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Selection of Surfactants, Co-surfactants, and Emulsifying agents in Nanosuspensions

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ABSTRACT:

Majority of the drugs and newly discovered pharmaceutical entities are hydrophobic and/or lyophobic in nature and have an inconsistent absorption rate, lowered bioavailability, and reduced stability. Nanosuspensions have emerged as a modern solution to these issues and it has facilitated the production of new therapeutic options along with other utilities as well. Nanosuspensions are biphasic colloid dispersions that have a submicron size (i.e. the particle size is usually less than one micron with an average particle size ranging between 200 and 600 nm), target the cells and tissues, and can show sustained stabilization over an extended period of time. Thus, it has evolved with time into an ideal advanced drug delivery system with an

admirable efficiency. Although there are multiple components of a nanosuspension, the ones that really stand out are surfactants, co-surfactants, and emulsifying agents, mainly due to their functional contribution to the formulation and stabilization. Surfactants are the surface-active agents that act by reducing the interfacial tension of the colloidal dispersion medium that prevents the nanosuspension from aggregating and settling down. It is amphiphilic in nature, consisting of a hydrophilic head and a hydrophobic tail. It increases the bioavailability of the drug while stabilizing the nanosuspension and improving its dispersibility, thus maintaining the particle size and colloidal structure at all time. Surfactants are ably aided by co-surfactants as well that have similar chemical properties and can bring down the interfacial tension to a more optimal level. Emulsifying agents also have a similar contribution to the stabilization and bioavailability of the nanosuspension, although its functionality is largely dependent on maintaining smaller proportion of particle size and preventing them from coalescing. Although all the three components have their fair share of advantages and challenges, the former outweighs the latter significantly. Therefore, a thorough understanding of the roles of each of them in a nanosuspension can go a long way in revolutionizing the nano-industry, especially in pharmacotherapeutics.

INTRODUCTION

For the successful formulation of drugs, a range of parameters play a critical role like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability. Through drug discovery programs more than 40% of the new chemical entities have been generated which are lipophilic or poorly water soluble compounds.[1,2] Nanoparticle engineering has been developed over the last decade and its application have been reported in the field of pharmaceuticals.[3] The application of nanotechnology can be used to solve the earlier mentioned problems. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9}m in which with the use of various techniques like Bottom-Up Technology and Top-Down Technology, the drug microparticles/ micronized drug powder is transferred to drug nanoparticles.[4] Nanosuspensions are submicron (below one micron, with an average particle size falling within the range of 200 to 600 nm[4,5]) colloidal dispersions of nanosized drug particles which are stabilized by surfactants[6] that solve the problems related to delivery of the low soluble active ingredients in water or instability due to environmental factors.[5] For e.g., Gera and co-workers used antisolvent sonoprecipitation method to formulate naringenin nanosuspension that was stabilized by polyvinylpyrrolidone K-90. During the process of nanosizing, crystalline naringenin was transformed into its amorphous form and contributed for enhanced dissolution 91 ± 4.4% as compared to plain naringenin (42 ± 0.41%) within one hour. Similarly, pharmacokinetic parameters i.e., maximum plasma concentration (C_{max}) and area under the curve ($AUC_{0\text{-}24h}$) values were improved by 2- and 1.8-folds respectively than pure naringenin.

ADVANTAGES AND DISADVANTAGES OF NANOSUSPENSIONS[7,8,9,10,11]

Advantages of nanosuspensions:

- The solubility and bioavailability of drugs will be enhanced.
- It is suitable for hydrophilic drugs.
- Higher drug loading is possible.
- Reduction in dose can be achieved.
- The physical and chemical stability of drugs is enhanced.
- Passive drug targeting is provided.
- Reduction in variation in fed/fasted conditions.
- The absorption from the absorption window is increased due to particle size reduction.

Disadvantages of nanosuspensions:

- Physical instability problems can occur for e.g., sedimentation and compaction.
- Transportation is difficult due to bulkiness.
- Difficulty in maintenance of dose uniformity.

PREPARATION OF NANOSUSPENSIONS:

Two methods namely "Bottom-up technology" and "Top-down technology" are mostly used for the preparation of nanosuspensions. In bottom-up technology, an assembling method is used to form nanoparticles like precipitation, supercritical fluid method, and in top-down technology, the disintegration of larger particles into nanoparticles occurs, for e.g., high-pressure homogenization and milling methods. There is third and final category which is the combination of both bottom-up and top-down technologies, which combines the advantages of both the methods to assist in nanosuspensions formulation.[12] Different methods for the formulation of nanosuspensions are indicated in

Figure *1*.[13] The principles of these methods are described in detail and their merits and demerits are shown in Table *1*.[14,15]

