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A REVIEW ON THE POSSIBLE EXPLANATIONS OF USING CASHEW (*ANACARDIUM OCCIDENTALE* LINN) NUT OIL TO FORM SEDDS

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Abstract

Nigeria is a country with rich varieties of nuts such as Anacardium occidentale (cashew nut). It is important to optimize the available local raw materials in our environment for the benefits of rising pharmaceutical companies in the country. To reduce inconveniences, it is better to reduce pharmaceutical formulations through the use of local oils (of excipient and surfactant properties). A work on cashew kernel oil extraction and it's physicochemical properties is beneficial, therewith, it can be utilized for making self-emulsifying properties such as self-emulsifying drug delivery system (SEDDS). SEDDS has oil and surfactant -based ability characterized with the potential of slow agitation that emulsified speedily in water. Certainly, cashew nut is an available and cheap nut in various parts of Nigeria, such as northern region, middle belt, and southern parts. The nut is rich in oleic acid, therewith, easily exploited for pharmaceutical applications and benefits. The self-emulsifying property in lowered interfacial tension (between the oil, and water interface), aided by surfactants (and cosurfactants) will give rise to boosted solubility (by minimized precipitation). The local nature of cashew invariably provides enough amount of oleic acid that aid formulations, advantageously to the pharmaceutical industries. The application locally-based products like cashew in pharmaceutical fields could not be overstated. One of the applications of cashew is formation of SEDDS. We cannot be able to form the SEDDS unless if we have details broaching about SEDDS. Therefore, this paper performs a review of SEDDS under certain headings. This paper makes a sufficient description of the items below: emulsions, self-emulsifying drug delivery systems (SEDDS), factors affecting SEDDS, method of preparing SEDDS, formulations SEDDS, components of SEDDS, characterization of SEDDS, stability of SEDDS, future, imitation, and the likes.

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1. INTRODUCTION

Nigeria is blessed with varieties of nuts and its oils such as arachis, cashew and groundnut oils. In recent times, there has been a need to optimize these locally available raw materials as excipients for the needs of Nigeria's growing Pharmaceutical manufacturing companies. To reduce the need for more ingredients in pharmaceutical formulations, it will be important to have locally available oil that possesses surfactant and excipient properties. Oleic acid is a surfactant with HLB value 1.6 and Oil Containing reasonable quantities of Oleic acid may possess Self Emulsifying properties (Gillian, 2021). In this research work Cashew kernel oil is extracted and its physicochemical properties studied. Its Oleic acid component was quantified to qualify its self-emulsifying properties in the formulation of Self Emulsifying Drug Delivery System (SEDDS). SEDDS are oil and surfactant-based preparations with the help of slow agitation that can be emulsified rapidly in water (Gillian, 2021).

Cashew nut is readily available in the southern and middle parts of the country. Cashew nut oil is rich in oleic acid and can be exploited as a biomaterial for pharmaceutical applications. By lowering the interfacial tension between the oil and water interface with the aid of surfactants and co surfactants, the self-emulsification feature provided will boosts solubility by minimizing precipitation (Agbongiarhuoyi et al., 2020). Provision of local and readily available materials with sufficient quantity of oleic acid will be an added value to the varieties of excipients available to the pharmaceutical industries to aid formulations. It is therefore paramount to identify, extract and characterize local oils and study its possible Self-emulsifying properties (Gillian, 2021). Therefore, this paper performs a review of SEDDS under certain headings.

2.1 The Cashew Tree, Emulsion and Self Emulsifying Delivery Systems

The cashew tree (**Anacardium occidentale**) is a tropical evergreen tree native to South America in the genus Anacardium that produces the cashew seed and the cashew apple accessory fruit. The tree can grow as tall as 14 metres (46 feet), but the dwarf cultivars, growing up to 6m (20 ft.), prove more profitable, with earlier maturity and greater yields. The cashew seed is commonly considered a snack nut (cashew nut) eaten on its own, used in recipes, or processed into cashew cheese or cashew butter (Furtado et al., 2021).

Cashew has a deep and widespread root system whose depth depends on the type of the soil, irrigation and the nutritional level of the crop. The trunk is short and irregular with the first branch growing close to the ground. Leaves are usually evergreen, elliptically ovate in shape with smooth margin and arranged in a spiral pattern towards the end of the stem. Plate I shows a cashew tree in its local habitat (Kind and Shillpa, 2016); Furtado et al., 2021). When the tree flowers, the leaves are gathered in pinnacle up to 26 cm long and bears close to 11 laterals as seen in most African species. When the flowers are open, they are receptive to pollen for few days which makes the stigma receptive even when pollen release may not occur immediately. This enhances cross pollination by insects against self-pollination as shown in Plate 1. Table 1 gives the botanical classification of cashew tree. The local names of cashew tree within the three major Nigerian languages are: Fisa (Hausa), Kaju (Yoruba) and Kashu (Igbo) (Dendena and Corsi, 2021).

Table 1: Classification of Cashew Tree

Common Name	Cashew
Kingdom	Plantae
Subkingdom	Tracheobionta
Phylum	Agnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Sapindales
Family	Anacardiacae

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Genus	Anacardium
Species	Occidentale

The Portuguese are mainly responsible for its distribution across Asia and Africa, as a result, the English name cashew derived its name from the local name "*Caju*" (Furtado et al., 2021). In the 1500s, the Portuguese explorers introduced the cashew tree to the east coast of Africa with the aim of soil conservation and afforestation. In the sixteenth century, it was introduced to the Western coast of Africa in countries such as Nigeria and Senegal. The cashew nut has experienced remarkable progress in its use, from afforestation and soil control to a major foreign exchange earner especially within the African sub region (Furtado et al., 2021)

The commercially available cashew (*Anacardium occidentale* L) belongs to the family Anacardiaceae botanica. Among the other species in the genus, cashew is the only one with economic value because of its succulent hypocarp and nutritious nuts (Furtado et al., 2021). In 2020 global production of cashew nuts was 4,180 tonnes with Vietnam the largest process or of cashew globally in 2020 (Idah et al., 2021).

Emulsions are colloidal solutions with both dispersed phase and dispersion medium being liquid. Thus finely divided droplets of one liquid are dispersed in another medium. These two immiscible liquids are mainly oil and water i.e. polar and non-polar solvents. Emulsions may be oil-in-water (o/w), in which oil droplets are dispersed in water or water-in-oil (w/o), in which water is dispersed in the oil (Gillian, 2021). Due to the various possible limitations with the GI system, hydrophilic macromolecular medicines, proteins primarily polysaccharides, therapeutic peptides, and DNA-based therapies, have low oral bioavailability. A range of tactics has been used to address this issue, including structural drug changes, addition of auxiliary agents, and the production of SEDDS.

