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MODIFIED OILS USED IN PREPARATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Self-Nano Emulsifying drug delivery system is a commonly utilized formulation technique in modern technology to improve solubility, especially in hydrophobic drugs. Oils, surfactants, and co-surfactants are the three main ingredients in a self-nano emulsion. Modified oils (hydrogenated oils) and natural oils are the two types of oils utilized in formulation. Because of their fluidity and solubilization capacity, hydrogenated oils are more commonly used in these applications. The particle size for nano-emulsion is between 20-200nm. The different advantages of self-nano emulsifying drug delivery system have been elaborated in the further article like showing better bioavailability, thereby increasing in patient compliance compared to conventional dosage form and hence it can increase the therapeutic efficacy. Oils are the most significant ingredient in the formulation for medication transit in the intestine and to improve adsorption. The main purpose of this review is to focus on the various types of modified oils like short chain, medium chain, long chain. A brief description on the various types of oil such as captex, capyrol, campul along with their chemical structure has been discussed below. The main aim of this article is to gather information about characteristics of various modified or hydrogenated oils that are used in preparation of self-nano emulsifying drugs. Since the characteristics of these oils vary their solubility efficiency will also be different. From this article it is concluded that Modified oils are mainly used for the preparation of self-nano emulsifying drugs as it increases the solubility of the drug thereby improving its stability.

KEYWORDS: Self-nanoemulsifying; Modified oils; Bioavailability; Nano-emulsion.

INTRODUCTION

One of the best method to improve the solubility of drug is self-emulsifying. In self-emulsifying drug delivery system, there are Self Nano-Emulsifying Drug Delivery System (SNEDDS) and Self-Micro-Emulsifying Drug Delivery System (SMEDDS). Delivery system for self-nano emulsifier consist of oils (modified or natural oil), surfactants, co-surfactants, drugs and for converting into solid self-nano then adsorbents are also used. As it is a stable emulsion for partitioning drug between oil and aqueous phase it will provide a large interfacial area and also provide improved bioavailability and better dissolution rate. As it is simple and cost-effective manufacturing facilities SNEDDS is a choice of formulation.[1]

Self-nano emulsifying is the best method for the development of hydrophobic drug. For drug with poor water solubility a solidification system is used to convert them into solid by in - cooperating the liquid excipient so that it will have properties of both liquid SNEDDS as well as solid SNEDDS. For increasing the dissolution rate the drug dispersed in polymeric carrier that has small particle size and a large surface area. Some of the method that used are kneading melting, solvent wetting method. Some of the method as drawback as well.[2] The most convenient method that used for enhancing the solubility and bioavailability of drug with poor water solubility is solid dispersion by surface modified technique. SNEDDS spread rapidly in gastrointestinal tract and When SNEDDS are consumed in the gastrointestinal tract, the digestive tract provides sufficient agitation for the self-emulsion process. As SNEDDS had limitation like high production cost, capsule shell has incompatibility problems, low drug probability and stability, drug leakage and precipitation, low drug loading, few choices of dosage forms and Irri reversible drugs/excipients precipitation SNEDDS are prepared as liquid dosage form is administrated as soft gelatin capsules.[3]

Advantage of SNEDDS

- It provides long-term stability as no Water is present, when it is orally given, there will be no palatability problems as they can be converted into capsules or tablet.
- It has more loading capacity because of high surfactant/co-surfactant ratio.
- In some cases, rapid onset of action is required so SNEDDS helps in enhancement of oral absorption of drug.[4]
- It can improve the physical stability of the formulation.
- Also help in filling it into unit dosage form
- The commercial viability will be increased.

- Reduces patient compliances or tolerability.

Application of SNEDDS

- To an extend it will help to overcome mucus gel barrier
- Delivery of biomolecules
- Drug targeting
- Solubility and bioavailability improvement[5]

Modified oil

Oils are the most important excipient that can be used in the dissolution of a drug which increase the transport of the drug through the lymphatic system which causes the drug to stay in intestine thus increase the absorption. Even though vegetable oil is safe, their use is limited as it has poor solubility in lipophilic drug and poor self-dispersing characteristics. Due to these characteristic modified hydrogenated oils are used as its final formulation.

