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SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM- A REVIEW

Mohit Chugh*[1], Anil Kumar Goyal[2] and Rajesh Asija[3]

[1]Research Scholar, Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan India.
[2]Associate Professor, Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan India.
[3]Principal, Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan India.

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***Corresponding Author**
Mohit Chugh
Research Scholar, Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan India.

ABSTRACT

For the purpose of improving bioavailability, self-nanoemulsifying drug delivery systems (SNEDDS) have become an essential formulation technique. Oil, surfactants, solvents, and cosolvents/surfactants are all components of SNEDDS. The main feature of these systems is their capacity to produce an oil-in-water (o/w) emulsion or micro emulsion after light agitation and aqueous phase dilution. The choice of SNEDDS components is heavily influenced by physicochemical characteristics, drug solubilization ability, and physiological destiny. These brand-new SNEDDS carriers seem to be helpful for regulating the rate at which poorly water-soluble medicines release.

KEYWORDS: Self Nano emulsification, Oral Delivery, Solubility, Surfactants.

INTRODUCTION

With the recent development in the focus on the biological targets and gene delivery a much more concentrated efforts have been made in exploring the lipid based delivery of the complex to deliver molecules as well. The data from one of the research say that out of 10000 leads identified during the NCE development almost about 50-60% of the leads had poor aqueous solubility.[1] Lack of solubility improvement techniques would actually kill a potential drug molecule. Thus, in recent years a significant shift has happen in developing and exploring the techniques that can be employed for the improvement in solubility of these compounds.[2]

Self Nanoemulsifying Drug Delivery System

SNEDDS are isotropic mixtures of an oil, surfactant and co-surfactant wherein the drug is present in dissolved state. They form fine oil-in-water emulsions when introduced into aqueous media under gentle agitation. The digestive motility of the stomach and intestine provides the required agitation necessary for self-emulsification in vivo (Orlagh M. Feeney et. al., 2016). Also, the finer the emulsion form the easier it is for the digestive enzyme to break it or form chylomicron which facilitates absorption.[3]

Excipients used in lipid based formulation One of the most diverse type or category of excipients available in today's world for the formulation scientist is lipids. They most amphiphilic in nature wherein fatty acid chain forms the lipophilic component of the molecule and the esterified portion of the chain working as hydrophilic component.[4] With growing competition there are lots of lipid components which are launched by the excipient companies to provide plenty of option to the formulator for designing their formulations. This particular works as two edge sword wherein the formulation scientist should keep couple of points in mind before concluding of the type of excipients to be used.[5]

The major important points to be look into before shortlisting the excipient are

- Miscibility with the components and the drug substance
- Room temperature morphology
- Digestive route and fate of digested components
- Chemical and physical stability of lipid component
- Compatibility with the capsule shell, in case it needs to be filled into capsule
- Safety data and other regulatory concerns
- Capacity to solubilize the components
- Viability in terms of cost effectiveness.[6]

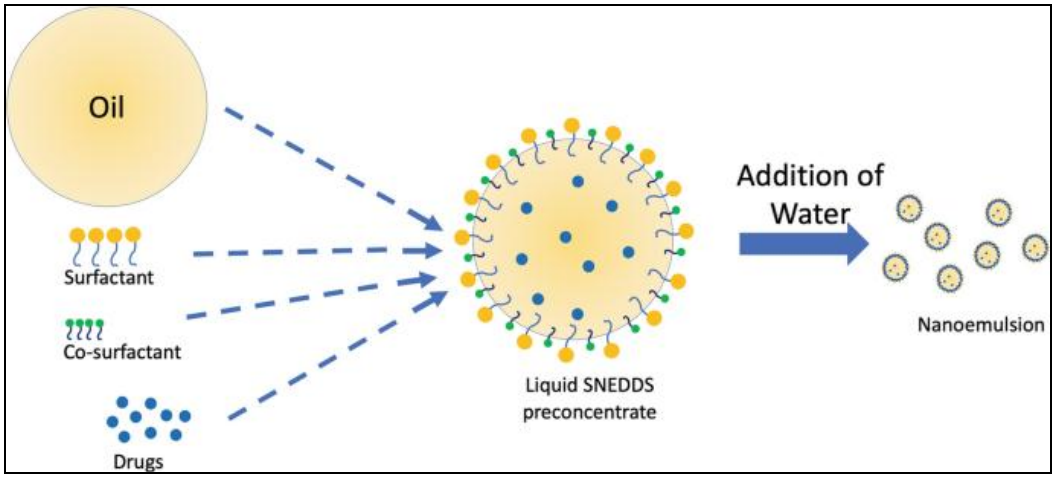

Figure 1: Schematic Diagram of SNEDDS.