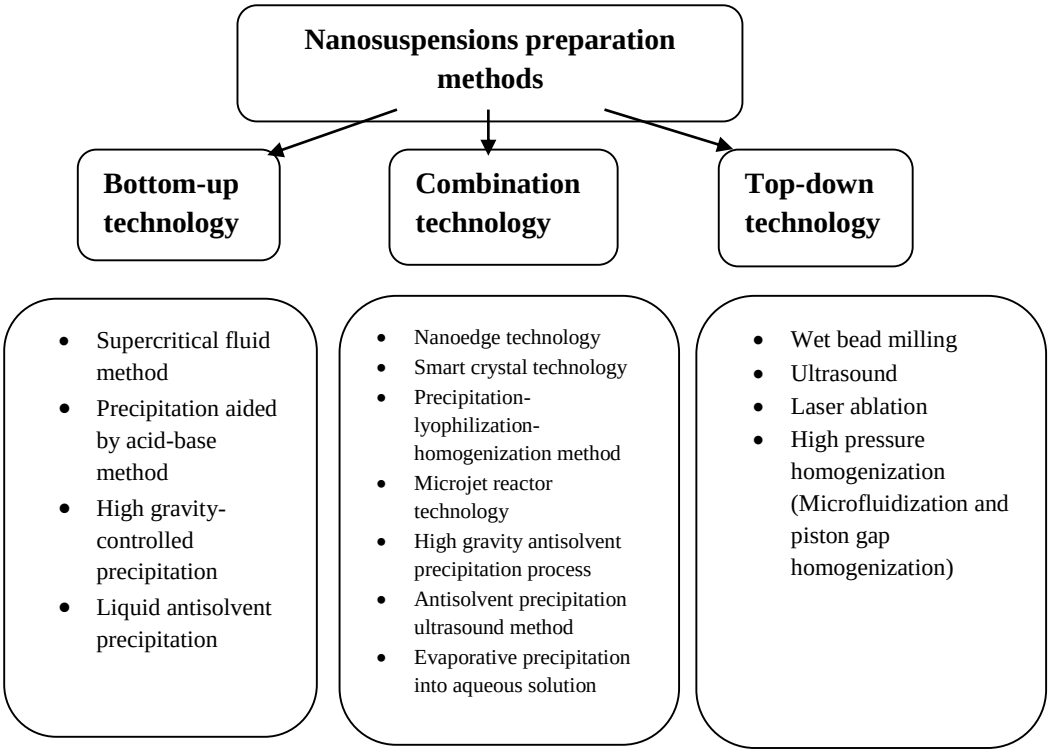

Figure 1 - Different Approaches for Preparation of Nanosuspensions

Table 1 - Preparative Techniques for Nanosuspensions with Merits and Demerits

Technique	Merits	Demerits
Precipitation	• Simple process. • Stable products. • Low requirement of energy. • Low equipment cost. • 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.
High-pressure homogenization	• Simple technique. • General applicability to most drugs. • Useful for formation of very dilute as well as highly concentrate nanosuspensions. • Aseptic production possible. • Low risk of product. • Contamination ease of scale-up.	• High number of homogenization cycles. • Pretreatment of micronized drug particles and pre-suspending materials before subjecting it to homogenization. Possible contamination of product could occur from metal ions coming through wall of the homogenizer.
Media milling	• High flexibility in handling. • Very few batch to batch variation in particle size. • High flexibility in handling large quantities of drugs. • Ease of scale up.	• Possible erosion of material from the milling pearls. • Require milling process for hours to days. • Prolonged milling may induce the formation of amorphous lead to instability.
Dry co-grinding	• Easy process. • Require short grinding time. • No organic solvent.	• Generation of residue of milling media.
Liquid emulsion/microemulsion template	• 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.
Melt emulsification	• Avoidance of organic solvents compared to the solvent diffusion.	• Formation of large particles. • Solvent diffusion.

There are multiple additives as shown in **Error! Reference source not found.**, which are a part of the nanosuspension formulation that have certain mechanism of action to enhance its effectiveness, with surfactants, co-surfactants, and emulsifying agents being the most important ones. Surfactant enhances dispersion by decreasing the interfacial tension; they can also function as wetting and deflocculating agents. Between two phases, they play a critical role in diminishing the interfacial tension and facilitating optimal dispersion. They can serve as suspending agents as well as wetting agents. Most commonly used stabilizing agents in the formulation of nanosuspensions are tweens and spans.[16]

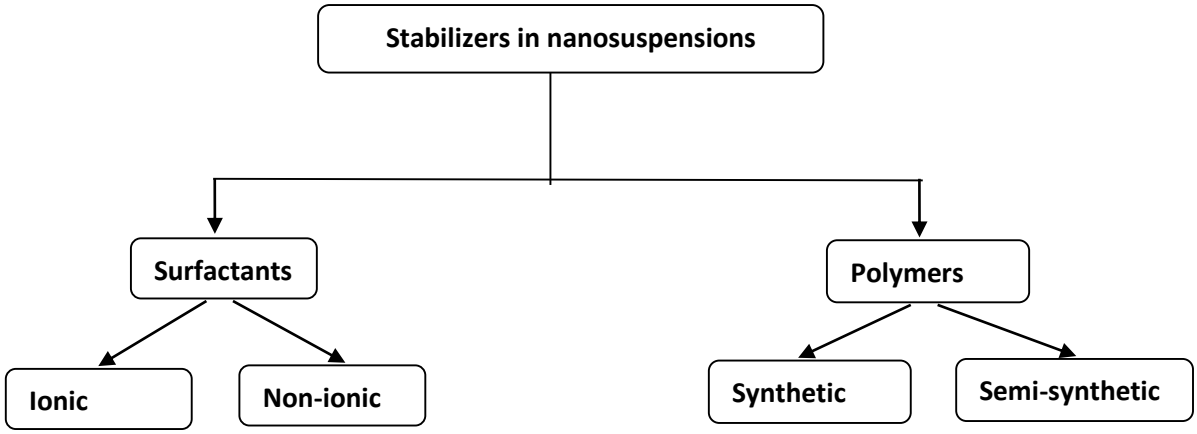

Figure 2 - Classification of stabilizers[5]

In addition to surfactants, co-surfactants are also added in the nanosuspensions to enhance the properties of surfactant. Co-surfactants act as additional surface-active agents and work together with surfactants to enhance their properties, such as solubilization, emulsification, dispersion, wetting, and foaming.[17] In the formulation of nanosuspensions employing microemulsions, the selection of a co-surfactant plays a crucial role. Co-surfactants significantly influence the phase behavior by its presence. Most commonly used co-surfactants for incorporation into the formulation and ensuring their safe use are bile salts, dipotassium glycyrrhizinate, and different solubilizers, including transcutol, glycofurol, ethanol, and isopropanol.[18]

Emulsifying agents mainly focus on breaking down the particles of larger sizes into smaller proportions, so that there is a uniform distribution of the active compounds.[19] They are majorly classified on the basis of their sizes into conventional emulsions (also known as coarse emulsions), microemulsions, and nanoemulsions.[20] The ones that are routinely used in nanosuspensions are the nanoemulsions whose sizes range from <200 to <100 nm. They are thermodynamically stable due to their kinetic stability conferred by reduced attractive forces and zero gravitational separation. They are not affected by parameters such as temperature and pH and have an influencing effect on the rheological behavior of the nanosuspensions as a whole.[21] Another advantage of nanoemulsifying agents is that they balance out the functions of the surfactants, resulting in its fewer requirements in the preparation of nanosuspensions. All three components have been discussed in more details in this review.