Natural oils are mixtures of triglycerides of different chain lengths and saturation rate. In case of some vegetable oils the melting point increase with increase in fatty acid chain length and decreases with the desaturation rate. Except for palm and coconut oil, natural oils are rich in long -chain tri-glycerides. Coconut and palm oils are used as it contains medium chained triglycerides. Because of their larger capacity for drug dissolution and higher oxidation resistance medium chain triglycerides are preferred.

To overcome the disadvantage of vegetable oils, hydrogenated vegetable oils are used so that they will be less susceptible to oxidation. Hydrogenated oils are prepared by hydrogenation of unsaturated bonds in oils which increases the stability. It is widely evaluated because of their digestion products similar end product of GIT digestion product. Due to high fluidity, solubilization capacity and self-nano-emulsifying potential, excipients like galactolipids are considered to be safe for the use of formulation of SEDDS. When natural oils are separated in their glyceride fractions, they will have positive influence on drug resorption will increase and oxidization susceptibility will decrease simultaneously. The physicochemical properties and hydrophilic lipophilic balance value of oil depend on fatty acids and esterification rate.[6]

Free fatty acids and monoglycerides are the most common products of dietary lipid lipolysis. Short and medium chain fatty acids (C_3-C_{12}) are readily absorbed by the enterocyte and primarily transferred to the systemic circulation as soluble fatty acids via the portal vein.

Long-chain fatty acids (C >12) go through a separate process, where they are esterified and organized into chylomicrons after being absorbed by the enterocyte. Triglycerides, apoproteins, cholesterol, and cholesterol ester make up the chylomicrons, which are enormous transport vesicles, Because of their huge size, chylomicrons are secreted into the lymphatic system rather than the portal vein. When combined with long-chain triglycerides, the chylomicrons may be used as carriers for delivery to the lymph, by passing the liver and lowering the risk of pre-systemic metabolism.[7]

Use of modified oils in lipophilic drugs

In case of lipophilic drug oil is one of the most important excipients in the self-emulsifying drug delivery system formulation, because it can solubilize large amounts of lipophilic drug or facilitate self-emulsification and most importantly it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Self-emulsifying formulations have been designed using both long and medium chain triglyceride oils with varying degrees of saturation. Furthermore, due to their low ability to dissolve significant amounts of lipophilic medication, edible oils which may be the logical and preferred lipid excipient choice for the development of SEDDS, are not usually used. Since these excipients form good emulsification systems with a large variety of surfactants approved for oral administration and have higher drug solubility qualities, modified or hydrolyzed vegetable oils have been frequently employed. They have formulative and physiological benefits, and the degradation products they produce are similar to the natural end products of intestine digestion. In Self-Emulsifying Oil Formulation (SEOF), novel semisynthetic medium chain derivatives, which are described as amphiphilic molecules with surfactant characteristics, are gradually and successfully replacing traditional medium chain triglyceride oils.[8]

Types of modified oils

To formulate SNEDDS, medium and long chain triglycerides oils that shows various degrees of saturation are used. The oils are selected on the basis of the ability of the oil to solubilize the drug and also should have influence on both formulation-loading capacity and drug absorption. Natural oils exhibit relatively low drug-loading capacity and poor emulsification efficiency but in case of modified oils they will enhance the drug solubility in the formulation.

1. **Short chain**

- Triglycerides of capric/caprylic acids:

Commercial names: Captex 300, 350, Labrafac cc, Crodamol GTCC

- Di-glycerides of capric/caprylic acids:

Commercial names: Campul MCM, Akoline MCM

- Monoglycerides of capric/capryl acids:

Commercial names: Capryl 90, Capryol PGMC, Imwitor742.

