CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com ***Review Article***

ROLE OF STABILIZERS IN NANOSUSPENSION – A REVIEW

Rajveer Bhaskar[1], Monika Ola[2], Rakeshsing Rajput[1]*, Harshjeet Sisode[1], Shailesh Chalikwar[1]

R. C. Patel of Pharmaceutical Education and Research Shirpur, Dist - Dhule 425405, (MS) 2018 -19 (Department of Pharmaceutical Quality Assurance)

[1*]Department of Pharmaceutical Quality Assurance, RCPIPER Shirpur (Dist-Dhule), India, Email – rr923530@gmail.com, Mobile no – 9637077234 / 8208256083, [1]RCPIPER Shirpur (Dist-Dhule), India, Email – harshjeetsisode536@gmail.com, Mobile no – 7775847170, [1]RCPIPER Shirpur (Dist-Dhule), India, Email – bhaskar007raj@gmail.com , Mobile no – 8275102109, [2]Email – monika.ola@rediffmail.com, Mobile no – 8275102108.

Article Received: December 2018 **Accepted:** February 2019 **Published:** March 2019

Abstract:

The Main goal of surfactants in the formation of nanoparticles is due to its high effect on the dispersion. Nano-suspension, as non- crystal systems, present characteristics and properties which depend not only on composition but also on the preparation method. Although interest in nano-Suspension was developed since about 20 years ago, mainly for nanoparticle preparation, it is in the last years that direct applications of nano-suspension in consumer products are being developed, mainly in pharmacy, drugs, personal care, health care, agrochemicals and cosmetics. These recent applications have made that studies on optimization methods for nano- suspension preparation be a requirement. This review is focused on the most recent literature on developments of nano-suspension as final application products and on the optimization of their preparation.

Keywords: *Nano-suspension, Stabilizers, Role, Techniques, Advantages, Disadvantages*

Corresponding author:

Rakeshsing Rajput,

Department of Pharmaceutical Quality Assurance,
RCPIPER Shirpur (Dist-Dhule), India,
Email – rr923530@gmail.com, Mobile no – 9637077234 / 8208256083

QR code

Please cite this article in press Rakeshsing Rajput et al., ***Role Of Stabilizers In Nanosuspension – A Review.,*** *Indo Am. J. P. Sci, 2019; 06(03).*

INTRODUCTION:

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability play a critical role in the successful formulation of drugs More than 40% the new chemical existence produced over drug discovery programs are poorly soluble in water or lipophilic chemical compounds and others. surface-active agent Play important roles in the formation of nano-suspension. Formulating a water insoluble drug has very often hard problem someone by the pharmaceutical research scientist. The formulation of nano- sized particles of drug generally belongs to the BCS class II and IV to improve their aqueous solubility leads to pass the gastrointestinal barriers. Microinization methods are always used to BCS class II drugs, that is good permeability and poor solubility and many methods are very helpfull to improve solubility of poorly soluble drugs, which include some methods like solubilization using co-solvent, salt form, microinization, surfactant dispersion, precipitation techniques and oily solution and some other methods like microemulsion, liposome, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they deficient in general bearing to all drugs. These kind of techniques are not suitable to solubilize some drugs which are not able to soluble in water and organic solvents. Nanotechnology generally used to solve the any problems related with these standard approaches for improve their solubility and oral bioavailability and it's a very challenging task in nanosuspension [1]. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. To prepare stable nanosuspension, surfactant and polymer play an important role.

Stabilization Principles

In English the term surfactant (surface-active-agent) select a substance which indicate some outermost interfacial commotion. It is feck look on that all amhiphiles do not release such activity; in impact, only the amphiphiles with approximates weigh up hydrophilic and lipophilic leaning are eventual to migrate to the surface or interfaceIt does not get if the amphiphilic partical is too hydrophilic or too hydrophobic, in which content it remain in one of the phases[2]. The manufacturing of nano-suspension implicit the formation of extra surface are and hence co-ordinate. As the Gibbs free energy change, similar with the formation of another interface is very use full to the nano-suspension are thermodynamically not stable and will certain to easily decrease their total energy by aggregated. The activation energy of these process aggregated of depends on its activation energy. This activation energy can be affected by adding stabilizers to the system [3]. The surface active agents, or surfctants, are molecule distinguished by the presence of both a polar and a nonpolar region which is termed as a head and tail in the structure of surfactant. Emulsifier is the common term that comprise detergents, dispersing agents, emulsifying agent, foaming agents, penetrating agents, and wetting agents [4]. Another group, the amphoteric or ampholytic emulsifier, can get anionic and cationic properties depend on the pH. Anionic surfactants are richly accepted as powerful irritants to human skin. Cationic stabilizers are obtain as at least disinterested annoying, but more cytotoxic other than anionic, while the innate annoyance of nonionic surface-active agent is examine to be the lowest. This categorization does not allow exact determination of the potential toxicity of each and every product [5]. In praxis, surface-active agent can at times be sorted as inactive ingredients in pharmaceutical forms or in other cases used as an active constituent. DLVO Theory applies to colloidal systems, and is not completely, considerable to "coarse" suspensions. However, it does put permeance as to how few suspension stabilizers function, and is associated for wholeness. The theory was expand isolated by Derjaguin and Landau and by Verwey, Overbeek in the 1940. The theory is found on the proposition that the emphasis acting on unplaced lyophobic (solvent-hating) colloidal molecules are due to some electrostatic revulsion and London-type van der Waals affinity forces. As two molecules in suspension perspective each other, in conclusion the repulsive energy will get apparent. As the particles are forced closer and closer together, the repulsion will reach the primary maximum and then, if the particles continue to move closer, the attractive force will strong and they will move into the primary least and coagulate. Stored the molecules are corroborated in such a means that they do not outlook each other more closely than the primary maximum, the particles should remain suspended. If the primary most of the exceeding weigh to the thermal energy of the atoms, the colloidal dispersion should be static and the atoms remain dispersed. Height of the elementory maximum, the force inhibition to coagulation, depending on zeta potential of the size and the electrolyte concentration in the sustained phase. Lyophilic colloids are stabilized by a conjuction of interplay of the electrical two fold layer and solvation. Both requirement be weaken for coagulation to become. Hydrophilic colloids are untouched by inferior concentrations of electrolyte,

but "salting out" can occur at sublimate concentrations of hardily hydrated ions [6].

