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ROLE AND MECHANISM OF STABILIZERS IN NANOSTRUCTURED LIPID CARRIER

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Abstract:

Nanostructured lipid carriers (NLC) are second generation lipid nano carriers. that is one of the promising nano-carriers that develop the effective targeted therapies. Solid lipid and liquid lipid which is bio-compatible and/or bio degradable used as a core matrix dispersed in stabilizer solution. However, despite the considerably simple structure, the assortment of good stabilizer for a certain drug is a challenging task because they are maintaining the nanosized particle size as long as possible after the formation of NLC. The bioavailability is also affected in the final formulation by cells and cell layers interactions that are maintained by stabilizers. This review describe the types of NLC, techniques to prepare NLCs and their advantages with limitation, Application of Stabilizers in different dosage form, classification of stabilizers, practical consideration for the selection of stabilizers and mechanism of stabilizer which is steric, electrostatic and electrosteric

Keywords: *Nanostructured lipid carrier, stabilizers, mechanism, electrosteric, application*

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INTRODUCTION:

NLC carrier was developed in 1999/2000 by Muller and itacquired 5 years to launch the first two products NanorepairQ10 cream (Dr. Rimpler, Wedemark, Germany) and Nan repair Q10 serum (Dr. Rimpler, Wedemark, Germany)in Munich/Germany in 2005. The third product Nanolipid CLR Restore (Chemisches Laboratorium, Berlin, Germany)was launched within a year [1]. NLC is one of the nanocarriers with the less time between discovery and market introduction. More than 30formulation are existing commercially in the span of twenty years. Solid lipid (SL) nanoparticles(SLN)is the first generation of lipid nanoparticles. SLN have been intensively planned as drug delivery systems for several routes of administration which is oral, parenteral, dermal, and topical delivery [2]. The crystallinity of solid lipids change the release properties of the SLNs. Directly after the development of SLN, lipids moderately crystallize in high-energy alterations with many imperfections in the crystal lattice[3]. The merged drug may be expelled from the lipid matrix when a polymorphic transition to low-energy alteration takes place during storage[2].To overwhelmed drug removal during storage, use of blends of lipids that do not form a highly ordered crystalline arrangement is needed. NLCs are the second generation lipid nanocarriers made by solid lipid matrix that are incorporated with liquid lipids (LL)[3]. NLCs have the capability to strongly arrest the drugs and stop the particles from coalescing by virtue of the solid matrix as compared to emulsions [1, 4]. In addition, the flexibility of the incorporated drug molecules is also drastically abridged in the solid phase. Furthermore, increase the drug loading capacity as compared to SLNs with the help of liquid oil droplets in the solid matrix. NLCs also have the leads over polymeric nanoparticles with low toxicity, biodegradability, drug protection, controlled release, and evasion of organic solvents during production. Recently, NLCs have been intensively formulated as delivery carriers for lipophilic and lipophobic drugs. The NLCs were formulated with a perspective to reach the industrial desires in terms of qualification and validation, scale up, simple technology, low cost etc.[5] With the help of solid lipid, liquid lipid and stabilizers the NLC is prepared. Steric and/or electrostatic technique is the most common approaches of stabilization. adsorbing of polymers onto the drug particle surface in case of Steric stabilization; whereas electrostatic stabilization is achieved by adsorbing charged molecules, both ionic surfactants or charged polymers, onto the particle surface [6]. as polymeric stabilizers include hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose (HPMC 3 cps), polyvinyl pyrrolidone (PVP K30) and poloxamer (Pluronic F68 and Pluronic F127) are Common pharmaceutical excipients that are use. Non-ionic surfactant stabilizers, such as polysorbate (Tween 80) and anionic surfactants such as docusate sodium (DOSS) or sodium lauryl sulphate (SLS) are also used [6, 7]. The use of suitable stabilizer in a naosuspension has to be done considering several factors. Molecular weight and Polymer length of a polymer acts as the thermodynamic driving energy for the physical adsorption on the surface of the particle. Polymeric stabilizer molecular weight is high then , the slower the rate of adsorption. Also long chain polymers high concentration may lower the rate of dis-solution which nullifies the advantage of nanomilling especially for low water soluble drugs. Further, stabilizers like sodium lauryl sulphate (SLS), Pluronic, at high concentration, sometimes offer task to producing patient friendly dosage form especially for pediatric group because of local gastric irritation. Vitamin E TPGS was used, which is enhanced the bioavailability of the drug, in vitro dissolution, and helped to stabilize the nanosuspension throughout wet milling process by avoiding the agglomeration of the drugparticles. Studies were reported in the previous about the significance of TPGS for enhancing the bioavailability of orally administered paclitaxel [8] and nifedipine[9]. The distinctive properties of Vitamin E TPGS as solubilizer, permeability enhancer and stabilizer led to the selection of this excipient for the nano system. Later throughout the stability study, particle size is increase that was observed due to crystal growth, justified the need of using an additional stabilizer.

1 TYPES OF NANOSTRUCTURED LIPID CARRIERS:

1.1 Type I: Highly imperfect solid matrix:

SL and LL are blended together then difference in the arrangement of lipids and special requirements in the crystallization process lead to a highly disordered, imperfect lipid matrix structure. They are offering the free space for drug molecules and amorphous clusters of drugs (Figure 1, I)[10].

1.2 Type II: Multiple oil/fat/water carrier:

liquid lipids are having higher solubility of drug compare to solid lipid. As per this, particles were produced with a high content of LL (oils). During the cooling phase miscibility gap of the two lipids (SL & LL) are occur. Because of this phase are separated. That means precipitation of tiny oily Nano compartments (Figure 1, II).In this multiple oil/fat/water, type II drug can be accommodated in

the solid, but at increased solubility in the oily parts of the lipid matrix[10].

1.3 Type III: Amorphous Matrix:

Lipids are blended in a way that avoid them from crystallizing. The lipid matrix is solid, but in an amorphous state (Figure 1, III) the absence of crystallization avoids drug expulsion by crystallization[10].

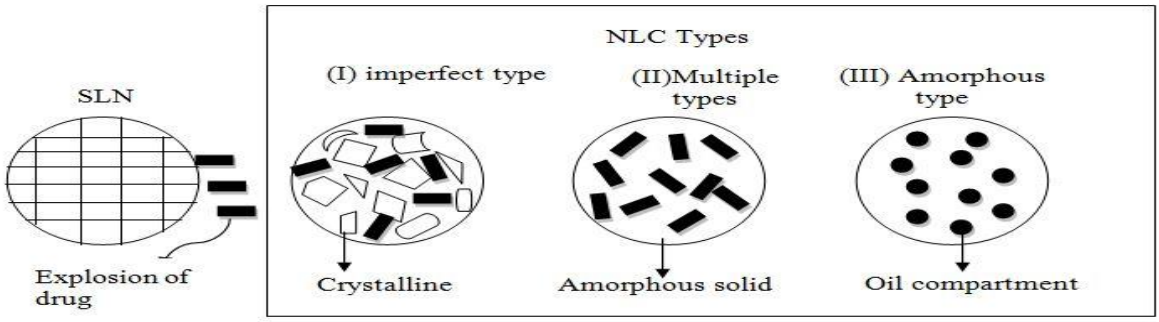


Figure no 01: Types of Nanostructured lipid carrier

Table no.1: Ingredient of Nanostructured lipid carrier (Solid lipid and Liquid lipid)

Solid lipids Chemical	description Chemical	Melting point	HLB		Liquid lipids	Chemical description	HLB
Monostearin	Glycerylmonostearate	66-68 °C	3.8		Transcutol HP	Diethylene glycol monoethyl ether	4.2
Geleol	Glyceryl stearate, Glycerylmonostearate 40-55 (Type I) EP	55-58 °C	3		Maisine™ 35-1	1-Monolinolein	4
Imwitor 900 K	Glyceryl stearate, Glycerol monostearate (Type ll)	54-64 °C	3		LauroglycolR 90	Propylene glycol monolaurate (type II) EP/NF	5
Compritol 888	ATO Glycerylbehenate NF	70 °C	5		Capryol 90	Propylene glycol monocaprylate (type II) NF	6
Precirol ATO 5	Glycerylpalmitostearate, Glycerol distearate (type I) EP	52-56 °C	2		Capryol PGMC	Propylene glycol monocaprylate (type I) NF	5
Stearic acid	n-Octadecanoic acid, Stearophanic acid	67-69 °C	15		Capmul MCM	Medium chain monoand diglycerides	5-6
Softisan154 / Hydrogenated	Triglyceride of C14-C18 fatty acids	55 °C	10		Capmul MCM C8	Glycerylmonocaprylate	5-6

