Compendium of Excipients for Parenteral Formulations

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Overview

The selection of excipients in parenteral formulation design is often both rational and empirical. It is rational in the sense that certain types of excipients are added to alter the formulation properties: i) buffers of appropriate pKa are added to control hydrogen ion concentration at a desired pH, ii) tonicifiers are added for biocompatibility, iii) surfactants are added when necessary to prevent aggregation, adsorption to surfaces, or increase solubility, iv) antioxidants are included to prevent unwanted oxidation of the drug, and so on. The inclusion of various classes of formulation components, and the concentration used is often quite rational, in that their behavior and properties are known, and they are added to prevent specific problems that would arise in their absence. On the other hand, however, the selection of the *exact* excipient used is far from rational; it is empirical in the first order, satisfying only one question, "Has it been used previously in a similar parenteral formulation?"

Many prototype formulations have been terminated because one or more of the selected excipients was not found in a previously approved parenteral product. In fact, there have been a handful of excipients with striking favorable properties, such as trehalose with its ability to confer solid state stabilization of several types of proteins, or EDTA and its antioxidants by metal ion chelation. These excipient compounds, and many others, have not been used widely, largely because of concerns with unknown toxicity, continued production supply, or cost.

Thus, the formulation scientist is often faced with a dilemma—which excipients are truly available for use (based on what has been used previously), and which are not? For example, PEG 400 has been added to several parenteral formulations, but what about PEG 1200, or PEG 4000? And at what concentrations, and by what route? Sodium citrate is an excellent buffer for many formulations at 5 mM, but is too painful in most instances for subcutaneous use at 50 mM. High concentrations of propylene glycol may be used in a slow intravenous infusion, but would produce unwanted hemolysis and pain if given by subcutaneous or intramuscular injection. It is often the case that the "safe level" of an excipient may depend on the route of administration. These are only a few examples of factors which must be considered when designing a formulation; there are dozens more based on empirical information required for efficient formulation design, but thus far a compendium has not been published. This review was written to fill this void.

Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc. The information found in this table comes from several sources, including package inserts, the Physician's Desk Reference (PDR '97), as well as personal correspondence from the companies supplying the products. The published excipient concentration was often given in different units, including: mg/mL, mOs, Molar, sodium equivalents, biological Units, Molal, weight percent, etc., and provided one of the greatest challenges in putting this compendium together. We sought to list all the excipients (where possible) in common units (i.e., mg/mL), so that a rapid comparison of the different formulations could be made at a glance. (This is not easy to do, for example, when comparing Tween 20 concentrations at 0.0001 M, 0.01% and 1 mg/mL; fortunately, the average molecular weight is known for most excipients, permitting a standardization of excipient concentrations). This standardization of excipient concentrations is perhaps the greatest value of this compendium, but also represents one of the greatest sources of potential error. The recalculation of excipient concentrations, often from scant or nondescriptive data, is not trivial and there may be an occasional discrepancy despite cross-checking with the original sources.[1] Nevertheless, this compendium represents a comprehensive survey of parenteral excipients used today, and is a resource for the parenteral formulation scientist.

Notes

In putting together this excipient compendium, there were a number of points that should be noted, so that the reader understands the limitations and assumptions in some of the calculations.

1) Concentrations are listed in weight/volume% unless otherwise noted. In some cases values are listed in volume/volume% or the manufacturer did not specify what kind of percentage they were using (and in this case it was assumed weight/volume %).

2) Sterile water for injection is included in the excipient list when used in solution formulations; however, in most

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[1] If discrepancies are found, e-mail them to nguyen.tue@gene.com for correction to subsequent compendiums of this nature.

cases the quantity or percentage of water in the formulation was not indicated by the manufacturer or identified only as q.s. We have kept the same conventions here.

3) Excipients listed are present in the drug formulation itself, and do not include excipients present in diluent (for example, when a lyophilized formulation is diluted with bacteriostatic water containing benzyl alcohol). In some cases, a diluent is supplied that contains several additional excipients and, in the case or provided diluent, these excipients are listed in the excipient category and designated with a "D" in addition to their usual excipient type (the D stand for present in diluent).

