# APPENDIX A

# MATERIALS USED FOR WATER DISPERSIBLE GRANULE FORMULATION

## 1. Lactose (lactose monohydrate)

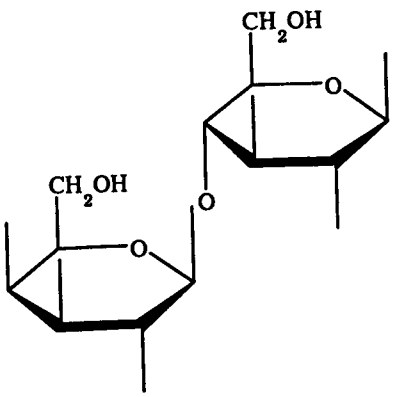


**Figure 32.** Structure of lactose

Lactose monohydrate is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety (The United States Pharmacopeial Convention, 2007).

| | |
|---|---|
| CAS name: | 4-*O*-β-D-galactopyranosyl-D-glucose |
| Additional name: | 4-(β-D-galactosido)-D-glucose; milk sugar; saccharum lactis; Aero Flo 20; Aero Flo 65; Aero Flo 95; Anhydrox; CapsuLac; Fast-Flo; FlowLac; GranuLac; InhaLac; HMS; Lactochem; Lactohale; Lactopress; Microfine; Microtose; Pharmatose; PrismaLac; Respitose; SacheLac; SorboLac; Super-Tab; Tablettose; Wyndale; Zeparox (Budavari *et al.*, 1999; Rowe *et al.*, 2003). |
| Molecular formula: | $C_{12}H_{22}O_{11}$ (anhydrous); $C_{12}H_{22}O_{11}\cdot H_2O$ (monohydrate) |
| Molecular weight: | 342.30 (anhydrous); 360.31 (monohydrate) |
| Properties: | Lactose occurs as white to off-white crystalline particles or powder (Rowe *et al.*, 2003). Freely but slowly soluble in water, practically insoluble in 96% ethanol (British Pharmacopoeia Commission, 2001). On hydrolysis with 2% $H_2SO_4$ or with |

emulsin lactose yields 1 mol D-glucose and 1 mol D-galactose. Reduces Fehlingprimes solution (Budavari *et al.*, 1999).

Functional category: Diluent for dry-powder inhalers; tablet and capsule diluent (Rowe *et al.*, 2003).

Hygroscopicity: Lactose monohydrate is stable in air and is unaffected by humidity at room temperature. However, the amorphous form, depending upon how it is dried, may be affected by humidity and can be converted to the monohydrate (Rowe *et al.*, 2003).

Safety: Lactose is widely used in pharmaceutical formulations as a diluent in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in persons with a deficiency of the intestinal enzyme lactase (Bedine and Bayless, 1973; Gudmand-Hoyer and Simony, 1977; Pray, 1990). Most adults consume about 25 g of lactose per day (500 mL of milk) without symptoms (Suarez *et al.*, 1995; Suarez and Savaiano Dennis, 1997).

| | |
|---|---|
| $LD_{50}$(rat, IP): | >10 g/kg |
| $LD_{50}$(rat, oral): | >10 g/kg |
| $LD_{50}$(rat, SC): | >5 g/kg |

Regulatory Status: Included in the FDA Inactive Ingredients Guide (IV injections; oral capsules and tablets). Included in nonparenteral and parenteral medicines licensed in the UK (Rowe *et al.*, 2003).