Based on the brief overview of nanosuspensions and the three main components that integrate to form the nanosuspensions drug delivery system, the objective of this review is to delve into further depth about the

roles of surfactants, co-surfactants, and emulsifying agents in the formation of nanosuspensions and the contribution to the process.

SURFACTANTS

Surfactants, also known as surface-active agents, are the compounds that are amphiphilic in nature and are used to stabilize and increase the dispersion ability of nanosuspensions. Surfactants consist of a head which is hydrophilic in nature which is complemented by a hydrophobic tail (see Figure 3).[22]

Surfactants are classified as ionic and non-ionic surfactants (as presented in the

Figure *4* and Table 2)[24]. Ionic surfactants are sub classified into anionic, cationic and amphoteric surfactants. In anionic surfactants, the hydrophilic group dissociates into anions in aqueous solutions, in cationic surfactants that dissociate into cations, and in amphoteric surfactants that dissociate into anions and cations often depending on their pH. The surfactants that do not dissociate into ions in aqueous solutions are non-ionic surfactants. Surfactants are also classified according to their solubility as hydrophilic and hydrophobic/ lipophilic (as presented in the

Figure 4). Ionic surfactants are generally hydrophilic surfactants, but nonionic surfactants can be either hydrophilic or lipophilic, depending on the balance of the hydrophilic group and lipophilic group. That means the solubility of nonionic surfactants depends on the balance between the two groups i.e. hydrophilic group and lipophilic group and their capacity to attract either water or oil.[23,24,25]

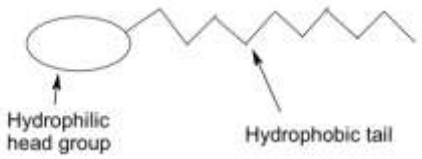

Figure 3 - Schematic Presentation of Surfactant[26]

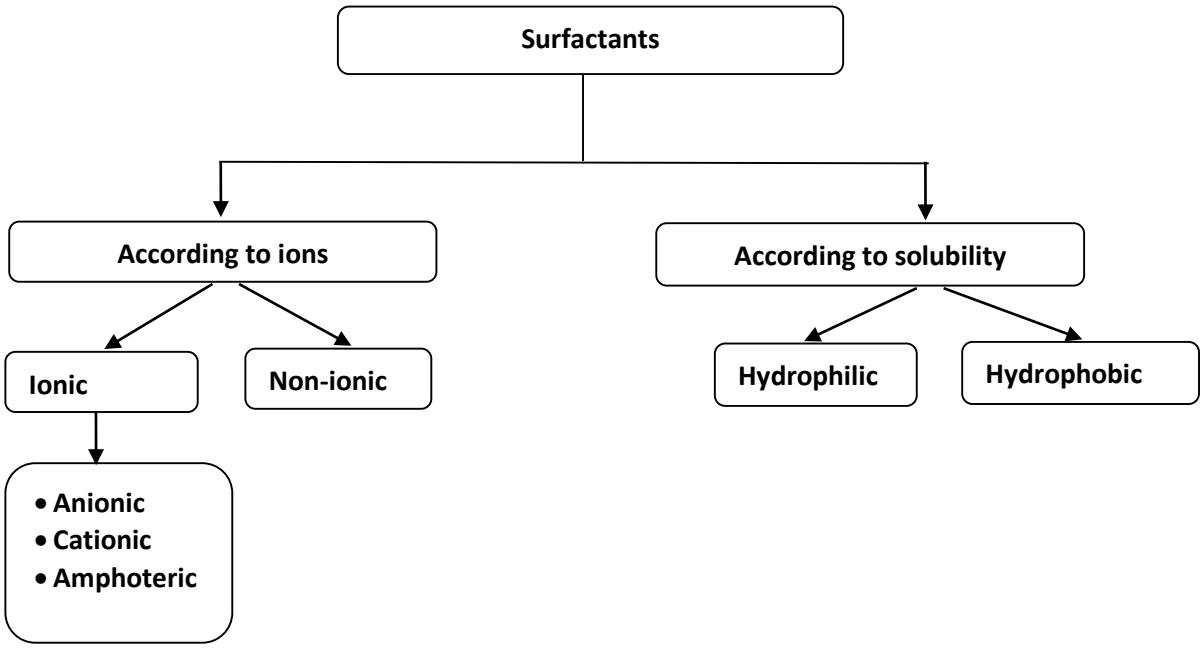

Figure 4 - Classification of Surfactants [23]

Table 2 - Special features and key challenges of the widely used Surfactants

Surfactant	Special feature	Key challenges
Anionic		
Sodium dodecyl sulfate[27]	• Is an anionic detergent that unfolds and denatures proteins, coating proteins in negative charge. It is added in excess to the proteins, so that the proteins intrinsic charge is covered, and a similar charge-to-mass ratio is obtained for all proteins. In this way, the migration rate of proteins will be dependent on their size, but not their intrinsic charge.	• Causes skin and eye irritation. • Lead cause of apthous ulcer when oral mucosa is exposed.
Sodium docusate[28]	• It is an anionic detergent. • Very efficient wetting, emulsifier, dispersing and solubilizing agent.	• Moderate to severe skin and eye irritant.
Sodium cholate[29]	• Promotes the leakage of nanoparticles into tissues through the vascular wall gap.	• Causes denaturation of proteins and low critical micelle concentration (CMC) value, which cannot be separated easily by dialysis.
Cationic		
DehyquartR A-CA[30]	• Increase the adhesion of positively nanocrystals to the negatively charged GIT wall, thus further enhancing the oral bioavailability.	• Moderate to severe skin and eye irritant. • Toxic to aquatic life.
Amphoteric		
Alkyl amido propyl amine N-oxide[31]	• Suitable for use in topical route	• Chronic ingestion in animal studies have found lower body weight, diarrhea, and lenticular opacities
Alkyl dimethylamine N-oxide[32]	• They are readily metabolized and excreted if ingested.	• Eye irritation due to amine oxides.
Alkyl betaine[33]	• Used in cosmetics, and is a common food component.	• Acute toxicity may be seen depending on the route of administration
Nonionic		
Tween 80	• Low cost, low polarity, low toxicity and high solubilization capacity.	• Slightly irritant to skin. Slightly harmful by inhalation.