2. **Medium chain**

- Glyceryl monooleate:

Commercial names: Peceol, Campul-GMO

- Glyceryl monolinoleate:

Commercial names: Maisine -35

3. **Long chain**

- Propylene glycol monocaprylate:

Commercial name: Campul PG-8, Sefsol 218

- Propylene glycol dicaprylate/caprate:

Commercial name: Miglycol 840, Captex 200

- Propylene glycol monolaurate:

Commercial name: Lauroglycol 90, Campul PG-12, Lauroglycol FCC.[10]

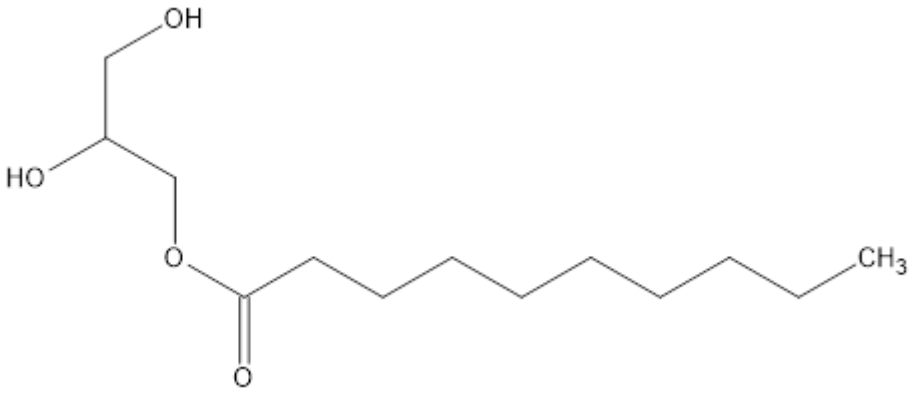
Medium chain triglycerides composed of triglycerides which have lipid chain ranging from C_8 to C_{10} like Capryol 90, Captex 300 whereas long chain consist of TG with the lipid chain lengths greater than C_{10}. Once these lipids are taken up by the stomach, they are broken down by gastric and pancreatic lipases into diglyceride, monoglyceride, and fatty acids. Once these are in the small intestine, they stimulate the release of endogenous gall bladder lipids, including bile salts, lipoprotein, phospholipids and cholesterol, which enhances the solubilization and adsorption ability of the intestinal tract via the formation of micelles. Comparing to medium chain lipids long chain lipids has more solubility.[9]

Due to better solubilizing ability and self-emulsification capacity for oral drug delivery in the intestine the clinically used enhancer is C_{10}. Sometimes it will only increase the drug transport through vein and limited ability to enhance the lymphatic transport of the drug. Long chain directly encapsulated into chylomicrons. Before entering the lymphatic system,

LCTs are encapsulated into chylomicrons, bypassing the first-pass hepatic metabolism. Even tough long chain triglycerides have the ability to pass the drug through lymph vessels. Sometimes it is difficult to emulsify.[10] To have the optimum properties and improve pharmacokinetics a mixture of MCTs and LCTs are used. Oil concertation had the highest effect on the particle size. The lipid constituents in all the SNEDDS formulation have variables with HLB values varying from 1 -6 and melting point varying from -78c to +78 c and mixtures of glycerides that contain fatty acid have HLB value ranging from 3-8. Several solubility enhancing surfactants approved for oral administration can be used in conjunction with semisynthetic derivatives to produce effective emulsion systems.[11]

Campul MCM C_8

It is a medium chain monoglycerides that shows both good solvent capacity for hydrophobic drugs as well as water penetrating capacity and upon hydration it will have self-dispersibility of liquid formulation. By encapsulating Capmul in high HLB surfactant, Capmul is likely to enhance emulsification during the dilution process with aqueous medium by increasing the interfacial fluidity of surfactant boundaries in the micelles.[12]

