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Excipient Selection In Parenteral Formulation Development

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Excipients are the integral part of pharmaceutical products development to achieve 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, inspite of proper excipients selection, judicious use during formulation manufacturing process based on their critical properties 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 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 excipient 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, Parenterals, Lyophilized, Suspension, formulation development

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 pharmacological activity of an active pharmaceutical ingredient or drug substance) has been recognized by USP & European Pharmacopoeia. Many excipient monographs do not address this aspect of excipient functionality or its control.

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 excipient that can be included in the formulation of parenteral drug product. For example, in Japan, the U.S., and the E.U., 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 an excipient is 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 excipient 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 an excipient in the GRAS (Generally Recognized as Safe) list or pharmacopoeia does not mean that the excipient has been deemed safe by the FDA for use in parenteral products.

EXCIPIENT USED IN LYOPHILIZATION

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].

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Lyoprotection is 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 finally, 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 excipient 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.

***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 injectables. 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.

Table 1: Critical process temperatures of various excipients used in Lyophilization [14]

Excipient	Tg'^{0}C	Tc^{0}C	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)
Raffinose	-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)
Sodium Hydroxide		--	
Tris base-65	-51	--	(5)
Tris acetate	-54	--	(5)
Tris HCl -65	-65	--	(5)
Tonicity Modifier			
Dextrose	-44		(8)
Collapse Temperature Modifier			
Dextran	-10	-9, -10,	
Ficoll	-19	-19.5, -20	
Gelatin	-9	-8	
Hydroxyethyl starch	--	-5	(21)

Table 2: List of excipients used in lyophilized formulation of small molecules, as marketed in USA [22,23]

Drug	Category	Excipients	Route of administration	Marketed name
Amifostine	Cytoprotective agent	---	IV infusion over 15-30 min	Ethyol® (MedImmune Oncology)
Amphotericin B cholesteryl sulfate	Antifungal	Sodium cholesteryl sulfate, Lactose, Tris, EDTA	IV infusion at 3-4 mg/kg/hr	Amphotec® (Sequus Pharmaceuticals)
Amphotericin B	Antifungal	Hydrogenated Soy phosphatidylcholine, Disteroylphosphatidyl glycerol, Cholesterol, α tocopherol, Sucrose, Disodium succinate	IV infusion at 3-5 mg/kg/hr	Ambisome® (Astellas)
Acyclovir sodium	Antiviral	--	IV infusion over 1 hr	Zovirax® (Glaxo Wellcome)
Allopurinol sodium	Anti-gout	--	IV infusion	Aloprim® (Nabi Biopharmaceuticals)