Surfactant	Special feature	Key challenges
		• Slightly irritant to eyes.
TPGS	• Improve bioavailability of orally administered drugs. • Increase drug solubility due to a nonionic surfactant. On the other aspect, TPGS can enhance drug permeation due to the P-gp inhibition effect.	• Mild to moderate toxic to aquatic life.
Poloxamer 188	• Exerts a protective action against oxidative stress and inflammation in tissue injury in various experimental models.	• No details are available.

When surfactants are used in optimum concentrations, it helps in the lowering of the surface free energy by reducing the solid-liquid interfacial tension. The facilitation of the electrostatic as well as steric repulsion of the nanosuspensions is achieved by the polymers and ionic type of surfactants together. The neutral polymers can cause an inhibition of the growth of the appropriate crystals and also result in gradual increase in the particle size, which is not a desirable property. Addition of surfactants that are ionic in nature to a non-ionic polymer takes care of the problem and allows more coverage of the surface than the surfactant alone.[34] When nanosuspensions are allowed to get exposed to a biological environment, it can undergo changes like precipitation, aggregation, and coagulation.[35] To make the molecule chemically stable, surfactants play a critical role by coating the lyophobic crystals with a hydrophobic portion. They also show a Brownian type of motion (the erratic random movement of microscopic particles in a fluid, as a result of continuous bombardment from molecules of the surrounding medium) that results in the improvement of physical stability along with the chemical stability.[36,5]

Key roles of surfactants

Determination of particle size

The particle size and distribution are largely dependent on the nucleation rate. It is based on the Arrhenius equation which delves into the effects of variables on the rate of nucleation.[37] It is important to note here that rate constant for nucleation is dependent on the surfactant concentration in an inverse manner. Therefore, increasing the concentration of the surfactant can decrease the overall surface tension.[38] This has a direct effect on the inhibition of the nucleation rate, which subsequently increases the time of crystallization.

Melting point depression

The melting point depression is dependent on the mixture and concentration of the drug crystals and the surfactants, although they do not always have a linear relationship. The surfactant concentration at the interface should be in harmony to its concentration in bulk. Thus, a negative Gibbs free energy is indicative of favorable absorption of the surfactant from the bulk to the interface. It is also important to note that the surfactant absorption is dependent on a number of other factors like ionic strength, solvent nature, temperature, pH, and the lateral interactions of the adsorbed molecules.[39]

Enhancing water-surfactant interaction

As mentioned before, a surfactant typically consists of a hydrophilic and hydrophobic component. As the name suggests, the hydrophilic part remains in contact with water while the orientation of the hydrophobic end is towards the surface of the particle. Thus, there is a lesser probability of damaging interaction between the aqueous part and the hydrocarbon. Thus, the water-surface interaction is much weaker at the surface than in the bulk area.[40]

Ostwald ripening

Since the surfactant influences the coefficient of diffusion as well as the solubility and surface tension of the nanosuspensions, they have an enormous effect on the Ostwald ripening process. In fact, Ostwald ripening is based on two parameters; the diffusion ability of the solute molecule and the crystal growth rate which is further determined by the attachment and detachment process. When a surfactant with high capacity of solubilizing is selected, it causes a rapid rise in the concentration of the particle in bulk which has a positive effect on the entire process.[5]

Crystallization rate

Surfactants play an influential role in the rate of crystallization of the nanosuspensions. The type of surfactant and the concentration at which it is dispensed are also important factors in this particular aspect.[41]

Intramolecular forces

The intramolecular forces are mainly under the control of two mechanisms, namely steric hindrance and electrostatic stabilization. Surfactants play a crucial role in the latter as the electrostatic stabilization is dependent on the interaction between the surface of the particle and the surfactant.[42] There is also a reduction in the electrostatic force due to the change in the dielectric medium constant. It plays an important role in diminishing the repulsive forces between the nanoparticles as well.[43]

Advantages of Surfactants

Surfactants play a plethora of roles in the formation and stabilization of nanosuspensions. It is important to list down the advantages of adding surfactants to nanosuspensions and they have been described in the Table 3.

Table 3 - Advantages of adding surfactants to nanosuspensions

Advantage	Description
Improvement in dispersibility	Surfactants prevent the nanoparticles from settling down over time. Shaking or any other form of agitation results in the nanoparticles being uniformly distributed again and again.
Improvement in the solubility	Surfactants make the water soluble drugs have more solubility by the formation of micelles which has the ability to encapsulate the hydrophobic molecule. Thus, the drug delivery becomes relatively easier.
Improved stability	Surfactants get adsorbed on the surface of the nanosuspensions, forming a protective layer and adding to the prevention of aggregation. It also contributes to the uniformity of distribution.

Advantage	Description
Increase in bioavailability of the drug	The poorly soluble drugs are absorbed and distributed in the body better, thus improving the bioavailability and leading to a favorable therapeutic outcome.
Size of the particles remain consistently small	During the preparation process of the nanosuspensions, surfactants act as a stabilizer while milling or homogenization, which helps to reduce and maintain the small size of the nanoparticles.
Control the release of the active ingredients	The release kinetics of the active ingredients in a nanosuspension can be instrumental in regulating the therapeutic ability and side effects. Surfactant has the ability to influence this release which adds to the advantages of it.
Increased compatibility with the biological systems	Since the nanosuspensions express its therapeutic effects on the biological systems, surfactants ensure that there is an increased compatibility to it, which enhances the bioavailability as well.
Easy to formulate	A preparation of a good suspension can be quite challenging, especially when the components are not well balanced and electrostatically compromised. Surfactants take care of both the aspects by prevention of aggregation and helping in the dispersion of the particles. Thus, this facilitates the large scale production of nanosuspensions as well.
Tuning of the surface properties	It is important to tune the surface properties of nanosuspensions so that the performances are tailored for specific applications. Surfactants help in the process of tuning as well, which plays a major role in influencing the interactions with different biological system.