For selections of excipients in SNEDDS based formulation few important criteria's needs to be kept in mind before finalizing them for formulation development.[7] Description of each of the ingredients are listed and discussed below.

Oil excipient

Oil is one the most important component of the SNEDDS based formulation wherein it is responsible for solubilization of the drug substance. It is also helpful in enhancing the lymphatic uptake of the drug to avoid the first pass metabolism and enhance bioavailability of the molecule. Typically, the molecular structure of the oil and its interaction with the surrounding is responsible for its emulsification tendency.[8] Thus, the oil is divided into three major categories.

Vegetable oil derivatives

The vegetable oil by themselves is known to be less stable and get rancid very quickly. The basic reason cited for this instability is the unsaturation of the oil, the more the unsaturated the oil the less is the stability. Thus, derivatives of vegetable oil mostly the hydrogenated vegetable oil are commonly used. The hydrogenation would remove the unsaturated bond in the molecule rendering it much more stable. Few of the examples of commercially available hydrogenated vegetable oils are

- Lubritab hydrogenated cottonseed oil
- Lipo hydrogenated soybean oil
- Cutina HR hydrogenated castor oil.[7]

Triglycerides vegetable oil

Triglycerides vegetable oil is known to be mixture of long chain triglycerides and medium chain triglycerides depending on the source from which they are obtained. The vegetable oil per se is known to be safe and can be easily digested by the body.[9] Mostly all vegetable oil are rich in unsaturated LCT in nature except few like coconut oil which are rich in saturated MCT. Generally, due to high solvation capacity and resistance towards oxidative stress the medium chain triglycerides are preferred over long chain triglycerides. In SNEDDS based formulation the use of vegetable oil are limited because of their poor dispersion property.[10]

Mixed partial glycerides

Partial hydrolysis of the vegetable oil leads to formation of ternary mixture of mono, di- and tri-glycerides. The degree of esterification and extent to which they are esterified the properties of partial glycerides change significantly. They have varying melting point, physical state and hydrophilic lipophilic balance.[11] Mostly, unsaturated fatty acids and medium chain triglycerides are used for improving the bioavailability of the formulation whereas the long chain saturated components are used to prepare the extended release formulation. Few examples in this category are:

- Capmul MCM Glyceryl monocaprylocaprate
- Maisine 35-1 Glyceryl monolinoleate
- Peceol Glyceryl monooleate

Surfactant excipient

The molecules which are used to stabilize the emulsion by arranging themselves in between the aqueous phase and oil phase are known as surfactants.[12] Surfactants are another major component of SNEDDS formulation as they are responsible for the stability of the formulation upon dispersion in water. Safety, toxicity and hydrophilic lipophilic balance are the important parameters looked into for the selection of surfactant. Generally, non-ionic surfactants are preferred.[13]

The HLB of the surfactant defines whether the formulation would be SEDDS or SMEDDS or SNEDDS. The critical HLB value cited is 12 wherein the surfactant with HLB of less than 12 are known to form SEDDS formulation and the surfactant with HLB more than 12 are known to form SMEDDS/SNEDDS formulation. The rationale for such selection is cited to the ability to have self dispersibility property in the gastrointestinal lumen.[14]

Surfactant which are naturally occurring are less toxic but have poor self emulsifying property thus, the most commonly used surfactants in SNEDDS based

formulation are polyethoxylated lipid derivative. Examples of surfactants commonly used in SNEDDS formulations are

- Brij Polyethoxylated alkyl ester
- Kolliphor Polyethoxylated glycerides
- Myrj Polyethoxylated fatty acid esters
- Tweens Polyethoxylated sorbitan esters.[15]

The surfactants are known to increase the gastric emptying time; however, it should be kept in mind to use the lowest possible surfactant concentration. The usual surfactant concentration used for SNEDDS based formulation is 40-60%. These high concentrations are needed to provide self dispersion property as well as stability to the system. Increase in surfactant concentration leads to decrease in droplet size and this reduction in droplet size leads enhance water penetration into the oil and faster solubilization. Surfactant can contribute to the enhancement of solvency tendency of oil component due to their amphiphilic nature. Thus, a large amount of drug can be incorporated in SNEDDS based approach.[16]

