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Excipients Use in Parenteral and Lyophilized Formulation Development

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Abstract

Excipients are the integral part of pharmaceutical product development to achieve the desired product profile (stability and efficacy). This review deals with understanding of the physicochemical properties of excipients used in parenteral formulation development for solution, suspension and lyophilized drug products. However, in spite of proper excipients selection, judicious use during formulation, manufacturing process based on their critical property that is also important to avoid negative effects such as loss of drug solubility, activity and stability. This paper deals with proper selection of excipients in lyophilized and parenteral drug products which gives high critical temperature, good bulking properties avoiding melt back and collapse with improved dried product appearance. We have also emphasized on appropriate selection of excipients for solution, suspension injectable dosage forms and linking their physiochemical properties with optimum manufacturing method with suitable case studies. This review will highlight various excipients related issues, optimizing product performance with documented references and practical approaches based on scientific justification. The reader will gain better understanding of excipients complexity during stability studies and resolving problems with practical approach.

Keywords

Excipients, Parenteral, Lyophilized, Suspension, Formulation Development

1. Introduction

Excipients are typically the major components in a drug product. Many formulations contain only a small percentage of the active drug molecules. Pharmaceutical excipients or additives are compounds added to the finished drug products to serve a specific function. They are added to increase bulk, aid manufacturing, improve stability, enhance drug delivery and targeting, and modify drug safety or pharmacokinetic profile. Ingredients that are used during drug product manufacturing, but may not be present in the finished drug product are also considered excipients (examples include water for lyophilized products, and inert gases in the head space of containers)[(1)]. In recent years the "functionality" of excipients in a dosage form (similar to the pharmacological activity of an active pharmaceutical ingredient or drug substance) has been recognized by USP & European Pharmacopoeia.

Excipients are traditionally referred to as inactive or inert ingredients to distinguish them from active pharmaceutical ingredients. Excipients may not be as inert as the term inactive suggests. Due to safety issues, several countries have restrictions on the type or amount of excipients that can be included in the formulation of parenteral drug product. For example, in Japan, U.S.A and EU amino mercuric chloride or thiomersal use is prohibited, despite the presence of these excipients in products in other regions [(2)].

As defined in Ph. Eur. and the British Pharmacopeia (BP), "Parenteral preparations are sterile preparations intended for administration by injection, infusion, or implantation into the human or animal body." In the present article, only sterile preparations for administration by injection or infusion into the human body will be surveyed [(3,4)]. Injectable products require a unique formulation strategy. The formulated product must be sterile, pyrogen-free, and, in the case of solution, free of particulate matter. No coloring agent may be

added solely for the purpose of coloring the parenteral preparation. The formulation should preferably be isotonic, and depending on the route of administration, certain excipients are not allowed. The injected drug by-passes natural defense barriers; hence, for any given drug, the risk of an adverse event may be greater or the effects difficult to reverse if administered as an injection rather than a non-Parenteral route. For this reason ultra high purity grades of excipients are available for parenteral administration. Sterility requirements demand that excipients are able to withstand terminal sterilization or aseptic processing. These factors limit the choice of excipients available [(2)].

Excipients which are already present in marketed formulations and accepted by the Food and Drug Administration (FDA) as safe, increases the assurance to a formulator that these excipients will probably be safe for a new drug product. But, this does not give complete assurance when combined with other excipients or drug molecules as this may lead to unwanted potentiation or synergistic toxic effects. However, regulatory bodies may favorably view an excipients previously approved in an injectable dosage form, and will require less safety data. A new additive in a formulated product always requires additional studies, adding to the cost and timeline of product development. Importantly, inclusion of excipients in the GRAS (Generally Recognized as Safe) list or pharmacopoeia does not mean that the excipients have been deemed safe by the FDA for use in parenteral products.

2. Excipients Used in Lyophilization

2.1. Bulking Agents and Lyoprotectants

Bulking agents forms the bulk of the lyophilized product and provide an adequate structure to the cake. These are generally used for low dose (high potency) drugs that do not have the necessary bulk to support their own structure. These are particularly more important when the total solid content is less than 2 %[(5)]. In such cases, a bulking agent is added to the formulation matrix. The structure of the lyophilized cake is important, since proper cake formation leads to proper pore formation that provides the means for vapor to escape from the product during the drying cycle[(6)] Lyoprotection defined as the stabilization and prevention of the degradation of a molecule both during freeze-drying and afterwards, during storage. Among disaccharides, sucrose and trehalose appear to be the most commonly used. In comparison to sucrose, trehalose seems to be a preferable lyoprotectant, because it has a less hygroscopicity, very low chemical, reactivity and inally, higher glass transition temperature (Tg) [(7,8,9)]. Critical temperature is the temperature above which the freeze-dried product loses macroscopic structure and collapses during freeze drying. Therefore, the excipients which provide higher critical temperature are preferred for lyophilization.