Self-Emulsifying Drug Delivery Systems (SEDDS) are oil and surfactant –based preparations with the help of slow of agitation that can be emulsified in water (Furtado et al., 2021). Arachis oil has been used for long as an excipient in manufacture of emulsions. This oil is known to possess up to 42% oleic acid (Wang et al., 2021). It is therefore important to identify local oils that has self-emulsifying properties.

Plate I: Cashew Plant at flowering stage (**www.researchgate.net**) The cashew fruit has two main parts; the cashew apple and cashew seed (fig 1.) The cashew apple arises from the enlargement of the pedicel which upon ripening becomes reddish yellow in colour of about 6-12 cm long. The cashew fruit (seed) is a drupe that is kidney-like in shape, which develops at the bottom of the apple (Furtado et al., 2021).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Common Cashew Tree Species in Nigeria

There are two types of cashew within the Anacardium occidentale species referred to as the dwarf and the common cashew. The difference in these cashew types depends on their size.

a) The dwarf type is usually shorter and reaches up to 6 m in height with a canopy of around 5 m wide. They begin to flower when they are about 5 m in height which falls within 2 – 3 years of planting; this gives them a marketable advantage (Anukam et al., 2015). The dwarf cashew tree can also be differentiated from the common types by nearness of their branches to the ground, the presence of smaller nuts, smaller stem diameter and lighter green leaves (Furtado et al., 2021).

b) The common type is more vigorous and bigger in size usually growing up to 14 m in height. They begin to flower when they are about three years, but do not produce marketable quantity until they are about 14 years. However, once they start producing, they produce up to 100 kg of nut every year (Furtado et al., 2021).

2.2 The Cashew Fruit

The cashew fruit is a kidney-shaped drupe that contains a single seed called the cashew nut as shown in Figure 1. The nut is surrounded by a double shell, from where the cashew nut shell liquid (CNSL) is obtained. The nut shell liquid is mainly anacardic acid containing a highly allergenic phenolic compound (Idah et al., 2021). The cashew fruit is a commercial product; while the nut is mainly exported, the apples are used as by-product in some places to make juice (Idah et al., 2021)

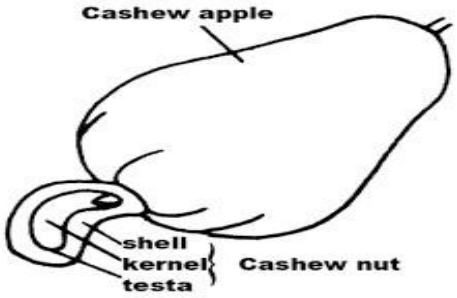

Figure 1: Diagram of the Cashew Fruit (www.researgate.net)

Nigeria comes the 5th position among the top ten exporters of cashew nuts from 2017 to 2021.The cashew industry therefore ranks the third in the world production of edible nuts.

Cashew nut is a high value edible nut which yields two „"Oils"""" Cashew nut shell liquid and Cashew Kernel oil.

Cashew Kernel or nut oil is found in the kernel of the cashew nut. It contains high proportion of unsaturated fatty acids as found in vegetable oil and has find its applications in Pharmaceutical and Cosmetic industries (Cassiday, 2019).

2.2.1 Harvesting of Cashew Nuts

The harvesting of cashew nuts is a crucial step in obtaining good quality nuts. Therefore, it is important to allow the fruit to fall to the ground without being plucked from the tree, then, collect and separate the nut from the apple daily to prevent having nuts from becoming yellowish in color. Separation of the nut from the apple is required to be done on the same day of collection in order to prevent moisture entrapment which will eventually reduce the quality of the nuts. It is also important to prevent pulp residue in the nut which will cause microbial spoilage (Yahaya et al., 2021).

2.2.2 Drying of the nuts

It is very important to dry the nuts properly in order to obtain high quality cashew nuts. In most communities cashew nuts are usually sun dried about three days, but it could take up to 1 week to dry in the rainy season (Yahaya et al., 2021). The dried cashew nuts are roasted in an open pan; drum roasted or by the use of any hot air method to obtain the readily available edible snacks known as roasted cashew nuts.

2.2.3 Pharmacological Benefits of Anacardium occidentale

The hydro-ethanol extract of cashew leaves has been reported to have gastro-protective and analgesic activities at a dose of 200 mg/ kg on laboratory rats (Oji et al., 2021). Hot decoction of new cashew leaves has shown wound healing potential while the matured leaves were found to inhibit the action of tyrosinase, an enzyme responsible for skin pigmentation problems (Furtado et al., 2021). Similarly, the aqueous leaf extracts of cashew have shown hypoglycemic potentials in streptozotocin

Frontier in Medical & Health Research

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induced diabetic rats at a dose of 175 mg/ kg body weight. Ethanol extracts of the leaves on the other hand have demonstrated antimicrobial activity against Staphylococus aureus, Pseudomonas aeriginosa, Escherichia coli, Candida albicans. Another study demonstrated that paediatric toothpastes containing cashew apple extract have the ability to inhibit Streptococcus mutans indicated in dental caries (Furtado et al., 2014). In a different study, the acetone stem bark extract of the cashew plant exhibited some degree of anti-inflammatory and anti-oxidant properties. Meanwhile, different parts of the cashew plant have been used ethnomedicinally by local medicine practitioners in the treatment of diarrhoea, headache and dermatitis (Oji et al., 2021).

2.3 Proximate Properties of Cashew Nuts

Although this may vary due to location and environmental factors, the moisture content of cashew nut oil is in the range of 0.1-0.5 % per gram of the oil (AOAC, 2016). The oil value which is the main source of energy reserve for the cashew seed is in form of lipids. It ranges from 44-46 % (Furtado et al., 2021). While the protein content is between 15 and 18% (Agbongiarhuoyi et al., 2020).

2.3.1 Amino acids of cashew nuts

There are up to 17 amino acids present in the cashew nut oil as with those having amino acid side groups being the most abundant, followed by those with aliphatic side groups. The amino acids present in the oil include: Glutamine, Arginine, and Leucine with 3.34, 1.37, and 1.2 respectively (Barkat et al., 2020).