Palm Oil							
Cetylpalmitate	Palmitylpalmitate, Hexadecylpalmitate	54 °C	10		Isopropyl myristate	Isopropyl tetradecanoate	2.82
Glyceryl Tripalmitate	Glycerol tripalmitate, Tripalmitin	64-66 °C			Isopropyl palmitate	Isopropyl hexadecanoate	1.62
GelucireR 43/01	Hard fat EP/NF (Mixture of triglycerides, diglycerides and monoglycerides)	43 °C	1		Imwitor 900 K	Glyceryl stearate, Glycerol monostearate (Type ll)	3

3 Techniques to prepare NLC:

There are many methods for preparation of NLC. That method is: high pressure homogenization (hot and cold), high shear homogenization/ultrasonication, Microemulsion technique, Solvent Emulsification evaporation Method, Solvent diffusion, Solvent injection/ Solvent displacement method, Water-in-oil-in-water double emulsion, Phase inversion and Membrane contactor Procedure of all the techniques with their advantages and disadvantages are summarized in Table no 2 and figure no 2-5

Table no. 02: Techniques for preparation of Nanostructured lipid carrier

Technique	Procedure	Advantages	Disadvantages	Ref.
High Pressure Homogenization (HPH)	**Hot HPH**: Drug is added into lipid and melted at +5-10^{0}C of melting point of solid lipid. Then added into the aqueous solution of surfactant (at same temp). Then pre-emulsion is prepared by using high shear device, then processed in a temperature controlled HPH. The nanoemulsion obtained recrystallizes on cooling at RT forming nanostructured lipid carrier **Cold HPH:** Lipid + drug melted together and cooled rapidly using ice or liquid nitrogen. A pre-emulsion is formed by homogenization of the particles in a cold aqueous surfactant solution then added into the HPH [fig2].	Widely used and well established technique. • Simple and very cost effective technique. • Product homogenous in particle size distribution with higher physical stability. • Aqueous and non aqueous dispersion media is used.	Complete avoidance of drug exposure to high temperature is not possible. • Not suitable for thermolabile drug.	[11]
High shear homogenization technique/ Ultrasonication	Lipid and drug are melted and combined with an aqueous surfactant at the same temperature and coarse emulsion is prepared using high shear mixture. Then coarse emulsion is converted to nanosized emulsion using ultrasonication. Finally, NLC are obtained by cooling down the hot nanoemulsion [Fig 3].	Feasible method, complex equipment is not required, high concentration of surfactants and co-surfactants are not required, method is free from organic solvents	Production of low dispersion quality products and possibility of metal contamination, high energy input is required.	[12]
Microemulsion Technique	Drug and lipids are melted to the 5-10 °C above the melting point of solid lipid and added to an aqueous surfactant solution at the same temperature. A hot microemulsion is formed which is poured into cold water forming nanoemulsion, which then recrystallizes to form NLC [Fig 4].	Rapid, reproducible and cost-effective method requires low energy input, industrial scale production is possible and easy to scale up, organic solvent free method.	• Strong dilution of particle suspension due to use of large volume of water. • High concentration of surfactant and co surfactant is not desired.	[13]
Solvent	Drug and lipids are dissolved in water-	Lipids are dissolved in	Production of very	[1

Emulsification evaporation Method	immiscible organic solvent, and then emulsified in an aqueous phase containing surfactants under continuous stirring. The organic solvent evaporates during emulsification, resulting in development of NLC.	a water immiscible solvent e.g., cyclohexane, chloroform. • Suitable for thermolabile drugs.	dilute nanoparticle dispersion which is not required. • Additional step is required. e.g. ultafiltration or evaporation. • Organic solvent may remain in the final preparation.	4, 15]
Solvent diffusion	Drug and lipids are dissolved in partially water miscible organic solvent and organic solvents are saturated with water to generate initial thermodynamic equilibrium. The transient o/w emulsion is transferred into water with continuous stirring, which leads to solidification of lipid phase forming NLC due to diffusion of the organic solvent.	(I)Lipids are dissolved in partially miscible solvent e.g. benzyl alcohol, Tetrahydrofuran. (II)Water miscible solvents are used to dissolve lipids.	•Ultrafiltration or lyophilisationtechniques are required. •Residue of organic solvent may remain in the final preparation.	[16, 17]
Solvent injection/ solvent displacement method	Basic principle of this technique is similar to the solvent diffusion technique. Drug and lipids are dissolved in a water-miscible solvent or water miscible solvent mixture and quickly injected into an aqueous phase containing surfactants through an injection needle [Fig 5].	Lipids are dissolved in water missicible solvent. e.g. ethanol, methanol, acetone. •Easy handling and fast production process without using sophisticated instrument (e.g., HPH).	Use of organic solvent.	[18]
Water-in-oil-in-water double emulsion	The drug is solubilized in the internal phase of double emulsion. An aqueous drug solution containing surfactant is emulsified in melted lipid by a high speed stirrer at an elevated temperature. The warm w/o nanoemulsion is then dispersed in the aqueous phase containing surfactant as the external phase of w/o/w emulsion at 2-3°C under mechanical stirring to obtain NLC. The NLC are then purified by ultra filtration.	Allows incorporation of hydrophilic drugs, organic solvent is not required.	Relatively dilute NLC dispersion is produced, large particle size of final formulation.	[19, 20]
Phase inversion	Drug and excipient are mixed together on magnetic stirrer, 3 heating and cooling cycles are carried out and then diluted with cold water causing phase inversion of the emulsion and breaking which results in the development of NLC.	Based on two step process. •Three temperature cycles (85–60–85°C) are required to reach inversion process. •Irreversible shock is induced by cold water (0°C).	Cumbersome technique	[21]
Membrane contactor	Lipid phase is passed through a porous membrane at temp 5-10 °C higher than melting point of solid lipid to the aqueous surfactant solution at same temperature. The lipid droplets are formed across the porous membrane dispersed in the aqueous phase. Further cooling of the entire system leads to development of NLC.	In this case, the lipid phase is pressed through the membrane pores to form small droplets. Under cooling at room temperature these droplets recrystallize forming the lipid nanoparticles	-	[22]

