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Review Article

Solid Lipid Nanoparticles: Overview on Excipients

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ABSTRACT

Nanotechnology is now a day's emerging fields in drug delivery approach. Solid lipid nanoparticles are colloidal particles of 1-1000 nm size and made up of lipids solid at room temperature, biodegradable, biocompatible. It gives controlled or sustained release and if surface modified then target release also. Compatible with Various route for administration and no toxicity problem make it versatile. Lots of methods available for preparation and scale up are also easy. For any of the dosage form it's important to select excipients on various criteria. This review gives brief idea about excipients and its suitability for solid lipid nanoparticles.

Key-words: Solid Lipid Nanoparticles, Nanotechnology,

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Introduction:

Solid lipid nanoparticles were introduced to get benefit of emulsion and liposome[1, 2]. Mainly SLN are made up of lipids which are solid at room temperature and biodegradable or biocompatible[3]. Using safe lipids drawback of polymeric nanoparticles toxicity can be overcome. SLN prepared with 2.5% lipid don't exhibit any cytotoxic effect[4]. There are various methods available for preparation like high pressure homogenization[5], microemulsion method[6], emulsification and ultrasonication[7], solvent evaporation[8], super critical fluid method[9],membrane contactor technique[10], Among them high pressure homogenization is most preferred in industrial scale as desired particle size can be achieved easily and no organic solvent required for preparation[11].

Solid lipid nanoparticles give controlled release drug delivery as here lipid matrix is present[2]. By surface modification we can also increase its residence time in blood plasma[4]. It also gives target drug delivery for brain or cancer tissue [12-15].

Drug is already solubilised in lipid so solubility and bioavailability of poorly water soluble drugs can be increased[5, 16]. Particle sizes with 100-200 nm will not up taken by RES system of liver and so bypass first pass metabolism.

Mainly two excipients are used in preparation of solid lipid nanoparticles. Lipids and stabilizer (surfactant).

Lipids which are biocompatible biodegradable and solid at room temperature are used. Fatty acid, fatty alcohol, triglycerides, mixture of mono-di glycerides wax and fat are used. In case of surfactant mainly non-ionic surfactant are used.

Mainly non-ionic surfactant are used which are compatible for the internal use.

Lipids

Main criteria for lipid selection are as following:

- Solubility of drug in melted lipids[17, 18]
- Chemical and physical nature of lipid also affects as lipid which forms more crystalline particles will lead to more drug expulsion[18, 19]. Lower crystalinity matrix higher would be degradation and vice versa[20].
  Transition to highly ordered lipid particles also leads to drug expulsion. If polymeric transition will occur in β form during storage then drug expulsion will be more prone[21].
- Drug incorporation rate decreases with following order: supercooled melt<α modification < β'modification < β modification [2].
- Thermodynamic Stability and Lipid packing Density[22]
- For topical purpose occlusive property also depends on degree of crystallinity of lipid [23].

Compritol ATO 888

Compritol ATO 888 most preferred excipient for SLN and have been used by numerous research groups. Solvent injection method was used to prepare SLN and sustained release with storage stability was achieved. Non fickian in vitro drug release was followed by Hixson Crowell model[24].

Compritol SLN prepared with pluronic F68 & SDS are GIT stable[25]. Spray drying of Compritol SLN was also made successful by decreasing lipid content and using carbohydrate by freitas and group[26].sugar prevents the aggregation of lipid particles and also retain stabilizer film around particles. Surajit das and co-worker found that entrapment efficiency is also good as compare to many other lipids as it is mixture of mono and di glycerides there is more space in lattice to accommodate for drug[27]. Compritol in combination with cacao butter was found to be beneficial as it increase entrapment efficiency of saquinavir[6]. compritol SLN are stable in dark light and increase in particle size on day light or artificial storage, same way zeta potential also vary with storage condition. It was found to be stable in plastic container instead of glass. SLN stored in siliconized vials at 8^0C was stable for 3 years[28].on storage at 40 ^{0}C SLN aggregates and forms gel[29].it was concluded that cooling rate during SLN preparation as high cooling rate induces less orders crystal formation and so drug loading is higher compared to other lipids[30]. compritol along with solubility enhancement found to be best for lymphatic targeting with compare to stearic acid, monostearin and tristearin[31].higher the fatty acid chain would be higher the lymphatic uptake[32].presence of mono and diglycerides also promotes solubility of drug in lipid matrix[18].