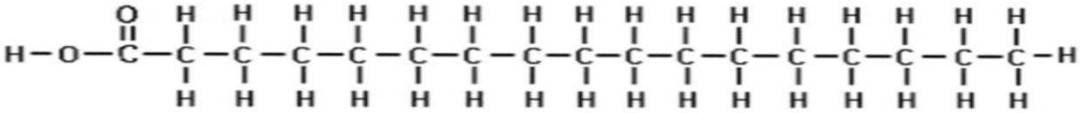
2.3.2 Lipids/Fatty acid composition of cashew nuts

Cashew nut oil has predominantly mono unsaturated fatty acid, (oleic acid C 18:1) and poly unsaturated fatty acid (linoleic acid C 18:2) up to 62 and 17 % respectively. The saturated fatty acids are palmitic acid and stearic acid. Oleic acid also called omega-9 is a mono-unsaturated fatty acid with a single double bond at C-9 and C-10 carbon atoms. It is an eighteen carbon chain compound with empirical formula C18H14O2 as shown in Figure 1.2. The saturated form of oleic acid is stearic acid (Figure 3). As a liquid, it is pale-yellow/brownish-yellow in colour (with a hard-like odour) that is insoluble in water. Oleic acid is known to be important in preventing obesity, cancer, coronary diseases and other health challenges (Furtado et al., 2021). In addition, stearic acid is known to possess a potent anti-inflammatory activity. As a fatty acid, it has a profound effect on liver metabolism, as such, is able to accelerate hepatic recovery in dysfunctional liver injury of laboratory rats (Saeed et al., 2019). It finds application in the pharmaceutical, cosmetic, soap and food industries.

On the other hand, palmitic acid is another signaling molecule with both anti-inflammatory and anti-diabetic properties. Replacing rat diet with palmitic acid leads to improvement in insulin sensitivity and reduction in fatty tissue inflammation (Barkat et al., 2020).

Linoleic acid has been approved recently for food as "generally recognized as safe" in the United State since 2008 (Figure 1.4). In addition to anti-cancer property, it is also known to prevent the development of atherosclerosis and modulate immune and inflammatory responses (David et al., 2020).

Plant sterols have been known for their ability to reduce cholesterol, however, cashew nut oil is not an approved source for this property because of their low level (Nasser et al., 2022). Cashew nuts contain phospholipids which serve as secondary messenger in plant growth as well as being a crucial component of the cell membranes of animals. Phosphatidyl choline is the most abundant with a content of about 276 mg/100 g. Others include phosphatidyl serine (51 mg/100 g), phosphatidyl ethanolamine and sphingomyelin in variable proportions (David et al., 2020).



Plamitic acid

Figure 2: Chemical Structure of Palmitic acid (www.chemsrc.com).

Volume 3, Issue 2, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

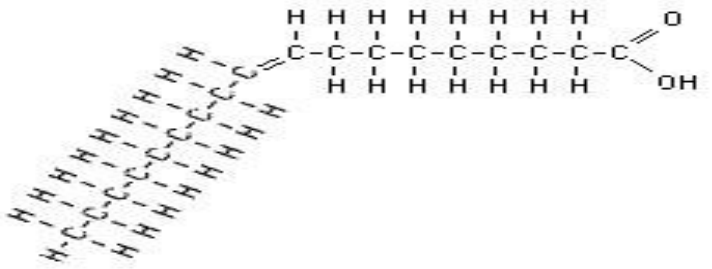


Figure 3: Chemical Structure of oleic acid (Adapted from David et al., 2020).

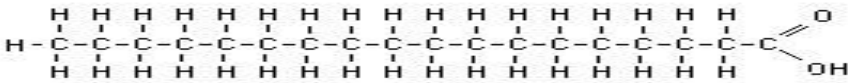


Figure 4: Chemical Structure of Stearic Acid (Nasser et al., 2022).

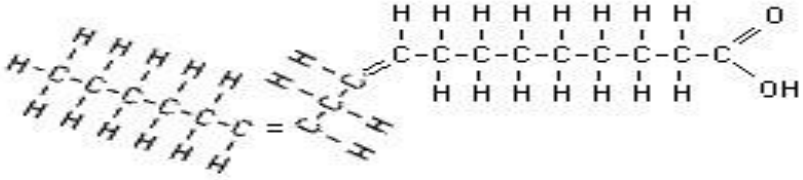


Figure 5: Chemical Structure of Linoleic Acid (Adapted from Furtado et al., 2021).

Plate II: Cashew Kernel and its oil (www.indiamart.com)

3.1 Pharmaceutical Emulsion

Pharmaceutical emulsions are colloidal solutions with both dispersed phase and dispersion medium being liquid. Thus finely divided droplets of one liquid are dispersed in another medium. These two immiscible liquids are mainly oil and water i.e. polar and non-polar solvents. Emulsions may be oil-in-water (o/w), in which oil droplets are dispersed in water or water-in-oil (w/o), in which water is dispersed in the oil (Gillian, 2021). Emulsions may also be multiple in nature in which the re-emulsification of w/o or o/w emulsions occurs in either water or oil to give o/w/o or w/o/w (Barkat et al., 2017). Some familiar food illustrate examples are milk which is an oil in water emulsion and margarine which is a water in oil emulsion (Idah et al., 2021).

3.2 Emulsion Formation

When two immiscible liquids (such as oil and water) are brought together, they form two separate layers with minimum area of contact due to low surface free energy (G). When energy is applied in to the system by mixing or agitation, the immiscible liquids will form various droplet sizes with resultant increase in surface free energy of the system. Thus, emulsions are thermo-dynamically unstable. This increase in surface free energy ΔG and the resultant increase in surface area ΔA is represented in equation (I) (Gillian, 2021) in which the surface tension is given by γ.

$$\Delta G = \gamma \Delta A \quad \text{(1)}$$

When droplets come in contact with each other, they will coalesce (merge together) so as to reduce the interfacial area (ΔA) and the free energy (ΔG). Thus

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

in emulsification, two competing processes are occurring together, one process requires application of energy and the formation of droplets while the other process involves the coalescence of droplets and the reduction of surface area and free energy.

For partially miscible oil and water phases, the droplets will eventually grow by Ostwald ripening; an irreversible mechanism that allows the growth of large droplets at the expense of smaller ones (Gillian, 2021)

3.3 Advantages and Disadvantages of Emulsion

3.3.1 Advantages of Emulsion

Emulsions can be used to deliver drugs that are poorly soluble in water but readily soluble in oils (Furtado et al., 2021). It can be used to mask the unpleasant taste and odour of drugs, when the drug is dissolved in the internal phase of an o/w emulsion. The external phase can then be formulated to contain the appropriate sweetening or flavouring agents. Drugs that are more stable in an oily phase compared to an aqueous medium can show improved stability in an emulsion dosage form. Intravenous emulsions of contrast media have been developed to assist in diagnosis. Emulsion can also be used to prolong the release of drugs (especially semisolid emulsions) thereby providing sustained release action. The oily phase can serve as a reservoir of the drug, which slowly partitions into the aqueous phase for absorption (Nandi, 2019).

3.3.2 Disadvantages of Emulsions

Emulsions are thermodynamically unstable and therefore should be formulated by stabilizing the emulsion from separation of the two phases by the addition of a third agent called surfactant. Pharmaceutical emulsions may be difficult to manufacture. Storage conditions may affect stability. Emulsions are bulky, difficult to transport, and prone to container breakages. They are liable to microbial contamination which can lead to cracking. This will make uniform and accurate dosing very difficult to be achieved (Furtado et al., 2021).

