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REVIEW ARTICLE

Excipients and Their Use in Injectable Products

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ABSTRACT: Formulation of a new drug product with excipients, that have been previously added to an approved injectable product, may save pharmaceutical companies developmental time and cost. The Physicians' Desk Reference (PDR) and Handbook on Injectable Drugs were reviewed, extracting all information on excipients. The information was consolidated into eight tables, categorizing excipients as 1) Solvents and Co-solvents, 2) Solubilizing, Wetting, Suspending, Emulsifying or Thickening agents, 3) Chelating Agents, 4) Antioxidants and Reducing Agents, 5) Antimicrobial Preservatives, 6) Buffers and pH Adjusting Agents, 7) Bulking Agents, Protectants, and Tonicity Adjustors, and 8) Special Additives. Where applicable, tables list frequency of use, concentration, and an example of a commercial product containing the excipient. Excipients which are included in the 1996 FDA 'Inactive Ingredient Guide,' but do not appear in the PDR or Handbook on Injectable Drugs, were included as a separate list.

Introduction

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. Preferably, the formulation will be isotonic, and depending on the route of administration (for instance, for intra-spinal or intra-cisternal routes), antioxidants and preservatives may not be allowed. For a given drug, the risk of adverse events is higher if it is administered as an injection versus a non-parenteral route. The requirement for sterility demands that the excipients be able to withstand autoclaving or other sterilization processes. These factors limit the choice of excipients available to the formulators.

Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their 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, creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data. A new additive in a formulated product will always require additional studies adding to the cost and timeline of product development.

The purpose of this paper is to present the various excipients that have been included in the formulation of injectable products marketed in the USA. This information is not readily available. A literature search indicates that the last paper dealing with this was published in 1980 (1). Products approved outside the US are not covered in this review. Also, sterile dosage forms not administered parenterally, such as solutions for irrigation, ophthalmic or otic drops, and ointments were excluded.

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Methodology

Physicians' Desk Reference published in 1994 & 1996 (2, 3), and Handbook on Injectable Drugs (4) were used as the primary source of information. Entries on all injectable drugs were summarized in an Excel worksheet. Each product was classified by Manufacturer, Trade name, Drug name, Route of Administration, SVP/LVP, pH of Product, Solvent Used, Solubilizing/Suspending Agent, Preservative, Antioxidant, Chelator and Other Formulation Additives.

The resulting Excel sheet had information on more than 700 products. This information was condensed into easy-to-read tables. Each table has been categorized based on the primary function of 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 was based on our experience in formulation development and on the published literature. Such simplification avoids duplication of entries and provides the audience with easy-to-read tables.

Some duplication was unavoidable. Tables VII and VIII contain some excipients which may have also been listed in the first six tables. Whenever the reference specifically designated a specific function to an ingredient it was re-listed in Tables VII and VIII. For example, glycine can be used as a buffer or as a stabilizing (protecting) agent. Therefore, glycine is listed in Tables VI and VII. Methyl paraben is a preservative (Table V) but also has a special function in Adriamycin RDF® formulation (Table VIII).

The concentration of excipients is listed as percentages weight by volume (w/v) or volume by volume (v/v). If the product was listed as lyophilized or powder, these percent-

TABLE I
Solvents and Co-solvents

Excipient	Frequency	Range	Example
Benzyl Benzoate	2	20% v/v	Depo-Testosterone® (Upjohn) 20% v/v
Cottonseed Oil	1	73.6% w/v	Depo-Testosterone® (Upjohn) 73.6% w/v
N,N Dimethylacetamide	1	6% w/v	Vumon® (Bristol Myers) 6% w/v
Ethanol	24	0.6–80%	Prograf® (Fujisawa) 80% v/v
Glycerin (Glycerol)	9	1.6–70% w/v	Multitest CMI® (Connaught) 70% w/v
Peanut oil	1	*	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG	4	0.15–50%	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	2	50–65%	VePesid® (Bristol Myers) 65% w/v
PEG 400	2	*	Ativan® (Wyeth-Ayerst)
PEG 3350	5	0.3–3%	Depo-Medrol® (Upjohn) 2.95% w/v
Poppyseed oil	1	1%	Ethiodol® (Savage) 1%
Propylene Glycol	25	0.2–75.2%	Terramycin Solution (Roerig) 75.2%
Safflower oil	2	5–10%	Liposyn II® (Abbott) 10%
Seasme oil	6	*	Solganal Inj.® (Schering)
Soybean oil	4	5–20% w/v	Intralipid® (Clintec) 20%
Vegetable oil	2	*	Virilon IM Inj.® (Star Pharmaceuticals)