**2. Polyethylene sorbitan monooleate (Tween 80)**

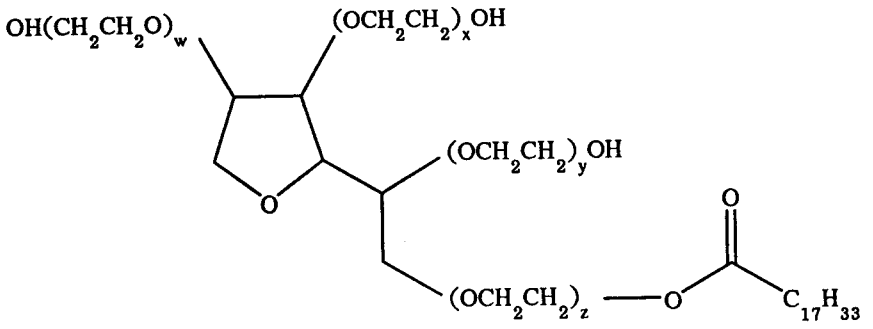


**Figure 33.** Structureof Tween 80 (w+x+y+z=20)

Tween 80 is an oleate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides (The United States Pharmacopeial Convention, 2007).

Additional name: polyoxyethylene (20) sorbitan monooleate; POE (20) sorbitan monooleate; polyoxyethylene 20 oleate; (Z)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-SMO; Drewpone 80K; Durfax 80; Durfax 80K; E433 ; Emrite 6120; Eumulgin SMO; Glycosperse O-20; Hodag PSMO-20; Liposorb O-20; Liposorb O-20K; Montanox 80; Protasorb O-20; Ritabate 80; Tego SMO 80; Tego SMO 80V; polysorbate 80 (Budavari *et al.*, 1999; Rowe *et al.*, 2003).

Molecular formula: $C_{64}H_{124}O_{26}$

Molecular weight: 1310

Properties: Lemon- to amber-colored, oily liquid. d 1.06-1.09 . Viscosity (25°C): 300-500 centistokes. Very sol in water; sol in alcohol, cottonseed oil, corn oil, ethyl acetate, methanol, toluene. Insol in mineral oil. pH of 5% aq soln between 6 and 8 (Budavari *et al.*, 1999).

Functional Category: Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent; as defoamers and emulsifiers in foods. Pharmaceutic aid (surfactant) (Budavari *et al.*, 1999; Rowe *et al.*, 2003).

Safety: Polysorbates are widely used in cosmetics, food products, and oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials (Rowe *et al.*, 2003). The WHO has set an estimated acceptable daily intake for polysorbate 80 calculated as total polysorbate esters, at up to 25 mg/kg body-weight (FAO/WHO, 1974).

$LD_{50}$(mouse, IP): 7.6 g/kg

$LD_{50}$(mouse, IV): 4.5 g/kg

$LD_{50}$(mouse, oral): 25 g/kg

$LD_{50}$(rat, IP): 6.8 g/kg

$LD_{50}$(rat, IV): 1.8 g/kg

Regulatory Status: Polysorbate 80 is GRAS listed, is accepted as food additives in Europe and included in the FDA Inactive Ingredients Guide (IM, IV, oral, rectal, topical, and vaginal preparations). Polysorbates are included in parenteral and nonparenteral medicines licensed in the UK (Rowe *et al.*, 2003).

**3. Polyvinyl pyrrolidone**

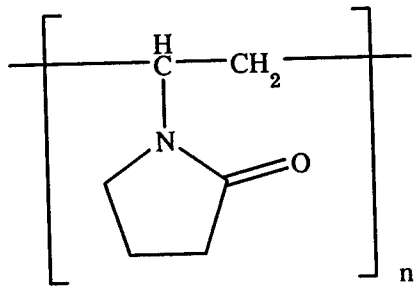


**Figure 34.** Structure of PVP

Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10 to 120 (The United States Pharmacopeial Convention, 2007).

CAS name: 1-vinyl-2-pyrrolidinone polymers; 1-Ethenyl-2-pyrrolidinone homopolymer

Addition name: poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvinylpyrrolidone; polyvidone; PVP; 1-vinyl-2- pyrrolidinone polymer; E1201; Kollidon; Plasdone; Periston; Protagen

Molecular formula: $(C_6H_9NO)_n$

Molecular weight: 2500-3000000 (approximate molecular weight of PVP K-30 is 50000)

Properties: Povidone occurs as fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder (Rowe *et al.*, 2003). Sol in water, alcohol, chloroform, formic acid, acetic acid, N - methylpyrrolidone, dichloromethane, methylcyclohexanone, ethyl enediamine, glycerol, diethyleneglycol, PEG 400. Insol in xylene, toluene, diethylether, ethylacetate, acetone, cyclohexanone, chlorobenzene, dioxane, carbon tetrachloride, mineral oil (Budavari *et al.*, 1999).