Drug	Category	Excipients	Route of administration	Marketed name
Alprostadil	Erectile dysfunction	β-cyclodextrin, Lactose	Intracavernosal	Edex® (Schwarz Pharma)
Alprostadil	Erectile dysfunction	Lactose, Sodium citrate, Benzyl alcohol	Intracavernosal	Caverject® (Phamacia and Upjohn)
Azathiopurine sodium	Immunosuppressive antimetabolite; management of severe rheumatoid arthritis	--	IV bolus, IV infusion	Imuran ® (Glaxo Wellcome)
Azithromycin	Antibiotic	Citric acid	IV infusion	Zithromax® (Pfizer)
Aztreonam	Antibiotic	L- arginine	IM, IV bolus, IV infusion	Azactam ® (Bristol Myers Squibb)
Carmustine	Antineoplastic	--	IV infusion	BiCNU® (Bristol Myers Squibb)
Cefazolin sodium	Antibiotic	--	IM, IV bolus, IV infusion	Kefzol® (Lilly)
Cefazolin sodium	Antibiotic	--	IM, IV bolus, IV infusion	Ancef ® (GlaxoSmith-Kline)
Chlorothiazide sodium	Diuretic and hypertensive	Mannitol, Thiomersal	IV bolus, IV infusion	Diuril® (Merck)
Cisplatin	Antineoplastic	Mannitol, Sodium chloride	IV infusion	Platinol® (Bristol Myers Oncology)
Colfosceril palmitate	Prevention and treatment of Respiratory disease syndrome in low birth weight infants	Cetyl alcohol, Tyloxapol, Sodium chloride	Intratracheal	Exosurf neonatal® (Glaxo Wellcome)
Cyclophosphamide	Antineoplastic	Mannitol	IM, IV bolus, IV infusion, IP,Intrapleural	Cytoxan® (Bristol Myers Squibb)
Dactinomycin	Antibiotic	Mannitol	IV bolus, IV infusion	Cosmegen® (Merck)
Dantrolene sodium	Muscle relaxant	Mannitol	IV bolus, IV infusion over 1 hr	Dantrium® (Procter & Gamble)
Daunorubicin HCl	Antibiotic	Mannitol	IV infusion	Cerubidine® (Bedford)
Dexrazoxane	Cardioprotective agent		IV	Zinecard® (Pharmacia & Upjohn)
Diltiazem	Antianginal	Mannitol	IV bolus, IV infusion	Cardizem® (Hoechst Marion Roussel)
Doxorubicin HCl	Antineoplastic	Lactose, Methyl paraben	IV	Rubex® (Bristol Myers Squibb)
Etoposide phosphate	Antineoplastic	Sodium citrate, Dextran 40	IV infusion over 30-60 min	Etopophos® (Bristol Myers Squibb)
Epoprostenol sodium	Antihypertensive	Mannitol, Sodium chloride Glycine	IV infusion	Flolan® (Glaxo Wellcome)
Ethacrynate sodium	Diuretic	Mannitol	Slow IV bolus, IV infusion	Sodium edecrin® (Merck)
Fludarabine phosphate	Antineoplastic	Mannitol	IV infusion over 30 min	Fludara® (Berlex)
Ganciclovir sodium	Treatment of CMV retinitis in Immune compromized patient		IV infusion at 5mg/kg over 1 Hr	Cytovene® (Roche)
Gemcitabine HCl	Antineoplastic	Mannitol, Sodium acetate	Mannitol Sodium acetate IV infusion over 30 min	Genzer® (Lilly)
Hemin	Treatment of acute intermittent porphyria related to mensuration	Sorbitol, Sodium carbonate	IV infusion	Panhematin® (Abbott)
Hydromorphone HCl	Opioid analgesic	-	IV, IM, SC	Dilaudid-HP® (Abbott)
Indomethacin sodium	NSAID		IV bolus	Indocin I.V. ® (Merck)