3.4 Self-Emulsifying Drug Delivery Systems

Many proteins and medical peptides have limited oral delivery. This limitation is due to the GI tracts enzymatic and absorption membrane factors and technologies have been investigated to solve these obstacles. SEDDS from the last few years have acquired much interest as prospective carriers for oral peptide and protein administration (Nandi, 2019).

Emulsions serve as drug carriers in pharmaceutical preparations even though they can likely improve the medicine's oral bioavailability by having poor absorption profiles (Wang et al., 2021). The prominent strategies for enhancing the stability of orally administered APIs are to use delivery systems of drugs that are based on lipids. According to the literature, the terminology for lipid-based techniques is highly debated. The initial droplet size is not the primary factor determining micro and nano emulsions (SMEDDS and SNEDDS). If the droplet size of emulsion is in the nanoscale range, the SNEDDS term should be used. SEDDS are oil and surfactant-based preparations with the help of slow agitation that can be emulsified rapidly in water. The chemical structure and physical properties of SEDDS physical qualities were essential determinants of application and tolerance. As a result, these variables must be established at the stage of preformulation (Idah et al., 2021).

Due to the various possible limitations with the GI system, hydrophilic macromolecular medicines, proteins primarily polysaccharides, therapeutic peptides, and DNA-based therapies, have low oral bioavailability. A range of tactics has been used to address this issue, including structural drug changes, addition of auxiliary agents, and the production of SEDDS nanocarriers, which are used in various studies as a prominent term for both self-nano- and self-micro emulsifying drug delivery systems (SNEDDS/SMEDDS) and emerge to be a successful method for oral medicines (Gillian, 2021). The preparation of SEDDS on an industrial level is economical and simpler than other nanocarriers, including liposomes, micelles, polymer-based nanoparticles, carbon nanotubes, or niosomes, because it is almost like the solution preparation (Furtado et al., 2021).

Self-emulsification can be influenced by the quality and nature of the concentration of surfactants, pair of oil/surfactant, and oil/surfactant ratio, and the physiological parameters in which it happens, including pH, and temperature. SEDDSs vary from conventional oral drug delivery systems in that

Frontier in Medical & Health Research

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digestion of enzymes significantly changes the excipients in the formulation (Anukam, 2020). Gastric and pancreatic lipases hydrolyze the lipids in the oil phase of SEDDSs in the GIT, releasing additional amphiphilic lipid digestion products. The solubilization of biliary lipids secreted in the bile is also quick and these released digested lipids. Different parameters are linked with the gastrointestinal lipolysis process during lipid digestion. These parameters include pancreatic and gastric lipase secretions, the difference in the small intestine‟s pH in and the stomach, pH of the lipase action, and secretions of the bile that allow solubilization of micelle by lipolysis products (Rossi et al., 2014).

Wide variety of nanocarrier systems are prepared from SEDDS, that appear to be the most appealing, at least from a present industrial standpoint, because their scaling and manufacture are very simple. In a proof of principle investigation, researchers were ready to build the first zeta potential altering SEDDS. But they were able to show that splitting phosphate groups from the surface of SEDDS and altering zeta potential from negative to positive, the shift was rather slight, ranging from −1 to +1 mV in the best scenario (Nandi, 2019). Moreover, excipients like octylamine, cetylpyridinium, or cetrimonium, can be included from a safety standpoint to have positive charges on SEDDs surface that was accessible after the cleavage of phosphate group. Furthermore, because both surfactants (cationic or anionic) were to be included in the same formulation, unwanted ionic interactions, including ion pairing, could not be ruled out (Saeed and Shola, 2019).

Apart from common methods like dispensability tests, turbidimetric evaluation, and viscosity tests, complex instrumental requirements like photon correlation spectroscopy (PCS) or dynamic light scattering (DLS), electro kinetic potential measurement, nondestructive spectroscopic techniques (LFDS, FTIR, RS), and numerous microscopic methods (SEM, PLM, EDS) have been defined. To achieve the greatest value, outstanding bioavailability, and tolerance of the dosage forms for human administration, all significant aspects must be identified during the preformulation stage of self-emulsifying drug delivery systems (SEDDS) (Guarrasi et al., 2022).

3.5 Factors affecting Formulation of SEDDS

1. Dose and nature of drug

Drugs delivered at extremely high doses are not appropriate for SMEDDS unless they show remarkable solubility in at minimum one of the ingredients, particularly the lipophilic phase. SMEDD has the most trouble administering drugs with low water and lipid solubility (usually with log P values of about) (Raffa et al., 2019).

2. Polarity of the lipophilic phase

The release of drug from microemulsions is regulated through parameters including polarity of the lipid matrix. The HLB, the length of chain and fatty acid degree of unsaturation, and the molecular weight of micronized all impact the polarity of the droplet for their ability to block crystallization and, therefore, establish and sustain the supersaturated state for a longer time (Furtado et al., 2021).

3.6 Components of SEDDS

The most important parameter for SEDDS are as follows:

1. Drug

The most important parameter for SEDDS formulation is the lipophilicity and hydrophobicity of a drug. A drug's log P should preferably be ≥2. The drug is formulated at a modest dose and should not be subjected to substantial first-pass metabolism (Tina, 2019).

2. Oil

Oil is necessary for the lipophilic drugs solubilization. It improves the drug's availability for quick absorption in the GI tract via the intestinal lymphatic system. The degree of esterification and kind of fatty acids and with regard to glycerol to create mono or diglycerides determine the physical, melting, and hydrophilic–lipophilic balance (HLB) features of glycerides. Six to twelve carbon chains present in MCTs and are delivered into the systemic circulation via portal blood. The intestinal lymphatic system transports LCT with more than 12 carbon chains. MCT is the most extensively utilized lipid formulation because of its improved quality of solubility, fluidity, and ability to resist oxidation (Pharmaceutical Codex, 2019).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

3. Surfactant

Surfactants lower the interfacial tension by forming an interfacial film, allowing for dispersion. During SEDDS formulation, the HLB value must be kept in mind. A surfactant with an HLB value greater than 12 is chosen to achieve better emulsification. It helps to disseminate the intended formulation quickly by forming small oil-in-water (o/w) droplets. Nonionic surfactants are commonly used in the formulation of SEDDS due to their nontoxic nature, despite the fact that they may produce a modest irreversible change in the permeability of the GIT wall. In GIT, a formulation of surface-active compounds that is 30–60% w/w results in improved self-emulsification. Surfactants in high amounts might irritate the wall of the GI tract (Gurrasi et al., 2022).