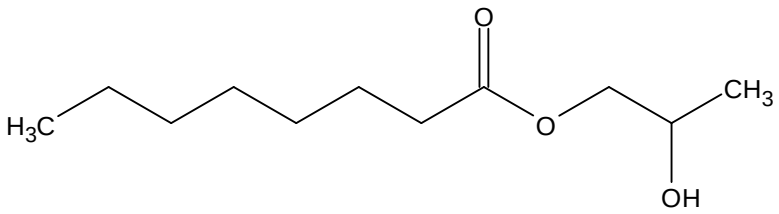


Structure of campul

Capryl 90

It is a medium chain fatty acid that has been widely used for pharmaceutical application especially the SNEDDS formulation that has maximum drug solubility. It has a good solubilization capacity. It can solubilize even a small concertation of drug. It is chosen among other formulation as it elucidates its specific action and mechanism. When absorption enhancers are given the local action and intestinal membrane should be considered and evaluated. It is also known as propylene glycol caprylate and consisting of propylene glycol esters of caprylic acid and it has monoesters and small fraction of diesters.[13] It acts as

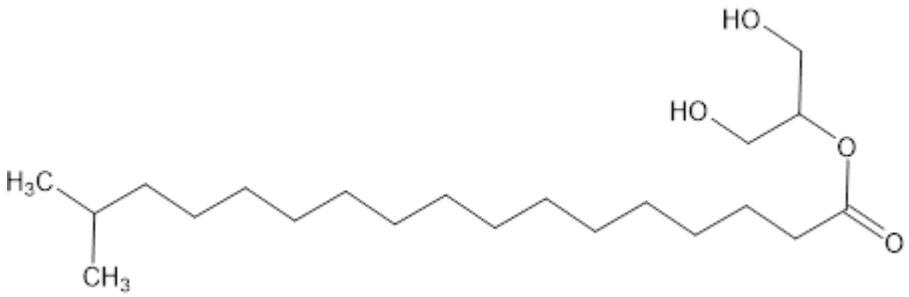
solubilizer for poorly soluble drugs and bioavailability enhancers and it is also used cosurfactant in topical formulation.[14]



Structure of capryl 90

Imwitor

It is an amphiphilic molecule that has surface activity. Furthermore, several hydroxyl groups inside Imwitor189 742's glycerol ester are free, which contributes to its polarity and excellent solvent characteristics for many medicines. This oil has low drug loading capacity[15]. Imwitor® 742 (caprylic/capric glyceride), a surface-active amphiphilic molecule, had the highest solubility of NDP and was chosen as an oil component. Imwitor® 742 can help lipid formulations penetrate the water barrier and self-disperse, and it has a high solvent capacity.[16]



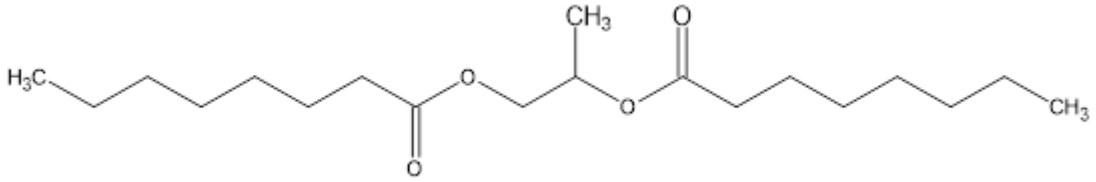
Structure of imwitor

Ghada et.al, had done a search Using imwitor and some other different compound in different concertation where he found that when lipid material such as imwitor concertation increase, the entrapment efficiency decreases that can increase the solubility of DZ in aqueous phase as the surfactant amount increases as the emulsifier's solubilizing effect increase.[17]

Captex

The medium chain triglycerides Captex-200 and Captex-355 are employed as a carrier, solubilizer, energy source, and viscosity modifier. These were originally used in the SEDDS CoQ_{10} formulation (Kommuru et al., 2001). Captex-355 is a medium-chain triglyceride that has been inter-esterified with coconut oil and is thoroughly refined and deodorised. It is

miscible with mineral and vegetable oils and soluble in a variety of organic solvents. In rats, it has an oral LD50 of >36 ml/kg, while in mice, it has an oral LD50 of >25 ml/kg. It can be used safely up to a concentration of 0.1 percent w/v, according to the current research.[18]

