REVIEW

Excipient–Drug Interactions in Parenteral Formulations

MICHAEL J. AKERS

Baxter Healthcare Corporation, Bloomington, Indiana 47402

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ABSTRACT: Excipients are added to parenteral formulations to enhance or maintain active ingredient solubility (solubilizers) and/or stability (buffers, antioxidants, chelating agents, cryo- and lyoprotectants). Excipients also are important in parenteral formulations to assure safety (antimicrobial preservatives), minimize pain and irritation upon injection (tonicity agents), and control or prolong drug delivery (polymers). These are all examples of positive or synergistic interactions between excipients and drugs. However, excipients may also produce negative effects such as loss of drug solubility, activity, and/or stability. This review article will highlight documented interactions, both synergistic and antagonistic, between excipients and drugs in parenteral formulations. The reader will gain better understanding and appreciation of the implications of adding formulation ingredients to parenteral drug products. © 2002 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 91:2283–2300, 2002

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INTRODUCTION

Well-referenced and useful publications are available listing every formulation component in all marketed parenteral drug products[1–5] (Food and Drug Administration web site[a]). The information in these publications has been invaluable to parenteral formulation scientists developing soluble, stable, resuspendable, manufacturable, and deliverable parenteral dosage forms. Formulation component precedence takes on high stature in the sterile product world because of significant toxicological and regulatory concerns. In other words, it is usually better to use a component that has a track record of relatively safe use in injectables and is likely not to raise concerns on the part of regulatory reviewers.

[a]www.fda.gov/cder/drug/iig/default.htm

Correspondence to: Michael J. Akers (Telephone: 812-355-7188; Fax: 812-332-3079; E-mail: michael_akers@baxter.com)

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This review article will not cover all excipients used in parenteral formulations because the aforementioned publications already do so. What this review article presents are examples of synergistic and antagonist interactions that have been reported for excipients used in parenteral formulations. Although extensive, this review will not be exhaustive in the effort to cite all published references on parenteral drug–excipient interactions. Pharmaceutical Excipients 2000[6] was a very helpful text in obtaining valuable information about drug–excipient interactions and compatibilities.

When one studies stability and compatibility issues in parenteral drug formulation, the packaging system also must be considered. Potential interactions between excipients and rubber closures in finished products are as much a concern as interactions between excipients and drugs. Therefore, some drug–sterile packaging interactions will be covered in this article.

Although this article will focus on chemical and physical compatibilities of drugs and excipients used as injectable products, readers must also be

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aware of the potential for any excipient and drug, either alone or in combination, when injected intravenously to cause certain problems. As Yalkowsky et al.[7] pointed out, some formulation-related problems associated with intravenous drug delivery include hemolysis, precipitation, phlebitis, and pain. Therefore, as scientists develop sterile product formulations, not only must they be concerned with physical and chemical interactions that may occur *in vitro*, but they must also be concerned with the potential for formulation-related problems occurring *in vivo*.

Drug–excipient interactions are studied in two basic ways. One is to perform traditional preformulation studies using full factorial or Plackett Burman type of experimental designs. A good example of this approach for parenteral formulation development is a preformulation study published by Peswani and Lalla.[8] Analytical methods such as differential scanning calorimetry (DSC),[9] isothermal microcalorimetry,[10,11] and fourier transform infrared (FT-IR) spectroscopy[12] are excellent tools for predicting drug–excipient interactions. The other approach for studying drug–excipient interactions is to conduct both short-term and long-term stability studies on various formulations of the drug and measure both chemical stability (usually by chromatographic techniques) and physical stability (e.g., by microscopic, electronic particle analysis, and circular dichroism techniques).

This review is organized according to major functions of parenteral excipients (solubilization, stabilization, preservation, and drug delivery aids). Several excipients serve more than one function [e.g., polyvinylpyrrolidone (PVP) as a complexing agent and as a freeze-drying bulking agent], so such excipients may be referenced in more than one segment of the article.

Table 1 lists all the major pharmaceutical excipients used in parenteral formulations. Table 2 provides a listing of lesser-used excipients that are found in 1–2 commercial parenteral formulations. References[1–5] provide much greater detail about the specifics of these excipients (e.g., concentration) and the products in which they are components (e.g., brand names, manufacturer).