4. Co-surfactant lowers the transitory negative value of interfacial tension even further.

It gives the interfacial film flexibility so that varied curvatures can be achieved for the creation of different micro emulsion concentrations. By adding co-surfactant, the higher amounts of surfactant (approximately 30 %) can be simulated (Pharmaceutical Codex, 2019). The contact enlargement at this moment results in the creation of finely scattered droplets. It will absorb more surfactant or a higher surfactant/co-surfactant ratio until the film is depleted enough to restore positive interfacial tension. Spontaneous emulsion is formed as a result of this. Cosurfactants are typically made up of medium-chain length alcohols (C3–C8) (Pharmaceutical Codex, 2019).

3.7 Method of Preparation of SEDDS

1. High pressure homogenizer

High pressure is required for the preparation of nano-formulation. Fine emulsion is formed depending upon the application of high sheer stress. There are two theories that can explain the droplet size including turbulence and cavitation. Nano-emulsion of smaller than 100 nm droplet size can be produced by this method. Various factors are responsible for the production of droplet size of nanoemulsion using high pressure homogenizers, i.e. type of homogenizer, composition of sample and the operating conditions of homogenizer including time, intensity, and temperature. High-pressure homogenization is commonly applied to produce nanoemulsions of food, medicinal, and biotechnological ingredients (Pharmaceutical Codex, 2019).

2. High energy approach

High mechanical energy is required for the high energy approach which leads the formation of nanoemulsion by mixing surfactants, oil, and co-solvent. Formulation of nanoemulsion extensively uses high energy methods. Strong disruptive forces are provided by the high mechanical energy that are used for breaking up the droplets of large size into droplets of nano size so that nanoemulsions produced would be of high kinetic energy. Basically, SNEDDS require low energy and depend upon the phenomena of self-emulsification (Pharmaceutical Codex, 2019).

3. Micro-fluidization

Micro-fluidizer is a device required by the method of micro-fluidization. The product is pushed toward the interaction chamber by the positive displacement pump. A micro channel is a small droplet channel found in this system. The product formed is then transferred to the impingement area through the micro channels where nano emulsion of very fine droplets is produced. Then, course emulsion is produced when the mixture of aqueous phase and oil phase is added into the homogenizer. Further processing leads to the formation of a transparent and homogeneously stable nanoemulsion (Pharmaceutical Codex, 2019).

4. Sonication method

One of the useful methods for the formation of SNEDDS is sonication method. With regard to cleaning and operation, the method of ultra-sonication is better as compared to other methods of high energy. In the emulsifications by ultra-sonication, the macro emulsions are broken down into nanoemulsion by the cavitation forces provided by the ultrasonic waves.

This process reduces the droplet size of the emulsion and leads to an emulsion of nano size. The mechanism of sonication is responsible for the reduction of the droplet size (Wahlgren et al., 2018).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

3.8 Lipid Base Formulations

Lipid based formulations offer a wide variety of formulations like solutions, suspensions, solid dispersions and self-micro emulsifying drug delivery systems (SMEDDS). The SMEDDS have attracted considerable interest after commercial success of immunosuppressive agent cyclosporine A (Neoral®) and the two HIV protease inhibitor ritonavir (Norvir®) and saquinavir (Fortovase®). Self-emulsifying formulations comprise isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvents which spontaneously emulsify when exposed to the fluids of the gastrointestinal tract (GIT) to form oilin-water emulsion or micro emulsion. The SMEDDS offer following advantages:

- Thermodynamic steadiness.
- Enhanced solubilization of bioactive substances
- Improvement in oral bioavailability by increasing solubility and efficient drug transport.
- Improved patient compliance.
- Reduced dosing frequency.
- Ease of manufacture and scale-up as compare to other lipid dosage forms.
- Reduction in inter-subject and intra-subject variability and food effects.
- Ability to deliver active biomolecules including peptides that are sensitive towards enzymatic hydrolysis in GIT.
- No influence of lipid digestion process unlike the other lipid-based drug delivery systems.

When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament (Pharmaceutical Codex, 2019).

Demerit of Lipid Formulation

1. Lack of good predicative in vitro models for assessment of the formulations.
2. This in vitro model needs further development and validation before its strength can be evaluated.
3. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.
4. Another is chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60 %) which irritate GIT.

The lipid formulation classification system was first introduced in 2000 and the extra „type" of formulation was added in 2006 (Obitte et al; 2017).

Type I

This system shows poor initial aqueous dispersion and requires digestion by pancreatic lipase/co-lipasen in GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. These are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatine capsules containing corn oil as lipidic component (Pharmaceutical Codex, 2019).

Type II

Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant content above 25 % (w/w). These formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allow efficient partitioning of drug between oil droplets and the aqueous phase from where absorption occurs (Pharmaceutical Codex, 2019).

Type III

Type III lipid based formulations, commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), are defined by inclusion of hydrophilic surfactant (HLB > 12) and co-solvent such as ethanol, polyethylene glycol and propylene glycol. Type III formulation can be further segregated into type IIIA and type IIIB formulations in order to identify more hydrophilic systems (type IIIB) where the content of hydrophilic surfactant and co-surfactant increases and the lipid content reduces (Pharmaceutical Codex, 2019).

Type III B

Formulations typically achieve greater dispersion rates when compared to type IIIA although the drug

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

precipitation risk on dispersion of the formulation is higher given the lower lipid content (Pharmaceutical Codex, 2019).

Type IV

These formulations commonly offer increased drug payloads when compared to the formulations containing simple glycerides lipids and also produce very fine dispersion when introduce in aqueous. An example of type IV formulation is the current capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase®) which contains TGPS as a surfactant and PEG 400 and PG as a cosolvent (Pharmaceutical Codex, 2019).

3.9 Mechanism of Self-Micron Emulsification

According to Reiss, the energy required to increase the surface area of the dispersion for selfemulsification process bear less importance when compared to the entropy change that favours dispersion. Self- micron emulsifying process is related to the free energy. 9 That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:

DG= S N p r 2s.....II

Where, DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets, and hence reduces the interfacial energy, and providing a barrier to avoid coalescence. In the case of self-micron emulsifying systems, the free energy required to form the emulsion is either very low or positive, or negative. Emulsification requires very little input energy involves destabilization through contraction of local interfacial region (Pharmaceutical Codex, 2019).

Phase Diagrams

The micro emulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a micro emulsion: an oil phase, an aqueous phase and a surfactant. If a co-surfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single pseudo-component. The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behaviour of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100 %. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs‟ phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the «phase behaviour» of the system at constant temperature and pressure. The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/ Sodium bis (2-ethylhexyl) sulfosuccinate (AOT)/water micro emulsions consists of multiple phases).Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilized by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However, examples of relatively stable micro emulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) micro emulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to micro dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralization). Such micro emulsions are probably very stable across a reasonably wide range of elevated temperature (Masucci and

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Little, 2019; Pharmaceutical Codex, 2019; Maphosa and Victoria, 2020; Park et al., 2020).