PREPARATION OF NANOSUSPENSION:

For the preparation of nanosuspensions, mostly two methods namely "Bottom up technology" and "Top down technology" are used, as shown in Figure 1 [7]. Bottom up technology is an assembling method to form nanoparticles like precipitation, microemulsion, melt emulsification method and top down technology involves the disintegration of larger particles into nanoparticles, examples of which are high-pressure homogenization and milling methods. The principles of these methods are described in detail and their merits and demerits are shown in Table 1 [8].

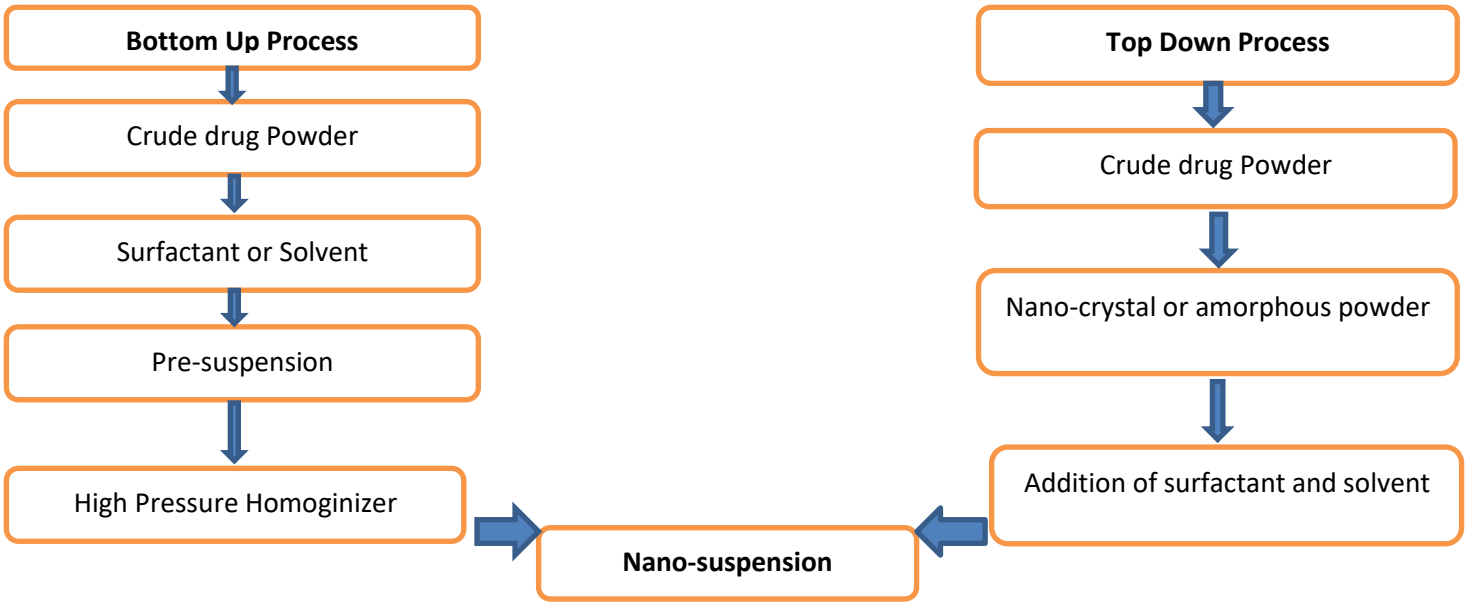


Figure 1: Approaches for preparation of nanosuspension.

Table 1: Preparative techniques for nanosuspension with Advantages and Disadvantages

Techniques	Principale	Advantages	Disadvantages
Media Milling (Nanocrystals)	Here,the main principle involved in the size reduction is "impaction". By this shear, the microparticles are braked down into nanoparticles. And it is connected to there circulating chamber so that continuous production will be carried out. It is suitable for both batch operation and continuous operation. By this,we canreduce the particle size upto < 200nm in30–60 min only.	Applicable to the drugs that are poorly soluble both aqeous and organic face. Very dilute as well as highly concentreted nano-supension can be prepared by handling 1mg/ml 400mg/ Drug quantity.	Nano-supension contaminated with materials eroded fr`om balls may be problematic when it is used for long theraphy. Scale Up is not easy due to mill size and weight.
High-Pressure Homogenization	High shear and high pressure are due to particle collisions; the particle size will be reduced.Here,we have to add viscosity enhancers to increase the viscosity of nanosuspension.In this methods we have to mainly concentrate on two parameter called pressure and homogenization cycles (depending on particle hardness analyzed by particle size and polydispersibility index)	Low risk of production contamination. Allow aseptic production of nanosuspension for parentral administred.	Prerequisite of microionized drug partical. Prerequsite of suspension formation using high-speed mixers before subjecting it to homogenization
Microemulsion as Template.	Microemulsions are thermodynamically stable and isotropically clear dispersion of the two immiscible liquids such as oil and water, and they were stabilized by an interfaceial film of surfactant and cosurfactant. In this, firstly, the microemulsion was prepared the dug solution was mixed to that prepared emulsion and drug loading efficiency was tested.	Simple process Small size particles Stable products Low need of energy High drug solubilization Uniform particle distribution Ease of manufacture	Use of high amount of surfactant and stabilizers Use of hazardous solvent

Precipitation Method	Precipitation has been applied for years to prepare submicron particles within the last decade, especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in a solvent. Then, this solution is mixed with a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water)leads to sudden super saturation of drug in the mixed solution and generation of ultrafine crystalline or amorphous drug solids This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary. Both rates are dependent on temperature: the optimum temperature for nucleation might lie below that for crystal growth, which permits temperature optimization	Simple process Stable products Low need of energy Low cost of equipment Ease of scale up	Growing of drug crystals needs to be limit by surfactant addition Drug must be soluble at least in one solvent Narrowly applying space, wide size distribution and potential toxicity of nonaqueous solvents

Classification of Surfactants

Surfactant is a general name for materials that possess surface activity; in solution they tend to orient at the level of the liquid. There are several common category of stabilizing agent: anionic, cationic, amphoteric and non-ionic. surface-active agent are amphiphilic molecules, i.e. part of the molecule is hydrophilic, and part is lipophilic. This combination of the two opposite affinities in the same molecule causes them to orient to the interface and thereby reduce the interfacial tension between the continuous and disperse phases, such as in emulsions and suspensions. Ionic stabilizers function primarily care of electrostatic emphasis, where as non-ionic stabilizers thing primarily through steric forces [9]. Surfactants can be classify in pursuance of the charge extant in the hydrophilic portion of the molecule (through dissociation in aqueous solution):

- Anionic surfactants
- Nonionic surfactants
- Cationic surfactants
- Amphoteric surfactants

Stabilizers Play important roles in the make a nano-suspension; stabilizer type and assiduity play an signification role in making a constant formulation. It must be competent of wetting the surface of the drug particles and provision a steric or ionic barrier. When drug-to-stabilizer rate was kept 1:0.5, it markedly improved stabilization of Nano-suspension.

