Enhancement of bioavailability of herbal drugs for treating viral therapy using SNEDDS as the delivery system

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Abstract. SNEDDS were developed with the objective of treating low bioavailability of drugs for antiviral drugs due to its low solubility. The scientist has increased their interest in improving bioavailability and absorption of poorly-water soluble drugs using Self-Emulsifying lipid technology. SNEDDS was an isocratic mixture contains an Oil, Surfactant, Co-surfactant, and Drug in accurate amount. The SNEDDS was primarily prepared as liquid-SNEDDS, but S-SNEDDS was more stable as compared to L-SNEDDS. As viral infection was major threat for people due to its limited efficacy and Serious adverse effects. The most damaging viral diseases was treated with help of SNEDDS as delivery system. They were a leading cause of morbidity and mortality. The plant and plant source were major source from which the extracted metabolites used for synthesis of drug through metabolic pathway. The phytochemicals and extracts were better and safe alternative for synthetic drugs. The phytochemicals like Curcumin, Myricetin, Apigenin etc. used as drug for treating antivirals using SNEDDS. This technique was used for quantitative and qualitative analysis. Also, the ternary phase diagram gives dramatic representation of Oil, surfactant and Co-surfactant which shows its concentration. Some characterization techniques were Droplet size, Zeta potential, XRD, DSC, FTIR, and TGA. Also, QbD provides a platform for systemic production of drug formulations. QbD was used for its better bioavailability.

Keywords: SNEDDS, Antiviral, Phytochemicals, Ternary Phase Diagram, Bioavailability

1 Introduction

Viral infection was a major threat to people because it has affected 3-5 million patients in recent years. The commonly used antiviral drugs mostly shows lower efficacy and significant adverse effects while treatment [1]. Viral infections were a major cause of foreboding and temporality. The damaging infections are Ebola, AIDS, Influenza, and SARS. Influenza was responsible for 3 million new cases of most infectious diseases and 3-5 lakhs deaths yearly [2]. The best antiviral drugs like interferon and Ribavirin are effective in-vitro against several viruses. There are 90 different antiviral agents available to treat selective viruses. The patient diagnosis has increased every year with help of Blood transfusion, and organ transplantation [3,4].

The phytochemicals were most active against viral infections with the help of SNEDDS formulations. Herbal extracts are used since primordial times and known for their antiseptic properties and endurable side effects [5]. With this mindset, many Pharmaceutical-industries make formulations including nano-suspension, SMEDDS, and SNEDDS were developed and used for the antiviral delivery of natural products. Around 80% of the people uses herbal extracts to show effect against viral infection [6]. Most plants contain vital oils as well as biologically active compounds like phenolic acid, flavonoids, terpenes, alkaloids, and proteins that show activity against vigorous infections. There are around 2500 registered global therapeutic species to treat infections and diseases. Thus, phytochemicals are majorly used to show effect against vigorous infections [7]. With consideration of this, pharmaceutical companies formulate SNEDDS for treating viral infections by considering phytochemicals as drug molecules [8].

The oral route was used for the delivery of drugs due to its safety, comfort, and low side effects. Whereas many drugs are difficult to formulate through oral dosage forms because of their low solubility, low permeability, poor bioavailability, and

delayed onset of action. To overcome this factor pharmaceutical industries, formulate a new dosage form technique to deliver drugs that was SEDDS which is divided into SMEDDS and SNEDDS.

SNEDDS was the modern method of transforming emulsion into a capsule-coated shell. SNEDDS was filled in a gelatin capsule for oral administration which was more convenient. SNEDDS was mainly an O/W type of emulsion and are lipid-based formulations that were used for delivery of poorly soluble active pharmaceutical ingredients [9]. This was an isotropic mixture comprised of Lubricant, Emulsifier, Co-Emulsifier, and Drug enclosed in a capsule shell. This isocratic means when drug from any part of an isocratic mixture it always gives the same amount of drug. When get in contact with water, SNEDDS can form a fine emulsion of nanometer-sized droplets less than 200nm [10–12]. Due to the small droplet size, they were transparent after dilution. SNEDDS was used for formulations of drugs in BCS class II - IV. A trial & error approach in the formulation is time-causing, cost-fruitless, and has no guarantee to obtain optimum formulation [13]. The ternary phase diagram gives an exact concentration of Lubricant, Emulsifier, Co-Emulsifier, and drug in the formulation.

Quality by Design term introduced by American scientist J. M. Juran for systematic planning and manufacturing to avoid the critical crisis. Later USFDA approved concept of QbD in pharmaceutical sciences [14]. QbD provides a platform for the systematic production of drug formulations. The QbD approach for applying DoE software for optimization of SNEDDS to reduce expenditure in terms of cost, time, resources[15].