Challenges associated with surfactants

Although surfactants have substantial advantages, there are some challenges that also need to be looked at. First and foremost is some surfactants may show a certain amount of cytotoxicity (for e.g., benzalkonium chloride >benzethonium chloride >sodium linear-dodecylbenzene – sulfonate (LAS) >potassium laurate >sodium dodecylsulfate >polyoxyethylene(20)sorbitan monolaurate >polyoxyethylene(20)sorbitan monooleate >betaine; these are presented according to toxicity ranking from the highest to lowest) and impaired bioavailability. Based on the ion of the hydrophilic group, the toxicity ranking of the surfactants is classified into four groups, which are cationic surfactants >anionic surfactants >non-ionic surfactants >amphipathic surfactants.[44] Secondly, the controlled and desired release of the active ingredient might be impaired by nanosuspensions. Thirdly, when the nanosuspension scales up from a laboratory to an industrial grade largescale production, the mixing, homogeneity, and stability can get affected. The cost of surfactants also adds substantially to the production of nanosuspensions. Lastly, surfactants face issues in complying with the regulatory guidelines as they can potentially negative impact on the environment as well as shown in Figure 5.[45]

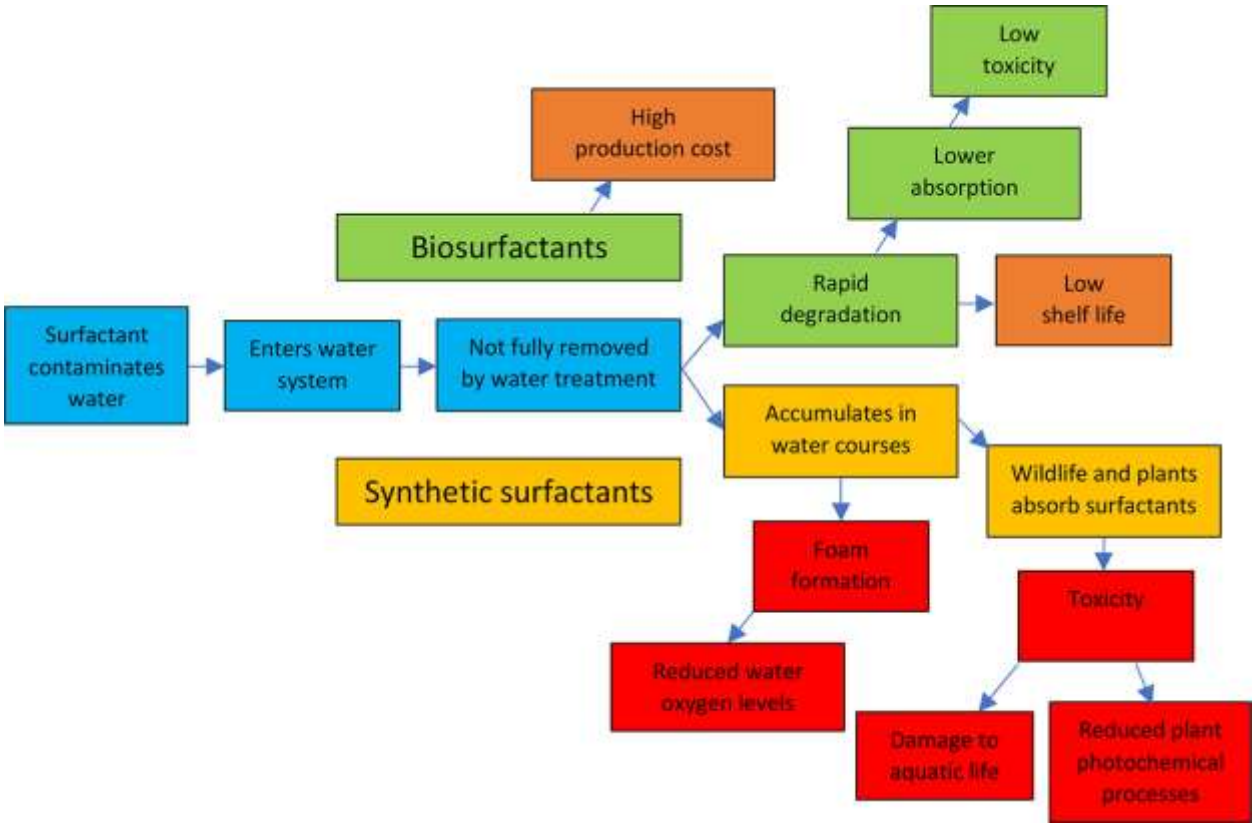

Figure 5- Graphic representation of negative impact of surfactants on the environment[37]

Co-surfactants

Co-surfactants are the agents used along with surfactants to increase the solubility of drugs by reducing the interfacial tension to a limit below that of the surfactants. There may be chances of increase in the particles size or aggregation of the particles due to limited mobility of surfactants to cover the surface of nanoparticles, during the recrystallization of solid lipids. Co-surfactants which are ionic or non-ionic in nature help in the stabilization of a system. They form dynamic micelles and hence reduce the interfacial tension.[46] Commonly used co-surfactants in the formulation of nanosuspensions are listed in **Error! Reference source not found.**.

Table 4 - Special features and key challenges of the widely used Co-surfactants

Co-surfactant	Special features	Key challenges
Benzalkonium chloride[47,48,49,50]	• It is a preservative which possesses properties of cationic surfactant. • It is very soluble in water, ethanol, and acetone. • Aqueous solutions of benzalkonium chloride foam when shaken have a low surface tension, detergent, and emulsifying properties.	• Regulatory: Changes in EU 2016/1950 and EU 528/2012 regulations, mean that benzalkonium chlorides are no longer approved for use in several biocidal products, such as consumer hand and body wash antiseptics.