Anionic surfactant

Anionic surface-active agent are those that away a -ve charge on the hydrophilic part. The generally category of anionic surfactant applied in this are containing carboxylate, sulfate, and sulfonate ions [10]. The most frequently allied cations are sodium, calcium, magnesium, and zinc, multivalent ions producing marked water isolubility. The straight chain is a saturated or unsaturated C12-C18 aliphatic group. The degree of water solubility is greatly affected by the length of the alky chain and by the presence of double bonds [11]. Depending on the chemical class and concentration, this group of surfactant may be irritating in certain conditions. Anionic Surfactants are dissociated in water in an amphiphilic anion*, and a cation*, which is in general an alcaline metal (Na+, K+) or a quaternary ammonium. They are the most commonly used surfactants.

Nonionic surfactant

Nonionic surfactants differ from ionic surfactants in the short-coming of charge on the particals. They are commonly lower affective than anionic or cationic surfactants. They are compatible with others types of surfactants, but they may diminish the antimicrobial activity of some preservatives [12]. The charcteristics of nonionic surfactants are essentially dependent on the propostion of hydrophilic or hydrophobic groups in the molecule. The hydrophilic parts contain the polyoxy ethylene, polyoxypropylene also polyol derivatives and her hydroxyl group. The hydrophobic character comprise saturates or not saturated fatty acid and fatty alcohols. By change the number of hydrophilic groups or the distance of the lipophilic

chain, compounds acquired with large range of hydrophilic and lipophilic balance (HLB) values. This is an empirical scale invented by griffitn that is useful to classify nonionic surfactants and to select surfactants mixtures for emulsification of particular oils [13]. Lipophilic surfactants (0< HLB < 10) atre known for their antiforming, water-in-oil emulsifying or wetting properties. Hydrophilic surfactants (10 < HLB < 20) have generally oil-in-water emulsifying or solubilizing properties. Due to the conditions of their fabrication, these surfactants are usually mixtures of associated substance, so there are sometimes variations in properties between different manufactures.Over many years, nonionic surfactants have become more and more important in the pharmaceutical field because of their ability to solubilize poorly soluble substances and their low toxicity [14]. The principal groups used in this domain are polyol derivatives, polyoxyethlene esters and ethers, and polaxamers, but other surfactants are also include in this classification, such as nonylphenyl ethers, polyvinyls alcohol, propylene glycol diacetate, or alkanolamides. This polyether sequencecy is applied as the lipophilic group is known as polyEO-polyPO block co-polymers, which are most oftentimes included in a apart class, e.g. polymeric surfactants, to be divide with later.

Cationic surfactants

The cationic group has a positively charged cationic. Negatively charged products strongly absorb cationic surfactants; some such products include hair, skin, and microorganisms. These type of surfactants are important pharmaceutically because of their bactericidal properties. Due to this activity, cationic surfactants are used on skin, in particular in the purify of injury and burns, or are used as preservatives. They may be very irritatble to the eyes and skin. These compounds are applied infrequently as emulsifiers. Furthermore, the use of quaternary ammonium groups as emulsifying agents in creams is restricted because of their incompatibility with soap, many anionic compounds, and different passive components such as that polymers (polyacrylate, carboxymethylcellulose) also used in these types of formulation. The principal cationic surfactants used in pharmaceutical preparation are quaternary ammonium salts, and the physiochemical properties and different application of these surfactants.

Amphoteric surfactant

Amphoteric surface-active-agents have deuce functional group, anionic and cationic. In part of it is the pH which compose which of the groups would administer, by side one or the other ionization: anionic at alkaline pH or cationic at acid pH. Near the so called isoelectric point, these stabilizers show both charges and are truly amphoteric, frequently with a least of interfacial activity and a inmate most of water solubility. Amphoteric stabilizers, especially the amino acid ones are thoroughly biocompatible, and are consumed in pharmaceuticals and cosmetics.

Excipients for Nanosuspensions

Nanosuspensions are suspensions where the molecule size of the intersperse phase is lower than 1µm (few authorities move 0.1µm), i.e. measured in nm. This are not new; they were already indicated to as colloidal systems either colloidal suspensions. Alone the knowledge of the period “nano” is novel. Since of their too succinct size, in the privation of variant cause, nanoparticles should bide in suspension for long time. However, as other disperse phases they will altogether and coalesce to form sizable particles, and Ostwald ripening may to break even occur. On condition that they settle out, the particles will be grossly hard to re-suspend. Nanosuspensions therefore need to be stabilized. Many of the same materials, surfactants and polymers used to stabilize conventional suspensions may also be usefull to fix nanosuspensions. However, since interfacial phenomena are involved and the surface area of disperse phase is very much increased in nanosystems, the level of incorporation of the polymers and stabilizers eventuality requirement to be increased accordingly. In sum, the DLVO theory will take effect to lyotropic nanoparticles [15]. Nanosuspensions may be classified as either systems containing solid nanoparticles, or those based on lipids. The methods of manufacture are very different for the two types of system, but some of the factors affecting nanosuspension stability are similar for both.

Aspects of Stabilizers In Nanosuspension

1 Pluronic

Nonproprietary Names

BP: Poloxamers , PhEur: Poloxamers, USP-NF: Poloxamer

Synonyms

Lutrol; Monolan; Pluronic; poloxalkol; poloxamera; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylenecopolymer; Supronic; Synperonic.