4.1 Formulation of SMEDDS

Upon dilution, the SMEDDS formulation immediately forms a clear dispersion and remains stable (Fig.1). The hydrophobic drug dispersed in the SMEDDS formulation remains solubilized it is absorbed. Efficient release of the drug from the formulation mainly depends on two factors, globule size and polarity of the droplets. In case of oil-in water micro emulsions, the polarities of oil droplets are not considerable, since the drug incorporated in the oil globules reach the capillaries.

Parameters to be considered in SMEDDS Formulation

1. Solubility of the drug in different oil, surfactants and cosolvents.
2. Selection of oil, surfactant and cosolvent based on the solubility of the drug, and of the phase diagram.

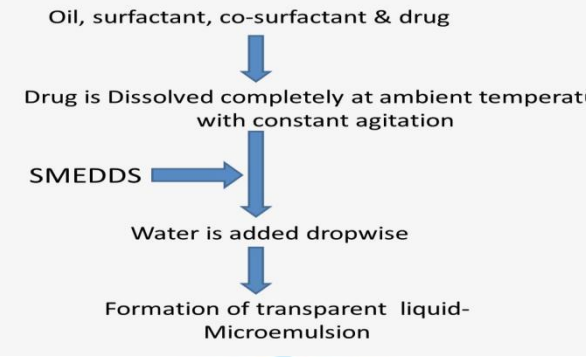

Figure 6: Flow chart for preparation of SMEDDS

Selection of suitable drug candidate

Lipid based formulations offer a potential platform for improving oral bioavailability of drugs specially those belonging to Biopharmaceutical Classification System (BCS) class II and class IV. A primary indication of the potential utility of lipid based formulation can be obtained by assessing the drug lipophilicity (log P) and its solubility in pharmaceutically acceptable lipid excipients, which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit. Another indicator of the potential for success of lipid based formulation is the observance of a strong positive food effect when the drug is administered with a fatty meal as opposed to dosing in the fasted (Abbas, 2022). For lipophilic drug compounds that exhibit dissolution dissolution-rate-limited absorption, SMEDDS can offer an improvement in rate and extent of absorption resulting in reproducible blood time profile. The systems SMEDDS usually provide advantage of increased drug loading capacity when compared with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents.2 The partition coefficient (log P) is the prime criterion of designing lipid based systems. High log P (greater than 4) is desirable for lipidic systems. Next physicochemical criteria that play an important role are melting point and dose. Low melting point and low dose are desirable for development of lipidic systems (Pharmaceutical Codex, 2019).

4. 2 Characterization of SEDDS

1. Centrifugation

In order to estimate metastable system, the optimized SEDDS formulation is diluted with purified distilled water. Then micro emulsion is centrifuged at 1000 rpm for 15 minute at 0°C and observed for any change in homogeneity of micro emulsions. This indicates the stability of product upon dilution (Pharmaceutical Codex, 2019).

2. Macroscopic Evaluation

Macroscopic evaluation analysis is carried out in order to observe the homogeneity of micro emulsion formulationAny change in color and transparency or phase separation occurring during normal storage condition (37±2°C) is observed in optimized micro emulsion formulation. The uniformity of globule size

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

ensures adequate drug distribution in the formulation (Pharmaceutical Codex, 2019).

Visual Assessment

To assess the self-emulsification properties, formulation is introduced into 100 ml of water in a glass Erlenmeyer flask at 25°C and the contents were gently stirred manually. The tendency to spontaneously form a transparent emulsion is judged as good and it is judged bad when there is poor or no emulsion formation. Phase diagram is constructed identifying the good self-emulsifying region. The formation of transparent product may be taken as end point to declare accomplishment of preparation (Pharmaceutical Codex, 2019; Cherney, 2022).

Determination of self-emulsification time

The emulsification time of SMEDDS is determined according to USP 22; dissolution apparatus about 2 mg of each formulation are added drop wise to 500 ml purified water at 37°C. Gentle agitation is provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time is assessed visually. This gives the formulator information regarding time lapsed during formulation (Sachan, 2010; Dash et al., 2014).

Droplet Size Determination

It is a precise method for evaluation of stability the size of droplets is measured by photoncorrelation spectroscopy (PSC) with Zetasizer. All measurements are carried out at scattering angle of 90°C and 25°C temperatures. Prior to measurement, micro emulsion is diluted into two steps with pure water then it is filtered through a 0.22µm filter just before it is added to cuvette. At first it is diluted with equal amount of water. In second step the mixture if further diluted to appropriate concentration for the measurement. That depends on droplet size (usually diluted 100-200 times). The globule size measurement helps to maintain the size distribution in desired range. Any deviations from this call for further trials (Pharmaceutical Codex, 2019).

Zeta Potential Measurement

Zeta potential for micro emulsion is determined using Zetasizer HAS 3000. Samples are placed in clear disposable zeta cells and results are recorded. Before putting the fresh sample cuvettes are washed with the methanol and rinsed using the sample to be measured before each experiment. The zeta potential values represent the surface charge of the dispersed globules. The higher the value of zeta potential more the stability is. This may be because of repulsion caused by individual globules during random movements in the continuous medium (Pharmaceutical Codex, 2019).

4.3 Stability Studies of SEDDS

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparation. The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. and many physical and chemical active substances in the formulation, the nature of container-closures used and the storage conditions. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods. Thus, stability studies may be restricted to the dosage form. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products. Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non-sterile products and changes in preservative efficacy. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation (Paul, 2019; Pharmaceutical Codex, 2019; Halim et al., 2023).

4.4 Importance of Stability Studies

- Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

- During the decomposition of the drug or product it may lead to toxic products.
- During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
- Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study (Casidey, 2019; Pharmaceutical Codex, 2019).

4.5 Types of Stability Studies on Drug Substances

A comprehensive pharmacopoeia protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

Physical Stability

The original physical properties such as appearance, colour, dissolution, palatability, suspend ability are retained. The physical stability may affect the uniformity and release rate; hence it is important for the efficacy and safety of the product.

Chemical Stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological Stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product (Pharmaceutical Codex, 2019; Raffa et al., 2019; Guarrasi et al., 2022).

Therapeutic Stability

The therapeutic effect (Drug Action) remains unchanged.

Toxicological Stability

Toxicological stability has no significant increase in the toxicity occurs.

4.6 Types of Stability Studies

Stability studies are used for testing the drug product for longer periods under varying conditions of temperature and Relative Humidity (RH). If the drug is to be distributed in different geographical regions and if shipping is required for transportation, in that case long term stability studies are of prime importance. Long term stability studies are performed by testing the sample at specific time intervals and conditions of external parameters are changed accordingly. Main objective of this study is to determine shelf-life of the drug product. Stability studies are mainly four types, they are Long term stability, Intermediate stability, Accelerated stability and In-use stability Studies (Jun et al., 2022; Koga et al., 2023). The type of stability studies and its storage conditions with respective time period were shown in Table 2.