Co-surfactant	Special features	Key challenges
		• Toxicity: Benzalkonium chlorides are known skin irritants, with occasional, rarer reports as allergens (skin sensitizers). Regarding acute toxicology data, benzalkonium chlorides are classified by the EPA as toxicity category II by the oral and inhalation routes and toxicity category III via the dermal route
Butanol [47,48,49]	• It is a preservative which possesses properties of cationic surfactant. • Has an acceptable pH. • Leads to small droplet size when added in microemulsion. • Stable during extended storage.	• It is harmful if swallowed. • Moderately irritates eye and skin. • Vapors may irritate the nose, throat and respiratory tract.
Glycerol[47,48,49]	• Possesses the properties of nonionic surfactant. • Low molecular weight. • Useful stabilizer for both oil-in-water and water-in-oil emulsions.	• Prolonged exposure to skin causes irritation. • Inhalation causes pulmonary edema. • It causes ocular irritation.
Sorbitol[47,48,49]	• Possesses the properties of nonionic surfactant. • Protect the integrity of nanoparticles. • Improves the reconstitution performance for ease of administration through various routes. • Acts as cryoprotectant.	• Prolonged exposure to skin causes irritation. • Inhalation causes respiratory tract irritation. • Ingestion causes digestive tract irritation.
Glycerol tristearate[47,48,49]	• Possesses the properties of nonionic surfactant. • Acts as lubricant and has excellent anti-friction properties. • Acts as crystallization accelerator.	• Prolonged exposure to skin causes irritation. • Inhalation causes pulmonary oedema. • It causes ocular irritation.
1-butanol[47,48,49]	• Act as a surfactant due to its amphiphilic nature, which allows it to lower surface tension and prevent coalescence. • It is a stronger surfactant because of larger alkyl group. • Soluble in water and most organic solvent.	• Inhalation or contact with material may irritate or burn skin and eyes. • In contact with fire, it leads to the production of irritating, corrosive and toxic gases. • Exhibits mild ecotoxicity.
Low molecular weight PEG[51,52]	• Possesses the properties of nonionic surfactant.	• Moderate to severe skin and eye irritant.

Co-surfactant	Special features	Key challenges
	• Exhibits low level of toxicity. • Provides affordable, stable, and biocompatible nanoparticles.	• Non-biodegradable. • Causes cytotoxicity.
Diethylene glycol monoethyl ether[53]	• It is an excellent solvent, carrier, viscosity modifier, humectant and penetration enhancer. • Due to its potent solubilizing property, improves the penetration levels and boosts the efficiency of active ingredients. • Possesses outstanding safety and versatility in both water and oil-based preparations • Increases the solubility of drugs in the skin	• Moderate to severe skin and eye irritant. • Causes, neurotoxicity, nephrotoxicity, occupational hepatotoxicity and reproductive toxicity includes developmental effects.
Propylene glycol[54]	• It is a clear-white liquid, readily soluble in water. • When used in small amounts, keeps products from melting in high heat or freezing when it is cold. • Helps active ingredients to penetrate the skin. • Improves the texture and stability of formulations.	• Moderate to severe skin and eye irritant. • Inhalation causes respiratory tract irritation. • It is neurotoxic. • Causes acute kidney injury.
Ethanol[55,47]	• It has a favorable interaction and compatibility with CO_2. • It enhances surfactant CO_2-soluble, foam stability and regeneration capacity.	• Inhalation or contact with material may irritate or burn skin and eyes. • Fire may produce irritating, corrosive and/or toxic gases. • Vapors may cause dizziness or asphyxiatio2n, especially when in closed or confined areas. • Runoff from fire control or dilution water may cause environmental contamination
Sorbitan monostearate[55,47]	• It is dispersible in oils when heated and cooled, and forms a gel in mineral oil at a 10% level. • It is used as an excellent water-in-oil emulsifier with hydrophillic-lypophillic balance (HLB) value of 4.7.	• Mild to moderate skin irritant.

In the formulation of nanosuspensions employing microemulsions, the selection of a co-surfactant plays a crucial role. The presence of a co-surfactant can significantly influence the phase behavior. For e.g., Bile salts,

dipotassium glycyrrhizinate, and different solubilizers, including transcutol, glycofurol, ethanol, and isopropanol, have been identified as suitable co-surfactants for incorporation into the formulation, ensuring their safe use.[18]

Key roles of co-surfactants

Generally, co-surfactants are short-chain amines or alcohols. Co-surfactants not only lower the interfacial tension but also help in changing the curvature of the reverse micelles. A schematic diagram illustrating the effect of chain length of the co-surfactant on the curvature is shown in Figure 6. A study was carried out on copper oxalate.[56] The co-surfactant chain length was varied from C-4 to C-10, i.e., 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, and 1-decanol. It has been observed in this study that there is an increase in the size of nanorods and the aspect ratio till C-6, beyond C-6, the aspect ratio decreases.[57] Also, the surfactant film rigidity decreases up to C-6, i.e., the curvature increases with the chain length and hence the aspect ratio of the nanorods increases. Beyond C-6, the co-surfactant alkyl chain interacts with the surfactant alkyl chain molecules resulting in a decrease in the inter droplet exchange rate. Therefore, leads to decrease in the aspect ratio.[58]

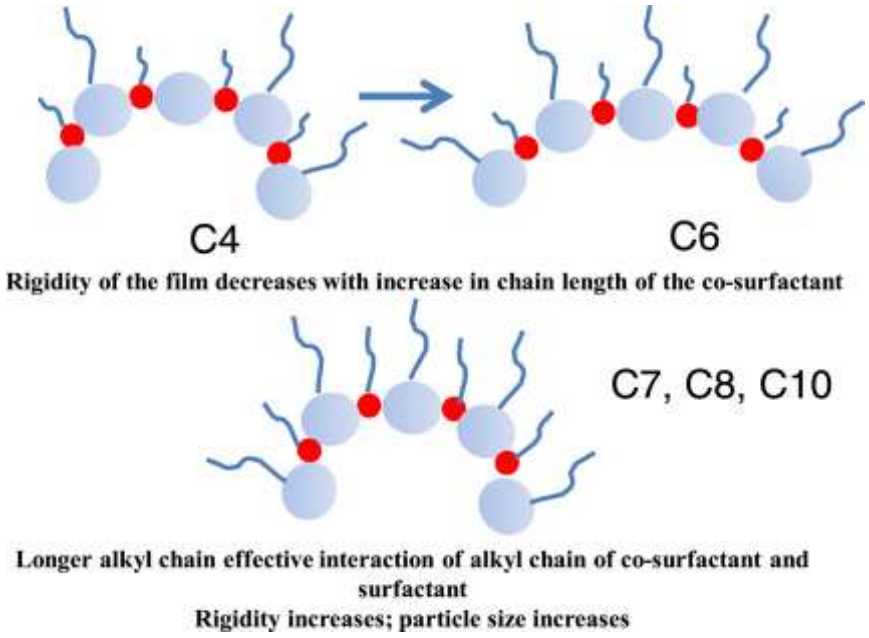

Figure 6 - Schematic diagram showing the effect of chain length of co-surfactant on the reverse micelles in microemulsion