Drug	Category	Excipients	Route of administration	Marketed name
Lansoprazole	Proton pump inhibitor	Mannitol, Meglumine, Sodium hydroxide	IV	Prevacid® (TAP)
Levothyroxine sodium	Hormone replacement	Mannitol, Sodium phosphate tribasic	IM, IV	Synthrod® (Knoll)
Melphalan HCl	Antineoplastic	Povidone, Diluent: Water, propylene, glycol, ethyl alcohol, sodium citrate	IV infusion over 15-20 min	Alkeran® (Celgene)
Methohexital sodium	Anesthetic	Anhydrous sodium carbonate	IV, IM	Brevital sodium® (KING)
Methyl prednisolone succinate Sodium	Hormone replacement	Sodium phosphate, Lactose, Benzyl alcohol	IM, IV bolus, IV infusion	Solu-Medrol® (Pfizer)
Metronidazole	Antibacterial	Mannitol	IV bolus, IV infusion	Flagyl® (Pfizer)
Mitomycin	Antineoplastic	Lactose	IV infusion	Mutramycin® (Bristol Myers Squibb)
Pamidronate disodium	Inhibition of bone resorption	Mannitol	IV	Aredia® (Novartis)
Pentostatin	Antineoplastic	Mannitol	Slow IV bolus, IV infusion	Nipent® (Supergen)
Phentolamine mesylate	Antihypertensive	Mannitol	IM, IV bolus, IV infusion	Regitine® (Novartis)
Pipecuronium bromide	Long acting neuromuscular blocking agent	-	IV bolus	Arduran® (Oryannon)
Pralidoxime chloride	Antidote for overdose due to anticholinesterase	-	IV bolus, IV infusion	Protopam® (Baxter Healthcare)
Remifentanil HCl	Analgesic	Glycine	IV infusion	Ultiva® (GlaxoWellcome)
Streptozocin	Antineoplastic	Citric acid	IV bolus, IV infusion	Zanosar® (Pharmacia & Upjohn)
Tazobactam sodium and Piperacillin sodium	Antibacterial combination	EDTA Sodium citrate	IV infusion	Zosyn® (Lederle)
Thiopental sodium	Short acting anesthetic	Sodium carbonate	IV infusion	Pentothal sodium® (Baxter)
Thiotepa	Antineoplastic	-	IV bolus, Intracavitary, Intravesical	Thioplex® (Immunex)
Thiothixene HCl	Antipsychotic	Mannitol	IM	Navane® (Pfizer)
Ticarcillin disodium	Antibacterial		IM, IV bolus, IV infusion	Ticar® (Smith Kline Beecham)
Tigecycline	Antibacterial		IV infusion	Tygacil® (Wyeth)
Topotecan	Antineoplastic	Mannitol, Tartaric acid	IV infusion	Hycamtin® (Smith Kline Beecham)
Trimetrexate glucuronate	Treatment of pneumonia	-	IV infusion	Neutrexin® (U.S. Biosciences)
Vancomycin HCl	Antibiotic	-	IV infusion	Vancocin HCl® (Lilly)
Vecuronium bromide	Muscle relaxant	Mannitol, Citric acid, Sodium phosphate dibasic	IV bolus, IV infusion	Norcuron® (Organon)
Vinblastine sulfate	Antineoplastic		IV bolus	Velban® (Lilly)
Warfarin sodium	Anticoagulant	Mannitol, Sodium chloride, Sodium phosphate, monobasic, monohydrate Sodium phosphate, dibasic, Heptahydrate	Slow IV over 2 min	Coumandin® (Bristol Myers Squibb)

***HCl** – hydrochloric acid; **i.v.** – intravenous; **i.m**. – intramuscular; **s.c.** – subcutaneous; **PDR-** Physicians Desk Reference; **EDTA** – ethylenediamine tetraacetic acid*

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)[24]. 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[25]. 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 [26]. 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 [27]. Tris buffer is known to release formaldehyde in peptide formulations stored at 70°C [28].

"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 [29,30,31]. Commonly used buffers in the parenteral formulations are Acetate, Citrate, Tartrate, Phosphate, Triethanolamine (TRIS).

EXCIPIENTS USED IN LIQUID INJECTION

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.

Preservatives: Antioxidants, Antimicrobial and Chelating agents.

The antioxidants are used to prevent/minimize the oxidation reaction of the drug or excipeints 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), Monothioglyercol 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 defined 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.

Table 3: Antimicrobial Preservatives

Excipient	Range	Example
Benzalkonium Chloride	0.02 % w/v	Celestone Soluspan (Schering) 0.02% w/v
Benzethonium Chloride	0.01%	Benadryl (Parke-Davis) 0.01% w/v
Benzyl alcohol	0.75-5 %	Dimenhydrinate Injection, USP (APP Pharmaceuticals) 5%
Chlorobutanol	0.25-0.5 %	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	0.1-0.315%	Humalog (Lilly) 0.315%
Myristyl gamma-picolinium Chloride	0.0195-0.169 % w/v	Depo-Provera (Pharmacia-Upjohn) 0.169% w/v
Paraben methyl	0.05-0.18%	Inapsine (Janssen) 0.18% w/v
Paraben propyl	0.005-0.1%	Xylocaine w/Epinephrine (Astra) 0.1% w/v
Phenol	0.15-0.5%	Calcimar (Rhone-Poulanc) 0.5% w/v
2-Penoxyethanol	0.50%	Havrix (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	0.001%	Antivenin (Wyeth-Ayerst) 0.001%
Thimerosal	0.003-0.012%	Atgam (Pharmacia-Upjohn) 0.01%

