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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.

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-

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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%

TABLE VI
Buffers and pH Adjusting Agents

Excipient	Example
Acetate	
Sodium	Miacalcin Injection® (Sandoz)
Acetic acid	Miacalcin Injection® (Sandoz)
Glacial acetic acid	Brevibioc Injection® (Ohmeda)
Ammonium	Bumex Injection® (Roche)
Ammonium hydroxide	Triostat Injection® (SmithKline Beecham)
Benzene sulfonic acid	Tracrium Injection® (Glaxo-Wellcome)
Benzoate Sodium/acid	Valium Injection® (Roche)
Bicarbonate Sodium	Cefotan Injection® (Zeneca)
Carbonate Sodium	HypoRho-D® (Bayer)
Citrate	
Acid	DTIC-Dome® (Bayer)
Sodium	Ceredase® (Genzyme)
Disodium	Cerezyme® (Genzyme)
Trisodium	Cerezyme® (Genzyme)
Diethanolamine	Bactrim IV® (Roche)
Glucono delta lactone	Quinidine® (Lilly)
Glycine	Hep-B Gammagee® (Merck)
Hydrochloric acid	Amicar® (Immunex)
Hydrogen bromide	Scopolamine (UDL)
Lactate acid/Sodium	Fentenyl citrate & Droperidol (Astra)
Lysine	Eminase Injection® (Roberts)
Maleic acid	Librium Injection® (Roche)
Methanesulfonic acid	DHE-45 Injection® (Sandoz)
Monoethanolamine	Terramycin Solution (Roerig)
Phosphate	
Acid (phosphoric)	Humegon® (Organon)
Monobasic potassium	Zantac Injection® (Glaxo-Wellcome)
Monobasic sodium*	Pregnyl® (Organon)
Dibasic sodium**	Prolastin® (Bayer)
Tribasic sodium	Synthroid® (Knoll)/
Sodium hydroxide	Optiray® (Mallinckrodt)
Sulfuric acid	Nebcin® (Lilly)
Tartrate acid/sodium	Methergine Injection® (Sandoz)
Tromethamine	Optiray® (Mallinckrodt)

* Sodium biphosphate, Sodium dihydrogen phosphate or Na dihydrogen orthophosphate.
** Sodium phosphate, Disodium hydrogen phosphate.

(Tracrium Inj., Atracurium besylate) or mesylate (DHE 45 Injection, Dihydroergotamine mesylate) salts. Glucono delta lactone is used to adjust the pH of Quinidine gluconate (Lilly). Benzoate buffer, at a concentration of 5%, is used in Valium Injection. Citrates are common buffers that can have a dual role as chelating agents. Lysine and glycine are amino acids which function as buffers and stabilize protein and peptide formulations. These amino acids are also used as lyo-additives and may prevent cold denaturation. Lactate and tartrate are occasionally used as buffer systems.

Table VII lists additives which are used to modify osmolality, and as bulking or lyo-cryo protective agents. Dextrose and sodium chloride are used to adjust tonicity in the majority of formulations. Some amino acids, glycine, alanine, histidine, imidazole, arginine, asparagine, aspartic acid, are used as bulking agents for lyophilization and may serve as stabilizers for proteins or peptides and as buffers. Monosaccharides (dextrose, glucose, lactose), disaccharide (sucrose), polyhydric alcohols (inositol, mannitol, sorbitol), glycol (PEG 3350), Povidone (polyvinylpyrrolidone), and proteins (albumin, gelatin) are commonly used as lyo-additives.