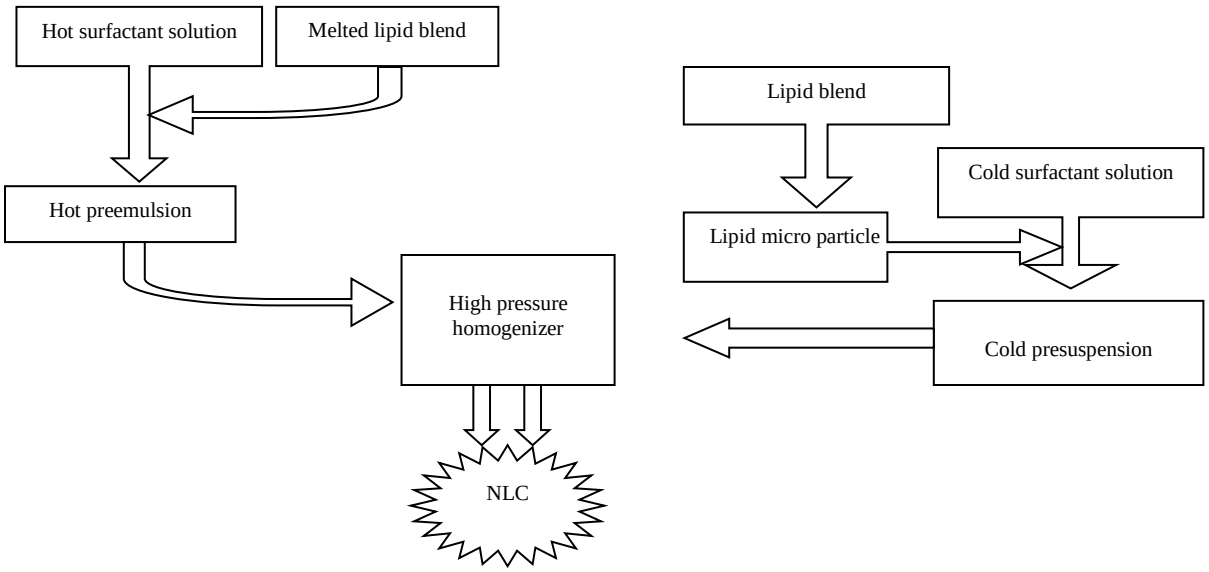


Fig2: Schematic overview of hot and cold High pressure homogenizer

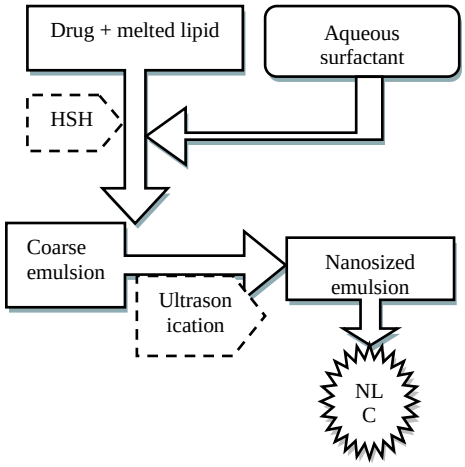


Fig 3: Schematic overview of High shear homogenizer /ultrasonication

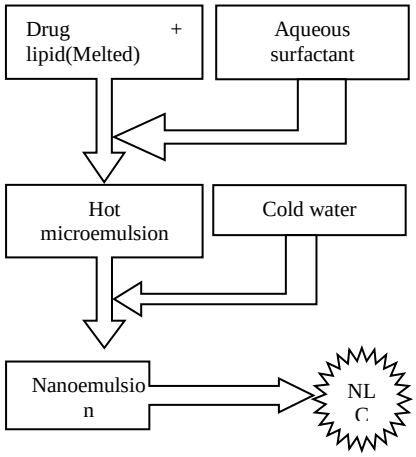


Fig 4: Schematic overview of Microemulsion

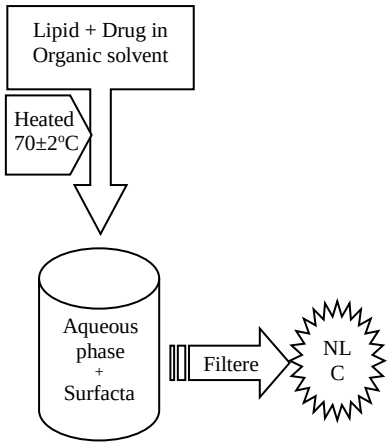


Fig 5: Schematic overview of Solvent injection method

4 Application of Stabilizer:

4.1 Topical delivery system:

For the skin diseasesTopical delivery is the preferred methoddue to reduced systemic side effects as compared to oral and parenteral administration.. It also reduces the first pass metabolism and maintains the concentration of drug at the site of action for longer periods especially for drugs with faster elimination.. The major task in topical delivery is the small amount of drug uptake due to the stratum corneum, which acts as a barrier to toxic molecules as well as therapeutics. In the recent years, lipid nanoparticles have gained attention as novel colloidal carriers for topical .use. NLC have various reward over conventional creams and emulsions in terms of providing controlled release,protection of the active component, increase permeability into the skin and lower the skin irritation[23] table no. 03 describe the various NLC formulations for topical delivery.

Table no. 03: Application of Stabilizer in Topical delivery system.

API	Solid lipid	Liquid lipid	stabilizer	Nature (stabilizer)	HLB (stabilizer)	Method	Partical size (nm)	Research highlights	Ref
Terbinafine HCl	GMS	Labrasol ®	Pluronic® F-127	Hydrophilic	18-23	HPH	128 ± 4.5	NLC formulation showed better permeation into the skin and reduced fungal burden in shorter duration of time as compared to marketed gel preparation.	[24]
Deoxyarbutin	Cetylpalmitate	MCT	Poloxamer 188	Hydrophilic	29	HPH & ultrasonication	500	NLC showed highest permeation into skin as compared to nanoemulsion and conventional emulsion.	[25]
Calcipotriol& Methotrexate	Precirol ® ATO5	Squalene	Myverol™	Lipophilic	3.8	HSH	270–320	Higher particle size with low squalene content Higher squalene proportions resulted in faster release Dual drug-loaded NLCs exhibited reduced skin permeation of calcipotriol but not methotrexate.	[26]
Acitretin	Precirol ® ATO5	OA	Polysorbate 80	Hydrophilic	15	Solvent diffusion	223 ± 8.92	NLC formulation was reported to significantly higher deposition of acitretin in human cadaver skin Demonstrated improvement in therapeutic response and reduction in local side effects	[27]
Ketoprofen	Compritol® 888 ATO Lipophile	Labrafac™ Lipophile	Lutrol® F-68	Hydrophilic	29	Nanoemulsification &ultrasonication	300–500	Improvement in both the dissolution and the skin permeation properties of drug	[28]

4.2 Oral delivery system:

Oral delivery system route is the most preferred and conventional route of administration because of some advantages such as painlessness, precise dosing, effortlessness of administration, patient conformity. However, a number of drugs have solubility issues and are low bioavailability due to the presence of various physical, chemical and enzymatic barriers in the gastrointestinal tract (GIT). Therefore, novel drug delivery systems are required to overcome these restrictions and improve therapeutic effectiveness leading to dose reduction and mitigation of side effects. Amongst various nanocarriers used, lipid nanoparticles such as SLN and NLC offer a number of advantages such as improved solubility, better permeability and bioavailability, improved stability by protecting the drug molecule from pH and enzymatic degradation, extended circulation time, reduced clearance and greater than before mean residence time (MRT)[29]. Table no. 04 describe the various NLC formulations for oral delivery

Table no. 04: Application of Stabilizer in Oral delivery system

API	Solid lipid	Liquid lipid	stabilizer	Nature (stabilizer)	HLB (stabilizer)	Method	Partical size	Research highlights	Ref
Vinpocetine	Monostearin	Miglyol ® 812	Lecithin	Amphiphilic	4-9	HPH	107–132 (nm)	Relative bioavailability of NLC formulation was 322% compared with suspension.	[30]
Lercanidipine Hydrochloride	Labrafil 2130M	Linseed Oil	Tween ® 80	Hydrophilic	15	Sovent evaporation	214.47	NLCs released drug in a controlled manner for a prolonged period of time as compared to plain drug	[31]
Oridonin	GMS	MCT	Soyabean lecithin	Amphiphilic	4-9	HPH	144.9	Relative bioavailability of Biotin modified NLC was 171.01%, while the value of non-modified NLCs was improved to 143.48%.	[32]
Baicalin	GMS	MCT	Soyabean lecithin	Amphiphilic	4-9	Emulsion–evaporation technique	244.7	Drug release showed a biphasic pattern with burst release initially and sustained release afterwards. Prolonged MRT and increased AUC compared to pure drug.	[33]
Resveratrol	Cetylpalmitate	Miglyol ® 812	Polysorbate 60	Hydrophilic	29	HSH &ultrasonication	150–250	Improved drug stability	[34]
Decitabine	Precirol ®ATO5	Transcutol®	Transcutol® HP and Tween ® 80	Hydrophilic	15	Cold HPH	116.64 ± 6.67	NLC had more stability and reduced crystallinity. Ex vivo gut permeation study showed 4-folds increment in the permeation of drug compared with the plain drug solution.	[35]
Fenofibrate	Compritol® 888 ATO	Labrafil ® M 1944CS	Soy Lecithin	Amphiphilic	4-9	Hot homogenization	100	Higher Cmax levels, along with higher AUC (fourfold) of NLC formulations in plasma, indicate enhancement in rate and extent of drug bioavailability.	[36]
Silymarin	Precirol ® ATO-5	Oleic acid	Tween ® 80 Lecithin (Lipoid E100)	Hydrophilic	15	Ultrasonication HPH	78.87	Relative oral bioavailability of NLC carriers in Beagle dogs was 2.54- and 3.10-fold that of marketed Legalon® and silymarin solid dispersion pellets	[37]