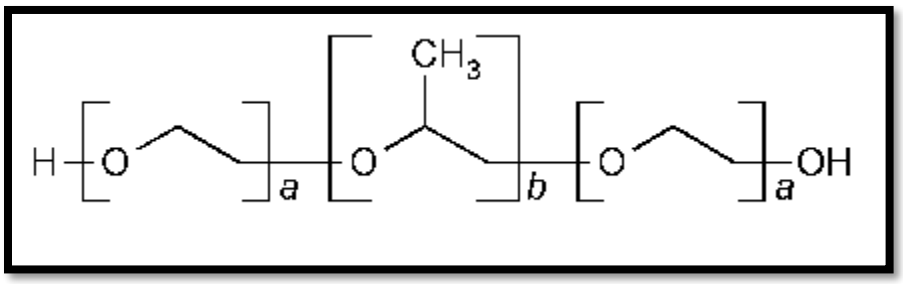
Chemical Name and CAS Registry Number

a-Hydro-o-hydroxypoly(oxyethylene)poly(oxypropylene) poly-(oxyethylene) block copolymer.

Empirical Formula and Molecular Weight
The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula HO(C2H4O)a(C3H6O)b(C2H4O)aH. The grades included in the PhEur 6.0 and USP32–NF27.

Melting point
16^{0}C for poloxamer 124, 52–57^{0}C for poloxamer 188, 49^{0}C for poloxamer 237, 57^{0}C for poloxamer 338, 52–57^{0}C for poloxamer 407.

Structural Formula



Functional Category
Dispersing agent, emulsifying agent, solubilizing agent, tablet lubricant, wetting agent.

Role in Pharmaceutical Nano system or Technology
Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents [16]. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available. Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes, and in the preparation of solid-dispersion systems [17]. Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers. Poloxamer 338 and 407 are used in solutions for contact lens care [18].

Stability and Storage Conditions
Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.

2 Polyoxyethylene Sorbitan Fatty Acid Esters

Non-proprietary Names

BP: Polysorbate 2 Polysorbate 40 Polysorbate 60 Polysorbate 80

JP: Polysorbate 80

PhEur: Polysorbate 20 Polysorbate 40 Polysorbate 60 Polysorbate 80

USP-NF: Polysorbate 20 Polysorbate 40 Polysorbate 60 Polysorbate 80

Synonyms
Polysorbate 20
Armotan PML 20; Capmul POE-L; Campul POE-L Low PV; Crillet 1; Drewmulse; E432; Durfax 20; E432; Eumulgin SML; Glycosperse L -20; Hodag PSML-20; Lamesorb SML-20; Liposorb L-20; Liposorb L-20K; Montanox 20; Nissan Nonion LT-221; Norfox Sorbo T-20; POESML; polysorbatum 20; Ritabate 20; Sorbax PML-20; sorbitan monododecanoate; Sorgen TW-20; T-Maz 20; T-Maz 20K; poly(oxy- 1,2-ethanediyl) derivatives; polyoxyethylene 20 laurate; Protasorb L-20; Tego SML 20; Tween 20.
Polysorbate 21

Crillet 11; Hodag PSML-4; Protasorb L-5; Tween 21.

Polysorbate 40

Crillet 2; E434; Eumulgin SMP; Glycosperse S-20; Hodag PSMP-20; Lamesorb SMP-20; Liposorb P-20; Lonzest SMP-20; Montanox 40; poly(oxy-1,2-ethanediyl) derivatives; polysorbatum 40; Protasorb P-20; Ritabate 40; sorbitan monohexadecanoate; Sorbax PMP-20; Tween 40.

Polysorbate 60

Atlas 70K; Atlas Armotan PMS 20; Capmul POE-S; Cremophor PS 60; Crillet 3; Drewpone 60K; Durfax 60; Durfax 60K; E435; Emrite 6125; Eumulgin SMS; Glycosperse S-20; Glycosperse S-20FG; Glycosperse S-20FKG; Hodag PSMS-20; Hodag SVS-18; Lamsorb SMS-20; Liposorb S-20; Liposorb S-20K; Lonzest SMS-20; Montanox 60; Nikkol TS-10; Norfox SorboT-60; Polycon T 60 K; polyoxyethylene 20 stearate; polysorbatum 60; Protasorb S-20; Ritabate 60; Sorbax PMS-20; sorbitan monooctadecanoate poly(oxy- 1,2-ethanediyl) derivatives; T-Maz 60; T-Max 60KHS; Tween 60; Tween 60K; Tween 60 VS.

Polysorbate 61

Crillet 31; Hodag PSMS-4; Liposorb S-4; Protasorb S-4; Tween 61.

Polysorbate 65

Alkamuls PSTS-20; Crillet 35; E436; Glycosperse TS-20; Glycosperse TS-20 FG; Glycosperse TS-20 KFG; Hodag PSTS-20; Lamesorb STS- 20; Lanzet STS-20; Liposorb TS-20; Liposorb TS-20A; Liposorb TS-20K; Montanox 65; Protasorb STS-20; Sorbax PTS-20; sorbitan trioctadecanoate poly(oxy-1,2-ethanediyl) derivatives; T-Maz 65K; Tween 65; Tween 65K; Tween 65V.

Polysorbate 80

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; polyoxyethylene 20 oleate; polysorbatum 80; Protasorb O-20; Ritabate 80; (Z)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Tego SMO 80; Tego SMO 80V; Tween 80.

Polysorbate 81

Crillet 41; Hetsorb O-5; Hodag PSMO-5; Protasorb O-5; Sorbax PMO-5; sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; T-Maz 81; Tego SMO 81; Tween 81.

Polysorbate 85

Alkamuls PSTO-20; Crillet 45; Glycosperse TO-20; Hodag PSTO-20; Liposorb TO-20; Lonzest STO-20; Montanox 85; Protasorb TO-20; Sorbax PTO-20; sorbitan tri-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Tego STO 85; Tween 85.

Polysorbate 120

Crillet 6

Chemical Names and CAS Registry Numbers

Polysorbate	Chemical name	CAS number
Polysorbate 20	Polyoxyethylene 20 sorbitan monolaurate	[9005-64-5]
Polysorbate 21	Polyoxyethylene (4) sorbitan monolaurate	[9005-64-5]
Polysorbate 40	Polyoxyethylene 20 sorbitan monopalmitate	[9005-66-7]
Polysorbate 60	Polyoxyethylene 20 sorbitan monostearate	[9005-67-8]
Polysorbate 61	Polyoxyethylene (4) sorbitan monostearate	[9005-67-8]
Polysorbate 65	Polyoxyethylene 20 sorbitan tristearate	[9005-71-4]
Polysorbate 80	Polyoxyethylene 20 sorbitan monooleate	[9005-65-6]
Polysorbate 81	Polyoxyethylene (5) sorbitan monooleate	[9005-65-6]
Polysorbate 85	Polyoxyethylene 20 sorbitan trioleate	[9005-70-3]
Polysorbate 120	Polyoxyethylene 20 sorbitan monoisostearate	[66794-58-9]

Empirical Formula and Molecular Weight

Approximate molecular weights for selected polysorbates are shown in Table.