Functional category: Povidone as pharmaceutic aid (dispersing, suspending and viscosity-increasing agent; tablet coating and binder). Thickener, dispersant, lubricant, film-forming agent and binder in cosmetics. Stabilizer, diluent, and dye dispersant in food. Dye dispersant in paper and textiles (Budavari *et al.*, 1999). Disintegrant; dissolution aid; suspending agent; tablet binder (Rowe *et al.*, 2003).

Safety: Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander. Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes (Wessel *et al.*, 1971). Povidone additionally has no irritant effect on the skin and causes no sensitization. A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight (FAO/WHO, 1983).

$LD_{50}$(mouse, IP): 12 g/kg

Regulatory Status: Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK (Rowe *et al.*, 2003).

**4. Sodium alginate**

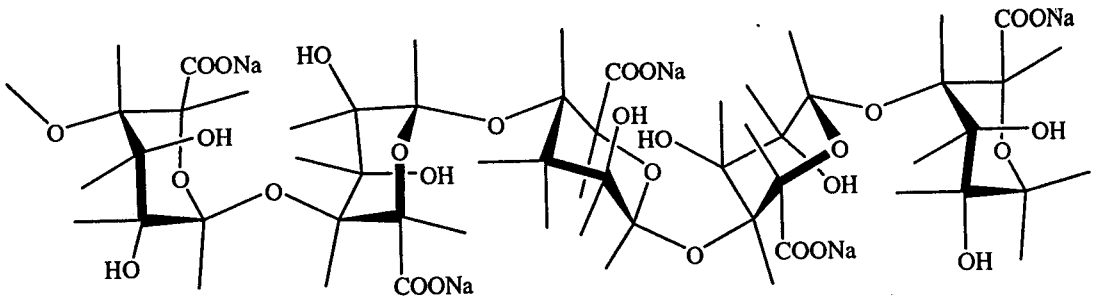


**Figure 35.** Structure of sodium alginate

Sodium alginate is the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali (The United States Pharmacopeial Convention, 2007). It consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid (Rowe *et al.*, 2003).

| | |
|---|---|
| CAS name: | Alginic acid sodium salt |
| Additional name: | sodium alginate; sodium polymannuronate; Kelcosol; Keltone; Protanal; Alto; Alman; Alloid; Allose (Budavari *et al.*, 1999; Rowe *et al.*, 2003). |
| Molecular formular: | $C_5H_7O_4COONa$ |
| Molecular weight: | 216 |
| Properties: | Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder (Rowe *et al.*, 2003). Sol in water, forming a viscous, colloidal soln. Insol in alcohol and in hydro-alcoholic solns in which the alcohol content is >30% w/w. Insol in chlo roform, ether, in aq acid solns when the pH is below 3 (Budavari *et al.*, 1999). |
| Functional category: | Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent (Budavari *et al.*, 1999; Rowe *et al.*, 2003). |
| Safety: | Sodium alginate is widely used in cosmetics, food products, and pharmaceutical formulations, such as tablets and topical products, including wound dressings. It is generally regarded as a nontoxic |

and nonirritant material (Rowe *et al.*, 2003). The WHO has not specified an acceptable daily intake for alginic acid and alginate salts as the levels used in food do not represent a hazard to health (FAO/WHO, 1992). Inhalation of alginate dust may be irritant and has been associated with industrial-related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to seaweed dust rather than pure alginate dust (Henderson *et al.*, 1984).

| | |
|---|---|
| $LD_{50}$(cat, IP): | 0.25 g/kg |
| $LD_{50}$(mouse, IV): | 0.2 g/kg |
| $LD_{50}$(rabbit, IV): | 0.1 g/kg |
| $LD_{50}$(rat, IV): | 1 g/kg |
| $LD_{50}$(rat, oral): | >5 g/kg |

**Regulatory Status:** GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets). Included in nonparenteral medicines licensed in the UK (Rowe *et al.*, 2003).