4.3 Pulmonary delivery system:

Pulmonary route is a promising noninvasive route for delivery of therapeutics for both local and systemic effects. Further, reward such as fast absorption of therapeutics due to large surface area (ca. 100 m2) and high vascularization (about 5 L min−1), unhurried drug metabolism because of low enzymatic activity besides circumventing the first-pass metabolism makes this route ideal for treatment of various diseases mainly for pulmonary diseases with potential for targeted delivery and reduction of side effects. This route has shown secure in the delivery of therapeutics for other diseases also such as cancer,

metabolic disorders like diabetes, acute pain, immune deficiencies, autoimmune diseases and infections[38, 39].Table no. 05 describe the various NLC formulations for Pulmonary delivery

Table no. 05: Application of Stabilizer in Pulmonary delivery system

API	Solid lipid	Liquid lipid	stabilizer	Nature (stabilizer)	HLB (stabilizer)	Method	Partical size (nm)	Research highlights	References
Celecoxib	Compritol®	Miglyol ® 812	Sodium taurocholate	Hydrophilic	16-17	HPH	217 ± 20	Controlled release of drug 888 ATO Cytotoxicity of NLC formulation due to prolonged release and cell internalization of nanoparticles Higher bioavailability and lower clearance	[40]
Doxorubicin	Precirol ® ATO 5	Squalene	Soybean phosphatidylcholine	Amphiphilic	4-9	HSH &ultrasonication	110 ± 20	Significantly decreased exposure of healthy tissues to cytotoxic effects	[41]
Rosuvastatin	Lauric acid	Capryol ™ 90	Cremophor RH40	Hydrophilic	13	Melt-emulsificationultrasonication	161 ± 3.38	Sustained release achieved over extended Time. Enhanced bioavailaibility and improved lung targeting	[42]
Tobramycin	Compritol® 888 ATO, Precirol ® ATO 5	Miglyol ® 812	Tween ® 80	Hydrophilic	15	Hot HPH	250	Sustained release and prolonged lung residence time	[43]
Paclitaxel	GMS	OA	Tween ® 80, 20 and 60			Emulsification	178-398	Better localization of drug within the lungs	[44]

4.4 Ocular delivery system:

The eye having unique anatomy, physiology and biochemistry which is highly protected organ. The existence of various anatomical barriers such as layers of cornea, sclera and retina including blood-aqueous and blood-retinal barriers together with presence of conjunctival blood supply, lymphatic tear turnover, nasolacrimal drainage and reflex blinking poses a great challenge for the delivery of therapeutics especially to the posterior segment of the eye. Topical administration is noninvasive and the most ideal route for administration of therapeutics especially to the anterior segment of the eye. However, the ocular bioavailability of the therapeutics is very low mainly because of short residence time at the target tissue and existence of anatomical barriers. Permeation of therapeutics topically to the posterior segment is less than 5%, thus the need for alternative invasive routes such as intravitreal and subconjunctival injections which are associated with risks such as infections, bleeding and loss of vision[45, 46]. In the recent years, NLC formulations have been investigated for their potential as an ocular delivery system as they can improve corneal permeation and thereby increase bioavailability in addition to being secure, non-invasive and patient compliant. Furthermore, the mucoadhesivenature of NLC enhanced their contact with the corneal membrane resulting in increase residence time, improve bioavailability and lower systemic and local side effects. NLC formulations have been check for the treatment of various disorders of the eye such as inflammation, infections,

glaucoma and also disorders affecting the posterior segment of the eye[47].Table no. 06 describe the various NLC formulations for ocular delivery.

Table no. 06: Application of Stabilizer in Ocular delivery system

Application	API	Solid Lipid	Liquid lipid	stabilizer	Nature	HLB	Method	Research highlights	Ref
Inflammation	Ibuprofen	Compritol® 888 ATO, Gelucire® 44/14, Stearylamine	Miglyol® 812 Transcutol® P	Cremphor EL (	Hydrophilic	13	Hot emulsion-ultrasonication	Apparent permeability coefficients were 1.28 and 1.36 times more than that of the control preparation. Prolonged precorneal retention time with steraylamine Controlled-release property. The AUC of the optimized NLC formulation was 3.99 times more than that of eye drops	[48]
Inflammation	Flurbiprofen	Compritol® 888 ATO, Gelucire® 44/14,	Miglyol® 812 N, Chitosan Oligosaccharides (COS)	Solutol® HS-15	Hydrophilic	14-16	Hot emulsion - ultrasonication	Delayed clearance and 7.7 fold increase in AUC of COS coated formulations. Solutol® HS-15, Miglyol® 812 N, Enhanced transcorneal permeation	[49]
Immunosuppression	Cyclosporine A	Thiolated polyethylene glycol monostearate, Precifac ATO® 5,	Miglyol® 840,	Tween® 80	Hydrophilic	15	Hot emulsion - ultrasonication	Systemic concentration was very low	[50]
Inflammation, edema	Triamcinolone acetonide	Stearic acid, Precirol® ATO5	Squalene	Lutrol® F68	Hydrophilic	29	HPH	Successfully delivered the lipophilic active to the posterior segment of the eye via the corneal and noncorneal pathways.	[51]
Inflammation	Indomethacin	Compritol® 888 ATO	Miglyol® 812/ 829 PEG	Tween® 80, Poloxamer 188,	Hydrophilic Hydrophilic	15 29	HPH	Higher drug concentration in all eye tissues as compared to SLN and chitosan coated SLN formulations	[52]

5 CLASSIFICATION OF STABILIZERS:

Various types of the stabilizers used for stabilization of nanoformulations. Such as PVP (Povidone), PVA (Polyvinyl alcohol), PEG (Polyethylene glycol), HPMC (Hypromellose), HPC (Hydroxypropyl cellulose), HEC (Hydroxyethyl cellulose), NaCMC (Carboxymethylcellulose sodium), SD (Docusate sodium), SLS (Sodium lauryl sulfate), PEI (Polyehtylene imine), TPGS (D-α-tocopheryl polyethylene glycol succinate), PEO (Polyethylene oxide) and PPO (Polypropylene oxide).that is classified in the figure no 06

6 Mechanism of stabilizer:

Electrostatic repulsion and steric stabilization are the two main mechanisms involved in the stabilization of colloidal nanosuspensions. Electrostatic stabilization occurs through an electrical double layer surrounding the colloidal particles, and steric stabilization is

completed when polymeric molecules are adsorbed or attached chemically[53, 54]. It is also probable to combine chemical functionalities within the same molecule to achieve both steric and electrostatic stabilization known as electrosteric stabilization [55, 56]. Ionic-polymers impart electrostatic repulsion from surfactant properties and steric stabilization from polymeric properties. Electrosteric stabilization can also be provided by using a combination of two different stabilizers, an ionic surfactant and a polymer, respectively [57]. Electrostatic, steric and electrosteric stabilization mechanisms are shown in Figure 7.

6.1 Electrostatic stabilization:

In the electrostatic stabilization the adsorption of ionic charges on the particle surface are occur resulting in mutual repulsive forces arises between the particles [58, 59]. The ionic strength of the medium significantly affected the repulsive forces. For a given colloidal system, an enhance in the ionic strength reduces the thickness of electrical double layer which leads to a decrease in the repulsion potential of the particles [60, 61]. Electrostatic stabilization is commonly used because of its simplicity and low cost [62]. Nonetheless, shortcomings are associated with this method. It is effective only in aqueous medium and is less effective after drying the formulation, as the ionized state is no longer maintained [62]. It is sensitive to changes in the ionic strength of the dispersion medium and is difficult to apply to multiple phase systems because different solids develop different electric potentials [63, 64]. Electrostatic stabilization is also susceptibleto processing such as heat sterilization. However, if the components of formulation are heat labile, alternative strategies like filtration sterilization can be used [58, 65].

6.2 Steric stabilization:

In the steric stabilization the adsorption or attachment of non-ionic amphipathic polymers on the particle surface thus preventingaggregation. The stabilizing moieties are mutually repulsive and because of this to effectively keep the particles at a distance from each other.They have to be attached, partially adsorbed or absorbed to the particle very strongly so that they can'taffect by Brownian collisions of particles. Polymericstabilization have several advantages compare to electrostatic stabilization, that is (i) The particles are re-disperse which is prepare by steric method[66, 67](ii) a very high concentration of nano-crystals can be accommodated and the dispersion medium can be completely removed [54, 68](iii) it is not sensitive after the addition of electrolytes below their 'salting out' rang [55, 69], and (iv) it is suitable for various phase systems[70].Sterically stabilized dispersions are generally sensitive to temperature changes. After the upon heating or coolingFlocculation may occur, but is reversible. However, if the ratio between the lopophilic to lipophobic parts of the polymer is such that their cloud points exceed the applied temperature variations, sterically stabilized dispersions show stability towards temperature changes [54, 71-74]. Povidone (PVP), Hypromellose (HPMC), Hydroxypropyl cellulose (HPC), block and graft co-polymers are the most usefullsteric stabilizers[54, 71-73, 75].