Organoleptic Physical Properties

Organoleptic properties consist of the color, odor and form of the dosage. Co-surfactants and surfactants being the active ingredient influence the shape and aroma of nanoemulsions.[59,60,61]

Physical Properties of Viscosity

The release of active substances from nanoemulsions is influenced by its viscosity. Higher the viscosity, the longer the release of the active substance will be from the preparation. Factors influencing the viscosity are the concentration, the type of material used, and different types of co-surfactants used. The viscosity of the nanoemulsions will increase with the increase in concentration and viscosity of the material.[62,61]

Physical Properties of Particle Size

Smaller the particle size, more kinetically stable is the nanosuspension. Although co-surfactants do not decrease the particle size but they occupy the gaps between the particles so that the emulsification process can be maximized.[61]

Physical Properties of Polydispersity Index

Polydispersity Index (PDI) is a value that shows the distribution of particle sizes. If the PDI value is >1, the preparation is categorized as heterogeneous. Heterogeneous preparations have many particles that aggregate so that the preparation is unstable. A PDI value that is closer to zero means the stability and distribution are better. Therefore, type of co-surfactant directly influences the PDI.[63,61]

pH Properties

pH of nanoemulsions increases or decreases based on the type of co-surfactant added.[64,61]

Advantages of co-surfactants

- A surfactant and co-surfactant combination helps in ultralow reduction in the interfacial tension which helps to maintain the size of the droplet at a nanometer.65 The interaction happens at the interface so that there is a better fluidity in the interface and it helps in the maintenance of the curvature of the nanosuspensions.
- It also balances out the hydro/lipophilicity with the immiscible phases and improves the miscibility in general.[66]
- Increases the fluidity of intersurface between dispersed droplets and outer phase.[67]
- It prevents the formation of liquid crystals, which further prevents process of microemulsification.[67]
- Influence the distribution of molecules of surfactants on intersurface, and contributes to its widening.[67]

For e.g., high concentration of surfactant is required for the fabrication of an optimum self-emulsifying drug delivery system (SEDDS) in order to reduce interfacial tension, but such high concentration of surfactant can be harmful, so to reduce the concentration of surfactants, co-surfactants are used. Organic solvents can be used as co-surfactant for SEDDS as they are able to dissolve a large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery e.g., ethanol, propylene glycol, and polyethylene glycol.[68]

Challenges associated with co-surfactants[69]

- Using very high concentrations of co-surfactants causes microemulsion instability and should be avoided.
- Can potentially cause negative impact on the environment.
- Can lead to increase in the particle size or aggregation of the particles due to limited mobility, during the recrystallization of solid lipids.

EMULSIFYING AGENTS

Emulsions are the mixture of two biphasic liquid forms in which the droplets are distributed throughout and they tend to separate from each other. An emulsifying agent mainly works by providing stability to the system by forming either molecular or particulate films surrounding the globules that have a tendency to disperse, especially when left standing for a long period of time.[70] Emulsifying agents can be classified based on the source from which it is derived as shown in Table 5. Roles of emulsifying agents are described in

Table *6*.[71]

Table 5 - Special features and key challenges of the widely used Emulsifying Agents

Emulsifying agent	Special features	Key challenges
Natural agents		
Agar	• Easy availability, inexpensiveness, cold-setting ability, nontoxicity, biodegradability	• High chances of contamination during isolation.
Acacia	• Shows antioxidant, anti-inflammatory, antibacterial (i.e., in periodontal disease), and lipidemic effects	• Irritation of nasal mucous, sinus, throat, respiratory tract and bronchus.
Semi-synthetic agents		
Methylcellulose	• Easy availability, inexpensiveness, sustainable, environmentally friendly and biocompatible.	• Causes eye irritation, skin sensitization, and chemical pneumonitis
Sodium carboxymethyl cellulose	• Good adhesive and emulsifying property.	• Chances of allergic reaction cannot be ruled out.
Synthetic agents		
Anionic: Sodium lauryl sulfate	• Used as surface-active, emulsifying, foaming, wetting, and dispersing agent.	• Cause skin, eye, and respiratory tract irritation. • Ingestion leads to GI tract irritation.
Cationic: Benzalkonium chloride	• It is used as an antimicrobial preservative, antiseptic, disinfectant, solubilizing agent, and wetting agent.	• Inhalation of vapor may cause irritation of upper respiratory tract. • Inhalation of high concentrations may cause CNS effects • Ingestion leads to GI tract irritation. • Causes skin and eye irritation.

Inorganic: Milk of magnesia	• It is alkaline in nature and forms a creamy white suspension with water.	• Side effects of nausea, vomiting and diarrhea if used in excess.

Table 6 - Roles of emulsifying agents in Nanosuspensions[72]

Role	Description
Reduction in surface tension	An emulsifying agent is capable of assisting in the reduction of surface tension and can bring it below 10 dynes per cm
Prevention of coalescence	It is absorbed around the globule rapidly in its dispersed phase in order to form a coherent film which prevents the nanosuspensions from coalescence.
Provision of stability	Emulsifying agents can build up the zeta potential and bring optimum stability to the system by managing its viscosity.
Function at a low concentration	Since an emulsifying agent can be effective at a low concentration, less quantity and concentration need to be dispensed

Advantages of emulsifying agents

Emulsifying agents are crucial in stabilizing the nanosuspensions. The advantages of emulsifying agents in nanosuspensions are described in detail in Table 7.

Table 7 - Advantages of Emulsifying Agents

Advantage	Description
Stability	Emulsifying agents help stabilize the nanosuspensions by reducing the surface tension and preventing particle aggregation.
Improved Solubility	They enhance the solubility of poorly water-soluble drugs, which can improve bioavailability.
Enhanced Bioavailability	By increasing the dissolution rate and surface area of the drug, emulsifying agents can improve its absorption and bioavailability.
Controlled Release	They can help in controlling the release rate of the drug from the nanosuspensions.
Versatility	A wide variety of emulsifying agents are available, allowing for flexibility in formulation design based on the specific drug and desired release profile.
Enhanced Stability	Emulsifying agents can improve the physical stability of the nanosuspensions by preventing particle growth and sedimentation.
Protection from Degradation	They can protect the drug from degradation by shielding it from environmental factors like light and oxygen.

