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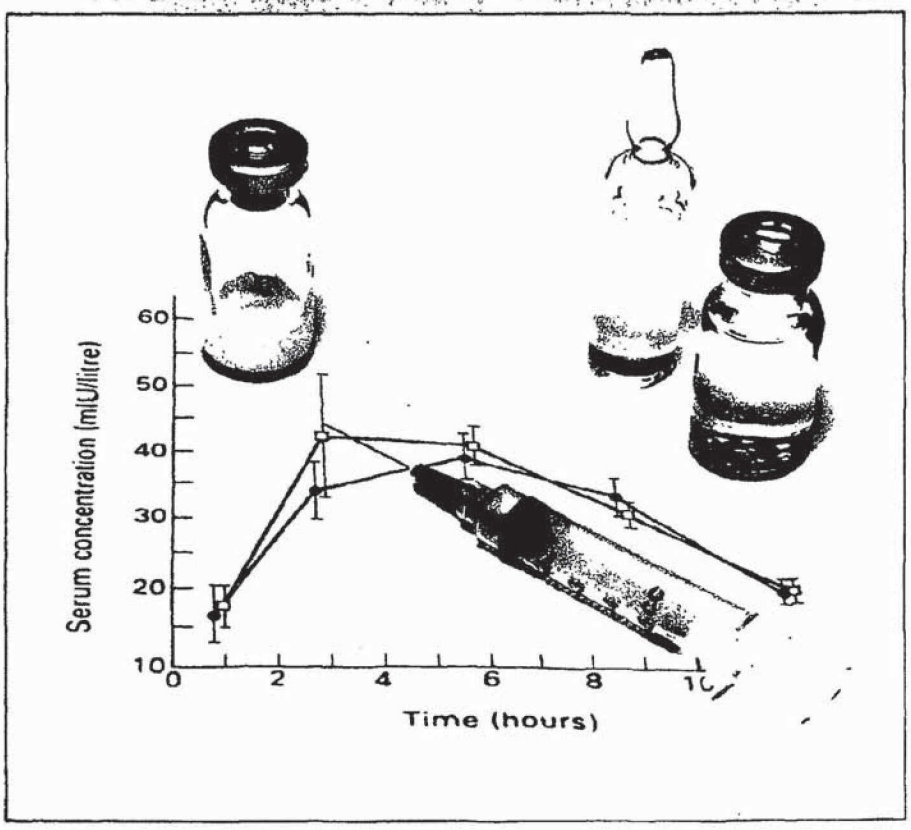
Pharmaceutical Dosage Forms:

Parenteral Medications

Volume 1

Second Edition, Revised and Expanded

Edited by Kenneth E. Avis, Herbert A. Lieberman, and Leon Lachman



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Library of Congress Cataloging-in-Publication Data

Pharmaceutical dosage forms, parenteral medications / edited by Kenneth E. Avis, Herbert A. Lieberman, and Leon Lachman. -- 2nd ed., rev. and expanded.
p. cm.
Includes bibliographical references and index.
ISBN 0-8247-8576-2 (v. 1 : alk. paper)
1. Parenteral solutions. 2. Pharmaceutical technology. I. Avis, Kenneth E. II. Lieberman, Herbert A.
III. Lachman, Leon.
[DNLM: 1. Infusions, Parenteral. 2. Technology, Pharmaceutical. WB 354 P536]
RS201.P37P48 1992
615'.19--dc20
DNLM/DLC
for Library of Congress

91-38063
CIP

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270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

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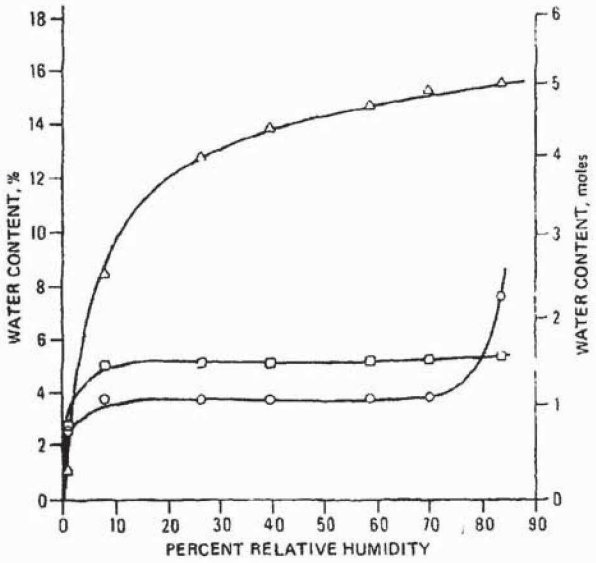

Figure 20 Relative humidity versus water content of hydrate forms of sodium cefazolin. -o-o-o-, Monohydrate; -□-□-□-, sesquihydrate; -△-△-△-, pentahydrate. (From Ref. 40.)