Mannitol: It is the most commonly and widely used excipients in the lyophilized products. Mannitol has a very high eutectic melting temperature (-1.4°C) after crystallization and is processed well in lyophilization. Crystallization of the bulking agent, however, might adversely affect the physical stability of the product in certain instances, for which, an amorphous bulking agent is preferred [(10)].

Lactose: It is a good bulking agent but is a reducing sugar and may undergo Maillard reaction with proteins leading to instability of the formulation [(11)]. The critical temperature of 1% lactose is -32°C.

Table 1. *Critical process temperatures of various excipients used in Lyophilization [(14)].*

Excipients	Tg'^0C	Tc^0C	references
Bulking Agent			
Sucrose	-32, -35	-34,-32	(14, 15, 16)
Lactose	-28	-31, -32	(5, 6, 17)
Trehalose	-27, -29	-29.5, -34	(5, 6, 8)
Mannitol	-35, -28	--	(5, 8)
Sorbitol	-46	-45	(6, 8, 18)
Glucose	-43	-40, -41.5, -43	(6,7,19)
Rafinose	-27	-26	(9)
Glycine	-62	--	(20)
Histidine	-33	--	(5)
PVP (K40)	-20	-23	(6, 8, 9)
Buffering Agent			
Sodium citrate	-41	--	(5)
Sodium phosphate	-45	--	(5)
Tris base-65	-51	--	(5)
Tris acetate	-54	--	(5)
Tris HCl -65	-65	--	(5)
Tonicity Modiier			
Dextrose	-44		(8)
Dextran	-10	-9, -10,	
Ficoll	-19	-19.5, -20	
Gelatin	-9	-8	
Hydroxyethyl starch	--	-5	(21)

Sucrose: It is having similar collapse temperature i.e -31°C (2%) as of lactose but it is not a reducing sugar and does not undergo Maillard reaction [(12)]. Sucrose has a higher density as compared to lactose which can cause slight collapse during drying.

Polyethylene glycol (PEG): It provides good cake structure and increases viscosity of water [(13)]. The 2% solution of PEG has a critical temperature of -22°C. Apart from lyophilization it is also used as a co-solvent and viscosity modifier in Parenteral including ophthalmics.

Polyvinyl pyrollidone (PVP): The low-molecular grades, Povidone K 12 and K 17 are used as solubilizing agents, dispersants and crystallization inhibitors, particularly for injectable. This application is used in particular for

antibiotics in solution or in lyophilized form. Povidones with higher K-values may not be administered parenterally as, due to their high molecular weights, they cannot be excreted by the kidneys and hence accumulate within the body. The povidone grades K12 and K 17 are used as solubilizers in parenteral applications. In addition Polyvinyl pyrollidone also provides cryo-protection to the product. The C-grades are supplied with low endotoxin levels ("pyrogen-free"). Bovine Serum Albumin (critical temperature of 0.5% solution of BSA is -9°C), Dextran (critical temperature of 2.0% solution of Dextran mw 9500 daltons is -12°C) due to its longer chain polymer of glucose gives higher viscosity and higher critical temperature. In addition other excipients which can be used for lyophilization are listed in Table 1 along with their critical process temperatures.

2.2. Buffering Agents

Control of pH is critical to avoid degradation of drug during processing, storage and reconstitution, thereby necessitating addition of buffering agent in the lyophilized formulation. The choice of buffer depends on the pH stability profile of active ingredient as drug needs to be reconstituted and stored for some time before it could be administered to the patient. For this purpose, the pH of maximum stability of drug should be known and maintained. Selection of a suitable buffer and its concentration is important for sensitive molecules.