Polysorbate	Molecular weight	Formula
Polysorbate 20	1128	C58H114O26
Polysorbate 21	523	C26H50O10
Polysorbate 40	1284	C62H122O26
Polysorbate 60	1312	C64H126O26
Polysorbate 61	607	C32H62O10
Polysorbate 65	1845	C100H194O28
Polysorbate 80	1310	C64H124O26
Polysorbate 81	649	C34H64O11
Polysorbate 85	1839	C100H188O28
Polysorbate 120	1312	C64H126O26

Functional Category
Dispersing agent; emulsifying agent; nonionic surfactant; solubilizing agent; suspending agent; wetting agent.

Role in Pharmaceutical Nanosuspension Formulation or Technology
Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a seriesof partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a single uniform compound. Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions.They may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for P-glycoprotein [19].

Stability and Storage Conditions

Structural Formula

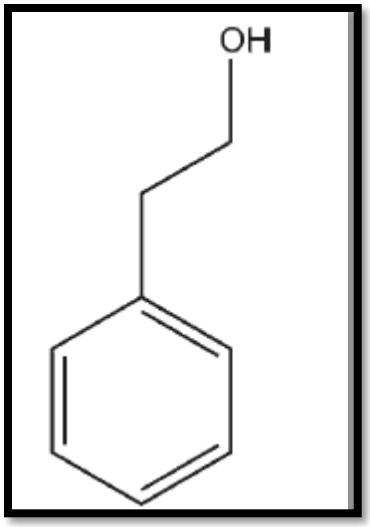
Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

3 Phenylethyl Alcohol
Nonproprietary Names
USP: Phenylethyl Alcohol

Synonyms
Benzeneethanol; benzyl carbinol; benzylmethanol; b-fenylethanol; b-fenethylalkohol; b-hydroxyethyl benzene; PEA; phenethanol; bphenylethyl alcohol; 2-phenylethyl alcohol; phenylethanol.

Chemical Name and CAS Registry Number
2-Phenylethanol [60-12-8]

Empirical Formula and Molecular Weight
C8H10O MW 122.17



Functional Category
Antimicrobial preservative.

Role in Pharmaceutical Nanosuspension Formulation or Technology
Phenylethyl alcohol is used as an antimicrobial preservative in nasal, ophthalmic, and otic formulations at 0.25–0.5% v/v concentration; it is generally used in combination with other preservatives [20]. Phenylethyl alcohol has also been used on its own as an antimicrobial preservative at concentrations up to 1% v/v in topical preparations. At this concentration, mycoplasmas are inactivated within 20 minutes, although enveloped viruses are resistant.

Stability and Storage Conditions
Phenylethyl alcohol is stable in bulk, but is volatile and sensitive to light and oxidizing agents. It is reasonably stable in both acidic and alkaline solutions. Aqueous solutions may be sterilized by autoclaving. If stored in low-density polyethylene containers, phenylethyl alcohol may be absorbed by the containers. Losses to polypropylene containers have been reported to be insignificant\ over 12 weeks at 30^0C. Sorption to rubber closures is generally small. The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

4 Hydroxypropyl methylcellulose

Nonproprietary Names
BP: Hypromellose, JP: Hypromellosem , PhEur: Hypromellose, USP: Hypromellose

Synonyms
Benecel MHPC, E464, hydroxypropyl methylcellulose, HPMC, hypromellosum; Methocel, methylcellulose propylene glycol ether; methyl hydroxypropylcellulose, Metolose, MHPC, Pharmacoat, Tylopur, Tylose MO, Hypromellose.

Chemical Name and CAS Registry Number
Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight
The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 208C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the various types of hypromellose. Molecular weight is approximately 10 000–1 500 000.

Functional Category
Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-

release agent; tablet binder; thickening agent; viscosity-increasing agent.

Role in Pharmaceutical Nanosuspension Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder [21]. in film-coating [22]. and as a matrix for use in extended release tablet formulations [23]. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0% . Depending upon the viscosity grade, concentrations of 2–20%w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include Any Coat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Structural Formula

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–90^{0}C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage [24]. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

5 Vitamin E Tocopherol Polyethylene Glycol Succinate

Nonproprietary Names

USP-NF: Vitamin E Polyethylene Glycol Succinate

Synonyms

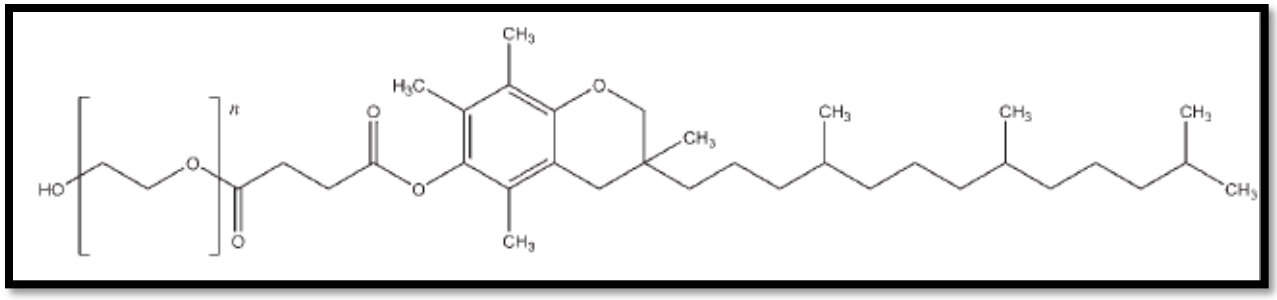
Speziol TPGS Pharma; tocofersolan; tocophersolan; tocopherol polyethylene glycol succinate; D-a-tocopheryl polyethylene glycol 1000 succinate; TPGS; vitamin E polyethylene glycol 1000 succinate; vitamin E TPGS; VEGS.