2 SNEDDS AS A DELIVERY SYSTEM

Types of SNEDDS

SNEDDS was an isocratic mixture comprised of Lubricant, Emulsifier, Co-Emulsifier and Drug in capsulated in gelatin shaped capsule. They give same amount of concentration from part of formulation as shown inFIGURE 1[16]. SNEDDS was nano-emulsifying drugs that are used for BCS Class II and Class IV drugs due to their low solubility [16].The BCS class I drugs were available 39% in market, whereas BCS class II drugs are 19% and Class IV are 33%, to overcome this scientist developed nano-formulations to improve solubility of drugs, the difference between SEDDS, SNEDDS & SMEDDS was shown in**Error! Reference source not found.**. Depending upon formulation SNEDDS are classified. SNEDDS are mainly classified in 2 types-

- Liquid SNEDDS
- Solid SNEDDS

Liquid SNEDDS – Liquid SNEDDS was first formed for the o/w type of emulsifying system. Lubricant, Emulsifier, Co-Emulsifier, and Drug enclosed in a soft gelatin capsule which when meets gastric fluid releases drugs and forms an emulsion [17]. Liquid SNEDDS require high poorly water-soluble drugs with large drug loading capacity and can be prepared quickly. Currently, the widely used formulation approach to produce S-SNEDDS was the adsorption of L-SNEDDS as a drug carrier [18]

Solid SNEDDS - Solid SNEDDS were more stable compared to liquid SNEDDS. The solid SNEDDS was growing platform to deliver drugs through the oral route. S-SNEDDS was a stable dosage form having high stability and ease of handling and can easily be administered by patients. In terms of pharmacokinetics S-SNEDDS were much better to fill in capsules compare to l-SNEDDS [19]. Solid SNEDDS was prepared by converting liquid or semisolid into powder form using techniques such as freeze drying, solid dispersion, melt granulation. Solid SNEDDS can be formulated in free-flowing powder, granules, pellets, tablets, and nanoparticles. The solid SNEDDS was formed when liquid SNEDDS are undergo through spray through to form solid nanoparticles which are more stable [16,19–23]

TABLE 1. Difference between SEDDS, SMEDDS and SNEDDS[10]

SEDDS	SMEDDS	SNEDDS
Oil droplet size ranging from 200nm-5um	Droplet size range between 100-300nm	Droplet size range >100nm
Turbid in appearance	Clear in appearance to turbid	Appearance is clear
HLB <12	HLB >12	HLB >12
Requires characterization of the ternary phase diagram	Requires characterization of the pseudo-ternary phase diagram	Requires characterization of the pseudo-ternary phase diagram

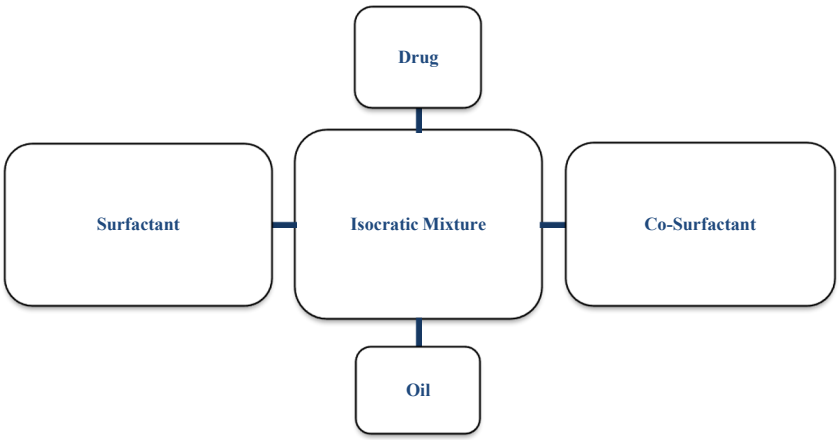

FIGURE 1. Isocratic Mixture Comprise of Oil, Surfactant, Co-Surfactant and Drug

3 VIRAL INFECTIONS

Viral infections were a major cause of foreboding and temporality. The viral infections were most hazardous for human health. It shows lower efficacy and significant adverse effects [24,25]. The patients which were treated with viral infections enlarge every year with the help of blood transfusion, organ transplantation, and the use of hypodermic syringes. There was no approved treatment to treat many viruses and limited vaccination available for certain viruses like Hepatitis A, Mumps, and Varicella [26]. Technological advancement overcomes us from viral diseases like Smallpox, Chickenpox, and Poliomyelitis. The influenza virus has more mutations so, new vaccines for the flu were developed yearly. The vaccines were preventative; thus, many pharmaceutical industries assume that the virus makes mutations, and they develop vaccines according to this, but this process was not accurate every time. Antiviral drugs were highly sensitive and require high patient compliance [1,27,28] The different classification of Antiviral drugs shown inFIGURE 2[26,29–32]. The viral diseases which affect most of the population were HIV, Herpes Virus, Influenza A & B, and Hepatitis virus.