4) If no excipients are listed, it means that no excipients were revealed by the manufacturer. In some cases, this is because there are no excipients in the formulation, but this should not be assumed. In some cases, there may be excipients present but the manufacturer has not disclosed them to us, largely for proprietary reasons. Specific follow-up about these drugs should be referred to the manufacturer.

5) The given drug concentration is usually the concentration of the compound listed in the drug name category, unless identified as otherwise. For example, many drugs are formulated as salts such that the salt name is listed in the drug name category (for example, mitoxantrone hydrochloride). However, in the drug concentration category, the concentration of the active component is usually listed (for example, equivalent to 2 mg/mL mitoxantrone free base), so as to have a correct concentration of the active drug form.

6) When concentrations of excipients and drugs are listed as a range it implies that these values could only be approximated. Frequently, a range is given because the product is available in a variety of storage containers, or having several dilution schemes. The ranges given are approximations only, based on the available information. In no way should these ranges be assumed to encompass all possible dilution schemes or configurations.

7) Preservatives (such as benzyl alcohol) that are present only in one configuration of a drug (for example in the multiple-dose product, but not in the single-use product) may be listed as a range (0–x%). This was to avoid making two or more records for essentially the same product configuration.

8) For drugs that are given as a salt form, the counter ion may not be listed as an excipient. To search for counter ions (like sodium or potassium) one may look in the drug name fields (where the entire salt is often listed) or in the comments section (where the quantity of the counter ion per gram of drug is often provided) as well as in the excipient section.

9) If a pH value is listed for a lyophilized product, in most cases, it is the pH of the drug after its initial reconstitution with diluent, not the pH at lyophilization.

10) The concentration values given for excipients and active drug product in lyophilized products are usually those present at the initial reconstitution step, and are not necessarily the concentrations present at delivery (often further dilution occurs). This applies to solution formulations as well. Further, excipient concentrations may not take into account additive effects from the diluent (for example, a drug containing sodium chloride and reconstituted with 0.9% Sodium Chloride usually lists the concentration of sodium chloride present in the undiluted state).

11) When the excipient concentration is calculated for a lyophilized product, it is usually done by dividing the weight of the material by the volume of liquid added. Note that this does not take into account the additive volume of mixing that occurs, so such values are to be considered only approximations. In cases where the manufacturer provided the total volume after mixing, this final volume was used for calculations.

12) For drugs requiring reconstitution/dilution, in most cases a diluent recommended by the manufacturer is identified. In cases where multiple compatible diluents are possible, or when dilution schemes are complicated, one will see the note "Consult PDR for appropriate dilution." In some cases, often when the recommended diluent is provided, the manufacturer would not reveal the identity of the diluent for proprietary reasons.

13) Finally, most of the entries herein have been sent to the manufacturer for their correction and final notes. Many manufacturers participated in checking the data; others did not. We want to make this compendium as correct as possible, and so if errors are found, please e-mail them to nguyen.tue@gene.com for correction.

Acknowledgments

This compendium would not have been possible without the diligent work of Milianne Chin. She compiled much of the data, engineered the database, and contacted dozens of different companies to ensure that the listings are up to date.