* No data available.

ages were derived based on the reconstitution volume commonly used. The tables list the range of concentration used, typical or most common concentration employed, and examples of products containing the excipient, specifically those which use extremely low or high concentrations.

Discussions

Table I list solvents and co-solvents used in parenteral products. Water for injection is the most common solvent but may be combined or substituted with a co-solvent to improve the solubility or stability of drugs. Oils like safflower and soybean are used in total parenteral nutrition products where they serve as a fat source and as carriers for fat-soluble vitamins. Ethanol and propylene glycol are used, either alone or in combination with other solvents, in more than 50% of parenteral co-solvent systems. It is surprising to see propylene glycol used more often than polyethylene glycols (PEGs) in spite of its higher myotoxicity and hemolyzing effects (5, 6). Probably, the presence or generation of peroxides in PEGs is a major limitation.

Table II includes a broad category of excipients whose function in formulation could be—(1) Viscosity imparting or suspending agents like carboxy methyl cellulose, sodium carboxy methyl cellulose, sorbitol, acacia, Povidone, hydrolyzed gelatin; (2) Solubilizing, wetting or emulsifying agents like Cremophore EL, sodium desoxycholate, Polysorbate 20 or 80, PEG 40 castor oil, PEG 60 castor oil, sodium dodecyl sulfate, lecithin or egg yolk phospholipid; (3) Aluminum monostearate which is added to fixed oil to form viscous or gel-like suspending medium. Polysorbate 80 is the most common and versatile solubilizing, wetting and emulsifying agent.

Only a limited number of chelating agents are used in parenteral products (Table III). They serve to complex heavy

TABLE II
Solubilizing, Wetting, Suspending, Emulsifying or Thickening Agents

Excipient	Frequency	Range	Example
Acacia	2	7%	Tuberculin Old Test® (Lederle) 7%
Aluminum monostearate	1	2%	Solganal Inj.® (Schering) 2%
Carboxy methyl cellulose	4	1%	Bicillin® (Wyeth-Ayerst) 0.55%
Carboxy methyl cellulose, sodium	9	0.1–0.75%	Lupron Depot® (TAP) 0.75% w/v
Cremophore EL*	3	50–65% w/v	Sandimmune® (Sandoz) 65% w/v
Desoxycholate sodium	1	0.4% w/v	Fungizone® (Bristol Myers) 0.41% w/v
Egg yolk phospholipid	3	1.2%	Intralipid® (Clintec) 1.2%
Gelatin, Hydrolzyed	1	16% w/v	Cortone® (Merck) 16% w/v
Lecithin	7	0.4–1.2% w/v	Diprivan® (Zeneca) 1.2% w/v
Polyoxyethylated fatty acid	1	7% w/v	AquaMephyton® (Merck) 7% w/v
Polysorbate 80 (Tween 80)	31	0.01–12%	Cordarone X I.v.®. (Wyeth-Ayerst) 10%
Polysorbate 20 (Tween 20)	5	0.01–0.4%	Calcijex® (Abbott) 0.4% w/v
PEG 40 castor oil**	1	11.5% v/v	Monistat® (Janssen) 11.5% v/v
PEG 60 castor oil***	1	20% w/v	Prograf® (Fujisawa) 20% w/v
Povidone (Polyvinyl pyrrolidone)	6	0.5–0.6% w/v	Bicillin® (Wyeth-Ayerst) 0.6% w/v
Sodium dodecyl sulfate (Na lauryl sulfate)	1	0.018% w/v	Proleukin® (Cetus) 0.018% w/v
Sorbitol	3	25–50%	Aristrospan® (Fujisawa) 50% v/v

* Cremophor EL: Etocas 35, polyethoxylated castor oil, polyoxyethylene 35 castor oil.
** PEG 40 castor oil; polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40.
*** PEG 60 hydrogenated castor oil: Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60.