Table 2: Types of Stability Studies

Types of Stability Studies	Storage Conditions	Minimum Time Period (Months)
Long Term	25±2°C and 60±5% RH or 30±2°C and 65±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

4.7 Stability Testing Methods

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature\humidity. The accelerated stability studies are easy to predict the degradation of the drug within short period of time. In the accelerated stability studies mainly the drug is performed at long-term storage. During this elevated temperatures are used to determine the products shelf-life. The main aim for the stability testing is to provide the acceptance level of fitness/ quality throughout the period during which they are available for the patience and should be fit for the acceptance of the drug by the patient. This helps the patient to be cured easily and the acceptance of the drug would be

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

easy and the known therapeutic uses of the pharmaceutical products manufactured. Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are (Pharmaceutical Codex, 2019):

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing (Pharmaceutical Codex, 2019).

1. Real-time Stability Testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time from inter-assay variation. While, testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst is able to distinguish the degradation day-today. The data can be increased by including the single batch of reference material for which stability characteristics have been established. In this the reagents and the instruments used should be in the consistency throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored (Anukam et al., 2020; Oji et al., 2021; Yayaha et al., 2021).

2. Accelerated Stability Testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies are easy to predict the shelf life thus reduces the duration to know the stability of the substance. In addition to temperature, stress conditions are applied such as moisture, light, pH and gravity. Due to the measurement of instability time is also reduced in comparison to the real-time testing. For the accelerated stability studies the stability projections are done at four different stress temperatures. However, projections are obtained when denaturing stress temperatures are avoided. The accelerated stability studies are easily predicted by the Arrhenius equation (Pharmaceutical Codex, 2019).

K =Ae-EaRT III

Where:

K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. k

T= Absolute temperature, k (Pharmaceutical Codex, 2019).

4.8 Stability Studies Methods of SEDDS

1. Thermodynamic Stability Studies

The samples are subjected to a number of cycles, usually hexaplicate, between temperatures of 4°C and 45°C.12 the formulations are then centrifuged at 3500 rpm for 30 min. This is followed by freeze-thaw cycles, usually triplicate, between -21°C and +25°C.All the formulations are kept at each temperature for not less than 48 hr. The formulation, that passes the thermodynamic stress tests, is further taken for the dispersibility test for assessing the efficiency of self-emulsification (Pharmaceutical Codex, 2019).

2. Robustness to Dilution

Nanoemulsions, resulting from dilution with various dissolution media, must be robust to all dilutions, and should not show any phase separation or drug precipitation even after 12 h of storage.

3. Liquefaction Time

This test is designed to estimate the time required by solid SEDDS to melt in vivo in the absence of agitation in the simulated GI tract conditions. One dosage form is wrapped in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round bottom flask containing simulated gastric fluid without pepsin maintained at 37±1°C, by means of thermo-regulated heating mantle (Govindan et al., 2024).

4.9 Dosage Form of SEDDS

Self-emulsifying capsule when capsules carrying liquid solution SE preparations are delivered, micro

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

emulsion droplets form in the GIT and disperse to reach the area of absorption. If the micro emulsion‟s phase separation is permanent, no increase in medication absorption may be expected. To solve this problem, sodium dodecyl sulfate was added to the SE formulation. Self-emulsifying sustained/controlled release the use of surfactants and lipids in the preparation of SE tablets has shown tremendous promise. SE pills are really helpful in preventing negative effects. Incorporating indomethacin into SE tablets, for example, may improve the drug‟s penetration across the GI mucosal membrane, thus lowering GI bleeding (Nasser et al., 2022).

Controlled/sustained release self-emulsifying pellets

Pellets can provide variety of advantages over conventional solid dosage forms, including production flexibility, lower intra- and inter-subject fluctuation in plasma profiles, and less GI discomfort without compromising drug absorption (Salawi et al., 2022).

Solid dispersions that self-emulsify: solid dispersions may increase the dissolving rate and bioavailability of drugs that are water insoluble, but they still have manufacturing and stability concerns. Using SE excipients can help you overcome these obstacles (Oji et al., 2021).

Semisolid SEDDS

Semisolid SEDDS are synthesized in situ utilizing lipidic ingredients comparable to those used in liquid SEDDS, but with a higher melting point than room temperature. These formulations are unique in that they do not contain co-surfactants, but only comprise lipids and surfactants. For the manufacturing of semisolid SEDDS lauryl macrogel-glycerides including gelucire 44/14, gelucire 50/13, derivatives of polyoxyethylene hydrogenated castor oil including cetyl alcohol derivative, Nikkol HCO50, and polyoxyethylene polyoxypropylene block polymer are the most frequently used surfactants and lipids. Such preparations have a greater viscosity than the comparable liquid SEDDS, resulting in increased medication stability and mobility during handling (Kini e al., 2016; Pharmaceutical Codex, 2019; Block, 2021).

However, because of lipids with high melting point, these formulations generally show poor emulsification efficiency in vivo, likely contributing to uneven drug absorption patterns. Several cases on the semisolid SEDDS, such as carvedilol and atorvastatin, have been for increasing their oral bioavailability. It was also revealed that semisolid SE formulations produced with glyceryl mono/dicaprylate, diethylene glycol monoethyl ether, propylene glycol monocaprylate, and gelucire 44/14, have improved physicochemical characteristics, due to the super saturation which prevents drug precipitation, these formulations showed significant levels of resistance to dilution and stability (Kini et al., 2016; Rao e al., 2017).

Self-emulsifying controlled release tablets

Self-emulsifying controlled release tablet (SECRET) is a more recent technical advancement in the S-SEDDS field for producing a controlled drug release profile. SECRET is a patented proprietary platform technology created by AlphaRx Inc. (Markham, Canada), in which tablets are formed with the help of liquid SE formulations by adsorbing onto the surface of rate-controlling polymers like HPMC, HPC, and others. These aids in the long-term release of the medication from the polymer matrix. Including systems have important meritorious features in formulation creation, such as site-specific delivery and improved intestinal wall permeability and solubility to aid medication dispersion in the gastrointestinal tract. The coenzyme Q10 SE controlled release hydrophilic matrices which use Avicel-112 and Kollidon V64 as release controlling polymers, have improved drug stability and controlled release properties significantly. The composition of SE tablets of carvedilol includes Aeroperl, MCC, HPMC, that significantly increase in vitro drug absorption in HCT-116 cell lines, perhaps owing to P-gp efflux inhibition. The capacity of solid SMEDDS tablets containing candesartan cilexetil dramatically increases the pace and extent of drug dissolution, that proves the better oral bioavailability. Diclofenac SE pellets produced with natural ingredients like goat fat and Tween 80 similarly showed a prolonged release profile of drug release (Pharmaceutical Codex, 2019).

