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Parenteral Products: Design and Optimization, Including Freeze Drying

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INTRODUCTION

A parenteral product can be defined as a sterile drug, solution, or suspension that is packaged in a manner suitable for administration by hypodermic injection either in the form prepared or following the addition of a suitable solvent or suspending agent (1). The delivery of drugs via the parenteral routes of administration has steadily increased over the past few decades due to the inherent advantages of reaching the systemic circulation quickly. The use of the parenteral routes will continue to increase and will even proliferate due to both the research in targeted (site-specific) delivery and the products derived from biotechnology.

The successful formulation of an injectable preparation requires a broad knowledge of physical, chemical, and biological principles as well as expertise in the application of these principles. Such knowledge and expertise are required to effect rational decisions regarding the selection of: (a) a suitable vehicle (aqueous, nonaqueous, or cosolvent); (b) added substances (antimicrobial agents, antioxidants, buffers, chelating agents, and tonicity contributors); and (c) the appropriate container and container components (2).

The majority of parenteral products are aqueous solutions, preferred because of their physiologic compatibility and versatility with regard to route of administration. However, cosolvents or nonaqueous substances are often required to effect solution or stability. Furthermore, the desired properties are sometimes attained through the use of a suspension or an emulsion. Although each of these dosage forms have distinctive characteristics and formulation requirements, certain physical-chemical principles are common. It is important to recognize that the pharmaceutical products

derived from biotechnology are on the increase and the formulation of these proteins and peptides requires some unique skills and novel approaches.

The general requirements of a parenteral product include those mandated for all dosage forms namely safety, effectiveness, stability and reliability. However, for those products which circumvent the body's most protective barriers and come into contact with internal body compartments, sterility, freedom from pyrogens, clarity and isotonicity become distinctive requirements. Therefore, the design and optimization of parenteral products must be approached around a "microcontamination control" theme, i.e., freedom from microbial, pyrogenic and particulate contamination.

STERILITY

While sterility is the complete absence of microorganisms, sterilization is a probability function that the treatment will render a product free of microorganisms. Since sterility testing is destructive it involves only a small fraction of the total batch. This is illustrated in Table 1 which shows that at a contamination level of 1 in a thousand, the batch would be accepted 98% of the time and even at a 1% level the batch would be accepted 82% of the time. To pass the batch with 95% confidence the contamination level would have to be above 15%. Hence, the official sterility test cannot be used to extrapolate with any certainty to the unsampled containers. Statistically, the chances of failing a batch are very low. Therefore, assurance of sterility must be designed into and implemented during the processing of a parenteral product.

TABLE 1 Probability* of Acceptance of Batches With Relationships to Sample Size

	% Contaminated Units in Batch				
0.1	1	5	10	20	50
C = 0.001	0.01	0.05	0.1	0.2	0.5
S = 0.999	0.99	0.95	0.9	0.8	0.5
P = 0.98	0.82	0.36	0.12	0.01	<0.00001

$*P = (1 - C)^N = S^N$

Where C represents the proportion of contaminated units in a batch and S the proportion of non-contaminated. P is the probability of selecting 20 consecutive sterile units (N = 20).

Agents with antimicrobial activity must be added to preparations packaged in multiple-dose containers unless prohibited by the monograph or unless the drug itself is bacteriostatic. They are often added to unit-dose solutions which are not sterilized at the terminal stage of their manufacture. In the case of multiple-dose preparations the antimicrobial agent is required as a bacteriostat to inhibit any microbes accidentally introduced while withdrawing doses. Antimicrobial agents may also serve a role as adjuncts in aseptic processing of products (e.g., prefilled syringes), where there may be product exposure during transfer, filling, and stoppering operations. Thus, should trace contamination occur during the manufacturing process, the antimicrobial agent may render the product sterile.

Consideration must be given to the stability and effectiveness of the antimicrobial agent in combination with the active ingredient and other added substances. Many papers have been published describing the incompatibilities or binding of preservatives with surfactants, pharmaceuticals, and rubber closures (3-8).

The effectiveness of antimicrobial agents can be tested by challenging the product with selected organisms to evaluate the bacteriostatic or bactericidal activity in a formulation. The challenge test described in the USP (9) should be performed with the formulation throughout and near the end of the expiration date to ensure that adequate levels of preservative are still available.

PYROGENS

Some lipopolysaccharide materials of bacterial origin can associate with varying amounts of proteins and phospholipids. This stimulates the production of endogenous pyrogens giving rise to febrile and other undesirable pharmacological responses. Pyrogens are the byproducts of bacterial contamination and must be guarded against in parenteral products. Water, ingredients, container components, administration sets and medical devices used in the preparation, packaging and administration of parenteral products must be maintained sterile and free of pyrogens. Chemically, pyrogens are water-soluble and heat resistant so they are not easily removed once introduced. Endotoxin derived from gram negative E. coli will produce a pyrogenic reaction in the rabbit at a concentration of 1 pg per Kg.

The major sources of endotoxin or pyrogenic contamination are the product components (water, excipients and the container), processing equipment and human emissions. Pyrogens can be avoided in parenteral products by (a) reducing airborne

bacterial contamination in processing areas, (b) using freshly distilled water, (c) having rigid specifications for ingredients, (d) compounding and sterilizing the solution within a 24 hour period and (e) rinsing equipment, containers and closures with water for injection and sterilizing within 24 hours.

CLARITY

Freedom from particulate contamination is one specification essential to ensure function and integrity of the product and safety for the patient. The attribute of freedom from undesirable particulates must not only be built into the product and exist when the product is released by the manufacturer, but must be maintained during shipping and storage and upon administration to the patient. The presence of foreign materials in solutions to be administered directly into the bloodstream has been of deep concern to drug-safety regulators, manufacturers, clinicians, and consumers. Not only do particulates constitute potential adverse clinical consequences, but the quality of the product becomes suspect when undissolved material is observed.

An appreciation of the magnitude of the problem of particulates can be illustrated by an example of "purity" and "impurity" of a material. A product that is 99.99% pure contains only 0.01% impurity, or 100 parts per million (ppm). Although this generally is a tolerable amount of impurity, even on a 100-fold smaller scale of 1 ppm, i.e., 1 mg/liter, such a level of insoluble impurity or contamination is equivalent to 120,000 particles (assuming a density of 1), 25 μm in diameter. This level of particulate contamination is well above the USP allowable limit for intravenous solutions. The number of spherical particles per milligram of substance can be calculated from the formula:

$$Particles/mg = \frac{1.91 \times 10^9}{dD^3} \qquad 1$$

where d is the density of the particle and D is the diameter in micrometers. Table 2 shows the number of solid, non-porous spherical particles in a milligram of insoluble impurity or contaminant at various diameters and densities.

Particulate matter in parenteral solutions has been a matter of concern to regulatory agencies and standard setting bodies for a number of years (10). Official standards for particulate matter in parenteral solutions are shown in Table 3.

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