Glyceryl monostearate & glyceryl monooleate

GMS contains glycerides of saturated fatty acids and usually melts at 50-55^{o}C.it is mostly preferred in cosmetics products. Its glycerol of stearic acid. While GMO melts at 35-40 ^{0}C. comparative study shows that GMO produces less ordered crystal structure so drug expulsion is low and also it provide sustained release than GMS. While drug entrapment in GMS is higher than GMO[33]. Esterification of glycerol by long chain fatty acids is responsible for high hydrophobicity of glycerides; this influences the lymphatic uptake of glycerides SLN[32].

Fatty acids

Stearic acid, palmitic acid tetradecanoic acid are used for reparation of SLN. Among all entrapment efficiency is found to be highest in stearic acids as length of fatty acid increases space to accommodate drug increases. Entrapment efficiency is very poor as compare to mono di and try glycerides[34]. While particle size is high in case of stearic acid as high melting point so it affects homogenization process[35]. As the carbon chain length increases drug release is retarded for long time. Degradation velocity is higher in stearic acid and palmitic acids as enzyme for the degradation are available in body. Fatty acid of C14 – C18 are more effective for lymphatic target[36].

Fatty alcohol

Stearyl alcohol has very low melting point compare to other lipids but it was found to be git stable on pH and electrolyte test[25].fatty alcohol like stearyl alcohol or cetyl alcohol will be digested by fatty alcohol dehydrogenase (FADH) in the liver as initro incubation of cetyl alcohol based SLN shoed 90% degradation after 24 hrs[37].

Wax

SLN prepared with cetyl palmitate shows better stability and less drug expulsion as compared to glycerides specially monoglycerides[32]. Cetyl palmitate has better invitro degradation rate and lower invivo toxicity as compared to compritol[38].

Bees wax and carnuba wax was used to prepare ketoprofen loaded SLN by where combination was found to be more effective for small particle size. Carnuba wax is more lipophilic (less free fatty acids and hydroxyl group) while bees wax is less lipophilic (high free fatty acid and hydroxyl group). So drug release found to be at higher rate in bees wax[39].

Cacao butter is triglycerides having better biocompatible and lower invivo toxicity than the semi synthetic lipids and easily obtained from theobroma cacao having 40% unsaturated fatty acids. aggregation is more prone if lipid concentration is increased by some extent[40].

Tristearin, Tripalmitin, Trilaurin

Triglycerides SLN are more stable as compare to mono and di glycerides SLN[29].

For parenteral purpose flocculating temperature may affect sterilization process,RH Muller found that trilaurin with poloxamer 188 is not stable when autoclaved[2]. As compared to medium chain tri glycerides long chain try glycerides promotes more lymphatic absorption[41].

Mainly four grades of dynasan are available in market. It is chemically mixture of di and try glycerides. Dynasan112 is pH and electrolyte sensitive lipid which shows heavy aggregation upon addition of electrolyte or artificial gastrointestinal media[25]. SLN Stored at 40 ^{o}C for 2 year will aggregate and convert into gel[29].

Triglycerides are not always converted into solid after cooling. They may remain in liquid state for several months and so emulsion of supercooled melt is prepared rather than SLN that may create stability and drug expulsion problem[42].

Table 1: Lipids their chemical composition and melting point[43, 44]

Lipids	% of Glycerides			Melting Point (^{o}C)
	Mono	Di	Try	
Compritol 888 ATO (glyceryl behenate)	12-18	52-54	28-32	70-75
Imwitor 900(GMS)	40-50	40	5	55-60
Dynasan 112	-	3	96	43-47
Dynasan 114 (Trimyristin)	-	4	95	55-58
Dynasan 116 (Tripalmitin)	-	3	96	61-65
Dynasan 118 (Tristearin)	-	2	97	70-73
Precirol ATO 5 (Glyceryl palmitostearate)	8-17	54	30	52-55
Witepsol S 51	4	33	62	30-32
Witepsol S 55	10	14	75	34-36
Softisan 154 (hydrogenated palm oil)	-	3	96	55-60

Surfactant

There are so many surfactant tried by various research group like poloxamer 188[24], poloxamer 407[24], tween 20[45], tween 60[46], tween 80[33], span 20[33], polyvinyl alcohol[47], cremophor EL[48], lecithin[4], sodium dodecyl sulphate[49], sodium glycolate[50].