Self-emulsifying controlled release capsules

These are made by coating liquid-filled soft-gelatin capsules with a thin layer of semipermeable polymeric material. The lipidic SE formulations give

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

the necessary therapeutic activity for a prolonged length of time due to their semipermeable character. An inflatable layer can also be added to the semipermeable layer to adjust the rate of medication release from the capsule shell. Cardiovascular medications, antiretroviral, anticancer treatments, corticosteroids, and immune suppressants such as nimodipine, cyclosporine, ritonavir, dexamethasone, vinblastine, and mepitiostane have all been reported to benefit from this method (Obitte et al., 2017).

The semipermeable coating is made up of cellulose acetate, cellulose acetaldehyde dimethyl acetate, cellulose acylate, and polyurethanes, while the expandable coat on the gelatin shell is made up of Carbopol, sodium carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), HPC, HPMC, and other materials. By converting SE formulations into SSEDDS using solidifying adsorption carriers, efficient delivery of SE formulations may be achieved. For controlled drug release over long periods of time, such formulations are encapsulated in mini capsules coated with sustained release polymers such as PVP K30 and acrylic resins (Pharmaceutical Codex, 2019; Ramya et al., 2019).

4.10 Applications

Lipids, surfactants, and cosolvents make up the SEDDS formulation. The system may form an o/w emulsion when separated by a water phase with modest stirring. SEDDSs deliver medications in small droplets with a balanced distribution, resulting in improved dissolution and permeability. As medicines can be loaded in the inner phase and supplied via lymphatic bypass sharing, SEDDSs protect drugs from enzymatic hydrolysis by in the GI tract and decrease presystemic clearance in the GI mucosa and hepatic first pass metabolism (Sachan et al., 2010; Bhosale et al., 2015).

4.11 Future Perspectives

In general, the technique appears to be highly advanced to efficiently control the enzymatic, sulfhydryl, and mucus barriers, giving convincing benefits over presumably all other delivery strategies in this area. SEDDS, on the other hand, has yet to attain its full potential in terms of overcoming the gut epithelial barrier. Improved information and comprehension of the destiny of HIPs and SEDDS on the intestinal epithelium is undoubtedly a precondition for such advancements. The first adjusting confocal/STED-laser microscopic evaluations of the cell uptake actions of peptides, surfactants, HIPs, and SEDDS marked with various colorful fluorescence dyes disclosed a wide range of achievable connections with epithelial cells, such as deposition of droplet on the cell membrane, SEDDS fusion with the cell membrane, and indeed the utilization of intact HIPs and droplets into cells. The majority of the parameters that govern HIPs and SEDDS‟ fate on the intestinal epithelium are unknown, but they are critical for building more effective SEDDS for oral macromolecular drug delivery. For example, the stability of HIPs in the intestinal fluid and on the cell, membrane appears to be one of them. The zeta potential and the kind of surfactants employed in SEDDS, both of which have permeation-enhancing qualities, are likely to be important considerations
(Pharmaceutical Codex, 2019; Salawi, 2022).

SEDDS‟ medicinal and economic potential has been greatly enhanced by the discovery of solid-SEDDS. Solid- SEDDS are considered state-of-the-art delivery vehicles for poorly water-soluble pharmaceuticals because to improve loading of drug, stability, precision dose, ease of processing and storage, and higher patient satisfaction. While developing solid SEDDS has gotten a lot of interest, there has not been much study done on the essential formulation characteristics that affect in vivo drug absorption. Similarly, only a few studies have compared the delivery performance of solid-SEDDS to that of liquid-SEDDS predecessors (Ramya et al., 2019). The extensive systematic research of the molecular relation between drug molecules, solid carriers, and lipid excipients are required to maximize in vivo absorption of drug molecules encapsulated in solid-SEDDS and unveil their full therapeutic value. Compare and contrast the solubilization behavior and in vivo pharmacokinetics of numerous drugs encapsulated in liquid- and solid-SEDDS to begin. Second, in order to explore and test the relationships within solid- SEDDS on the nanoscale, it is proposed that a variety of impactful physicochemical, biophysical analysis techniques, and surface sensitive, be used for the clarification of the optimal parameters that ultimately leads to the improvement

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

of biopharmaceutical performance for given therapeutics (Ramya et al., 2019). parameters that impact GI absorption effectiveness include charge and size of the oil droplet in the emulsion produced. As an alternative to standard SEDDS, numerous preparations have been created to provide modified emulsified formulations.

Self-micro emulsion formulations, preformulated freeze dried emulsions, surfactant dispersions, microencapsulated emulsions, pellets that are self-emulsifiable, solid SESs and lipid/cross-linked polymeric matrices are just a few examples. Upon water dilution, all of such formulations will yield fine oil droplets or micelle dispersions. Currently, pharmacological products developed as SEDDS, such as CsA, ritonavir, and saquinavir, are freely accessible on the market. As roughly 40% of novel drug compounds are hydrophobic, it predicts that further drug products for the pharmaceutical industry will be formed as SEDDS in the coming years (Nasiktar et al., 2024).

4.12 Limitations

The absence of reliable predictive in vitro models for the assessment of SEDDSs and other lipid-based formulations is one of the barriers to their development. Traditional dissolution procedures are ineffective because these formulations may be dependent on gut digestion prior to drug release (Chen et al., 2010). An in vitro model of the duodenum‟s digestion processes has been constructed to imitate this. Before the strength of this in vitro model can be assessed, it must be refined and validated. In addition, because development will be based on in vitro–in vivo correlations, several prototype lipid-based formulations must be produced and evaluated in vivo in an appropriate animal model. Chemical instability of medications and high surfactant concentrations in formulations (about 30–60%) that irritate the GIT are a few other downsides. Furthermore, it is known that volatile cosolvents in traditional selfmicro emulsifying formulations diffuse into the shells of soft or hard gelatin capsules, causing lipophilic drugs to precipitate. Due to the dilution impact of the hydrophilic solvent, the drug‟s precipitation propensity may be increased when diluted. Simultaneously, validating formulations with several components becomes more difficult (Pharmaceutical Codex, 2019; Agbongiarhuoyi et al., 2020).

5. Conclusion

The local nature of cashew invariably provides enough amount of oleic acid that aid formulations, advantageously to the pharmaceutical industries. The application locally products such as cashew in pharmaceutical fields could not be overstated. One of the uses of cashew is formation of SEDDS. The SEDDS can be formed using details about SEDDS. Thus, this paper performs a review of SEDDS under certain headings. This paper makes a sufficient description of the items below: emulsions, self-emulsifying drug delivery systems (SEDDS), factors affecting SEDDS, method of preparing SEDDS, formulations SEDDS, components of SEDDS, characterization of SEDDS, stability of SEDDS, future, imitation, and the likes. We therefore accept the null hypothesis which says that cashew nut oil cannot be used to prepare stable emulsion alone without the addition of oleic acid.

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