Table 4: Chelating agents

Excipient	Range	Example
Calcium disodium EDTA*	0.01-0.1%	Wydase (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	0.01-0.11%	Calcijex (Abbott) 0.11% w/v
Sodium EDTA	0.20%	Folvite (Lederle) 0.20%
Calcium Versetamide Na	2.84%	OptiMARK (Mallinckrodt)
Calteridol	0.023%	Prohance (Bracco Diagnostics, Inc.)
DTPA**	0.04-1.2%	Omniscan™ (GE Healthcare) 1.2%

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

TABLE 5: Antioxidants and Reducing Agents

Excipient	Range	Example
Acetone sodium bisulfite	0.2 - 0.4 % w/v	Novocaine (Sanofi-Winthrop) 0.4% w/v
Argon	100 %	Used to fill headspace of lyophilized or liquid products. TechneScan MAG3(Covidien)
Ascorbyl palmitate	-	Visudyne (QLT)
Ascorbate (sodium/acid)	0.1-4.8 % w/v	Vibramycin (Pfizer) 4.8% w/v

Excipient	Range	Example
Bisulfite sodium	0.02-0.66% w/v	Amikin (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	0.00028-003 % w/v	Aquasol A (Astra) 0.03% w/v
Butylated hydroxy toluene (BHT)	0.00116–0.03% w/v	Aquasol A (Astra) 0.03% w/v
Cystein/ cysteinate HCl	0.07–1.3% w/v	Acthrel (Ferring) 1.3% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	0.10%	Numorphan (Endo Lab) 0.10%
Gentisic acid	0.02 % w/v	OctreoScan (Mallinckrodt) 0.02% w/v
Gentisic acid ethanolamine	2%	M.V.I. 12 (Astra) 2%
Glutamate monosodium	0.1% w/v	Varivax (Merck) 0.1% w/v
Glutathione	0.01% w/v	Advate (Baxter) 0.01% w/v
Formaldehyde sulfoxylate sodium	0.075 – 0.5 % w/v	Terramycin solution (Pfizer) 0.5% w/v
Metabisulfite potassium	0.10%	Vasoxyl (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	0.02–1% w/v	Intropin (DuPont) 1% w/v
Methionine	0.01-0.15 %	Depo-subQ provera 104 (Upjohn)
Monothioglycerol (Thioglycerol)	0.1-1%	Terramycin solution (Pfizer) 1%
Nitrogen	100%	Used to fill headspace of lyophilized or liquid products
Propyl gallate	0.02%	Navane (Pfizer) 0.02%
Sulfite sodium	0.05-0.2% w/v	Enlon (Ohmeda) 0.2% w/v
Tocopherol alpha	0.005 – 0.075%	Torisel (Wyeth) 0.075%
Alpha Tocopherol hydrogen succinate	0.02% w/v	Fluarix (GSK) 0.02% w/v
Thioglycolate sodium	0.66% w/v	Sus-Phrine (Forest) 0.66% w/v

Solubilizing agents

The agents which help in dissolving or increase the drug solubility into the formulation are known as solubilizing agents, the solubilising 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.

Table 6 below provides list of solvents, solubilizing agents and co-solvents which are currently in use in the approved formulations.

Table 6: Solvents and Co-solvents used in Injectables[32]

Excipient	Range	Example
Benzyl benzoate	20 – 44.7% w/v	Delestrogen 40 mg/mL (Bristol Myers) 44.7% w/v
Castor oil	11.50%	Delestrogen 40 mg/mL (Bristol Myers)
Cottonseed oil	73.6 – 87.4 w/v	Depo Testosterone (Pfizer) 73.6% w/v
N,N dimethylacetamide	6 – 33% w/v	Busulfex (Orphan Medical) 33%
Ethanol/ethanol dehydrated	0.6 – 100%	Prograf (Fujisawa) 80% v/v, Alprostadil (Bedford Lab) 100%
Glycerin (glycerol)	1.6 – 70 % w/v	Multitest CMI (Pasteur Merieux) 70% w/v
N-methyl-2-pyrrolidone	*	Eligrad 7.5 mg (Sanofi)
Peanut oil	*	Bal in Oil (Becton Dickinson)
PEG**	0.15 – 50 %	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	50 – 65%	VePesid (Bristol Myers) 65% w/v
PEG 400	11.2 – 67 % v/v	Busulfex (Orphan Medical) 67%
PEG 600	5% w/v	Persantine (Dupont-Merck)
PEG 3350	0.3 – 3 %	Depo-Medrol (Upjohn) 2.95% w/v
PEG 4000	0.3 - 3%	Invega Sustenna (Janssen)
Poppyseed oil	*	Ethiodol (Savage)
Propylene glycol	0.0025 – 80 %	Ativan (Wyeth-Ayerst) 80%
Safflower oil	5 - 10%	Liposyn II (Abbott) 10%
Seasme oil	100 %	Solganal Injection (Schering)
Soybean oil	10% w/v	Diprivan Injection (Zeneca)
Vegetable oil	*	Virilon IM Injection (Star Pharmaceuticals)

