluconazole) Injection Iso-osmotic Dextrose Diluent. VIAFLEX Plastic Container, 100mL
Frozen Products
<ul style="list-style-type: none"> AZACTAM (aztreonam injection). GALAXY Plastic Container, 50mL FORTAZ (ceftazidime injection). GALAXY Plastic Container, 50mL VANCOMYCIN Injection, USP. GALAXY Plastic Container, 200mL ZOSYN (Piperacillin and Tazobactam Injection). GALAXY Plastic Container, 100mL

Table 2. Example: Formulation Optimization - Variables

Variable	Test Level
Drug Concentration	1g/50mL, 2g/50mL
Buffer Concentration	0, 0.2 and 0.4% sodium citrate per g /of drug
Target pH	6.0, 6.6, 7.0

Table 3. Example: Formulation Optimization – Test Intervals

Type of Product	Storage Condition	Test Intervals
Liquid	25° C	0, 2, 4 and 6 months
	5° C	0, 2, 4 and 6 months
	40° C	0, 1, 2, 3 and 6 months
Frozen	-20° C - Frozen	0, 2, 4 and 6 months
	5° C - Thawed	0, 1, 2, 3 and 4 weeks
	25° C - Thawed	0, 24, 48, 72 and 96 hours

Note: Thawed testing performed at 0 and 6 months of frozen storage

(Continued from p. 41)

If precipitation of drug occurs, the long-term stability of the drug in the frozen state is much more enhanced than in the liquid state. If the drug remains a concentrate, the degradation rate or kinetics could change relative to liquid state. Although the pres-

ence of drug in glassy state may enhance the stability in comparison to a concentrate, the existence of drugs in a glassy state above -20°C is not common.

In optimizing the drug formulations for stability, it is extremely important to understand the effect of each formulation factor as well as combination effects. A multi-factorial design can be utilized to understand these effects. Such studies will help to meet regulatory requirements.¹

Tables 2 and 3 (see left) illustrate an example of formulation optimization design and relevant storage conditions to evaluate these factors. During the formulation studies, monitoring and evaluation of impurities/degradation products is critical, because one or more impurities/degradation products may become the limiting factors for meeting overall specifications and achieving the desired shelf life. These studies will form the basis for qualification of impurities as required by the ICH Q3B guideline.² In addition, pH, visual inspection, particulate matter, and color are essential parameters to be monitored. ■

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REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Guideline Q 8 (R1): Pharmaceutical development. Geneva, Switzerland; 2008.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Guideline Q 3 B (R2): Impurities in new drug products. Geneva, Switzerland; 2006.