Solubility Effects

Many parenteral formulations require additives, either solvent or solute excipient, to increase and/or maintain solubility of the active ingredient in the solution. Sweetana and Akers[13] summarized seven basic approaches for solubilization of parenteral drugs as follows:

1. Salt formation
2. pH adjustment
3. Use of co-solvents
4. Use of surface-active agents
5. Use of complexation agents
6. Change formulation from solution to a dispersed system, oily solution, or a more complex formulation such as a microemulsion or liposome
7. "Heroic" approaches involving the use ofnon-commercially approved types and/or concentrations of solvents or excipients

This section will highlight some of the interactions between drugs and solubilizing agents, focusing on co-solvents, surfactants, suspending and emulsifying agents, complexation agents, and oils or lipids. Some examples of unpredicted interactions of excipients and drugs to enhance drug solubility are listed in Table 3.

Co-Solvents

There are approximately 20 different co-solvent agents used in approved parenteral products. However, the most commonly used co-solvents in parenteral formulations are ethanol, glycerin, propylene glycol, sorbitol, polyethylene glycol (both 300 and 400), dimethylacetamide, Cremophor EL, and *N*-methyl-2-pyrrolidone.

Glycols are widely used solubilizing agents, but can cause some stability or compatibility problems. Glycerol is used not only as a co-solvent for improving solubility of poorly water-soluble drugs, but also as a tonicity-adjusting agent (e.g., in insulin formulations). In freeze-dried formulations, glycerol can serve as a plasticizer, lowering the glass transition temperature of the product without the significant change in water content or activity.[14] In certain formulations containing unstable peptides, the presence of glycerol will increase the mobility of the freeze-dried formulation matrix, leading to peptide deamidation. Sorbitol has been reported to increase the degradation rate of penicillins in neutral and aqueous solutions.[15] On a more positive note, propylene glycol will potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction of methylparaben and polysorbate 80.[16]

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Table 1. A Listing of Major Excipients Used in Sterile Product Formulations (Both Commercial and Developmental)

- Solvent systems
  - Co-solvents
    - Propylene glycol
    - Glycerin
    - Ethanol
    - Polyethylene glycol (300 and 400)
    - Sorbitol
    - Dimethylacetamide
    - Cremophor EL
  - Oils
    - Sesame
    - Soybean
    - Corn
    - Castor
    - Cottonseed
    - Peanut
    - Arachis
    - Ethyl oleate
    - Isopropyl myristate
    - Glycofurol
    - Petrolatum
- Solubilization agents
  - Co-solvents
    - See above
  - Surface-active agents
    - Polyoxyethylene sorbitan monooleate (Tween 80)
    - Sorbitan monooleate
    - Polyoxyethylene sorbitan monolaurate (Tween 20)
    - Lecithin
    - Polyoxyethylene–polyoxypropylene copolymers (Pluronics®)
  - Complexation agents
    - Hydroxypropyl-β-cyclodextrin
    - Sulfobutylether-β-cyclodextrin (Captisol®)
    - Polyvinylpyrrolidone
    - Amino acids (arginine, lysine, histidine)
- Stabilization agents
  - Buffers
    - Acetate
    - Citrate
    - Tartrate
    - Phosphate
    - Triethanolamine (TRIS)
  - Antioxidants
    - Ascorbic acid
    - Acetylcysteine
    - Sulfurous acid salts (bisulfite, metabisulfite)
    - Monothioglyercol
  - Chelating agents
    - Ethylenediaminetetraacetic acid (EDTA)
    - Sodium citrate
  - Cryo- and lyoprotectants and bulking agents
    - Mannitol
    - Glycine
    - Sucrose
    - Lactose
    - Trehalose
    - Dextran
    - Povidone
    - Sorbitol
  - Competitive binding agents
    - Serum albumin
    - Heta-starch
- Tonicity-adjusting agents
  - Sodium chloride
  - Glycerin
  - Mannitol
  - Dextrose
- Antimicrobial preservative agents
  - Phenol
  - Meta-cresol
  - Benzyl alcohol
  - Parabens (methyl, propyl, butyl)
  - Benzalkonium chloride
  - Chlorobutanol
  - Thimerosal
  - Phenylmercuric salts (acetate, borate, nitrate)
- Delivery polymers
  - See Table 6

Co-solvents are known to cause hemolysis. In a study conducted by Fuet et al.[17] comparing the hemolytic effects, both *in vitro* and *in vivo*, of a variety of co-solvents (ethanol, propylene glycol, polyethylene glycol, dimethylisosorbide, and dimethylacetamide), complexing agents (nicotinamide), and surfactants (Pluronic L64 and emulphor EL-719), solutions most prone to elicit a hemolytic response were those containing propylene glycol, dimethylisosorbide, and nicotinamide). However, these authors found that the hemolytic effects of propylene glycol can be alleviated by the addition of either a tonicifying agent or polyethylene glycol 400.