The buffering agent should have a high collapse temperature, be non-volatile and have a high glass transition temperature (Tg). A high collapse temperature would facilitate a faster primary drying, and its non-volatile nature would prevent pH drift, that might be detrimental to the product stability. Additionally, a high glass transition temperature (Tg) would ensure stability during storage. In this context, acetate buffer is not used due to its volatile nature, as it can be partially lost during lyophilization. Crystallization of buffer components can also lead to a drastic shift in pH, resulting in degradation of the active component. Sodium and potassium phosphate salts are not often used in the lyophilization, since these crystallize during cooling and in frozen solution, which leads to a decrease in pH of about 4 units. Shalave et al. studied citrate, succinate and tartrate buffer for their crystallization behavior and its effect on pH of the formulation. Citrate buffer was found to be the most preferred as it remained amorphous, with the shift in pH being minimal, in comparison to succinate and tartrate, which crystallized during lyophilization. Tris buffer is known to release formaldehyde in peptide formulations stored at 70°C"pH memory" is a term used to denote the relationship between pH-activity and pH stability profiles, in the solution and dried state respectively, as the pH of the solution before drying has an impact on the rate of chemical reactivity in the resulting amorphous material. Commonly used buffers in the Parenteral formulations are Acetate, Citrate, Tartrate, Phosphate, Triethanolamine (TRIS).

3. Excipients Used in Liquid Injection

3.1. Tonicity Adjusting Agents

Parenteral formulations should be isotonic with human plasma so as to avoid damage to the tissues. However, not all drugs at their recommended dosage are isotonic with blood, thus requiring the addition of a tonicity adjusting agent to the formulation. The most commonly used tonicity agent is dextrose, while others, such as glycerol and sodium chloride are less commonly used. Other commonly used tonicity adjusting agents are Glycerin and Mannitol.

3.2. Preservatives: Antioxidants, Antimicrobial and Chelating Agents

The antioxidants are used to prevent/minimize the oxidation reaction of the drug or excipients over the shelf life of the product whereas antimicrobial agents are used to prevent the growth of micro-organisms in the drug product. The most commonly used antioxidants in the sterile formulations are Ascorbic acid, Acetylcysteine, Sulfurous acid salts (bisulfite, metabisulfite), Monothioglycercol etc. The commonly used antimicrobial agents are Phenol, Meta-cresol, Benzyl alcohol, Parabens (methyl, propyl, butyl), Benzalkonium chloride, Chlorobutanol, Thimerosal,

Phenylmercuric salts (acetate, borate, nitrate) etc. In addition to the antioxidant and antimicrobial a chelating agent can be deined as a substance whose molecules can form several bonds to a single metal ion. Against the general understanding several single dose preparations contain preservatives due to legacy.

3.3. Solubilizing Agents

The agents which help in dissolving or increase the drug solubility into the formulation are known as solubilizing agents, the solubilizing agents can be broadly classified into surfactants and co-solvents. The surfactants increase the dissolution by reducing the surface tension of the drug substances whereas, co-solvents are defined as a solvent that in conjunction with another solvent can dissolve a solute. Few examples of surfactants are Polyoxyethylene sorbitan monooleate (Tween 80), Sorbitan monooleate Polyoxyethylene sorbitan monolaurate (Tween 20), Lecithin, Polyoxyethylene polyoxypropylene copolymers (Pluronics). Examples of co-solvents are Propylene glycol, Glycerin, Ethanol, Polyethylene glycol (300 and 400), Sorbitol, Dimethylacetamide and Cremophor EL etc.

3.4. Complexing and Dispersing Agents

Complexation is sometimes used to improve the solubility of drug in the solvent especially water. Cyclodextrins have emerged as very effective additive compounds for solubilizing hydrophobic drugs. In the parenteral$_b$ dosage form, modified cyclodextrins, such as hydroxypropyl- -cyclodextrin and sulfobutylether- -cyclodextrin have been reported to solubilize and stabilize many injectable drugs, including dexamethasone, estradiol, interleukin-2, and other

proteins and peptides without apparent compatibility problems.