Cosolvent excipient

Another major component of the formulation is cosolvent in the lipid based delivery system. Generally, water soluble co-solvents are used in formulation to have variety of benefits. The co-solvent helps in dissolving the hydrophilic surfactant in large quantity in the hydrophobic oil components by acting as common solvent. It also helps in stabilizing the nanoemulsion formed upon dispersion by aligning themselves in between the surfactant molecules. The most important advantage of having the co-solvent in the SNEDDS based system is due to its ability to increase the solvation property of oil for the hydrophobic drug.[17]

Few examples of the most commonly used co-solvent in SNEDDS based formulations are as follows

- Glycerin
- Polytheylene glycol
- Propylene glycol
- Ethanol
- Transcutol

The co-solvent plays vital role in SNEDDS formulation, however, at the same time few thing need to be kept in mind while their selection and amount to be used. The alcohol (ethanol) has the tendency to migrate into the capsule shell thereby enhancing the chances of drug precipitation with the capsule. Thus, alcohol should be avoided or minimized its used in case the SNEDDS formulation has to be filled in capsule shell. Also, the solubility of co-solvent with the oil component is limited and beyond a certain point the excess quantity added lead to generation to two phases in the system.[18]

Additional ingredient

To have a complete formulation of SNEDDS based approach although oil, surfactant and co-solvent are important components. Few other components are also added to provide stability to the formulation. Many a times antioxidants which are soluble in oily components are added to prevent both drug substance and oil components from getting degraded. The commonly used antioxidant in SNEDDS formulations are

- Propyl gallate
- Alpha tocopherol
- Butylated hydoxyl anisole
- Butylated hydroxyl toulene

At times other ingredients may also be added depending on the formulation challenge and problem we are trying to resolve. Preservative may be added in case large amount of microbial promoting component are added. Type of capsule shell (HPMC or gelatin) can be used in case formulation is to be dispensed in solid form.[19]

Challenges in Snedds System

There are few challenges also associated with SNEDDS delivery system. One of the major challenges is the ability to solubilize drug the mixture of oil and surfactant/co-surfactant. The crucial part of SNEDDS successful formulation is its ability to solubilize the drug within itself which prevent drug from precipitating / crashing out in the gastrointestinal tract. The ability of SNEDDS to form nano emulsion gives it the advantage over the other form of delivery system.

Another major challenge for the development of SNEDDS formulation is taste masking of drug, lipid and surfactants. The bitter and acrid taste of drug, lipid and surfactant should be masked for better patient acceptability and drug dosing regimen compliance. Most of the drugs currently are bitter in taste when taken with oil the nausea and vomiting sensation may increase due to synergistic effect. This may lead to non-compliance of the drug therapy and the potential advantage of this delivery system may not be explored. Thus, it is most important to have taste masked lipid formulation for better acceptability of formulation and benefit to patients.[18]

Industries currently apply additional techniques to make them industrially and commercially viable by converting them into solid dosage forms. The few techniques used along are listed below:

Direct capsule filling of solution/suspensions: A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell during expected shelf life of product. For such kind of formulations, the bulk fill reservoir needs maintenance of temperature at which formulations is pourable viscosity and subsequently filled in capsules. The challenge additionally lies in fact that, in molten state it's essential to avoid phase separation and sedimentation of the dispersed drug. The filling temperature is one of the crucial parameters for capsule filling and has to be at least 2°C above the temperature at which the apparent

viscosity of the drug-excipient mixture significantly increases during cooling.

Spray cooling: Spray cooling also known as spray congealing is a process whereby the molten mass (containing drugs and mainly solid lipids) is sprayed into a cooling chamber. During contact with the cooling air and traversing the chamber, the molten droplets congeal and re-crystallize into spherical solid particles which are subsequently collected as fine powder. The fine powder may then be processed for development of solid dosage forms like tablets or directly filled into hard shell capsules.

Spray drying: Spray drying is defined as a process by which a liquid dispersion/solution is sprayed into a hot air chamber to evaporate the organic/aqueous solvent(s). The process yields solid microparticles. Equipment described for spray cooling can be used for spray drying. Before spray drying, the formulation is prepared bydissolving/dispersing excipient(s) along with drug in organic solvent(s).[9]

Adsorption on solid carriers: Liquid lipid formulations can easily be transformed into free flowing powders by adsorption onto solid carriers for ease handling. The adsorption process is simple and involves addition of the liquid formulation onto the carrier of choice by mixing in a blender. The carriers used for this purpose include calcium silicate, magnesium aluminometasilicate, silicon dioxide, or carbon nanotube. Carrier selection is governed by their adsorption abilities and the flowability of the mixture after adsorption.