Cremophor EL (polyoxyl 35 castor oil) has been approved as a solvent in commercial injectable dosage forms containing paclitaxel, diazepam, propanidid, and alfaxalone. It is compatible with many organic solvents and aqueous solutions. However, compounds containing phenolic hydroxyl groups may cause precipitation of Cremophor EL.

Surfactants

Surfactants serve a variety of very important functions in parenteral formulations. Among the most important are stabilizing proteins against aggregation. Tween 20 (polyoxyethylene sorbitan monolaurate) was shown to greatly reduce the

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Table 2. Examples of Special or Uncommon Excipients Used in Injectable Drug Products

Excipient	Product	Manufacturer
Acacia	Tuberculin Old Test (ID)	Lederle
Acetone sodium	Talwin (IM)	Sanofi Winthrop
Aluminum monostearate	Solganal	Schering
Benzenesulfonic acid	Tracrium	Glaxo Smith Kline
Benzyl benzoate	Depo-testesterone	Pharmacia
Cyclodextrin (alpha)	Alprostadil	Schwarz
Diethanolamine	Bactrim	Roche
Desoxycholate sodium	Fungizone	Bristol Myers Squibb
Formaldehyde	Some vaccines	Lederle, Connaught, Merck
Gelatin, hydrolyzed	Some vaccines	Merck
Gelatin, purified	Lupron Depot	TAP
Hydroxypropyl-β-cyclodextrin	Itraconazole	Janssen
Imidazole	Kogenate	Bayer
Monoethanolamine	Terramycin (IM)	Roerig
N,*N*-dimethylacetamide	Vuman	Bristol Myers Squibb
	Busulfan	Orphan
Polyoxyethylated fatty acid	AquaMephyton	Merck
PEG 40 castor oil	Monistat	Janssen
PEG 60 castor oil	Prograf	Fujisawa
Sodium lauryl sulfate	Proleukin	Cetus
Sulfobutylether-β-cyclodextrin	Ziprasidone mesylate	Pfizer
Triacetin	Prepidil Gel (ICV)	Pharmacia

rate of formation of insoluble aggregates of recombinant human factor XIII caused by both freeze thawing and agitation stresses[18] (Fig. 1). Maximum protection occurs at concentrations close to the critical micelle concentration of Tween 20, independent of initial protein concentration. In another report, Tween 20 at a 1% (w/v) concentration caused precipitation of a relatively hydrophobic protein (*Humicola lanuginosa lipase*) by inducing non-native aggregates.[19]

Tween 80 is well known to protect proteins against surface-induced denaturation.[20] Tween 80 was demonstrated to reduce hemoglobin aggregation in solution by preventing the protein from reaching the air–liquid interface or the liquid–surface interfaces.[21] Polyoxyethylene surfactants such as Tween 80 can form peroxide impurities after long-term storage. Knepp et al.[22] concluded that Tween 80 and other nonionic polyether surfactants undergo oxidation during bulk material storage and subsequent use and the resultant alkyl hydroperoxides formed can contribute to the degradation of proteins. In such formulations, they further reported that thiols such as cysteine, glutathione, and thioglycerol were most effective in stabilizing protein formulations containing peroxide-forming nonionic surfactants.

The nonionic surfactant octoxynol 40 (ethoxylated alkyl phenol, Igepal CA897, GAF), was found to solubilize an otherwise insoluble complex of a nonsteroidal anti-inflammatory drug and a quaternary ammonium antimicrobial preservative

Table 3. Examples of Esoteric Excipients Used as Solubilizers

Generic Name	Brand Name	Manufacturer	Excipient
Ciprofloxacin	Cipro IV	Bayer	Lactic acid
Doxorubicin HCl	Adriamycin RDF	Pharmacia	Methyl paraben
Ergotrate Maleate	Ergonovine maleate	Lilly	Ethyl lactate
Polyestradiol phosphate	Estradurin	Wyeth	Niacinamide
Zomepirac	Zomax	McNeil	Tromethamine[105]