Table 2. *Excipients used in different drug formulations.*

Drug	Category	Excipients	Route administration
Alprostadil	Erectile dysfunction	b-cyclodextrin, Lactose	Intracavernosal
Alprostadil	Erectile dysfunction	Lactose, Sodium citrate, Benzyl alcohol	Intracavernosal
Azathiopurine sodium	Immunosuppressive antimetabolite; management of severe rheumatoid arthritis	--	IV bolus, IV infusion
Azithromycin	Antibiotic	Citric acid	IV infusion
Aztreonam	Antibiotic	L- arginine	IM, IV bolus, IV infusion
Carmustine	Antineoplastic	--	IV infusion
Cefazolin sodium	Antibiotic	--	IM, IV bolus, IV infusion
Cefazolin sodium	Antibiotic	--	IM, IV bolus, IV infusion
Chlorothiazide sodium	Diuretic and hypertensive	Mannitol, Thiomersal	IV bolus, IV infusion
Cisplatin	Antineoplastic	Mannitol, Sodium chloride	IV infusion
Colfosceril palmitate	Prevention and treatment of Respiratory disease syndrome in low birth weight infants	Cetyl alcohol, Tyloxapol, Sodium chloride	Intratracheal
Cyclophosphamide	Antineoplastic	Mannitol	IM, IV bolus, IV infusion, IP,Intrapleural
Dactinomycin	Antibiotic	Mannitol	IV bolus, IV infusion
Dantrolene sodium	Muscle relaxant	Mannitol	IV bolus, IV infusion over 1 hr
Daunorubicin Hcl	Antibiotic	Mannitol	IV infusion
Dexrazoxane	Cardioprotective agent		IV
Diltiazem	Antianginal	Mannitol	IV bolus, IV infusion
Doxorubicin HCl	Antineoplastic	Lactose, Methyl paraben	IV
Etoposide phosphate	Antineoplastic	Sodium citrate, Dextran 40	IV infusion over 30-60 min
Epoprostenol sodium	Antihypertensive	Mannitol, Sodium chloride Glycine	IV infusion
Ethacrynate sodium	Diuretic	Mannitol	Slow IV bolus, IV infusion
Fludarabine phosphate	Antineoplastic	Mannitol	IV infusion over 30 min
Ganciclovir sodium	Treatment of CMV retinitis in Immune compromized patient		IV infusion at 5mg/kg over 1 Hr
Gemcitabine Hcl	Antineoplastic	Mannitol, Sodium acetate	Mannitol Sodium acetate IV infusion over 30 min
Hemin	Treatment of acute intermittent porphyria related to mensuration	Sorbitol, Sodium carbonate	IV infusion
Hydromorphone Hcl	Opioid analgesic	-	IV, IM, SC
Indomethacin sodium	NSAID		IV bolus

Buffers added to a formulation to adjust and stabilize pH and optimize drug solubility and stability, for parenteral preparations, it is desirable that the product pH be close to physiologic pH. Selection of a buffer concentration (which contributes to the ionic strength of the formulation) and a buffer species is important. For example, citrate buffers in the

range of 5–15 mM are typically used in formulations but increasing the buffer concentration to 50 mM will result in excessive pain on sub-cutaneous injection and toxic effects due to chelation of calcium in the blood. Table 6 lists buffers and chemicals used for pH adjustment and maintenance of the drug product pH range, phosphate, citrate, and acetate are the most common buffers used in Parenteral products. Citrates are common buffers that serve a dual role as chelating agent. Lactate and tartrate are occasionally used as buffer systems. Acetates are good buffers at low pH, but they are not frequently used for lyophilization because of the potential sublimation of acetates.