**Not applicable or no data available **PEG molecular weight not specified*

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 dosage form, modified cyclodextrins, such as hydroxypropyl-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 without apparent compatibility problems[33].

Table 7: Buffers and pH Adjusting Agents

Excipients		pH Range	Examples
Acetate	Sodium	2.5–7.0	Syntocinon (Novartis)
	Acetic acid	2.5–7.2	Syntocinon (Novartis)
	Glacial acetic acid	3.5–7.0	Brevibloc (Ohmeda)
	Acetic acid	2.5–7.2	Syntocinon (Novartis)
	Ammonium	6.8–7.8	Bumex Injection (Roche)
Ammonium sulfate		-	Innovar (Astra)
Ammonium hydroxide		-	Triostat (Jones Medical)
Arginine		7.0–7.4	Retavase (Boehringer)
Aspartic acid		5.0–5.6	Pepcid (Merck)
Benzene sulfonic acid		3.25–3.65	Nimbex (Glaxo Wellcome)
Benzoate sodium/acid		3.5–6.9	Valium (Roche)
Bicarbonate, sodium		5.5–11.0	Cenolate (Abbott)
Boric acid/sodium			Comvax (Merck)
Carbonate, sodium		4.0–11.0	Hyperab (Bayer)
Carbon dioxide		-	Serentil (Boehringer) used to fill headspace
Citrate	Acid	2.5–9.0	DTIC-Dome (Bayer)
	Sodium	3.0–8.5	Amikin (Bristol Myers)
	Disodium	6.1	Cerezyme (Genzyme)
	Trisodium	6.1	Cerezyme (Genzyme)
Diethanolamine		9.5–10.5	Bactim IV (Roche)
Glucono delta lactone		5.5–7.0	Quinidine Gluconate (Lilly)
Glycine/glycine HCl		2.5–10.8	Hep-B Gammagee (Merck)
Histidine/histidine HCl		5.0–6.5	Doxil (Sequus)
Hydrochloric acid		Broad range	Amicar (Immunex)
Hydrobromic acid		3.5–6.5	Scopolamine (UDL)
Lysine (L)			Eminase (Roberts)
Maleic acid		3.0–5.0	Librium (Roche)
Meglumine		6.5–11.0	Magnevist (Berlex)
Methanesulfonic acid		3.2–4.0	DHE-45 (Novartis)
Monoethanolamine		8.0–9.0	Terramycin (Pfizer)
Phosphate	Acid	6.5–8.5	Saizen (Serono Labs)
	Monobasic potassium	6.7–7.3	Zantac (Glaxo-Wellcome)
	Dibasic potassium	6.7–7.3	Aminosyn (Hospira)
	Monobasic sodium*	2.5–8.0	Pregnyl (Organon)
	Dibasic sodium**	2.5–8.3	Zantac (Glaxo-Wellcome)
	Tribasic sodium		Synthroid (Knoll)
Sodium hydroxide		Broad range	Optiray (Mallinckrodt)
Succinate sodium/disodium		5.0–6.0	AmBisome (Fujisawa)
Sulfuric acid		3.0–7.0	Nebcin (Lilly)
Tartarate sodium/acid		2.5–6.2	Methergine (Novartis)
Tromethamine (Tris)		6.5–9.0	Optiray (Mallinckrodt)

** Sodium biphosphate, sodium dihydrogen phosphate, or Na dihydrogen orthophosphate. ** Sodium phosphate, disodium hydrogen phosphate.*

Buffering agents:

Buffers are 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 7 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 [33].