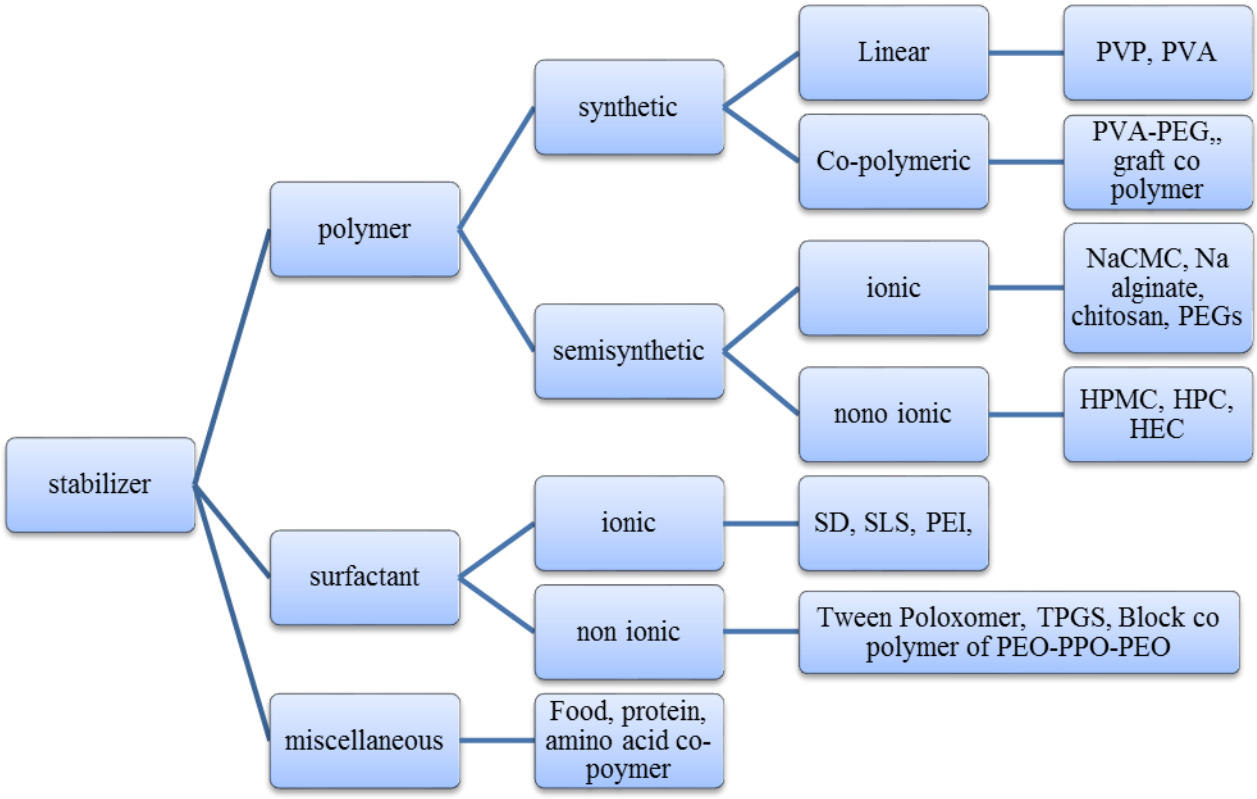
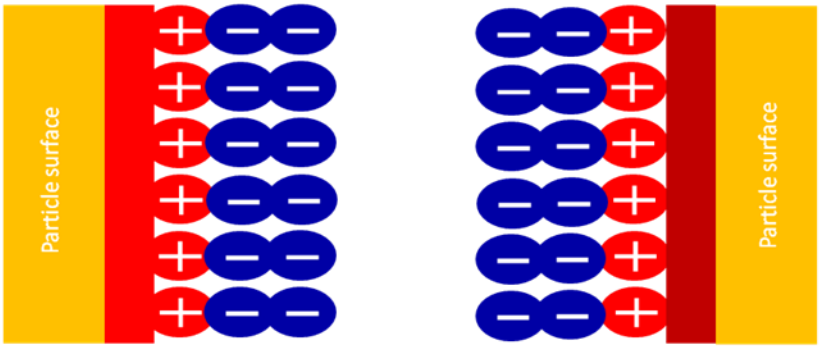


Figure no 06: Classification of Stabilizers



Placement of ionic charges on particle surface result in mutual repulsive forces between particles

Electrostatic stabilization

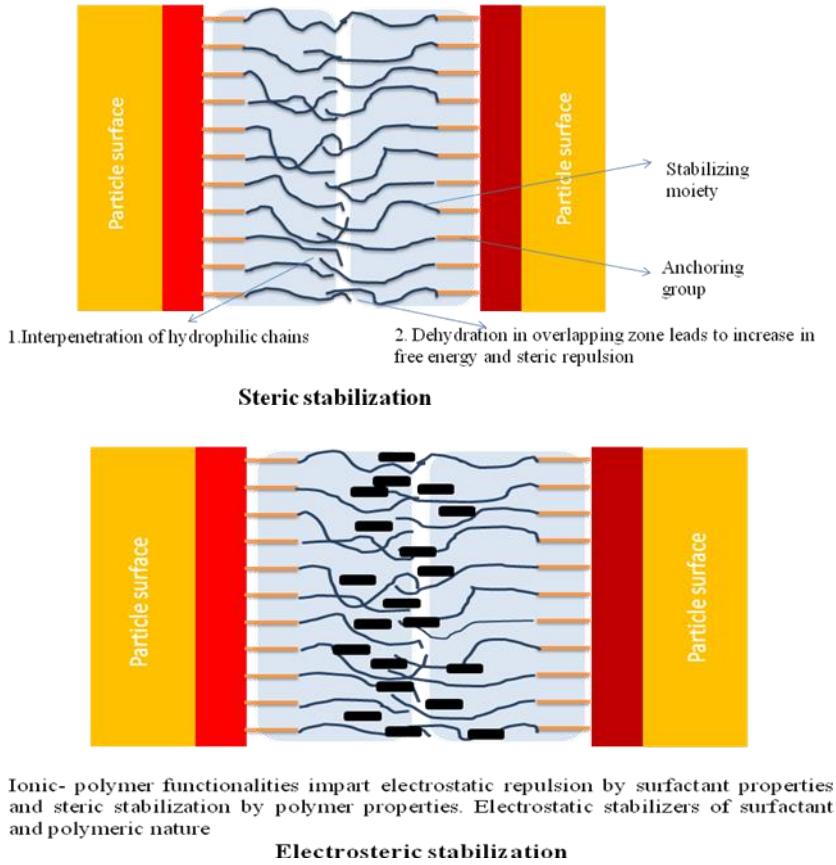


Figure 6: Schematic illustration of electrostatic, steric and electrosteric stabilization.