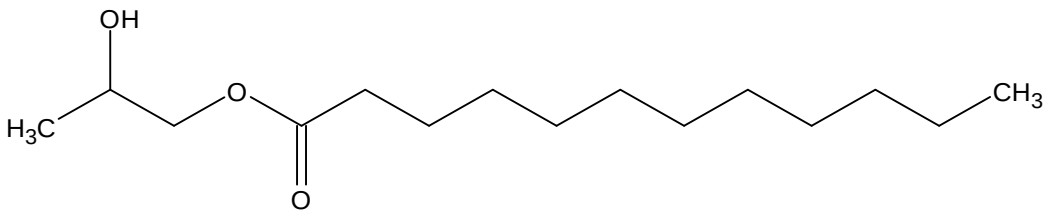


Structure of captex

Patil p et al, in his research study found that Because both Captex 200 and Miglyol 840 (both chemically, propylene glycol dicaprylate/ dicaprate, diglycerides) could dissolve bigger amounts of ketoprofen, it was possible to create more concentrated SEDDS. Because of their nonpolar nature, other triglycerides have a lower affinity for ketoprofen. Captex 200 was chosen among the two oils for future research. Aerosil considerably enhanced the viscosity of Captex 200 (7-13 cP). The surface of Aerosil (fumed silica) contains polar silanol (Si-OH) groups, making it hydrophilic.[19]

Propylene glycol monolaurate

It will strengthen the affinity with the cell membrane. To increase the oral bioavailability, it has to form mixed micelles formation. It is a non-irritanting skin emollient. In a study it showed that the APRS for atenolol, diltiazem, hydrocortisone and tazifylline increased upon the addition of ethanol to miglyol. It is synthesized by propylene glycol monolaurate by esterification of propylene glycol with lauric acid.[20]

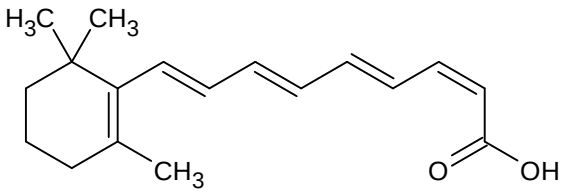


Structure of propylene glycol monolaurate

Cremophor RH 40-PEG 40

It is also known as hydrogenated castor oil. It is waxy liquid in nature and also has maximum water content of 0.2%. PEG -30, -40, -35, -33 hydrogenated castor oil can be used at 100% concertation. It comprised of 130 cosmetic ingredients. castor oil triglycerides consist of ricinoleic acid residues, 7% are oleic acid ,3% linoleic acid,2% palmitic acid, 1% stearic acid

and trace amount of dihydroxysteric acid. There is different type of castor oil like glyceryl triricinoleyl polyethylene glycol, fatty acid esterification. Hydrogenated castor oil 12-hydroxystearic triglyceride, PEG-40 hydrogenated castor oil can be used as oil in oral, topical and parenteral drug delivery systems.

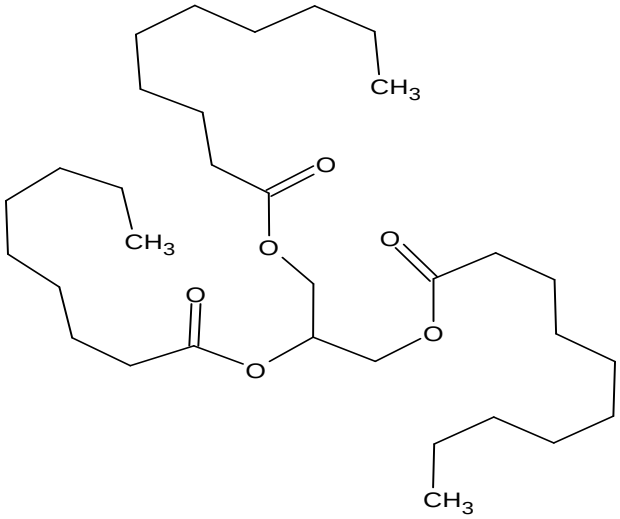


Structure of cremophor

PEG-40 hydrogenated castor oil can be used as direct food additives. PEG -40 has properties like hydrophilic, non-ionic solubilizer for fat soluble vitamins A, D, E, K and its clarity in alcohol solution. It is non-irritant.[21]