For e.g., in a study by Khan et al naringenin SNEDDS (Self-nanoemulsifying drug delivery systems SNEDDS, are isotropic, thermodynamically stable mixtures of oil, surfactant, co-surfactant, and drug which form oil-in-

water nanoemulsion when it comes in contact with aqueous phase) were prepared by water titration method using triacetin, tween 80 or cremophor EL and transcutol HP based on the emulsification efficiency and solubilization capacity. In vitro drug release from SNEDDS was found to be higher ($p < 0.005$) than that of pure naringenin. Also, absorption of the drug increased. This improvement in drug release and bioavailability of naringenin was due to the nano-sized droplets and improved solubility of naringenin in the SNEDDS formulation.

Challenges associated with emulsifying agents

Although emulsifying agents serve number of purposes, there are challenges that also need to be considered while selecting the appropriate one for a nanosuspension. Following challenges are listed in Table 8.[73,74]

Table 8 - Challenges associated with Emulsifying Agents

Challenge	Description
Toxicity	Some emulsifying agents can be toxic or cause irritation, which may limit their use, especially for parenteral or ophthalmic formulations.
Compatibility Issues	Not all emulsifying agents are compatible with all drugs, and finding the right combination can be challenging.
Complex Formulation Process	The formulation process can be complex and may require extensive optimization to achieve the desired properties.
Stability Concerns	Over time, emulsifying agents can degrade or interact with other formulation components, leading to instability.
Potential for Allergic Reactions	Some emulsifying agents can cause allergic reactions in sensitive individuals.
Cost	High-quality or specialized emulsifying agents can be expensive, increasing the overall cost of the nanosuspension formulation.
Regulatory Hurdles	Regulatory approval for new emulsifying agents can be difficult to obtain, which may limit their use in pharmaceutical applications.

In summary, while emulsifying agents play a crucial role in stabilizing nanosuspensions and enhancing drug delivery, their selection and use must be carefully considered to balance efficacy, safety, and stability.

Interactions among surfactants, co-surfactants, and emulsifying agents, and strategies to optimize the system

One of the biggest challenges that nanosuspensions intend to address is their low bioavailability, dispersibility, and limited absorption. All the three components, i.e., surfactants, co-surfactants, and emulsifying agents, play a crucial role in addressing the challenge by complementing each other. Surfactants are mainly involved in reducing the size of the particles and inducing stability among the colloids by inducing stability of the droplets and reducing the interfacial tension significantly. Thus, it maintains a homogenization in the nanosuspensions and it is ably aided by co-surfactants. Co-surfactants have a similar molecular composition as a surfactant and it interacts at monolayers to maintain interface fluidity and curvature. Sometimes a surfactant is not able to bring down the interfacial tension to permissible levels alone and it requires a co-surfactant to achieve better mixing.[75] The utility of these two components is further enhanced by the use of an emulsifying agent. They are mainly attributed to the breakdown of large active molecules into small ones so that they remain evenly distributed throughout the nanosuspensions and sedimentation is prevented. All the three of them work in coordination with each other that the particle size is maintained at the desired level, the nanosuspensions is stable and well-dispersed, have improved bioavailability and remain viable for a

long time. There are certain strategies that are adapted to balance out the effects of each of the individual components and optimize the system. Excessive surfactants in a nanosuspension increase the chances of certain side effects and toxicities and also hamper the reduction ability of the interfacial tension. Co-surfactants are effective in compensating for both the aspects as it a lesser toxic profile and an enhanced ability at tension reduction.[76] Moreover, both of them share a balanced amphiphilic nature that helps in phase partitioning and improved miscibility. Although the function of emulsifying agents is to maintain stability and increase bioavailability of nanosuspensions, it caters to a different route of action. Therefore, addition of emulsifying agents also reduces the requirement of surfactants and co-surfactants in a nanosuspension.

Future perspectives of surfactants, co-surfactants, and emulsifying agents

The future perspectives of the components of nanosuspensions i.e. surfactants, co-surfactants, and emulsifying agents as described above have a wide range of applications. They play a very significant and crucial role in delivering novel pharmaceuticals, especially the nanomedicines and the micellar drug carriers.[77] Moreover, the colloidal system shall ensure the stability of future formulations along with its longer duration optimization. It can also find its application in precision medicine and other personalized care as they become more tailored to individual requirements. They can also develop a smart responsive action by modifying and accommodating itself to the external stimuli with respect to several aspects like temperature, pH, and light. Additional antimicrobial properties can also get integrated to these components in the future as they strive to get more environmentally safer and compliant to regulatory laws. The introduction of artificial intelligence and computational methods can improve the predictivity of nanosuspensions. Overall, the future beholds an elaborate intradisciplinary collaboration that can take nanosuspensions to new heights.

Patents[78]

Table 9 - Comprises various Patents based on Nanosuspension Technology[78]

Nanosuspensions	**Company**
Hydrosol	Novartis
Nanomorph™	Soligs/Abbott
NanoCrystal™	Élan NanoSystems
DissoCubes®	SkyePharma
Nanopure	PharmaSol
Nanoedge™	Baxter

Conclusion

Surfactants, co-surfactants, and emulsifying agents are indispensable components of nanosuspensions. However, the selection of these in formulation of nanosuspensions plays a crucial role. The creation of stable and optimally bioavailable colloid system hinges on a thorough understanding of their properties and functionality; in this article we have tried to aggregate the same. The interactions between the components of nanosuspensions and the challenges faced in their selection have also been the emphasized in this review. Though the wide spectrum of surfactants, co-surfactants, and emulsifying agents are available their selection should balance the efficacy, safety, stability, economics involved in the formulation, and production of nanosuspensions.

Disclosure of financial and competing interests

The authors confirm that this article content has no conflicts of interest and have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript.

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