Chemical Name and CAS Registry Number

4-O-(2-Hydroxyethyl)-1-O-[2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)- 3,4-dihydrochromen-6-yl]butanedioate [9002-96-4] and [30999-06-5]

Empirical Formula and Molecular Weight

C33O5H54(CH2CH2O)20–22 =1513



Functional Category
Absorption enhancer; antioxidant; emulsifying agent; granulation aid; ointment base; solubilizing agent; surfactant; suspending agent; tablet binder.

Role in Pharmaceutical Nanosuspension Formulation or Technology
Vitamin E polyethylene glycol succinate is an esterified vitamin E (tocopherol) derivative primarily used as a solubilizer or emulsifying agent because of its surfactant properties. Structurally, it is amphipathic and hydrophilic, unlike the tocopherols, and therefore it is a water-soluble derivative that can be used in pharmaceutical formulations such as capsules, tablets, [25] hot-melt extrusion, [26] microemulsions,[27] topical products, [28] and parenterals [29]. One of the most important applications is its use as a vehicle for lipid-based drug delivery formulations. It can also be used as a source of vitamin E. Vitamin E polyethylene glycol succinate has been characterized with respect to its mechanism of action and studied as a Pglycoprotein inhibitor [30] .

Typical Properties
Acid value ≤ 41.5
Critical micelle concentration 0.02% by weight (378C)(1)
HLB value ≈13.2
Melting point 37–41^{0}C
Solubility Miscible in water in all parts. Specific gravity 1.06 (at 45^{0}C)

Stability and Storage Conditions
Vitamin E polyethylene glycol succinate is stable at ambient room temperature for up to 4 years. It reacts with alkalis and acids. Aqueous solutions of vitamin E polyethylene glycol succinate are stable over a pH range of 4.5–7.5 and can be further stabilized with propylene glycol.

6 polyvinylpyrrolidone

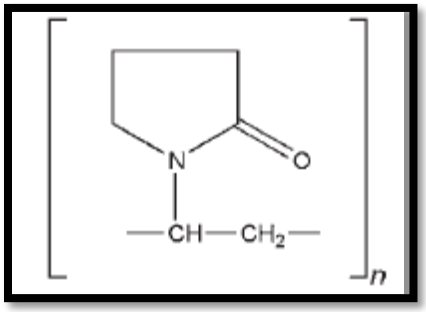
Nonproprietary Names
BP: Povidone
JP: Povidone
PhEur: Povidone
USP: Povidone

Synonyms
E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Chemical Name and CAS Registry Number
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight
(C6H9NO)n 2500–3 000 000

Structural Formula



Functional Category
Disintegrant, dissolution enhancer, suspending agent, tablet binder.

Role in Pharmaceutical Nanosuspension Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes [31]. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms . Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.
See in Table.

Table: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations.

Typical Properties

Acidity/alkalinity pH = 3.0–7.0 (5% w/v aqueous solution); pH = 4.0–7.0 (5% w/v aqueous solution) for Povipharm K90.
Density (bulk) 0.29–0.39[3] g/cm3 for Plasdone.
Density (tapped) 0.39–0.54[3] g/cm3 for Plasdone.
Density (true) 1.180 g/cm^3
Flowability 20 g/s for povidone K-15; 16 g/s for povidone K-29/32.
Melting point Softens at 150^{0}C. Moisture content Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Stability and Storage Conditions

Povidone darkens to some extent on heating at 150^{0}C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130^{0}C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

7 Albumin

Nonproprietary Names

BP: Albumin Solution, PhEur: Human Albumin Solution, USP: Albumin Human.

Synonyms

Alba; Albuconn; Albuminar; albumin human solution; albumin humani solutio; Albumisol; Albuspan; Albutein; Buminate; human serum albumin; normal human serum albumin; Octalbin; Plasbumin; plasma albumin; Pro-Bumin; Proserum; Zenalb.

Chemical Name and CAS Registry Number

Serum albumin [9048-49-1]

Empirical Formula and Molecular Weight

Human serum albumin has a molecular weight of about 66 500 and is a single polypeptide chain consisting of 585 amino acids. Characteristic features are a single tryptophan residue, a relatively low content of methionine 6 residues, and a large number of cysteine 17 and of charged amino acid residues of aspartic acid 36, glutamic acid 61, lysine 59, and arginine 23.

Structural Formula

Primary structure Human albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges.
Secondary structure Human albumin is known to have a secondary structure that is about 55% a-helix. The remaining 45% is believed to be divided among turns, disordered, and β structures. Albumin is the only major plasma protein that does not contain carbohydrate constituents. Assays of crystalline albumin show less than one sugar residue per molecule.

Functional Category
Stabilizing agent; therapeutic agent.

Role in Pharmaceutical nanosuspension Formulation or Technology
Albumin is primarily used as an excipient in parenteral pharmaceutical formulations, where it is used as a stabilizing agent for formulations containing proteins and enzymes. Albumin has also been used to prepare microspheres and microcapsules for experimental drug-delivery systems [32]. As a stabilizing agent, albumin has been employed in protein formulations at concentrations as low as 0.003%, although concentrations of 1–5% are commonly used. Albumin has also been used as a cosolvent for parenteral drugs, as a cryoprotectant during lyophilization [33], and to prevent adsorption of other proteins to surfaces. Therapeutically, albumin solutions have been used parenterally for plasma volume replacement and to treat severe acute albumin loss. However, the benefits of using albumin in such applications in critically ill patients has been questioned [34].

Typical Properties
Acidity/alkalinity **pH** = 6.7–7.3 for a 1% w/v solution, in 0.9% w/v sodium chloride solution, at 20^0C.
Osmolarity A 4–5% w/v aqueous solution is isoosmotic with serum.
Solubility Freely soluble in dilute salt solutions and water. Aqueous solutions containing 40% w/v albumin can be readily prepared at pH 7.4. The high net charge of the peptide contributes to its solubility in aqueous media. The seven disulfide bridges contribute to its chemical and spatial conformation. At physiological pH, albumin has a net electrostatic charge of about–17. Aqueous albumin solutions are slightly viscous and range in color from almost colorless to amber depending on the protein concentration.

Stability and Storage Conditions
Albumin is a protein and is therefore susceptible to chemical degradation and denaturation by exposure to extremes of pH, high salt concentrations, heat, enzymes, organic solvents, and other chemical agents. Albumin solutions should be protected from light and stored at a temperature of 2–25^0C or as indicated on the label.