7 List of stabilizer with their mechanism of stabilization:

Stabilizer efficacy and their properties are studied and check the relationship between stabilizer properties and their potential for the specific drug that is published in the some articles [7, 76-81].these properties are summaries in the figure no.07

Table no 07: List of stabilizers together with their mechanism of stabilization

Stabilizing agent(s)	Mechanism of Stabilization	Drug compound	Formulation type	Techniques for making nano-crystals	Ref
POLYMERS(SYNTHETIC)					
PVP K15	Steric	Danazol	Nanosuspension	Ball milling	[82]
PVA	Steric	Nitrendipine	Nanosuspension	Precipitation-ultrasonication	[83]
POLYMERS (SEMISYNTHETIC)					
HPMC	Steric	Ibuprofen	Nanosupension	Precipitation under sonication followed by microfluidization	[84]
HPMC	Steric	Nifedipine	Freeze dried nanosuspension	High pressure homogenization	
HPMC	Steric	Spironolactone	Nanosuspension	Antisolvent precipitation	[85]
HPMC	Steric	Naproxen	Nanosuspension	Media milling	[86]

Plantacare® 2000 (decylglucoside)	Steric	Lutein	Cream and gel containing Freeze dried nanosuspension	High pressure homogenization(HPH)	[87]
SURFACTANTS (IONIC)					
SLS	Electrostatic	Curcumin	Nanosuspension	Nanoprecipitation	[88]
SLS	Electrostatic	Ketoprofen	Matrix Pellet containing nano-crystals	Bead milling followed by spray drying and melt pelletization	[89]
SURFACTANTS (NONIONIC)					
TPGS	Steric	Itraconazole	Freeze dried nanosuspension	Ball milling followed by freeze drying	[90]
Tween 80	Steric	Spironolactone	Nanocapsules	Nanoprecipitation	[91]
Tween 80	Steric	Baicalein	Nanosuspension	Antisolvent recrystallization followed by HPH)	[92]
Tween 80	Steric	Quercetin	Nanosuspension	Bead milling	[93]
Poloxamer 188	Steric	Simvastatin	Nanosuspension	Sonoprecipitation	[94]
Poloxamer 188	Steric	Piroxicam	Orally disintegrating	tablet HPH	[95]
Poloxamer 188	Steric	Diclofenac	Nanosuspension	HPH	[96]
Poloxamer 188	Steric	Naproxen	Nanosuspension	Milling	[82]
Poloxamer 338	Steric	Azithromycin	Freeze dried nanosuspension	HPH	[97]
Poloxamer 407	Steric	Paclitaxel	Nanosuspension	Stabilization of nano-crystal method	[98]
Poloxamer 407	Steric	Cyclosporine	Nanosuspension	Media milling	[99]
COMBINATION OF STABILIZERS					
Capryol 90 and Solutol HS 15	Steric	Atovaquone	Freeze dried nanosuspension	Microprecipitation followed by HPH	[100]
PVP K30 and SLS	Electrosteric	Celecoxib	Nanosuspension and tablet	Emulsion diffusion (solvent exchange) followed by spray drying	[101]
Lutrol F127 and SLS	Electrosteric	Itraconazole	Nanosupension	HPH	[102]
HPMC and SLS	Electrosteric	Miconazole	Nanosuspension	High energy milling	[103]
Tween 80, Poloxamer 188 and Sodium cholate	Electrosteric	Amphotericin B	Nanosuspension	HPH	[104]
Lecithin and Tyloxapol	Electrosteric	Budenoside	Nanosuspension	HPH	[105]
Poloxamer 188 and Lecithin	Electrosteric	Oridonin	Nanosuspension	HPH	[106]
Poloxamer 188 & Phospholipon 90	Electrosteric	Clofazimine	Nanosuspension	HPH	[107]

8 Practical considerations for the selection of stabilizers:

There are some factors that are affected in the stabilizers efficacy and properties. For example (I) drug related parameter which is zeta potential, log P enthalpy of melting, drug solubility in stabilizer solution. (II) Stabilizer related parameter that is concentration of stabilizer, molecular weight, surface energy, Hydrophobicity and affinity for drug etc. These factors are summarized in the figure no 08