Melt granulation: Melt granulation or thermoplastic pelletization is a single step process that transforms drug-excipient powder blend into granules or pellets. Typically, lipid-based binders are used between15% and 25% w/w level depending on the fineness of the powder mixture. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement.[20]

Melt extrusion/extrusion spheronization : Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions. Lipid-based excipients have been included in the past as additives to classic extrusion formulations in order to enhance the dissolution or bioavailability of poorly soluble drugs. This approach has been successfully tried for 17β-estradiol and two model drugs(methyl and propyl parabens) with surfactants such as sucrose monopalmitate (Surfhope® D-1616), lauroylpolyoxyl glycerides (Gelucire®™ 44/14) and polysorbate 80 (Tween® 80).[21]

Supercritical fluid based methods: Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. The coating process entails dispersing the drug particles (as powder) in a supercritical fluid containing one or more coating materials dissolved therein. Various lipid-based or lipidrelated excipients have been studied with this process. Examples include controlled-release applications using glyceryl trimyristate (Dynasan™ 114) and stearoyl polyoxylglycerides (Gelucire® 50/02).[21]

All the above techniques do not keep lipid formulation in their original form ie. Liquid. Thus, techniques should be applied to mask the taste of lipid formulation. Literature suggests most commonly used techniques for taste masking of the bitter drug are listed below (not limited to)

- Complexation
- Prodrug formation
- Drug coating
- Drug entrapment in matrix
- Ion exchange resign
- Over encapsulation
- Salt formation
- Addition of sweetener and flavor

Complexation is known to cover the drug molecule and prevent it from interaction with the taste buds thereby masking the bitter taste of drug. However, it cannot be used for all kind of molecules and sometime drug may remain inside the cavity and do not come out at all. For prodrug and salt formation a chemical change in the drug is required which may change the entire physicochemical and pharmacological property of the drug, thus is less preferred.

Commonly used approach of taste masking for the lipid based product is use of inert material wherein it needs to be converted into solid form. The conversion of liquid SNEDDS to solid takes place by absorption of liquid SNEDDS over an inert carrier. These systems can be converted to solid intermediates like powders, granules and pellets by various techniques and can be filled in hard gelatin capsules or can be compressed into tablets after blending with suitable tableting excipients. The overall advantage of converting drug into SNEDDS is compromised by conversion to solid form and in turn converting it into tablet or capsule. The basic reason or rationale for converting to solid form is unpleasant taste of the lipid formulation which leads to lesser patient compliance. However, the challenge with this technique of taste masking is the loss of the liquid form of the drug which could have been more positive if taste masked in the liquid form itself without conversion into solid.[22]

Taste assessment of SNEDDS formulation

Another major challenge is the real assessment of the taste of formulation without getting exposed to the drug substance directly. The frequent taste evaluations by healthy human may unnecessary expose them to the

untoward effect of drug. Thus, the industries have shifted focus towards the electronic tongue for the evaluation of the taste of the formulations.[23]

The taste perceived by human tongue can be classified into five categories salty, sour, sweet, bitter and umami.[24]

Various sensory mechanism gives rise to the taste describe before after consumption of material. The possible mechanisms that may give rise to taste perception are listed below:

Taste Mechanism

Sour taste: Hydrogen ion blockage of sodium or potassium channel
Saltiness: Sodium ion efflux through apical sodium channel
Sweet taste: G protein coupled receptors
Bitter taste: G protein coupled receptors

The detailed mechanism and exact reason for taste is still not understood fully. The pharmaceutical drug substances most have a bitter taste. Chemical compounds dissolved at the site of receptors give the taste of the material which is perceived by individual.[25] On similar mechanism, the sensors of the electronic tongue detect the dissolved organic and inorganic materials.

The sensors of the electronic tongue have different reaction with the sensors just like human tongue. The information or signal provided by each sensor is complementary and the combination of all sensor response gives a unique pattern. It is easy to control the detection threshold of the sensors thus can provide more informative results depending on the requirement. Electronic tongue helps in reducing the overall turnaround time for the taste assessment of the product thereby making it much more cost effective. Since it is majorly free from human intervention thus, it free from bias as well.[26]

Variety of pharmaceutical applications for which the electronic tongue could be used is as follows:

- Bitterness quantification of drug substance;
- Aids in development of matching placebo for the blinded studies or clinical trials;
- Regular monitoring of final formulation;
- Indirect assessment of coating over the core formulations having a bitter taste;
- Comparison between marketed product and test product.

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