# APPENDIX B

# MATERIALS USED FOR EMULSIFIABLE CONCENTRATE FORMULATION

## 1. Butylated hydroxytoluene (BHT)

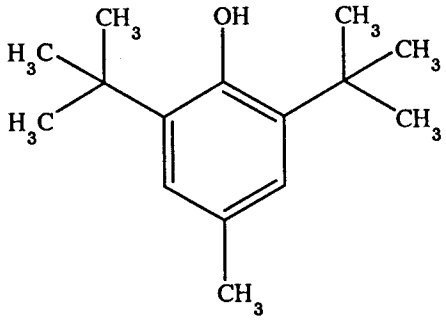


**Figure 36.** Structure of BHT

CAS name: 2,6-Bis(1,1-dimethylethyl)-4-methylphenol

Additional name: 2,6-di-*tert*-butyl-4-methylphenol; 2,6-di-*tert*-butyl-*p*-cresol; 3,5-di-*tert*-butyl-4-hydroxytoluene; dibutyled hydroxytoluene; BHT; Antrancine 8; Tenox BHT; Ionol CP; Sustane; Dalpac; Impruvol; Vianol; Agidol; Embanox BHT; Nipanox BHT; Sustane; Tapanol (Budavari *et al.*, 1999; Rowe *et al.*, 2003).

Molecular formula: $C_{15}H_{24}O$

Molecular weight: 220.35

Properties: Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic odor (Rowe *et al.*, 2003). Insol in water. Freely sol in toluene, sol in methanol, ethanol, isopropanol, methyl ethyl ketone, acetone, Cellosolve, petr ether, benzene, most other hydro carbon solvents. Soly in liquid petrolatum (white oil): 0.5% w/w. More sol in food oils and fats than butylated hydr oxyanisole. Good soly in linseed oil (Budavari *et al.*, 1999).

Functional category: Antioxidant (Rowe *et al.*, 2003).

Safety: Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract and is metabolized and excreted in the urine mainly as glucuronide conjugates of oxidation products. Although there have been some isolated reports of adverse skin reactions, butylated hydroxytoluene is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant (Juhlin, 1981; Roed-Peterson and Hjorth, 1976). The WHO has set a temporary estimated acceptable daily intake for butylated hydroxytoluene at up to 125 μg/kg body-weight (FAO/WHO, 1991).

$LD_{50}$(guinea pig, oral): 10.7 g/kg
$LD_{50}$(mouse, IP): 0.14 g/kg
$LD_{50}$(mouse, IV): 0.18 g/kg
$LD_{50}$(mouse, oral): 0.65 g/kg
$LD_{50}$(rat, oral): 0.89 g/kg
$LD_{50}$ (mice, oral): 1.04 g/kg

Regulatory status: GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, nasal sprays, oral capsules and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK (Rowe *et al.*, 2003).

**2. Polyethylene sorbitan monooleate (Tween 80)**

(See Appendix A)