Excipients in pharmaceutical suspension

Parenteral suspension is useful dosage from 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:

1. Flocculating / suspending agents.
2. Wetting agents.
3. Solvent systems
4. Preservatives
5. Antioxidants
6. Chelating agents
7. Buffering agents
8. Tonicity adjusting agents

Flocculating/suspending agents

The controlled flocculation approach uses a flocculating agent(s) 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 [34]

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 7 to 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.

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 [35,36].

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 [37].

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 [38].

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 final formulation [39].

Table 8: Antioxidants/chelating agents[40]

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
Antioxidants (propagation termination oil soluble)	
Ascorbic acid ester	0.01-0.15
Butylated hydroxy toluene	0.005-0.02
Tocopherols	0.05-0.075
Chelating agent	
Ethylene diamine tetra acetic acid salt	0.01-0.075

CRITERIA FOR THE SELECTION OF EXCIPIENT

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

1. Influence of excipient on the overall quality, stability, and effectiveness of drug product.
2. Compatibility of excipient with drug and the packaging system.
3. Compatibility of excipient with the manufacturing process, for example, preservatives may be adsorbed by rubber tubes or filters, acetate buffers will be lost during lyophilization process, etc.
4. The amount or percentage of excipients that can be added to the drug product.
5. 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 9 list excipients and their use along with route of administration
6. 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.
7. 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.
8. The length or duration of time that the drug product will be used once the multidose injection is opened [41].

TABLE 9: Pharmaceutical Excipients, Use and Route of Administration [41]

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
Dichlorodifluoromethane	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

Polyoxyethylene castor	oil Base, emulsifying agent, solubilizing agent, stabilizer	iv
Polyoxyethylene hydrogenated castor oil Base	emulsifying agent, solubilizer, stabilizer, suspending agent, vehicle	iv
Polyoxyethylene sorbitan monolaurate	Emulsifying agent, solubilizing agent, surfactant	iv, im, sc
Potassium pyrosulfite	Stabilizer	iv, sc, im
Potassium thiocyanate	Stabilizer	iv
Purified soybean oil	Solubilizer	iv
Sodium acetate, anhydrous	Buffer, pH adjuster, solubilizing agent, stabilizer	im
Sodium carbonate, anhydrous	Buffer, solubilizing agent	iv, im, ic
Sodium dihydrogen phosphate monohydrate	Buffering agent	ic
Sodium gluconate	Stabilizer, vehicle	iv, im
Sodium pyrophosphate, anhydrous	Dispersing agent, isotonicity, stabilizer	iv, im, is
Sodium sulfite	Antioxidant, stabilizer	iv
Sodium thioglycolate	Antioxidant, stabilizer	iv, im, sc
Sorbitan esters of fatty acids	Emulsifying agent, solubilizing agent, surfactant, stabilizer, suspending agent, vehicle	iv
Succinic acid	pH adjusting agent	iv
α-Thioglycerol	Antioxidant	iv, im, sc
Trienthanolamine	Buffer, pH adjuster, solubilizing agent, stabilizer	iv
Zinc chloride solution	Stabilizer	sc

Regulatory Perspective

Based on available safety testing information, the International Pharmaceutical Excipients Council (IPEC) has classified excipients into following classes[42]:

1. New chemical excipients: These excipients require a full safety evaluation program. It is estimated that the cost of safety studies for a new chemical excipient is about $35 million over 4 –5 years. E.U. directive 75/318/EEC states that new chemical excipients will be treated in the same way as new actives. In the U.S. a new excipient requires a Drug Master File (DMF) to be filed with the FDA. Similarly, in Europe a dossier needs to be established. Both the DMF and dossier contain relevant safety information. IPEC Europe has issued a guideline (Compilation of Excipient Master Files Guidelines) providing guidance to excipient producers on constructing a dossier to support MAA (Marketing Authorization Application) while maintaining confidentiality of the data [2].
2. Existing chemical excipient—first use in man: This class implies that animal safety data exists and that the excipient may have been used in some other route of administration (e.g., from oral to parenteral), new dosage form, higher dose, etc. may require additional safety information.
3. New modifications or combinations of existing excipients: These excipients indicate a physical interaction *not* a chemical reaction. No safety evaluation is necessary in this case.