Table 3. *List of excipients used in lyophilized formulations.*

Drug	Category	Excipients	route of administration
Lansoprazole	Proton pump inhibitor	Mannitol, Meglumine, Sodium hydroxide	IV
Levothyroxine sodium	Hormone replacement	Mannitol, Sodium phosphate tribasic	IM, IV
Melphalan Hcl	Antineoplastic	Povidone, Diluent: Water, Propylene glycol, ethyl alcohol, sodium citrate	IV infusion over 15-20 min
Methohexital sodium	Anesthetic	Anhydrous sodium carbonate	IV, IM
Methyl prednisolone succinate Sodium	Hormone replacement	Sodium phosphate, Lactose, Benzyl alcohol	IM, IV bolus, IV infusion
Metronidazole	Antibacterial	Mannitol	IV bolus, IV infusion
Mitomycin	Antineoplastic	Lactose	IV infusion
Pamidronate disodium	Inhibition of bone resorption	Mannitol	IV
Pentostatin	Antineoplastic	Mannitol	Slow IV bolus, IV infusion
Phentolamine mesylate	Antihypertensive	Mannitol	IM, IV bolus, IV infusion
Pipecuronium bromide	Long acting neuromuscular blocking agent	-	IV bolus
Pralidoxime chloride	Antidote for overdose due to anticholinesterase	-	IV bolus, IV infusion
Remifentanil Hcl	Analgesic	Glycine	IV infusion
Streptozocin	Antineoplastic	Citric acid	IV bolus, IV infusion
Tazobactam sodium and Piperacillin sodium	Antibacterial combination	EDTA Sodium citrate	IV infusion
Thiopental sodium	Short acting anesthetic	Sodium carbonate	IV infusion
Thiotepa	Antineoplastic	-	IV bolus, Intracavitary, Intravesical
Thiothixene Hcl	Antipsychotic	Mannitol	IM
Ticarcillin disodium	Antibacterial		IM, IV bolus, IV infusion
Tigecycline	Antibacterial		IV infusion
Topotecan	Antineoplastic	Mannitol, Tartaric acid	IV infusion
Trimetrexate glucuronate	Treatment of pneumonia	-	IV infusion
Vancomycin HCl	Antibiotic	-	IV infusion
Vecuronium bromide	Muscle relaxant	Mannitol, Citric acid, Sodium phosphate dibasic	IV bolus, IV infusion
Vinblastine sulfate	Antineoplastic		IV bolus
Warfarin sodium	Anticoagulant	Mannitol, Sodium chloride, Sodium phosphate, monobasic, monohydrate Sodium phosphate, dibasic, Heptahydrate	Slow IV over 2 min

3.5. Excipients in Pharmaceutical Suspension

Parenteral suspension is useful dosage form for administering insoluble or poorly soluble drugs. The larger surface area of disperse drug may help to ensure a high degree of availability for absorption. Parenteral suspension provides more prolonged release from the injection site than a comparable solution.

Typical excipients used in Parenteral suspensions include following:

Flocculating / suspending agents.
Wetting agents.
Solvent systems
Preservatives
Antioxidants
Chelating agents
Buffering agents
Tonicity adjusting agents

Table 4. *Antimicrobial agents.*

Excipients	range	Example
Benzalkonium Chloride	0.02 % w/v	Celestone Soluspan
Benzethonium Chloride	0.01%	Benadryl
Benzyl alcohol	0.75-5 %	Dimenhydrinate Injection, USP
Chlorobutanol	0.25-0.5 %	Codine phosphate
m-Cresol	0.1-0.315%	Humalog
Myristyl gamma-picolinium Chloride	0.0195-0.169 %	Depo-Provera
Paraben methyl	0.05-0.18%	Inapsine
Paraben propyl	0.005-0.1%	Xylocaine
Phenol	0.15-0.5%	Calcimar
2-Penoxyethanol	0.50%	Havrix
Phenyl mercuric nitrate	0.001%	Antivenin
Thimerosal	0.003-0.012%	Atgam

3.6. Flocculating / Suspending Agents

The controlled flocculation approach uses a flocculating agents to from loosely bound aggregate or flocs in a controlled manner that settles rapidly but redisperses easily upon agitation. An appropriate amount or flocculating agent is added that result in maximum sedimentation volume & prevents cake formation. Electrolytes, surfactant and hydrophilic colloids have been typically used as flocculating agents. Electrolytes & surfactants reduce the electrical forces of repulsion between particles & allow the flocs to form, which in turn is influenced by the surface charge on the particles.

E.g. Electrolytes used in Parenteral Suspensions.

Potassium/sodium chloride
Potassium/sodium citrate
Potassium/sodium acetate

The surface charge of the system can be measured by the zeta potential. The zeta potential must be controlled so as to lie within a range (generally less than 25 mV) to obtain a flocculated, noncaking suspension with maximum sedimentation. Hydrophilic colloids (generally negatively charged) not only affect the repulsive force but also provide mechanical barrier to the particles. For e.g. a 25% PVP solution is used in combination with polysorbate 80 (2%) acts as a stabilizer to provide a stable injectable 30% aqueous powder suspension.

Some viscosity building agents used in formulation of injectable suspension are:

Sodium carboxymethyl cellulose
Acacia
Gelatin
Methyl cellulose
Polyvinyl pyrrolidone.

