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Excipients: Their Role in Parenteral Dosage Forms

Introduction

The term pharmaceutical excipient or additive denotes compounds that are added to the finished drug product for a variety of reasons. Most often such excipients are the major components of the drug product, with the active drug molecule being present only in a small percentage. Excipients have also been referred to as inactive or inert ingredients to distinguish them from the active pharmaceutical ingredients. However, in many instances excipients may not be as inert as some scientists may believe. Several countries have restrictions on the type or amount of excipient that can be included in the formulation of parenteral drug products due to safety issues. For example, in Japan the use of amino mercuric chloride or thimerosal is prohibited, even though these excipients are present in several American products.

As defined in the *European Pharmacopeia* (EP 1997) and the *British Pharmacopeia* (BP 1998), "Parenteral preparations are sterile preparations intended for administration by injection, infusion, or implantation into the human or animal body." However, in this article, only sterile preparations for administration by injection or infusion into the human body are surveyed [1,2]. Injectable products require a unique formulation strategy. The formulated product has to be sterile, pyrogen free, and in the case of solutions, free of particulate matter. No coloring agent may be added solely for the purpose of coloring the parenteral preparation. Preferably, the formulation should be isotonic, and depending on the route of administration, certain excipients may not be included. For a given drug, the risk of an adverse event may be higher or the effects may be difficult to reverse if it is administered as an injection versus a nonparenteral route, since the injected drug bypasses natural defense barriers. The requirement for sterility demands that the excipient be able to withstand terminal sterilization or aseptic processing. These factors limit the choice of excipients available to the formulator.

Generally, a knowledge of which excipients have been deemed safe by the Food and Drug Administration (FDA) or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for a new drug product. However, there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug molecule creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and frequently require fewer safety data. A new additive in a formulated product always requires additional studies adding to the cost and timeline of product development.

In Japan, if the drug product contains an excipient with no precedence of use in Japan, the quality and safety attributes of the excipient must be evaluated by the Subcommittee on Pharmaceutical Excipients of the Central Pharmaceutical Affairs Council concurrently with the evaluation of the drug product application [3]. Precedence of use means that the excipient has been used in a drug product in Japan, and is administered via the

same route and in a dose level equal to or higher than the excipient in question in the new application.

This article is a comprehensive review of the excipients that have been included in the injectable products marketed in the United States, Europe, and Japan. A review of the literature indicates that only a few articles have been published which specifically deal with the selection of parenteral excipients [4–9]. However, excipients included in other sterile dosage forms not administered parenterally are not covered here, such as solution for irrigation, ophthalmic or otic drops, and ointments. Additional information on the excipients used in parenteral products can be found in Vols. 1–4, 6, 11, and 13–15 of this encyclopedia.

Several sources of information were used to summarize the information compiled in this article [4–7, 10, 11–14]. Formulation information on the commercially available injectable products was entered in a worksheet, which is the source of the tables presented here. Each table has been categorized based on the primary function of the excipient in the formulation. For example, citrates are classified as buffers and not as chelating agents, and ascorbates are categorized as antioxidants, although they can serve as buffers. This classification system minimizes redundancy and provides a reader-friendly format. The concentration of excipients is given as percent weight by volume (w/v) or volume by volume (v/v). If the product was listed as lyophilized or powder, the percentages were based on the reconstitution volume commonly used. The tables list the range of concentration and examples of products containing the excipient, especially those which are used in extremely low or high concentrations. A column in Tables 1–5 indicates the frequency with which these excipients are used in parenteral products.

Types of Excipients

Solvents and Cosolvents

Table 1 list solvents and cosolvents used in parenteral products. Water for injection is the most common solvent but may be combined or substituted with a cosolvent to improve the solubility or stability of the drugs [15,16]. The dielectric constant and solubility parameters are among the most common polarity indices used for solvent blending [17,18]. Ethanol and propylene glycol are used alone or in combination with other solvents in more than 50% of parenteral cosolvent systems. Surprisingly, propylene glycol is used more often than polyethylene glycols (PEGs) in spite of its higher myotoxicity and hemolyzing effects [19–22]. The hemolytic potential of cosolvents is as follows [19]:

Dimethyl acetamide < PEG 400 < ethanol < propylene glycol < dimethylsulfoxide

It is possible that the presence of residual peroxide from the bleaching of PEG or the generation of peroxides in PEG may result in the degradation of the drug in the cosolvent system. It is important to use unbleached and peroxide-free PEGs in the formulation.

Oils like safflower and soybean are used in parenteral nutrition products where they serve as a fat source and carriers for fat-soluble vitamins. The United States Pharmacopeia, USP, requirements for injectable oils are as follows [3]:

- Fixed oils of vegetable origin
  Saponification value, 185–200
  Iodine number, 79–128; Japan Pharmacopeia recommends a value between 79 and 137

TABLE 1 Solvents and Cosolvents

Excipient	Frequency	Concentration Range	Example
Almond oil	1	NA[a]	Poison ivy extract (Parke Davis)
Benzyl benzoate	3	20–44.7% w/v	Delestrogen® 40 mg/mL (Bristol Myers), 44.8% w/v
Castor oil	1	NA[a]	Delestrogen® 20 mg/mL (Bristol Myers), 44.8% w/v
Cottonseed oil	2	73.6–87.4% w/v	Depo-Testadiol® (Upjohn), 87.4% w/v
N,N-Dimethylacetamide	1	6% w/v	Vumon® (Bristol Myers), 6% w/v
Ethanol	24	0.6–80%	Prograf® (Fujisawa), 80% w/v
Glycerin (glycerol)	11	1.6–70% w/v	Multitest CMI® (Pasteur Merieux), 70% w/v
Peanut oil	1	NA[a]	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG	5	0.15–50%	Secobarbital sodium (Wyeth-Ayerst), 50%
PEG 300	3	50–65%	VePesid® (Bristol Myers), 65% w/v
PEG 600	1	5% w/v	Persantine® (Dupont-Merck)
PEG 400	2	NA[a]	Ativan® (Wyeth-Ayerst)
PEG 3350	5	0.3–3%	Depo-Medrol® (Upjohn), 2.95% w/v
Poppyseed oil	1	NA[a]	Ethiodol® (Savage)
Propylene glycol	25	0.2–75.2%	Terramycin solution (Pfizer), 75.2%
Safflower oil	2	5–10%	Liposyn II® (Abbott), 10%
Sesame oil	6	NA[a]	Solganal® (Schering)
Soybean oil	4	5–20% w/v	Intralipid® (Clintec), 20%
Vegetable oil	2	NA[a]	Virilon IM® (Star Pharmaceuticals)

[a]No data available.

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