**3. Sorbitan monooleate (Span 80)**

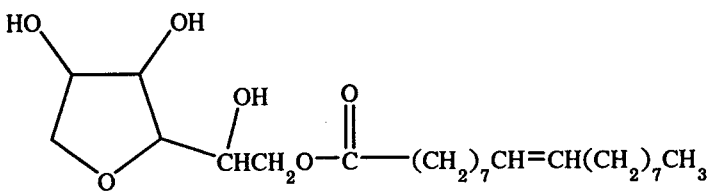


**Figure 37.** Structure of Span 80

CAS name: (Z)-Sorbitan mono-9-octadecenoate

Addition name: sorbitan oleate; Span 80; Ablunol S-80; Arlacel 80; Armotan MO; Alkamuls SMO; Capmul O; Crill 4; Crill 50; Dehymuls SMO; Drewmulse SMO; Drewsorb 80K; E494; Emsorb 2500; Glycomul O; Glycomul O; Hodag SMO; Lamesorb SMO; Liposorb O; Montane 80; Nikkol SO-10; Nissan Nonion OP-80R; Norfox Sorbo S-80; Polycon S80 K; Proto-sorb SMO; Protachem SMO; S-Maz 80K; Sorbester P17; Sorbirol O; Sorgen 40; Sorgon S-40-H; Tego SMO (Budavari *et al.*, 1999; Rowe *et al.*, 2003)

Molecular formula: $C_{24}H_{44}O_6$

Molecular weight: 429

Properties: Sorbitan monooleate occurs as yellow viscous liquid with a distinctive odor and taste (Rowe *et al.*, 2003). Acid num ber: 5-8. Saponification value: 140-160. Hydroxyl value: 193-215. Sol in ethanol, isopropyl alcohol, mineral oil, vegetable oil. Insol in water, propylene glycol (Budavari *et al.*, 1999).

Functional category: Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent (Rowe *et al.*, 2003). Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent (Budavari *et al.*, 1999).

Safety: Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters (Austad, 1982; Boyle and Kennedy, 1984; Finn and Forsyth, 1975; Hannuksela *et al.*, 1976). The WHO has set an estimated acceptable daily intake of sorbitan monooleate at up to 25 mg/kg body-weight calculated as total sorbitan esters (FAO/WHO, 1982).

Regulatory Status: Certain sorbitan esters are accepted as food additives in the UK. Sorbitan esters are included in the FDA Inactive Ingredients Guide (inhalations; IM injections; ophthalmic, oral, topical, and vaginal

preparations). Sorbitan esters are used in nonparenteral medicines licensed in the UK (Rowe *et al.*, 2003).

**4. Soybean oil**

Soybean oil is the refined fixed oil obtained from seeds of the soya plant *Glycine max* Merr. (Fabaceae). It may contain suitable antioxidants (The United States Pharmacopeial Convention, 2007).

CAS name: Soybean oil

Addition name: soja bean oil; soyabean oil; soya bean oil; alchem IVO-114; Lipex; Lipex; Shogun CT (Rowe *et al.*, 2003).

Properties: Soybean oil is a clear, pale-yellow colored, odorless or almost odorless liquid, with a bland taste that solidifies between -10°C and -16°C (Rowe *et al.*, 2003). The flavor of crude soybean oil has been described as paint-like and grass-like, and is somewhat distasteful to the palate of occidentals. Viscosity in centipoises: 172.9 at 0°C; 99.7 at 10°C; 50.09 at 25°C; 28.86 at 40°C. Acid value 0.3-3.0. Saponification value 189-195. Iodine value 127-138. Thiocyanogen value 77-85. Diene no. 0.7. Hydroxyl value 4-8. Reichert-Meissl value 0.2-0.7. Polenske value 0.2-1.0. Miscible with absolute alcohol, ether, petroleum ether, chloroform, carbon disulfide (Budavari *et al.*, 1999).

Functional Category: Oleaginous vehicle; solvent (Rowe *et al.*, 2003).

Safety: Soybean oil is widely used intramuscularly as a drug vehicle or as a component of emulsions used in parenteral nutrition regimens; it is also consumed as an edible oil. Generally, soybean oil is regarded as an essentially nontoxic and nonirritant material (Rowe *et al.*, 2003).

$LD_{50}$(mouse, IV): 22.1 g/kg

$LD_{50}$(rat, IV): 16.5 g/kg

Regulatory Status: Included in the FDA Inactive Ingredients Guide (IV injections, oral capsules, and topical preparations). Included in nonparenteral (oral

capsules; topical bath additives) and parenteral (emulsions for IV injection or infusion) medicines licensed in the UK (Rowe *et al.*, 2003).