Table 5. *Chelating agents.*

Excipients	range
Calcium disodium	0.01-0.1%
EDTA*	0.01-0.05%
Disodium EDTA	0.01-0.11%
Sodium EDTA	0.20%
Calcium Versetamide Na	2.84%
Calteridol	0.023%
DTPA**	0.04-1.2%

*EDTA = Ethylenediaminetetra acetic acid
**DTPA = Diethylenetriaminepenta acetic acid

Table 6. *Buffering Agents.*

Excipients	range
Sodium acetate	0.01%
Sodium phosphate,monobasic	0.14%
Sodium phosphate monobasic, dihydrate	0.5%
Sodium chloride	45%
Mannitol	5%

3.7. Wetting Agents

Various nonionic surfactants and non-aqueous solvents like glycerin, alcohol & propylene glycol are types of wetting agents commonly used in injectable suspensions. Wetting agents reduce the contact angle between the surface of the particle & the wetting liquid to obtain maximum wetting efficiency, surfactants with hydrophilic lipophilic balance (HLB) value in the range of 7to 9 should be selected. The usual concentration of surfactants varies from 0.05% to 0.5% depending on the solid contents of the suspension. Care should be taken in terms of the amount used, excessive amounts may cause foaming or caking or provide an undesirable taste/odor to the product.

3.8. Surfactants (Wetting Agent)

Lecithin, Polysorbate 20, Polysorbate 80, Pluronic F-68, Sorbitan trioleate (span 85) are used, as surfactants in injectable suspensions for e.g. in the preparation of a non-aqueous suspension of Cefazolin sodium in peanut oil, addition of polysorbate 80 at concentration greater than 0.17% resulted in deflocculated suspension which was difficult to redisperse. Microscopic examination revealed extensive agglomeration and crystal growth of cefazolin sodium in the presence of polysorbate 80.

3.9. Solvent System

Solvent systems used in parenteral suspension are classified as either aqueous or non-aqueous vehicles. Choice of a typical solvent system depends on solubility, stability &

desired release characteristics of the drug. Non-aqueous vehicles include both water miscible and water immiscible vehicles. Water for injection is generally the preferred solvent system. However, non-aqueous water miscible agents are used as co-solvents with water for injection to promote the solubility & stability in parenteral preparation. Examples of water miscible non-aqueous vehicles include ethanol, glycerin, propylene glycol and n–lactamide. The use of water miscible co-solvents can lead to undesirable side effect for e.g. intramuscular injection of propylene glycol-water, ethyl alcohol-water & polyethylene glycol (PEG) 400 water mixtures was found to cause muscle damage as measured by in vitro release of creatinine kinase from isolated rat skeletal muscle.

Table 7. *Pharmaceutical Excipients use and route of Administration.*

Excipients	uses	Administration
Aluminum chloride	Potentiating agent	sc, im
Aluminum hydroxide	Adsorbent	sc, im
Aminoethyl sulfonic acid	Buffer, isotonicity, stabilizer, vehicle	iv, im
Ammonium acetate	pH adjusting agent	im
Anhydrous stannous chloride	Reducing agent	iv
L-Arginine	Buffer, stabilizer, solubilizer	iv, im, sc
Asepsis sodium bicarbonate	Stabilizer	iv
Butylhydroxyanisol	Antioxidant, stabilizer	iv
m-Cresol	Preservative	iv, im, sc, ic
L-Cysteine	Stabilizer	iv
Cysteine hydrochloride	Antioxidant, stabilizer	iv, im
Dichlorodiluoromethane	Propellant	iv
Diethanolamine	Buffer, solubilizer, stabilizer	iv
Diethylenetriaminepentaacetic acid	Stabilizer	iv
Ferric chloride	Stabilizer	iv
Highly purified yolk lecithin	Emulsifier	iv
Human serum albumin	Preservative, stabilizer	iv, im, sc
Hydrolyzed gelatin	Stabilizer	sc
Inositol	Stabilizer, vehicle	iv, im
Lidocaine hydrochloride	Soothing agent	im
D,L-Methionine	Stabilizer	im, sc
Monobasic sodium phosphate	Buffer, Isotonicity, adjust pH	iv, im, sc
Oleic acid	Dispersing agent, solvent	iv
Phenol red	Coloring agent	sc

3.10. Tonicity Agents

Isotonicity of the Parenteral suspension for subcutaneous or intramuscular administration is desired to prevent pain; irritation and tissue damage at the site of administration, the aqueous solution of tonicity agents used in Parenteral suspensions include dextrose & various electrolytes .