The excipient included in the GRAS list does not mean that the excipient can be used in Injectables; the excipients which are meant for IV/IM/SC/IP etc need to be mentioned in GRAS list and then only the excipient qualifies to be used for parenteral dosage form.

The United States and Europe require all excipients to be declared, along with their quantity, on the label (what is put on the immediate container) if the product is an injectable preparation. In Japan, only the excipient names are required in the labeling (information that is included with the product, such as a package insert); E.U. Article 54(c) requires that all excipients must be declared on the labeling if the medicinal product is an injectable, a topical, or an eye preparation The European guide for the label and package leaflet also lists excipients with special issues and are addressed in Annex 31[43]. Table 10 is a summary of some of these ingredients commonly used as parenteral excipients and the corresponding safety information that should be included in a leaflet. A package leaflet must include a list of information on those excipients, knowledge of which is important for the safe and effective use of the medicinal product. Similarly, 21 CFR 201.22 requires prescription drugs containing sulfites to be labeled with a warning statement about possible hypersensitivity.

According to the Notes for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04), the choice of excipients, their grade, compatibility, concentration, and function should be described in the P2 section of the Common Technical Document. It is necessary to justify inclusion of all ingredients in the drug product and describe their intended function. A specification of ±10% at the end of shelf-life is acceptable except for antioxidants and preservatives where performance data from PET or stability data may justify broader limits. Bioburden and endotoxin limits of excipients used in the manufacture of sterile medical products shall be stated. Individual testing of excipients may be omitted.

If an excipient is present in Ph. Eur or other major pharmacopoeia, the monograph specifications are usually acceptable in the registration file. For excipients not described in any pharmacopoeia, specifications should include physical characterization, identification tests, purity test, assay, and impurity tests. A certification must be included to confirm that excipients are of non-animal (specifically non-ruminate) origin. If this is not the case, a regulatory agency will require documentation to demonstrate freedom from viral and transmissible spongiform encephalopathies (TSE) and Bovine Serum Encephalopathy (BSE) risks [44].

Currently, there are concerns regarding TSE via animal derived excipients such as gelatin [45]. TSEs are caused by prions that are extremely resistant to heat and normal sterilization processes. TSEs have a very long incubation time with no cure. In the current regulatory environment, if given a choice, it is beneficial to select non-animal-derived excipients. Concerns about bovine serum albumin or human serum albumin (HSA) because of possible derivation from virus-contaminated blood remain.

European Commission directive EMEA/410/01/rev2 requires manufacturers to provide a "Certificate of Suitability" or the underlying "scientific information" to attest that their pharmaceuticals are free of TSEs.

Below are the few points which are to be considered in selecting an excipients and its supplier for parenteral products.

Table 10: Excipients for Label and Corresponding Information for the Package Leaflet [46]