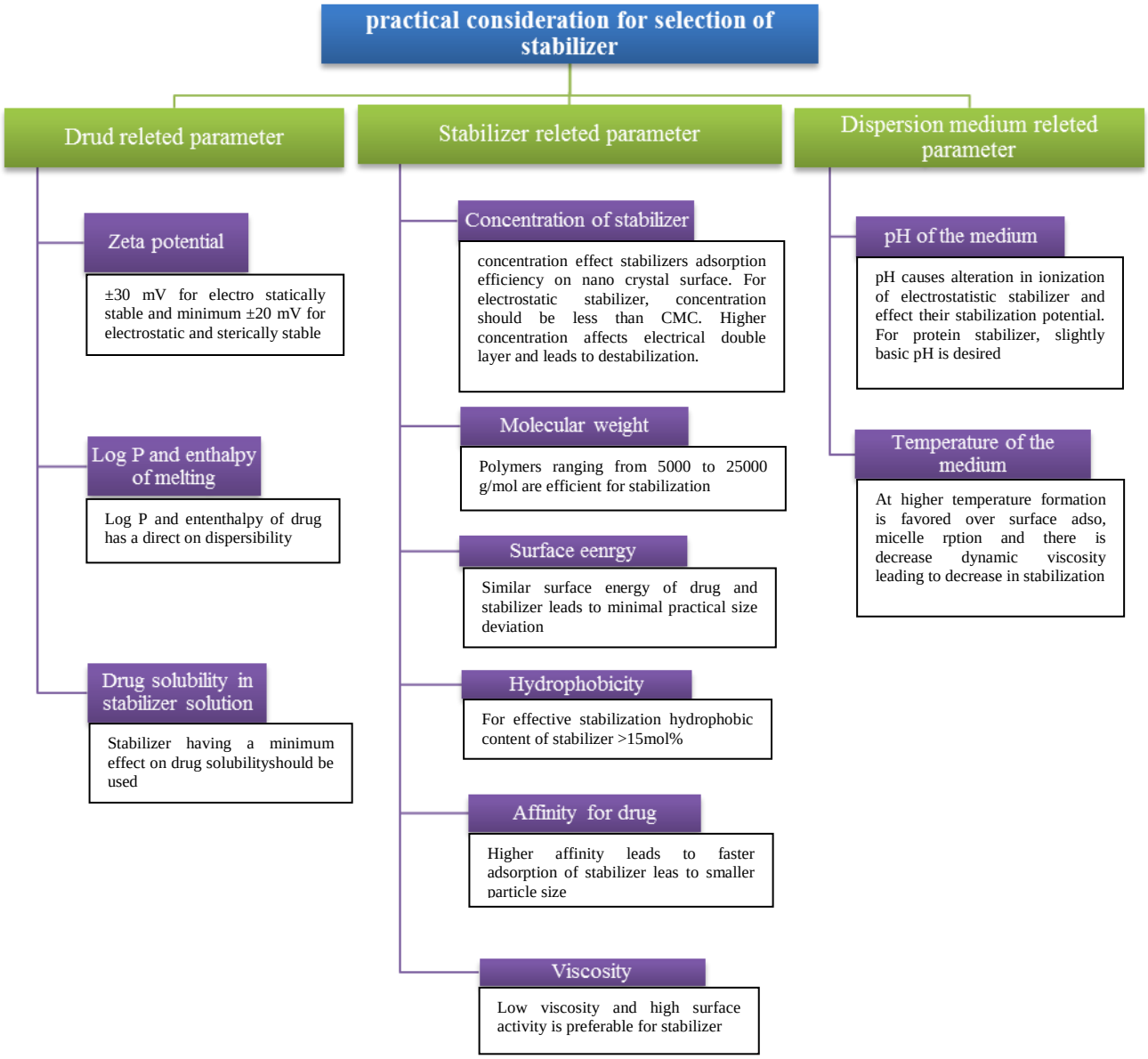


Figure no 08: Practical considerations for the selection of stabilizer

9 STABILIZERS:

9.1 Poloxamers:

Poloxamers are synthetic polymers which is made by the series of closely related block copolymers of ethylene oxide and propylene oxide[108-110]. This is also evaluated as a steric stabilizer[101].Poloxamers is mostly used in field of pharmacy and biomedicine as thermo-sensitive hydrogels, nanoparticle and micelle carriers, particle surface coatings, and tissue scaffolds[111, 112].Poloxamers are made-up by adding ethylene oxide to polyoxypropylene glycol, which is a produce from the reaction between propylene oxide and propylene glycol. These amphiphilic block polymers, comprised of hydrophobic polypropylene oxide (PPO) and hydrophilic polyethylene oxide (PEO) chains, are regarded as more advantageous nanocrystal stabilizers than, i.e., traditional homopolymers.Both polymeric Stabilizers i.e., poloxamer 407 (Pluronic® F127) and poloxamer 188 (Pluronic® F68) are non-ionic linear triblock copolymers build up from hydrophobic central segment of PPO and 2 lipophobic side segments of PEO. While the lipophobicPEO segments surround the drug crystals providing steric hindrance and preventing particle co-agglomeration and growth, the adsorption on the crystal surface is driven by lipophilic interactions of the lipophilic PPO chains. Depending on the used drug compound, the F68 may exert less kinetic restriction in the adsorption process and earlier diffusion due to its lower molecular weight compared to F127 (8400 g/mol vs. 12,600 g/mol)[7].In addition to the linear PEO–PPO–PEO type Poloxamers, there exists reverse structured poloxamers, i.e., Pluronic® Reverse 17R4, having a reverse structure as compared to Pluronic®. 17R4 presents a block copolymer with terminal secondary hydroxyl groups, and is also called a telechelic polymer (PPO–PEO–PPO). However, the linear PEO–PPO–PEO type structures are generally reported as more efficient in nanocrystal stabilization, since the telechelic polymer structure of 17R4 may promote inter-particle bridging and aggregation after nanocrystallization[108].In the past studies it was reveal that the combination of TPGS and Pluronic was shown to be a potential particle size growth inhibitor[113].Additionally, amphiphilic polymers can reduce the interfacial tension and enhance the wettability of nanocrystals. The poloxamers facilitate a reduce in zeta potential with rising molecular weight (poloxamer F68 < F127).The decline in zeta potential suggests a formation of a sterically stabilized polymer layer. The decrease is even highlighted by rising poloxamer concentration, especially with poloxamerF127[108, 110, 114].Danhier et al. compared poloxamer stabilized anti-cancer multi-targeted kinase inhibitor MTKi-327 nanocrystalline formulation with other nanocarrier systems, PEGylated PLGA nanoparticles, polymeric micelles, and also to Captisol solution[115].However, the rate of crystal growth of the drug was slightly faster in case of Pluronic F-68 as compared to Pluronic F-127, during storage.This may be due to the fact that the crystal growth inhibition is mainly due to the lipophilic polypropylene oxide group (PPO) in the Pluronic polymer. As the influence of the strength of lipophilic hydrogen bonding on the crystal growth is a kinetic process, it gets manifested over time during the stability study. Similar observation was also reported by [113]

9.2 Vitamin E TPGS:

Pharmaceutical industries is used Vitamin E TPGS as an excipient, nutraceuticaland cosmetic application. Esterification of the carboxylic group of crystalline D-_-tocopheryl succinate with polyethylene glycol 1000 (C33O5H54(CH2CH2O)n) is made the Vitamin E TPGS.Vitamin E TPGS has exhibit the improved bioavailability properties of poorly absorbed drugs, vitamins and micro-nutrients by acting as an absorption and permeability enhancer[116]. In the vitamin E Vitamin E TPGS is a highly stable form, because it is stable when exposed to oxygen, heat, light, or oxidizing agentsHowever, it is unstable to alkali.when stored in an unopened container at room temperatureVitamin E TPGS is recognized to be a stable excipient with a shelf-life of 4 yearsImportantlyunder the conditions of heat sterilizationVitamin E TPGS is stableAccording to Zhang et al., Vitamin E TPGS is having the advantages of PEG and Vitamin E in application of various nanocarriers for drug delivery, including extended half-life of drugs in plasma and enhanced cellular uptake of the drugs[116].Vitamin E TPGS has an amphiphilic structure exerted by the hydrophobic alkyl tail and the lipophobic polar head, with a lypophobic/hydrophobic balance (HLB) value of 13.2 and a relatively low critical micelle concentration (CMC) of 0.02% w/w. when developing various drug delivery systems, including prodrugs, micelles, liposome's and nanoparticlesThese properties make Vitamin E TPGS an interesting molecular biomaterial. By the inhibition of P-glycoprotein (P-gp) these novel drug delivery systems are, in turn, able to reach sustained, controlled and targeted drug delivery, as well as to overcome the efflux by multidrug resistance (MDR) proteins as a promoter of oral cancer drug delivery[117].Vitamin E TPGS show relatively smaller particle size as compared to Pluronic (both F68 and F127) or sodium lauryl sulphate (SLS)[73].Multidrug resistance (MDR) is one of the

main factors that is influence in the failure of anticancer chemotherapy. Already in 2006 and 2009, Feng and coworkers published positive results on the delivery of biodegradable poly(lactide) and poly(lactide)-co-poly(glycolide)—vitamin E derivative—based nanoparticle formulations for the oral delivery of paclitaxel and docetaxel cancer drugs [117]. Later on, e.g., Wang et al. prepare novel multifunctional camptotechin derivative SN-38 loaded alpha-tocopheryl polyethylene glycol succinate (TPGS)/poly(lactic-co-glycolic acid) (PLGA) nanoparticles by a modified solvent extraction/evaporation method: 200 nm spherical particles with smooth surfaces, narrow size distribution, appropriate surface charge, and successful drug-loading into the nanoparticles.Cytotoxicity of the TPGS/PLGA/SN-38 nanoparticles was increased by 3.6 times compared to the free SN-38against the MDR.Mechanistically, the TPGS/PLGA/SN-38 nanoparticlesenhanced the uptake of the loaded drug by clathrin-mediated endocytosis, and the intracellular nanoparticles escaped the identification of P-gp by MDR cells.modulate the efflux microenvironment of the P-gp pump, the mitochondria and the P-gp domain with an ATP-binding siteAfter the SN-38 was released from the TPGS/PLGA/SN-38 nanoparticles in the MDR cells, TPGS or/and PLGA it is hypothesis [118],after which the drug penetrate the nucleus of the MDR cells and induced the cytotoxic effect[118].In drug nanocrystals, Vitamin E TPGS has been broadly studied due to the above-mentioned activity in vivo. Ge et al. formulated ursolic acid nanocrystalsusing TPGS1000 as a stabilizer via an antisolvent precipitation technique [119].The optimum drug:stabilizer ratio was found and that is 0.4:1 as per this composition very fine and homogeneous particles were formed (particle size 127 nm and polydispersity index 0.15).When compared to bulk drug dispersion the bioavailability was 27.5-fold and Cmax value was 9-fold higher.Theenhanced bioavailability was partly explained to be due to the P-gp inhibition effect of TPGS1000 on the intestinal epithelium cells.

9.3 Effect of SLS:

SLS significantly improved the intrinsic solubility of the drug, there is a high chance that during the processing, Ostwald ripening can occur. This type of observation can be elaborated by Liftshitz, Slyozov and Wagner (LSW) theory [120] As per theLSWtheory, rate of Ostwald ripening can be elaborated by the following equation:D(d)3/dt=64_Vm2cD/9RT, where _ is the interfacial tension, Vm(molar volume of the dispersed compound), c (bulk solubility), D (diffusion coefficient in the solvent), R (gas constant) and T (absolute temperature). As per this theory, most of the parameters are constant except the interfacial tension and bulk solubility. Since the bulk solubility ofthe drug improved by addition of 1% SLS, the rate of Ostwald ripening also increased. Although SLS was main factor for the drop in interfacial tension during the initial stage, however the enhancement of surface area with increase of milling timeimproved the interfacial tension which leads to time dependent Ostwald ripening during the nanomilling process.[73]

9.4 Celluloses:

Celluloses are polymers. That is obtaining from natural origin, that are frequently utilized as nontoxic and nonirritating substances in pharmaceutical industries. Hydroxypropyl methyl cellulose (HPMC) is the most useful cellulose in pharmaceutical industries,categorized as a semisynthetic non-ionic polymer. HPMCmolecular weight is between 10,000 and 1,500,000 g/mol.alkali cellulose is treated with chloromethane and propylene oxide that produce the HPMC, purified afterwards andground to fine powder.Exposing of HPMC to anhydrous hydrogen chloride in order to induce depolymerization after this process different molecular weights, meaning basically varying viscosity grades of the polymer is obtain. HPMC is used as a lipobhobic polymer in oral controlled drug delivery systems[121]. HPMC is also accepted for ocular drug delivery as an ophthalmic lubricant and tear substitute because of an inactive ingredient [122]The helpful characteristics of HPMC support the use of HPMC in the preparations of ophthalmic drug delivery systems that features is low toxicity, elongated contact with the mucosa and, most of all, a highly swellable nature, conferred beneficial effects on the release kinetics of the incorporated drug [122-124].because of High degree substitution of the methoxy and hydroxypropoxy groups in molecular structure of HPMC,which can effectively attach onto the brinzolamide nanocrystal particle surfaces via hydrogen bonding[125]With its relatively high molecular weight, polymeric HPMC support an effective steric stabilization for brinzolamide[126]Overall, the intraocular pressure lowering the effect with the formulated formulations seemed to be remarkable in hypertensive rats[127]