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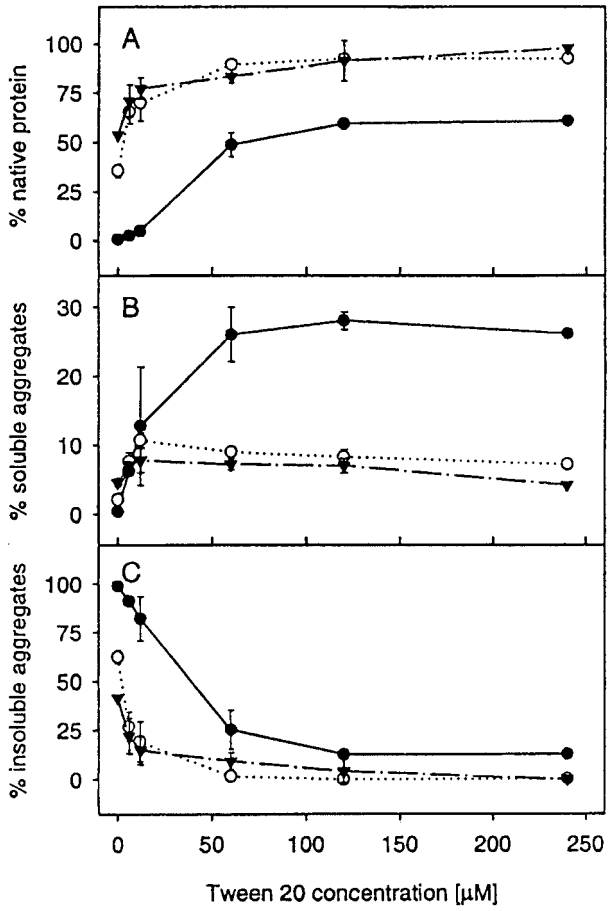

Figure 1. Recovery of native rFXIII (A) and formation of soluble (B) and insoluble (C) aggregates after 10 freeze–thaw cycles of 1 mg/mL (●), 5 mg/mL (○), and 10 mg/mL (▼) as a function of Tween 20. (From Krielgaard et al., J Pharm Sci, 87, 1593–1603, © 1998 John Wiley & Sons, Inc., reproduced with permission.)

mixture in an ophthalmic formulation.[23] This is a rather unique drug–excipient interaction in which the interaction of the excipient involves not only a drug, but also a drug–preservative combination that is otherwise incompatible.

Complexing and Dispersing Agents

Cyclodextrins have emerged as very effective additive compounds for solubilizing hydrophobic drugs. In the parenteral dosage form area, modified cyclodextrins, such as hydroxylpropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin have been reported to solubilize and stabilize many injectable drugs, including dexamethasone, estradiol, interleukin-2, and other proteins and peptides[24] without apparent compatability problems.[25] There are still only a few approved products worldwide that contain cyclodextrins (see Table 2). However, based on the literature and scientific meeting presentations, there will be a higher number of cyclodextrin-containing injectable formulations in the future.

The only reports of incompatibilities with cyclodextrins involve certain antimicrobial preservatives, primarily parabens.[26,27] One preliminary report described both sulfobutylether-β-cyclodextrin and hydroxylpropyl-β-cyclodextrin accelerating the degradation of an unidentified water-soluble drug to its insoluble degradant form.[28] The authors concluded that both the type and degree of substitution of the proximal hydroxyl groups in the cyclodextrin cavity will influence the potential for cyclodextrin additives to accelerate chemical degradation of drugs. As cyclodextrins become more prominent in injectable drug product development, there likely will be more reports of incompatibilities along with the expected reports describing solubility and stability enhancements.

Cyclodextrin-containing formulations (either 0.1 M sulfobutylether-β-cyclodextrin or 0.1 M hydroxylpropyl-β-cyclodextrin) were shown to cause less damage to venous epithelial cells at the site of injection compared with formulations containing organic co-solvents.[29] PVP (povidone) is a generally compatible polymeric excipient. However, it can form molecular adducts (a positive reaction with respect to iodine therapy topically) and will complex with some preservatives such as thimerosal.[6] Lecithin is a commonly used emulsifying and stabilizing agent in intramuscular and intravenous injections, primarily the intravenous fatty or lipid emulsions used in parenteral nutrition. Lecithin also is a component of some liposomal formulations. Polaxamers (e.g., Poloxamer 188, BP) are nonionic polyoxyethylene–polyoxypropylene copolymers used as emulsifying agents in intravenous fat emulsions. They have also been used in several patented protein formulations as stabilizers and sustained release injectables in development as solubilizing and stabilizing agents.[30] Polaxamers, like the polysorbates, can form peroxide impurities over time and are incompatible with antimicrobial preservatives such as phenol and paraben.

Oils/Lipids

Many commercially available parenteral products contain lipophilic or oleaginous solvents. Examples of injectable lipid solvents include ethyl

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