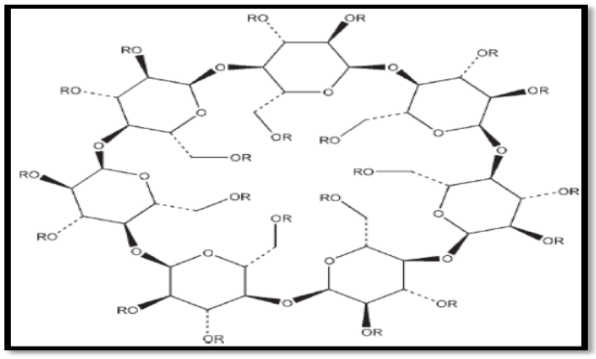
8 Cyclodextrins
Nonproprietary Names
BP: Alfadex Betadex, PhEur: Alfadex Betadex, USP-NF: Alfadex Betadex, Gamma Cyclodextrin

Synonyms
Cyclodextrin Cavitron, cyclic oligosaccharide, cycloamylose, cycloglucan; Encapsin, Schardinger dextrin.
α-Cyclodextrin alfadexum; alpha-cycloamylose, alpha-cyclodextrin, alpha-dextrin, Cavamax W6 Pharma, cyclohexaamylose, cyclomaltohexose.
β-Cyclodextrin beta-cycloamylose, beta-dextrin, betadexum, Cavamax W7 Pharma.
Cycloheptaamylose, cycloheptaglucan, cyclomaltoheptose, Kleptose.g-Cyclodextrin Cavamax W8 Pharma; cyclooctaamylose, cyclomaltooctaose.

Chemical Name and CAS Registry Number
α-Cyclodextrin [10016-20-3]
β-Cyclodextrin [7585-39-9]

Empirical Formula and Molecular Weight
α-Cyclodextrin C36H60O30 972, β-Cyclodextrin C42H70O35 1135

Structural Formula



Note: the structure of betadex (β-cyclodextrin) with 7 glucose units is shown.
R=H for 'natural' α, β, and γ-cyclodextrins with 6, 7 and 8 glucose units, respectively
R=H or CH3 for methyl cyclodextrins

R=H or CHOHCH3 for 2-hydroxyethyl cyclodextrins
R=H or CH2CHOHCH3 for 2-hydroxypropyl cyclodextrins

Functional Category
Solubilizing agent; stabilizing agent.

Role in Pharmaceutical Nanosuspension Formulation or Technology
Cyclodextrins are crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are α-, β-, and γ-cyclodextrin, which have respectively 6, 7, and 8 glucose units. Cyclodextrins are 'bucketlike' or 'conelike' toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex. Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. β-Cyclodextrin is the most commonly used cyclodextrin, although it is the least soluble. It is the least expensive cyclodextrin; is commercially available from a number of sources; and is able to form inclusion complexes with a number of molecules of pharmaceutical interest. However, β-cyclodextrin is nephrotoxic and should not be used in parenteral formulations. β-Cyclodextrin is primarily used in tablet and capsule formulations. In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a nonaqueous solvent. In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug; to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation [35]. Cyclodextrins have also been used in the formulation of solutions [36], suppositories [37], and cosmetics [38].

Typical Properties
Compressibility 21.0–44.0% for β-cyclodextrin.
Density (bulk) α-cyclodextrin: 0.526 g/cm^3, β-cyclodextrin: 0.523 g/cm^3, γ-cyclodextrin: 0.568 g/cm^3
Desnsity (tapped) α-cyclodextrin: 0.685 g/cm^3, β-cyclodextrin: 0.754 g/cm^3, γ-cyclodextrin: 0.684 g/cm^3
Density (true) α-cyclodextrin: 1.521 g/cm^3 , γ-cyclodextrin: 1.471 g/cm^3
Melting point α-cyclodextrin: 250–260^{0}C, β-cyclodextrin: 255–265^{0}C, γ-cyclodextrin: 240–245^{0}C.
Moisture content α-cyclodextrin: 10.2% w/w, β-cyclodextrin: 13.0–15.0% w/w; γ-cyclodextrin: 8–18% w/w.
Particle size distribution β-cyclodextrin: 7.0–45.0 µm
Solubility α-cyclodextrin: soluble 1 in 7 parts of water at 20^{0}C, 1 in 3 at 50^{0}C.
β-cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20^{0}C, 1 in 20 at 50^{0}C; practically insoluble in acetone, ethanol (95%), and methylene chloride.
γ-cyclodextrin: soluble 1 in 4.4 parts of water at 20^{8}C, 1 in 2 at 45^{0}C.

Stability and Storage Conditions
β-Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place [39].

9 Glyceryl Monostearate

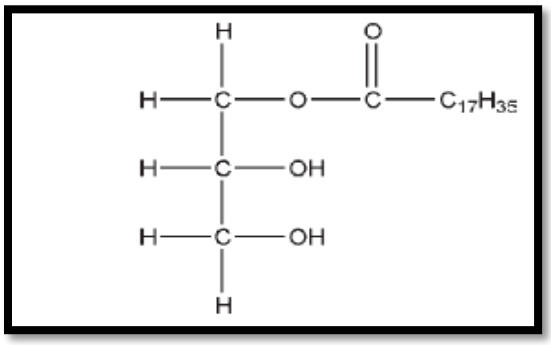
Nonproprietary Names
BP: Glyceryl Monostearate 40–55, JP: Glyceryl Monostearate, PhEur: Glycerol Monostearate 40–55, USP-NF: Glyceryl Monostearate, Note that the USP32–NF27 also includes a specification for monoand di-glycerides that corresponds to glyceryl monostearate 40–55 in the PhEur 6.0.
Synonyms
Capmul GMS-50; Cutina GMS; 2,3-dihydroxypropyl octadecanoate; Geleol; glycerine monostearate; glycerin monostearate; glycerol monostearate; glyceroli monostearas; glycerol stearate; glyceryl stearate; GMS; HallStar GMS; Imwitor 191; Imwitor 900; Kessco GMS; Lipo GMS; monoester with 1,2,3-propanetriol; monostearin; Myvaplex 600P; Myvatex; 1,2,3-propanetriol octadecanoate; Protachem GMS-450; Rita GMS; stearic acid, monoester with glycerol; stearic monoglyceride; Stepan GMS; Tegin; Tegin 503; Tegin 515; Tegin 4100; Tegin M; Unimate GMS.