other celluloses:

hydroxypropylcellulose, (HPC, approx. 50,000–1,250,000 g/mol), hydroxyethylcellulose(HEC), and methylcellulose (MC, approx. 10,000–200,000 g/mol) are the other semisynthetic non-ionic polymers which is as

nanocrystalstabilizerswheresome of the cellulose hydroxyl groups are hydroxypropylated (HPC), hydroxyethylated (HEC) ormethylated (MC), correspondingly. in oral and topical applicationsHPC and MC are used, whereas in ophthalmic and topical drug deliveryHEC is applied. These homopolymers always containlipobhobicbackbone chains. These polymers can adsorb on the particle surfaceto form a hydrodynamic boundary layer by hydrogen bond.As described, cellulose ethers (HPMC and MC) contain ahigh degree of substitution as methoxy or hydroxypropoxy groups, which can prepare hydrogen bondswith the drug and inhibit the crystal growth.This degree of substitution determines the stability ofthe nanocrystal suspensions. For instance, lipophilic drug surfaces without polar functionalgroups may be best for HPC to physically adsorb and produce steric stabilization, since thehydrogen bonding between the polymer and drug tends to interfere with the stabilization activity of polmer[128].With polymeric stabilizers, the molecular weight was related to the viscosity, which must be taken into account: high viscosity of the milled dispersions reduce the milling efficiency [58]. In conclusion, HPMC produced nanocrystals efficiently with better storage stability [129].The smallest nanocrystals were provided by PVP due to the less dispersion viscosity. However, the process parameters had a strong effect on the properties of the PVP containing products.

9.5 Soluplus:

Soluplus® (BASF) is a pharmaceutical additives prepare by the polyethylene glycol, polyvinyl acetate and polyvinyl caprolactame-based graft copolymer (PVAc-PVCap-PEG). Primarily, Soluplus® was established in order to enhance drug solubilization properties of poorly soluble active pharmaceutical ingredients (APIs). Model drug studies of Soluplus® based formulation development have been developed in the fields of hot melt extrusion, spray drying, high shear dispersions, electrospinning/electrospraying, microwave radiation, solvent casting, solvent evaporation, ball milling, physical/co-milling blends, and thermal heating applications[130, 131]. Yang et al. investigated Soluplus® and HPMC stabilized fenofibrate nanosuspensions [132]. Nanocrystals were prepared by the media milling technique. In this case, Soluplus® produced considerably smaller particles (344 nm) than HPMC (642 nm). Soluplus® is also stabilized the Nanosuspension. beacause of weaker Oswald ripening with Soluplus, when Soluplus® micelles entrapped dissolved fenofibrate by the slow diffusion.Physical mixture of fenofibrate and Soluplus® studies for Bioavailability, that indicated Soluplus® altered themembrane permeability in the intestines, which increased also the drug permeation.With both of the nanocrystalline formulations, the plasma-concentration curves showed double peaks, indicating different absorption sites for fenofibrate in GI tract.Linn et al. tested Soluplus® forits capability that found a permeation enhancing effect of Soluplus®which is improve intestinal drug absorption.danazol, fenofibrateanditraconazoleBCS class II compoundswere tested both in vivo in beagle dogs and in vitro in transport experiments across Caco-2cell monolayers[133].Gadadare et al. studied top-down and bottom-up approaches for producing Soluplus® stabilized repaglinidenanocrystals[134].

9.6 Hydrophobins:

Hydrophobins are surfactant proteins from filamentous fungi, and they can suddenly form self-assembling monolayers to hydrophobic–hydrophilic interfaces.Valo et al. studied beclomethason enanocrystals and hydrophobin is used as a stabilizer[135].small nanocrystals were formed, by antisolvent precipitation technique, but their stability is not good for long period of time. They combined two cellulose binding domains to hydrophobin via genetical engineering for improving the long term stability[136].Engineered utilized the hydrophobin as a stabilizer for itraconazole nanocrystals with the aid of cellulose binding domains, nanocrystals were immobilized to cellulose nanofibrils,nanocrystals produced by an antisolvent precipitation technique. This increased their stability. As compared to commercial Sporanox 1.3-fold bioavailability is enhanced in nanocrystalline formulation. The role of the cellulose material is crucial for drug release profiles. When hydrophobin stabilized, itraconazolenanocrystals were imbedded into red pepper nanocellulose or the microcrystalline cellulose matrix, the in vitro drug release was immediate[137].

9.7 Cyclodextrins:

Cyclodextrins are used in pharmaceutical formulations because they can improve the solubility of poorly water-soluble drugs, via complex formation,[138]. emulsion solvent diffusion method used in a study with indomethacin, cyclodextrins used as a stabilizer [139]. The prepare indomethacin nanocrystals were 300–500 nm in particle size, and cyclodextrin networks were formulated via intermolecular relations between cyclodextrin molecules stabilizing the particles. α-form of crystal was presented in indomethacin nanocrystal, while γ-form was presented in original bulk drug, which improved the dissolution of nanocrystals even more. The dissolution from nanocrystals was rapid and complete.

9.8 PVA:

Xia et al. formulated PVA stabilized nitrendipinenanocrystals with the help of precipitation-ultrasonication method[83]. They noticedthe new drug crystals were most likely in an amorphous stateafter the precipitation[120],but when extra energy, such as ultrasonication, was put into the system, the high-energy amorphous state tended to transform to a more stable crystalline form. Based on XRPD analysis, the crystallinity was improved by ultrasonication[83]. Precipitated nitrendipine produced lipophilic surfaces, which was fast covered by PVA. However, the crystal growth still continued, because the absorption was not fast enough. The external mass transfer and adsorption rate were intensified, , when the ultrasound was applied to the suspension. As a result,As a result, PVA sheltered the drug nanocrystal surfaces, and the system reached surface energy and enthalpy minimum values meaning adsorption equilibrium with the sterically stabilized drug nanocrystals. In this case, the ultrasonication after the precipitation process caused the fast change of amorphous form into the more stable crystalline form. simultaneously , aggregate formation was hindered with a higher adsorption rate of stabilizer on the nanocrystal surfaces.

9.9 cationic charged chitosan:

Kurakula et al. studiedatorvastatin nanocrystals and cationic charged chitosan is used as a stabilizer[140]. Nanocrystals were prepare by the probe sonication method. The impact of charge density (different molecular weights of chitosan) on nanocrystal stabilization was studied. The smallest nanocrystals, 394 nm, were reached with low cationic charged type of chitosan. In this case, the stabilization effect was due to both steric and electric stabilization.

10 Conclusion:

From the last decade in the biomedical field Nanoparticulate delivery systems have been extensively used. Amongst the a variety of types of nanocarriersNLC system have great efficient delivery of therapeutics by various routes of administration such as pulmonary, topical, intranasal, ocular and oral routes. Because of their small size and of crossing the BBB even without surface functionalization makes them an excellent applicant for delivery of therapeutics across the brain. Further the additives used in the NLC that are biodegradable, biocompatible, non-irritating and mainly approved with GRAS status. Also they are easy to scale up and can be change to achieve optimize and desired particle size and release profile, improved drug loading and higher stability of the therapeutics. Also the no of NLC dermal and other formulation are available in the market.

11 Future prospective:

The NLCs have a very auspicious future as nearly 40% of the new drug compounds are hydrophobic. the numbers of research groups working with NLC as well as the number of publications in this area have distinctly increased from the last 5 years. It reflects that more and more scientists in academia have realized the capability of the NLCs and have started to develop it.in countries like Germany, Canada, China and also in countries such as Slovenia and Poland Research groups are placedThere is no breakthrough for a delivery system if only academic research groups are developing it. Success can be possible if pharmaceutical industry takes up developments as well to guarantee a broad application of a carrier system. Contract research organisation engaged with research and development of newer drug delivery systems develop pharmaceutical solutions adapted to the needs of many different pharmaceutical companies, that means the technology will spread to many companies and not only localized inside one particular company using this new technology just limited to their own drugs. It appears that more drug products will be formulated as NLC because of the obvious

12 Conflict of interest:

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

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