Freeze-Drying. From a historical standpoint the process of freeze-drying, often referred to as *lyophilization*, received its initial thrust during World War II when whole blood and blood plasma became lifesaving elements, and adequate supplies were jeopardized because of stability and shipping problems associated with these natural biological products. Soon after World War II, the pharmaceutical industry began considering the process for the preparation of sterile injectable dosage forms which could not be formulated into stable solutions. At the same time the food industry began employing freeze-drying to process and package foods, an application that continues to grow. Another application that has been receiving research attention is the preservation of biological substances, especially those of high worth or in short supply. Vital organs and tissues are also preserved by freeze-drying. Substances that degrade in solution become candidates for freeze-drying. This precludes storage of the product in a deep-frozen state which presents solubility problems, is costly, and there is always the risk of degradation. Often, freeze-drying offers the only means to stabilize the product or may be a convenient way to stockpile material for defense or emergency purposes and of course shipment and storage of dry material are less expensive than that in solution form. Although there are those who would consider freeze-drying only as the last resort, there are others who view it as a panacea—a way to get into clinical trials quickly or a way to exclude contaminants and inert particles, especially in comparison with powder filling. Certainly, freeze-drying does offer the ad-

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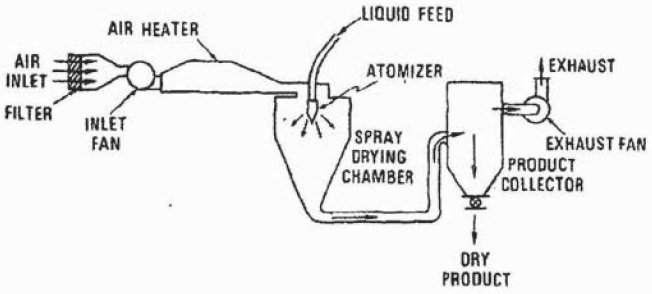

Figure 21 Schematic drawing of spray dryer.

vantage over powder filling of accuracy of dosage, since the drug is filled into the final container as a solution. Microgram quantities can be filled precisely. Powder filling is used where the required dosage is represented by a large quantity of the drug or where the solubility is not adequate to freeze and as previously described with powder filling, sterilization of the powder is possible prior to filling.

The process of freeze-drying illustrated in Figure 22 involves: (1) dissolving the drug and excipients in a suitable solvent, generally water; (2) sterilizing the bulk solution by passing it through a bacteria-retentive filter; (3) filling into individual sterile containers; (4) freezing the solution by placing the open containers on cooled shelves in a freeze-drying chamber or prefreezing in another chamber; and (5) applying a vacuum to the chamber and heating the shelves in order to sublime the water from the frozen state. The desired characteristics of a freeze-dried pharmaceutical dosage form include: (1) an intact cake occupying the same shape and size as the original frozen mass; (2) sufficient strength to prevent cracking, powdering, or collapse; (3) uniform color and consistency; (4) sufficient dryness to maintain stability; and (5) sufficient porosity and surface area to permit rapid reconstitution. Of course, as with any injectable dosage form, freedom from contamination (i.e., microorganisms, pyrogens, and particulates) is an essential attribute.

The desired characteristics can be achieved by proper formulation of the product and by employing optimum freeze-drying cycles. The development of a suitable formulation and a freeze-dry cycle requires knowledge of some basic properties, such as: (1) eutectic temperature; (2) temperature effect on solubility; (3) thermal properties of the frozen solution; (4) degree of supercooling; (5) heat transfer properties of the freeze-dryer shelves, metal trays, glass vials, and the frozen product; and (6) equipment design and equipment capability. Formulating the solution to be freeze-dried must be done with a view toward the characteristics required at the time of reconstitution and administration. The drug alone often does not provide the solid content or characteristics appropriate for the finished product, and inert or relatively inert substances such as lactose or mannitol must be added prior to freeze-drying to provide the necessary bulk and desired characteristics.

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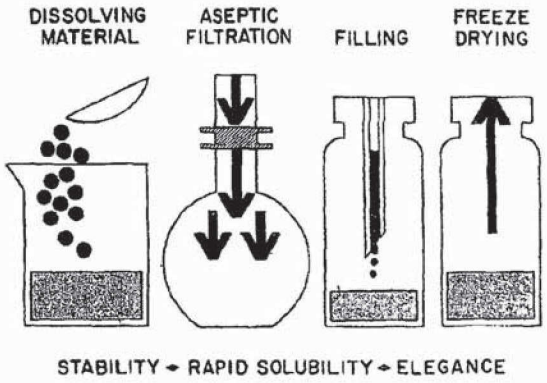

Figure 22 Freeze-drying process.

For a systematic approach to the development of a suitable freeze-dried product, knowledge of the various stages of the process is necessary. The main stages can be classified as freezing and drying. The initial freezing process is of critical importance since it will influence the pattern of the sublimation phase. The latter phase must occur from the solid state throughout the cycle. Appropriate cooling cycles must be determined in order to obtain an appropriate structure of the frozen mass, which is a function of the rate of freezing and the final freezing temperature. The rate of freezing also affects the size of ice crystals. The slower the rate of freezing, the larger the ice crystals that form. Freezing of the solution is most conveniently accomplished in the chamber to be employed for drying, by placing the containers of solution on a shelf that is cooled by a circulating refrigerant, such as Freon, Cellusolve, or trichlorethylene. If the frozen system exhibits metastable or amorphous-glassy structures, these structures may need to be ruptured by appropriate thermal treatments (a succession of cooling and rewarming periods), thereby inducing crystallization of the amorphous material and adequate crystal size necessary for efficient sublimation.

The most commonly employed method of drying pharmaceuticals is condensation at low temperatures whereby, through the principal mode of conduction, heat is transferred to the frozen product to effect vaporization. By further introducing a cold surface into the system at a temperature below that of the frozen product, the water vapor evolved by the drying material will be condensed as ice on the refrigerated surface. The process is illustrated in Figure 23, together with the temperature gradient during the drying cycle. Factors influencing the rate of vaporization have been discussed extensively [67, 68]. The faster heat can be applied, the faster the drying proceeds, provided that (1) the temperature of the product remains below its liquefying point, and (2) a sufficiently low pressure is maintained in the system by efficient vacuum pumps. If a sufficiently low pressure is not maintained, the temperature of the product will rise until a phase separation occurs, resulting in the partial softening or puffing of the product.

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