Chemical Name and CAS Registry Number

Octadecanoic acid, monoester with 1,2,3-propanetriol [31566-31-1]

Empirical Formula and Molecular Weight
C21H42O4 358.6

Structural Formula



Functional Category
Emollient; emulsifying agent; solubilizing agent; stabilizing agent; sustained-release agent; tablet and capsule lubricant.

Role in Pharmaceutical Nanosuspension Formulation or Technology
The many varieties of glyceryl monostearate are used as nonionic emulsifiers, stabilizers, emollients, and plasticizers in a variety of food, pharmaceutical, and cosmetic applications. It acts as an effective stabilizer, that is, as a mutual solvent for polar and nonpolar compounds that may form water-in-oil or oil-in-water emulsions [40]. These properties also make it useful as a dispersing agent for pigments in oils or solids in fats, or as a solvent for phospholipids, such as lecithin. Glyceryl monostearate has also been used in a novel fluidized hot-melt granulation technique for the production of granules and tablets [41] . Glyceryl monostearate is a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms [42]. Sustained-release applications include the formulation of pellets for tablets [43] or suppositories, and the preparation of a veterinary bolus [44].Glyceryl monostearate has also been used as a matrix ingredient for a biodegradable, implantable, controlled release dosage form [45]. When using glyceryl monostearate in a formulation, the possibility of polymorph formation should be considered. The aform is dispersible and foamy, useful as an emulsifying agent or preservative. The denser, more stable, b-form is suitable for wax matrices. This application has been used to mask the flavor of clarithromycin in a pediatric formulation [46].

Typical Properties
A wide variety of glyceryl monostearate grades are commercially available, including self-emulsifying grades that contain small amounts of soap or other surfactants. Most grades are tailored for specific applications or made to user specifications and therefore have varied physical properties.
HLB value 3.8
Flash point ≈240^{0}C
Melting point 55–60^{0}C
Polymorphs The a-form is converted to the b-form when heated at 50^{0}C [47].
Solubility Soluble in hot ethanol, ether, chloroform, hot acetone, mineral oil, and fixed oils. Practically insoluble in water, but may be dispersed in water with the aid of a small amount of soap or other surfactant.
Specific gravity 0.92

Stability and Storage Conditions
If stored at warm temperatures, glyceryl monostearate increases in acid value upon aging owing to the saponification of the ester with trace amounts of water. Effective antioxidants may be added, such as butylated hydroxytoluene and propyl gallate. Glyceryl monostearate should be stored in a tightly closed container in a cool, dry place, and protected from light.

10 Sodium Alginate

Nonproprietary Names
BP: Sodium Alginate, PhEur: Sodium Alginate,USP-NF: Sodium Alginate

Synonyms
Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; natrii alginas; Protanal; sodium polymannuronate.

Chemical Name and CAS Registry Number
Sodium alginate [9005-38-3]

Empirical Formula and Molecular Weight
Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of Dmannuronic acid and L-guluronic acid. The block structure and molecular weight of sodium alginate samples have been investigated [48].

Functional Category
Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Role in Pharmaceutical nanosuspension Formulation or Technology
Sodium alginate is used in a variety of oral and topical pharmaceutical formulations [49]. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; [50] it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets [51], capsules, and aqueous suspensions. The effects of particle size, viscosity and chemical composition of sodium alginate on drug release from matrix tablets have been described [52]. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the moreconventional microencapsulation techniques which use organicsolvent systems. It has also been used in the formation of nanoparticles [53]. The adhesiveness of hydrogels prepared from sodium alginate has been investigated, and drug release from oral mucosal adhesive tablets, buccal gels, and vaginal tablets based on sodium alginate have been reported. The esophageal bioadhesion of sodium alginate suspensions may provide a barrier against gastric reflux or site-specific delivery of therapeutic agents [54]. Other novel delivery systems containing sodium alginate include ophthalmic solutions that form a gel in situ when administered to the eye; [55] an in situ forming gel containing paracetamol for oral administration; nasal delivery systems based on mucoadhesive microspheres; and a freeze-dried device intended for the delivery of bone-growth factors [56]. Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides. In addition, sodium alginate microspheres have been used in the preparation of a footmouth disease DNA vaccine and in an oral vaccine for Helicobacter pylori; chitosan nanoparticles coated with sodium alginate may have applications in mucosal vaccine delivery systems [57]. Therapeutically, sodium alginate has been used in combination with an H2-receptor antagonist in the management of gastroesophageal reflux, and as a hemostatic agent in surgical dressings. Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties. Sponges composed of sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressings or as tissue engineering matrices [58]. Lyophilized wound healing wafers composed of sodium alginate have been found to exhibit large reductions in viscosity following gamma irradiation [59].

Typical Properties
Acidity/alkalinity *pH* ≈ 7.2 (1% w/v aqueous solution) ***Solubility*** Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.
Viscosity (dynamic) Various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 20^0C, will have a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions.(36–38) Above pH 10, viscosity decreases.

Stability and Storage Condition
Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years. Solutions should not be stored in metal containers. Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity [60]. Solutions are ideally terilized using ethylene oxide, although filtration using a 0.45 μm filter also has only a slight adverse effect on solution viscosity [61]. Heating sodium alginate solutions to temperatures above 70^0C causes depolymerization with a subsequent loss of viscosity. Autoclaving of solutions can cause a decrease in viscosity, which may vary

depending upon the nature of any other substances present. Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity . Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used. The bulk material should be stored in an airtight container in a cool, dry place.

CONCLUSION

Numbers of drug candidates are identified but most of them are poorly soluble. In this case, nanosuspension can be considered as a optimistic dosage form. Various production techniques mentioned in this review can be successfully used to solve the poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. To build a stable formulation, surfactants plays an important role. Frequently used surfactants along with their details are reported in this article. A nanosuspension formulation not only solves the poor solubility problems, but also improves drug efficacy.

Conflict of interest

The authors confirm that this review article content no conflict of interest

Acknowledgment:

The principle author acknowledges the financial assistance provided by R.C.Patel Institute of Pharmaceutical Education and Research (RCPIPER), Shirpur Dist, Dhule.

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