TABLE VII
Bulking Agents, Protectants, and Tonicity Adjustors

Excipient	Example
Alanine	Thrombate III® (Bayer)
Albumin	Biociate® (Arco)
Albumin human	Botox® (Allergan)
Amino acids	Havrix® (SmithKline Beecham)
L-Arginine	Activase® (Genentech)
Asparagine	Tice BCG® (Oganon)
L-Aspartic acid	Pepcid® (Merck)
Calcium chloride	Phenergan Injection® (Wyeth-Ayerst)
Citric acid	Sensorcaine-MPF® (Astra)
Dextrose	Betaseron® (Berlex)
Gelatin hydrolyzed	Acthar® (Rhone-Poulanc Rorer)
Glucose	Iveegam® (immuno-US)
Glycerin	Tice BCG® (Oganon)
Glycine	Atgam Injection® (Upjohn)
Histidine	Antihemophilic Factor, human (Am. Red Cross)
Imidazole	Helixate® (Armour)
Inositol	OctreoScan® (Mallinckrodt)
Lactose	Caverject® (Upjohn)
Magnesium chloride	Terramycin Solution® (Roerig)
Magnesium sulfate	Tice BCG® (Oganon)
Mannitol	Elspar® (Merck)
Polyethylene glycol 3350	Bioclate® (Arco)
Polysorbate 80	Helixate® (Armour)
Potassium chloride	Varivax® (Merck)
Povidone	Alkeran® (Glaxo-Wellcome)
Sodium chloride	WinRho SD® (Univax)
Sodium succinate	Actimmune® (Genentech)
Sodium sulfate	Depo-Provera® (Upjohn)
Sorbitol	Panhematin® (Abbott)
Sucrose	Prolastin® (Bayer)

Special Additives

These additives have been included in pharmaceutical formulation to serve specific functions (Table VIII). Below is a summary of the special additives along with their intended use—

(1) Calcium gluconate injection (American Regent) is a saturated solution of 10% w/v; calcium d-saccharate tetrahydrate 0.46% w/v is added to prevent crystallization during temperature fluctuations.
(2) Cipro IV® (Ciprofloxacin, Bayer) contains lactic acid as a solubilizing agent for the antibiotic.
(3) Premarin Injection® (Conjugated Estrogens, Wyeth-Ayerst Labs) is a lyophilized product that contains simethicone to prevent formation of foam during reconstitution.
(4) Dexamethasone acetate (Dalalone DP, Forest, Decadron-LA, Merck, Dalalone DP Injection, UAD Labs) and Dexamethasone Na phosphate (Merck) are available as suspension or solution. These dexamethasone formulations contain creatine or creatinine as an additive.
(5) Adriamycin RDF® (Doxorubicin hydrochloride, Pharmacia) contains methyl paraben, 0.2 mg/mL, to increase dissolution (10).
(6) Ergotrate maleate (Ergonovine maleate, Lilly) contains 0.1% ethyl lactate as a solubilizing agent.
(7) Estradurin Injection® (Polyestradiol phosphate, Wyeth-Ayerst Labs) uses Niacinamide (12.5 mg/ml)

TABLE VIII
Special Additives

Excipient	Example
Acetyl tryptophanate	Human Albumin (American Red Cross)
Aluminum hydroxide	Recombinant HB® (Merck)
Aluminum phosphate	Tetanus Toxoid Adsorbed® (Lederle)
Aluminum potassium sulfate	TD Adsorbed Adult® (Connaught)
E-Aminocaproic acid	Eminase® (Roberts)
Calcium d-saccharate	Calcium Gluconate (American Regent)
Caprylate sodium	Human Albumin (American Red Cross)
8-Chlorotheophylline	Dimenhydrinate (Steris)
Creatine	Dalalone DP® (Forest)
Creatinine	Hydrocortone Phosphate (Merck)
Diatrizoic acid	Conray (Mallinckrodt)
Gamma Cyclodextrin	Cardiotec (Squibb)
Ethyl lactate	Ergotrate maleate® (Lilly)
Ethylenediamine	Aminophylline® (Abbott)
L-Glutamate sodium	Kabikinase® (Pharmacia)
Iron ammonium citrate	Tice BCG® (Oganon)
Lactic acid	Cipro IV® (Bayer)
D,L-Lactic and Glycolic acid copolymer	Zoladex® (Zeneca)
Maltose	Gamimune® (Bayer)
Meglumine	Magnevist® (Berlex)
Niacinamide	Estradurin® (Wyeth-Ayerst)
Paraben methyl	Adriamycin RDF® (Pharmacia)
Protamine	Insulatard NPH® (Novo Nordisk)
Simethicone	Premarin Injection® (Wyeth-Ayerst)
Sodium saccharin	Compazine Injection® (Smith-Kline Beecham)
Tri-n-butyl phosphate	Venoglobulin® (Apha Therapeutic)
von Willebrand factor	Bioclate® (Arco)
Zinc	Lente Insulin® (Novo Nordisk)

TABLE IX
List of Excipient from 1996 FDA 'Inactive Ingredient Guide'