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
			paravertebral	sarracenia purpurea, pitcher plant distillate	Sarapin	High Chemical Company	Solution	multidose vial
		6.0 - 7.0	IV - intravenous	Provides Rose's recommended daily intake of essential	5.4% NephrAmine "	R&D Laboratories Inc.	Solution	glass containers
acacia	7.0		ID - intradermal	Old Tuberculin	Tuberculin, Old, Tine Test	Lederle Laboratories	Solution	disposable
acacia (gum arabic)	7.0		ID - intradermal	tuberculin, purified protein derivative	(PPD) Tine Test	Lederle Laboratories	Solution	multiple-puncture
acetate	0.059	4.0	IV - intravenous	filgrastim (recombinant methionyl human	Neupogen ®	Amgen, Inc.	Solution	single dose vial
acetate		neutral	SC - subcutaneous	Lente (R) human insulin zinc suspension	Novolin ® L	Novo Nordisk Pharmaceuticals	Suspension	vials
acetate		neutral	SC - subcutaneous	Lente (L) Purified Pork Insulin Zinc Suspension, USP	Lente (L) Purified Pork Insulin Zinc Suspension,	Novo Nordisk Pharmaceuticals	Suspension	vials
acetic acid	0.435		IV - intravenous	ritodrine hydrochloride	Yutopar	Astra USA, Inc.	Solution	vial
acetic acid			SC - subcutaneous	leuprolide acetate	Lupron Injection	TAP Pharmaceuticals	Solution	multidose vial
acetic acid			IM - intramuscular	calcitonin-salmon	Calcimar ® Injection; Synthetic	Rhone-Poulenc Rorer	Solution	vials
acetic acid			IV - intravenous	albumin (human), 25%	Albuminar ®-25	Armour Pharmaceutical	Solution	vials
acetic acid		6.9 ± 0.5	IV - intravenous	albumin (human) 5%	Albuminar ®-5	Armour Pharmaceutical	Solution	bottles
acetic acid		3.5 - 5.5	IV - intravenous	vincristine sulfate, USP	Oncovin ®	Eli Lilly & Company	Solution	vials
acetic acid	0.01	~4.0	IV - intravenous	flumazenil	Romazicon ™	Roche Laboratories	Solution	vials
acetic acid	<2.5 (w/w)		SC - subcutaneous	goserelin acetate implant	Zoladex ®	Zeneca Pharmaceuticals	Solid Implant	disposable
acetic acid	0.46	3.0 - 4.5	IV - intravenous	mitoxantrone hydrochloride	Novantrone	Immunex Corporation	Solution	multidose vials
acetic acid		2.5 - 4.5	IM - intramuscular	oxytocin	Oxytocin Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid		~5.9	IM - intramuscular	neostigmine methylsulfate	Prostigmin Injectable	ICN Pharmaceuticals	Solution	multidose vial
acetic acid	0.225		IM - intramuscular	calcitonin-salmon	Miacalcin ®	Sandoz Pharmaceuticals	Solution	vial
acetic acid		6.4 - 7.2	IM - intramuscular	tetanus immune globulin (human) primarily IgG	Hyper-Tet ®	Bayer Corporation-Biologi	Solution	prefilled
acetic acid		4.0	IV - intravenous	rocuronium bromide	Zemuron ™ Injection	Organon	Solution	multidose vial
acetic acid (ampul)			IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals,	Lyophilized	single dose vials
acetic acid (glacial)	0.2	4.2 ± 0.3	IV - intravenous	octreotide acetate injection	Sandostatin ®	Sandoz Pharmaceuticals	Solution	ampuls

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
acetic acid NF			IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
acetic acid NF		4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
acetone sodium	0.1	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin Injection (cartridge needle)	Sanofi Winthrop	Solution	cartridge needle
acetone sodium	0.2	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin injection (multidose vial)	Sanofi Winthrop	Solution	multidose vials
acetone sodium	0.4		spinal anesthesia	procaine hydrochloride	Novocain	Sanofi Winthrop	Solution	ampuls
acetone sodium	≤ 0.2	3.2 - 6.0	spinal anesthesia	tetracaine hydrochloride	Pontocaine Hydrochloride 1% Solution	Sanofi Winthrop	Solution	ampuls
alanine	0.668 - 1.11	6.0 - 7.5	IV - intravenous	antithrombin III (human)	Thrombate III ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
albumin	0.25	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
albumin	<10.0		IM - intramuscular	rabies virus prepared from strain	Imovax ® Rabies Vaccine	Connaught Laboraties Inc.	Freeze-dried	single dose vial
albumin (human)	≤1.25		IV-intravenous	Antihemophilic Factor (recombinant)	Bioclate ™	Armour Pharmaceutical	Lyophilized	single-dose
albumin (human)	≤0.3	6.8 ± 0.4	IV-intravenous	Immune Globulin Intravenous (human) (IGIV)	Gammagard ® S/D	Baxter Healthcare Corporation	Lyophilized	single use bottles
albumin (human)	0.04-1.0		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
albumin (human)	≤1.0		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
albumin (human)	0.4-1.0		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
albumin (human)	0.0063 - 0.05		IM - intramuscular	botulinum toxin type A	Botox ®	Allergan Inc.	Lyophilized	ampuls
albumin (human)	5.0		IV - intravenous	urokinase for injection	Abbokinase	Abbott Laboratories	Lyophilized	vial
albumin (human)	0.25	6.9 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ®	Amgen, Inc.	Solution	single dose vial
albumin (human)	0.25	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
albumin (human)	3.0	6.8 ± 0.4	IV - intravenous	immune globulin IV (human) primarily IgG	Gammar ®-IV	Armour Pharmaceutical	Lyophilized	single dose vials
albumin (human)	1.0 - 2.0		IV - intravenous	monoclonal antibody purified human	Monoclate-P ® Factor VIII: C Pasteurized	Armour Pharmaceutical	Lyophilized	single dose vial
albumin (human)	1.25		SC - subcutaneous	interferon beta-1b	Betaseron ®	Berlex Laboratories	Lyophilized	single use vial
albumin (human)	1.0		IV - intravenous	cytomegalovirus immune globulin intravenous	CytoGam ®	MedImmune, Inc.	Sterile Liquid	single dose vial
albumin (human)	0.5		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
albumin (human)	0.5		IM - intramuscular	interferon alfa-2a, recombinant	Roferon ®-A	Roche Laboratories	Solution	vial