Tricaprin

It consists of monoglycerides and fatty acids that will increase the intestinal permeation of peptides. Triglycerides that contain C_{10} fatty acids are called tricaprin that are found in milk fat, coconut oil. It is one of the medium-chain triglycerides that has fatty acid of 8 to 12 carbons. When it is consumed the MCT will not be absorbed by the lymphatic system like other fats instead of that it will be transported to the liver directly. So, it will metabolize carbohydrates like fats.[22]

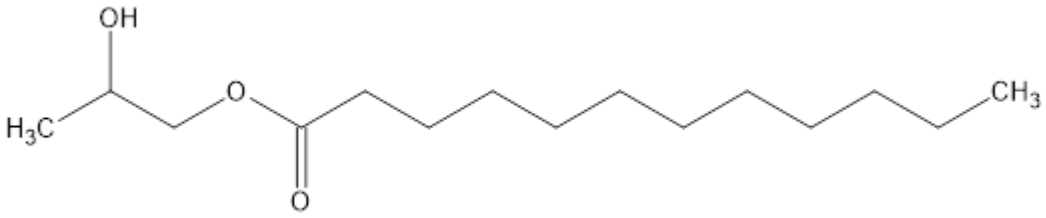


Structure of tricaprin

Ranhotra et al in a study found that tricaprin will give an average energy of 6.9 when compared to other conventional fats. In some other studies also found that it will be less effective for body fat than other long chain fats.[23]

lauroglycol FCC

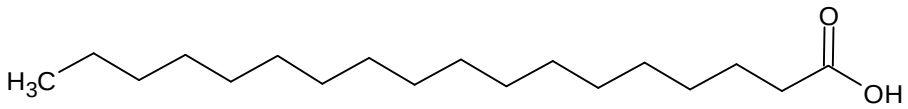
For the development of SEDDS/SMEDDS/SNEDDS of various pharmaceuticals for solubility, dissolution, permeation, and in vivo absorption bioavailability enhancement, Lauroglycol-FCC has also been explored as the oil phase.[24] Propylene glycol or polyethylene glycol are the hydrophilic heads of the molecules, whereas the lipophilic components are a combination of saturated or unsaturated C_8–C_{12} fatty acids.[25]



Structure of lauroglycol FCC

Labrafil

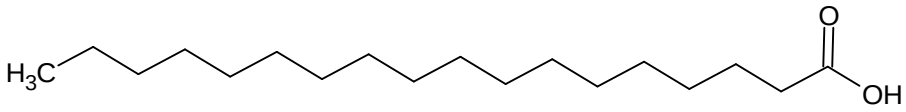
It is a medium chain triglyceride. Labrafil® M 1944 CS is made up of mono-, di-, and triglycerides, as well as mono and di-fatty esters of polyethylene glycol 300 (PEG), with oleic acid as the main fatty acid.[26] Oleic acid has a carbon chain length of 18, showing greater lipophilicity. It has greater hydrophilicity and surfactant-like properties. Many drugs have shown significant improvements in bioavailability following administration of long-chain triglyceride (LCT) solutions compared with medium-chain triglyceride (MCT) solutions, probably due to the more efficient lymphatic circulation. It is concluded that using labrafil will be more effective.[27]



Structure of labrafil

Peceol

It is a type of medium chain triglycerides and also known as glyceryl monoolerate that has high solubility. it is a glyceride-rich excipient. It consists of monounsaturated fatty acid that has better absorption.[28]



Structure of peceol

CONCLUSION

Self-nano emulsification is widely used now a days in drug delivery system. In self-nano emulsion modified oils have more advantage than vegetable oils because it will prevent from oxidative degradation and help in increasing the absorption and thus it will improve the bioavailability. Mainly this is used in the case of hydrophobic drug which are less soluble in water. It is also important in lipophilic drug as it will help in the transport of drug through intestinal. Different type of oils is available with different solubility that helps in increase the solubility and absorption. Thus increase the bioavailability.

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