Surfactants are required to stabilize the dispersion of SLN and also prevent aggregation. HLB value is mainly considered for selections of surfactant as if HLB is lower than 9 are lipophilic while and more than 9 will be hydrophilic. Sometimes blends of two surfactants are also used which provide more stability[17].

Also smaller particle size can be achieved by with higher surfactant ratio[39]. Drug entrapment is also increased with higher amount of surfactant. Surfactant acts as stabilizers. Stability mainly indicated by zeta potential and range for electrical stabilization is 40 mv and for steric stabilization 30 mv[29].

Surfactant imparts significance influence on crystallization temperature and polymorphic transition of lipids[50].ionic surfactant(sodium glycolate) retain α modification while non ionic surfactant(cremophor) retain β modification[51].

Sometimes change in pH and electrolyte will lead to steric destabilization and poloxamer 188 at law zeta potential gives steric stabilization[25].

Enzymatic degradation was also found to be slower by using poloxamer 407 steric stabilizer, while cholic acid soium salt accelerating degradation and tween 80 has not pronouncing effect on enzymatic degradation[52].

For parenteral purpose toxicity also matters so surfactant must be of GRAS status like lecithin poloxamer 188, tween 80, sodium glycolate[53]. Some excipient may lead to blood coating and change pharmacokinetic profile when administered paranterally. Compritol with tween 80 and poloxamer 188 don't show any effect but span 85 may lead to RBC aggregation[54]. Excipient should not elicit any allergic reaction like cremophor EL was found to be allergic in paclitaxel emulsion for parenteral use[55].

Soya lecithin purports enough zeta potential to electrostatically stabilize trilaurin SLN formulation.poloxamer will only provide steric stabilization while lipoid will give electrostatic stabilization.

For slow clearance and prevent liver uptake PEG is used as surface coating material as it is less prone to binding with plasma protein and other biological material. Pegylation is also found to be effective for this purpose. Other material like poloxamer and Brij was also tried.

Only coating with polysorbates found to be effective for CNS pharmacological effect as they cross BBB while poloxamer and cremophor are not effective. Coupling with cationic albumin is able to cross BBB. For brain targeting of Vincristine two different surface coating material was studied tween 80 and vitamin E (TGPS). Here brain content was found higher with tween 80 coating as compared to TGPS[12].

Gelucire 50/13 and 44/14 can also be used as stabilizer. Gelucire 50/13 was successfully used to prepare SLN of Repaglinide for oral and Triclosan for dermal application[56].Gelucire also inhibit p- gp efflux pump an so increase absorption after oral administration[57].

Drug candidate

BCS Class II drugs are most suitable candidates for SLN preparation as they have prominent solubility and bioavailability problem like valsartan[24], Ofloxacin[58], Saquinavir [6].

Drug molecule which undergo first pass metabolism and rapid inactivation are also good candidates as SLN are not uptake by RES and so don't undergo hepatic metabolism like Simvastatin[59] , Nitrendipine[60]. controlled release over long time is achieved in topical like Triptolide[61], Tretinoin[62], Resveratrol[63] or systemic drug delivery anti TB agent[64]. Surface modification also does

same for parenteral administration. Drug degradation is also prevented in case of photodegradable drug like tretinoin [62].

To enhance absorption where p-gp efflux is hurdle for drug absorption specially in anticancer drug like Doxorubicin[65].

It enhance the concentration of drug in brain as they cross BBB efficiently like in case of Nevirapine[66], Idebenone[67].

Topical drug delivery is possible for various skin problem especially inflammation and cosmetic purpose eg. Aceclofenac[68] , CoQ10 [69], Clotrimazole[27].

Conclusion

Lots of method available for preparation of SLN but still there is need of excipient which is safe and fulfil all aspects for SLN workability. Especially for parenteral purpose, excipient which is safe and resists change during sterilization is required.

Declaration of Interest

Author indicates no potential conflict of interest.

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