Name	Threshold Level	Information for the Package Leaflet
Arachis oil	Zero	Whenever arachis oil appears, peanut oil should appear beside it. If you are allergic to peanut or soya, do not use this medicinal product.
Benzoic acid and benzoates	Zero	It may increase the risk of jaundice in newborn babies.
Benzyl alcohol	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.
	90 mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.
Castor oil polyoxyl and castor oil polyoxyl hydrogenated	Zero	May cause severe allergic reactions.
Chlorocresol	Zero	May cause allergic reactions
Ethanol	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per dose
	100 mg to 3 g per Dose	This medicinal product contains . . . vol % ethanol (alcohol), i.e., up to . . . mg per dose, equivalent to . . . mL beer . . . mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children, and high-risk groups such as patients with liver disease or epilepsy.
Fructose	Zero	If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
	5 g	Contains x g fructose per dose. This should be taken into account in patients with diabetes mellitus
Galactose	Zero	If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. SPC proposal: Patients with rare hereditary problems of galactose intolerance (e.g., galactosaemia) should not take this medicine.
	5 g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.
Glucose	5 g	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.
Heparin (as an excipient)	Zero	May cause allergic reactions and reduced blood cell counts, which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin containing medicines.
Organic mercury compounds (such as thiomersal phenyl-mercuric nitrate, acetate, borate)	Zero	This medicinal product contains (e.g., thiomersal) as a preservative and it is possible that you/your child may experience an allergic reaction. Tell your doctor if you/your child have/has any known allergies. Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.
Parahydroxybenzoates and their esters	Zero	May cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm
Phenylalanine	Zero	This medicine contains phenylalanine. May be harmful for people with phenylketonuria.
Potassium	Less than 1 mmol per dose	This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e., essentially “potassiumfree.”
	1 mmol per dose	This medicine contains x mmol (or y mg) potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.
	30 mmol/L	May cause pain at the site of injection.
Propylene glycol and esters	400 mg/kg adults 200 mg/kg children	May cause alcohol-like symptoms.
Sesame oil	Zero	May rarely cause severe allergic reactions.
Sodium	Less than 1 mmol per dose	This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially “sodium-free.”
	1 mmol per dose	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet
Sorbitol	Zero	If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Soya oil (and hydrogenated soya oil)	Zero	(Medicinal product) contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

Future Direction and Conclusion

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 [47].

Chitosan,β-1,4-linked glucosamine, a naturally occurring, biodegradable, nontoxic polycationic biopolymer, is being investigated for its potential as across-linked microsphere matrix to deliver Antineoplastic drugs.

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[48]. Such bio-polymers are finding increased application as a matrix to deliver parenteral drugs for prolonged delivery [49].

Polyanhydrides degrade primarily by surface erosion and possess excellent in vivo compatibility. In 1996 the FDA approved a polyanhydride-based drug implantable delivery system to the brain for the chemotherapeutic agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU).

Several phospholipid-based excipients are finding increased application as solubilizing agents, emulsifying agents, or as components of liposomal formulations. The phospholipids occur naturally and are biocompatible and biodegradable, for example, eg. phosphatidylcholine, soybean phosphatidylcholine, hydrogenated soybean phosphatidylcholine (HSPC), dimyristoyl phosphatidylcholine (DMPC), distearoyl phosphatidylcholine (DSPC), 1,2 dioleoyl-sn-glycero-3-phosphocholine (DOPC), distearoyl phosphoethanolamine (DSPE), L-alpha-dimyristoylphosphatidylglycerol (DMPG), 1,2-dipalmitoyl-sn-glycero-3-phosho-rac-(1-glycerol).

Poloxamer or pluronic are block copolymers comprised of polyoxyethylene and polyoxypropylene segments. They exhibit reverse thermal gelation and are being tried as solubilizing, emulsifying, and stabilizing agents.

Sucrose acetate isobutyrate (SAIB) a high viscosity liquid system converts into free flowing liquid when mixed with 10–15% ethanol[50]. Upon subcutaneous or intramuscular injection, the matrix rapidly converts to a water-insoluble semi-solid capable of delivering proteins and small molecules for a prolonged period. SAIB is biocompatible, and it biodegrades to natural metabolites.

Several other biodegradable, biocompatible, injectable polymers are being investigated for drug delivery systems. They include polyvinyl alcohol, block copolymer of PLA-PEG, polycyanoacrylate, polyanhydrides, cellulose, alginate, collagen, modified HSA, albumin, starches, dextrans, hyaluronic acid and its derivatives, and hydroxyapatite.

Recent concerns about swine flu and other infectious diseases have regenerated interest in new vaccines and adjuvants to improve immune response. Some of the adjuvants included in marketed vaccines in Europe but still being evaluated include AS03 and AS04 (GSK) and MF-59 (Novartis). AS04 is composed of 3-Odesacyl-4-monophosphoryl lipid A. It is present in Cervarix, which was approved in 2010. Newer adjuvants being tested include saponin-based (QS-21, Quil A, ISCOM) or emulsion-based (SA03).

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