Ammonium sulfate	Pentetate (DTPA) calcium trisodium
Benzyl chloride	Poloxamer 165
Butyl paraben	PEG 4000
Caldiamide sodium	PEG 600
Calteridol calcium	Polyglactin
Castor oil	Polylactide
Cellulose (microcrystalline)	Polyoxyethlene fatty acid esters
Cholesterol	Polyoxyethylene sorbitan monosterate
Deoxycholic acid	Polyoxyl 35 Castor oil
Diatrizoic acid	Polysorbate 40
Dicyclohexyl carbodiimide	Polysorbate 85
Diethyl amine	Potassium hydroxide
Dimyristoyl lecithin	Potassium phosphate, dibasic
Dimyristoyl phosphatidyl-glycerol	Sodium bisulfate
Disofenin	Sodium chlorate
Docusate sodium	Sodium hypochloride
Edamine	Sodium iodide
Exametazime	Sodium pyrophosphate
Gluceptate sodium	Sodium thiosulfate, anhydrous
Gluceptate calcium	Sodium trimetaphosphate
Glucuronic acid	Sorbitan monopalmitate
Guanidine HCl	Stannous chloride
Iofetamine HCl	Stannous fluoride
Lactobionic acid	Stannous tartrate
Lecithin hydrogenated soy	Starch
Lidofenin	Succimer
Medrofenin	Succinic acid
Medronate disodium	Sulfurous acid
Medronic acid	Tetrakis (1-isocyano-2-methoxy-2,methyl-propante) copper (I) Te
Methyl boronic acid	Thiazoximic acid
Methyl cellulose	Trithiazoximic acid
Methylene blue	Urea
N-(carbamoyl-methoxy polyethylene-glycol 2000)-1,2-distearoyl	Zinc acetate
N-2-hydroxyethyl piperazine N'-2' ethane sulphonic acid	Zinc chloride
Nioxime	Zinc oxide
Nitric acid	2-ethyl hexanoic acid
Oxyquinoline	PEG vegetable oil

as a solubilizing agent. Hydeltrasol® (Merck) also contains niacinamide.

(8) Aluminum in the form of aluminum hydroxide, aluminum phosphate or aluminum potassium sulfate is used as adjuvant in various vaccine formulations to elicit an increased immunogenic response.

(9) Zoladex® (Goserelin acetate, Zeneca) is administered subcutaneously as microspheres. These spheres are made of D,L-lactic and glycolic acid copolymer. Lupron Depot Injection® (TAP) are lyophilized microspheres of gelatin and glycolic-lactic acid for intramuscular injection.

(10) Gamma cyclodextrin is used as a stabilizer in Cardiotec® at a concentration of 50 mg/mL.

(11) Sodium caprylate (sodium octoate) has antifungal properties, but it is also used to improve the stability of albumin solution against effects of heat. Albumin solution can be heat pasteurized by heating at 60°C for 10 hours in the presence of sodium caprylate. Acetyl tryptophanate sodium is also added to albumin formulations.

(12) Meglumine (N-methylglucamine) is used as an excipient and to form in-situ salt. For example, diatrizoic acid, an X-ray contrast agent, is more stable when autoclaved as meglumine salt than as sodium salt (11). Meglumine is also added to Magnevist®, a magnetic resonance contrast agent, formulation.

(13) Surprisingly, sodium saccharine is used in Stelazine® and Compazine® formulations; our guess is that it serves as a stabilizer and tonicity adjuster.

(14) Tri-n-butyl phosphate is present as an excipient in human immune globulin solution (Venoglobulin®). Its exact function in the formulation is not known, but it may serve as a scavenging agent.

(15) von Willebrand factor is used to stabilize recombinant antihemophilic factor (Bioclate®).

(16) Maltose serves as a tonicity adjuster and stabilizer in immune globulin formulation (Gamimune N®).

(17) Epsilon amino caproic acid (6-amino hexanoic acid) is used as a stabilizer in anistreplase (Eminase injection®).

(18) Zinc and protamine have been added to insulin to form complexes and control the duration of action.

Recently, FDA has published 'Inactive Ingredient Guide' which lists all the excipients in alphabetical order. Each ingredient is followed by the route of administration (for example, iv, oral) and, in some cases, the range of concentration used in the approved drug product. However, this list does not provide the name of commercial product(s) corresponding to each excipient. Table IX is a summary of all the excipients which are included in the 'Inactive Ingredient Guide,' but do not appear in PDR or Handbook on Injectable Drugs.

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