TABLE III
Chelating Agents

Excipient	Frequency	Range	Example
Calcium disodium EDTA*	9	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	34	0.01–0.1%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.2%
DTPA**	1	0.04%	Magnevist® (Berlex) 0.04%

* EDTA = Ethlenediaminetetraacetic acid.
** DTPA = Diethylenetriaminepentaacetic acid; Pentetic acid.

metals and therefore can improve the efficacy of antioxidants or preservatives. In our opinion, calcium EDTA has an advantage over tetrasodium salt by not contributing sodium and not chelating calcium from the blood.

An antioxidant as a class is defined as those compounds that can act as reducing agents or may serve as free radical scavengers. Table IV summarizes the antioxidants, their frequency of use, concentration range and examples of products containing them. Sulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products despite several reports of incompatibilities and toxicity (7, 8). Butylated hydroxy anisole, butylated hydroxy toluene and propyl gallate are primarily used in semi/non-aqueous vehicles because of their low aqueous solubility. Ascorbic acid/sodium ascorbate may serve as an antioxidant, buffer, and chelating agent in the same formulation.

Benzyl alcohol was the most common antimicrobial preservative present in parenteral formulations (Table V). This is consistent with other surveys (9). Parabens are the next most common preservatives. Thirty-nine products had a combination of methyl and propyl parabens; eleven had only methyl, and one had only propyl paraben. Thimerosal was surprisingly common, especially in vaccines, even though some individuals have sensitivity to mercurics. Chlorocresol is purported to be a good preservative for parenterals, but our survey did not find any examples of commercial products containing chlorocresol.

Table VI lists buffers and chemicals used to adjust the pH of formulations. Phosphate, citrate, and acetate are the most common buffers used in parenteral products. Mono and diethanolamine are added to adjust pH and form corresponding salts. Hydrogen bromide, sulfuric acid, benzene sulfonic acid and methane sulfonic acids are added to drugs which are bromide (Scopolamine HBr, Hyoscine HBr, UDL), sulfate (Nebcin, Tobramycin sulfate, Lilly), besylate

TABLE IV
Antioxidants and Reducing Agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Ascorbate (sodium/acid)	7	0.1–4.8% w/v	Vibramycin® (Roerig) 4.8% w/v
Bisulfite sodium	28	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol® (Astra) 0.03%
Butylated hydroxy toluene (BHT)	3	0.00116–0.03% w/v	Aquasol® (Astra) 0.03%
Cystein/Cysteinate HCl	2	0.07–0.10% w/v	Acthar Gel® (Rhone-Poulanc) 0.1% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (DuPont) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt)
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	2	0.1% w/v	Varivas® (Merck) 0.1% w/v
Formaldehyde sulfoxylate sodium	9	0.075–0.5% w/v	Terramycin Solution (Roerig) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	29	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Monothioglycerol (Thioglycerol)	6	0.1–1%	Terramycin Solution (Roerig) 1%
Propyl gallate	2	0.02%	Navane® (Roerig)
Sulfite sodium	7	0.05–0.2% w/v	Enion® (Ohmeda) 0.2% w/v
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

TABLE V
Antimicrobial Preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	74	0.75–5%	Dimenhydrinate® (Steris) 5%
Chlorobutanol	17	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	3	0.1–0.3%	Humatrope® (Lilly) 0.30%
Myristyl gamma-picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Upjohn) 0.169% w/v
Paraben methyl	50	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	40	0.01–0.1%	Xylocaine w/Epinephrine (Astra) 0.1% w/v
Phenol	48	0.2–0.5%	Calcimar® (Rhone Poulanc) 0.5% w/v
2-Phenoxyethanol	3	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	46	0.003–0.01%	Atgam® (Upjohn) 0.01%

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