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
albumin (human)	0.167		IM - intramuscular	interferon alfa-2a, recombinant	Roferon ®-A (powder)	Roche Laboratories	Powder (sterile)	vial
albumin (human)	0.1		IL - intralesional	interferon alfa-2b, recombinant	Intron A	Schering Corporation	Powder	vial
albumin (human)	0.1		IM - intramuscular	interferon alfa-2b, recombinant	Intron A (solution)	Schering Corporation	Solution	vials
albumin (human)	0.6		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
albumin (human)	0.4 - 0.8		IV - intravenous	antihemophilic factor (human) (Factor VIII, AHF)	Humate-P ™	Armour Pharmaceutical	Lyophilized	single dose vial
albumin human USP	1.0		IV - intravenous	alglucerase injection	Ceredase ®	Genzyme Corporation	Solution	glass bottle
alcohol	30.5 (v/v%)	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
alcohol	6.8 (v/v)		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin	Glaxo-Wellcome	Solution	ampul
alcohol	6.1 (v/v)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate	D.H.E. 45 ®	Sandoz	Solution	ampuls
alcohol	10.0	~9.5	IM - intramuscular	pentobarbital sodium injection	Nembutal Sodium Solution	Abbott Laboratories	Solution	ampul
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin (Digoxin) Injection	Glaxo Wellcome	Solution	ampuls
alcohol	10.0	12.0	IV - intravenous	phenytoin sodium injection, USP	Dilantin	Parke-Davis	Solution	steri-vials
alcohol	10.0		IM - intramuscular	ketorolac tromethamine	Toradol	Syntex Laboratories	Solution	Tubex cartridge
alcohol (Ph. Helv)	32.9 (v/v)		IV - intravenous	cyclosporine concentrate for injection USP	Sandimmune ®	Sandoz Pharmaceuticals	Solution	Ampul
alcohol (USP)	0.61 (v/v)	4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
alcohol (USP)	6.1 (v/v%)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate injection, USP	D.H.E. 45 ® or Dyhdergot ®	Sandoz	Solution	ampuls
alpha	1.0		IM - intramuscular	oxytetracycline	Terramycin	Roerig	Solution	multidose vial
aluminum	≤0.17		IM-intramuscular	Diphtheria and Tetanus Toxoids and Acellular	Acel-Imune	Lederle Laboratories	Suspension(aft	multidose vial
aluminum	≤0.0001		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
aluminum	≤0.034	~ 7.4	IM-intramuscular	Diphtheria & Tetanus Toxoids and Acellular	Tripedia ™	Connaught Laboratories, Inc.	Solution/Suspe	vial
aluminum	≤0.16		IM - intramuscular	combinantion of refined tetanus & diphtheria toxoids	Tetanus & Diphtheria Toxoids Adsorbed (Adult	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	refined tetanus toxoid	Tetanus Toxoid Adsorbed, aluminum	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	diphtheria & tetanus toxoids & Pertussis Vaccine	Tri-Immunol	Lederle Laboratories	Suspension(aft	multidose vials

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