3.11. Preservatives

Antimicrobial agents are required for parenteral products that are intended for multiple dosing, in order to protect the product from accidental microbial contamination during clinical usage & maintain sterility. Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.

Benzyl alcohol (0.9% to 1.5%)
Methylparaben (0.18%to0.2%)
Propylparaben (0.02%)
Benzalkonium chloride (0.01% to 0.02%)
Thiomersal (0.001% to 0.01%)

Benzalkonium chloride is used in ophthalmic dosage forms & not in injectable dosage forms.

Propyl and methyl parabens are referred to chemically as Propyl and methyl esters of p-hydroxy benzoic acids.

Because of the inherent chemically reactive nature of preservatives, stability & compatibility problems need to be evaluated for their usage in the formulation.

Table 8. *Antioxidants/chelating agents.*

Compound	Typical Concentration (%w/w)
Ascorbic acid	0.02-0.1
Sodium bisulfite	0.1-0.15
Sodium meta bisulfite	0.1-0.15
Sodium formaldehyde sulfoxylate	0.1-0.15
Thiourea	0.005

Table 9. *Antioxidants (oil soluble).*

Ascorbic acid ester	0.01-0.15
Butylated hydroxy toluene	0.005-0.02
Tocopherols	0.05-0.075

4. Criteria for the Selection of Excipients

The following key points should be considered in selecting excipients for parenteral products:

Influence of excipients on the overall quality, stability, and effectiveness of drug product. Compatibility of excipient with drug and the packaging system. Compatibility of excipients with the manufacturing process, for example, preservatives may be absorbed by rubber tubes or liters, acetate buffers will be lost during lyophilization process etc. The amount or percentage of excipients that can be added to the drug product.

Route of administration. The USP, Ph. Eur, BP do not allow preservatives to be present in injections intended to come in contact with brain tissues or CSF. Thus intracisternal, epidural, and intradural injections should be preservative free. Also, it is preferred that a drug product to be administered via intravenous (IV) route be free of particulate matter. However, if the size of the particle is well controlled, like in fat emulsion or colloidal albumin or amphotericin B dispersion, it can be administered by IV infusion. Table 7 list excipients and their use along with route of administration Dose volume. All LVPs and those SVPs where the single dose injection volume can be greater than 15 ml are required by the EP/BP to be preservative free (unless justified). The USP recommends that special care be observed in the choice and the use of added substances in preparations for injections that are administered in volumes exceeding 5 ml.

Whether the product is intended for single or multiple dose use. According to USP, single dose injections should be free of preservative. The FDA takes the position that even though a single dose injection may have to be aseptically processed, the manufacturer should not use a preservative to prevent microbial growth. European agencies have taken a more lenient attitude on this subject. The length or duration of time that the drug product will be used once the multidose injection is opened. Several new excipients, such as cyclodextrins, are being evaluated to improve solubility or stability of parenteral drugs. Currently, there are two FDA-approved parenteral products that utilize alpha and gamma cyclodextrins. Beta-cyclodextrin is unsuitable for Parenteral administration because it causes necrosis of the proximal kidney tubules upon intravenous and subcutaneous administration.

Biodegradable polymeric materials (polylactic acid, polyglycolic acid, and other poly-alpha-hydroxy acids) have been used as medical devices and as biodegradable sutures since the 1960s. Currently, the FDA has approved for marketing only devices made from homopolymers or co-polymers of glycolide, lactide, caprolactone, p-dioxanone, and trimethylene carbonate.

5. Conclusion

Several new excipients, such as cyclodextrin, are being evaluated to improve solubility or stability of parenteral drugs. Currently, there are two FDA-approved parenteral products that utilize alpha and gamma cyclodextrin. Beta-cyclodextrin is unsuitable for parenteral administration because it causes necrosis of the proximal kidney tubules upon intravenous administration. Biodegradable polymeric materials (polylactic acid, polyglycolic acid, and other poly-alpha-hydroxy acids) have been used as medical devices and as biodegradable sutures since the 1960s. Injectable formulations are used with intravenous, subcutaneous, intramuscular, and intra-articular administration. The drug is stored in liquid or if unstable, lyophilized form. These include solubilizers, stabilizers, buffers, tonicity modifiers, bulking agents, viscosity enhancers/reducers, surfactants, chelating agents, and adjuvants. In this review we discus all excipients and there percentage.

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