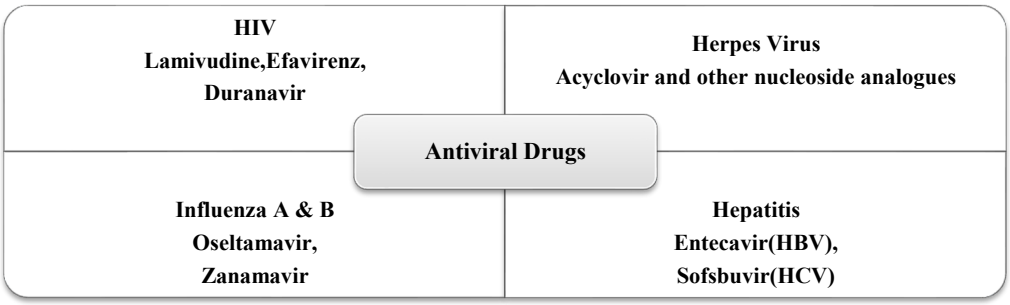

FIGURE 2. Classification of Antiviral Drugs

4 VIRUS

Viruses are intracellular parasites composed of DNA & RNA inside a protein that cannot carry out metabolic processes, they attach and enter the host cell to use its energy for the survival of DNA & RNA. It was difficult to kill viruses that were present inside the host cell as antiviral drugs kill viruses but they also damage host cells. Thus, it was difficult to make

curative drugs or vaccines to treat vigorous infections. HIV was responsible for AIDS targets $CD4^+$ helper T cells. HIV infection begins with interaction with glycoprotein [33,34]. Hepatitis means swelling of the liver. The Hepatitis virus was a series of 5 viruses that cause liver inflammation. HBV also known as oncovirus was majorly responsible for hepatitis-related deaths due to liver-damaging properties [30]. Herpes virus causes contagious sores, most commonly around the mouth or on the genitals. Infections were classified based on part of the body infected. The Herpes Simplex virus was challenging to treat because it can enter a latent state. They enter the host cell by binding different glycoproteins on the surface of the virus [31]. Influenza virus was neuraminidase inhibitors that block viral neuraminidase enzymes and shows activity. The Influenza virus was commonly broadened through association with blood or body fluids which has a deadly outbreak in Africa. Virus comprised of negative sense ss RNA encapsulated in viral capsid. It enters the host cell through the host glycoprotein. The SARS -coronavirus enclosed of positive ss-RNA [34].

5 PHYTOCHEMICALS FOR TREATING VIRAL INFECTIONS

Plants and plant source were considered as a major source from which the extracted secondary metabolites were used for the synthesis of the drug through a metabolic pathway with the help of genetic engineering. The extraction techniques were studied based on plant nature i.e., fruits, leaves, roots, bark, etc. The different phytochemicals having antiviral activity was shown in

TABLE ***2***). This technique was mainly used for quantitative and qualitative analysis of phytocompounds especially, the need to extract thermolabile drugs and oxidizable products [35]. The techniques used for the separation of phytochemicals are column chromatography, flash chromatography, Thin-layer chromatography, HPLC, and HP-TLC while, UV-visible spectroscopy, IR spectroscopy, NMR, and Mass chromatography are used for structural elucidation [36,37]. The classes that was medically active such as flavonoids, polyphenols, alkaloids, tannins, carotenoids, polysaccharides, and poly-unsaturated fatty acids are extracted from plants and are important for antiviral activities which cause huge endemic in different parts [38]The medicinal plants contain active ingredients which was present in leaf, stem, root, bark, and fruit which forms fine powder, when it goes under solvent extraction in presence of polar (water, methanol) and non-polar (chloroform, toluene) solvents it shows in-vitro antiviral activity. The TLC, HPLC, and MS analyzed active fractions which goes under in-vivo evaluation further goes under clinical trials and then form phytochemical which shows antiviral property as shown in FIGURE 3[5].

TABLE 2. Classification of different phytochemicals to treat antiviral activity using SNEDDS.

Phytochemicals	Antiviral Activity	Delivery System	Reference
MYRICETIN	HIV, RLV, Influenza	SNEDDS	39
APIGENIN	Influenza A, Hepatitis C virus, Enterovirus-71	SMEDDS, SNEDDS, o/w and w/o emulsion	40
BAICALIN	DENV, HIV, HBV, Influenza virus, Enterovirus 71	SNEDDS, SMEDDS, Nanoparticles	41
CURCUMIN	CHIKV, Norovirus, Influenza, HBV, HCV, HPV, HIV,	SNEDDS, SMEDDS, Nanoparticles	42
QUERCETIN	Influenza A, JEV, EBV, HCV	SNEDDS, Nano-emulsion, Nanocarriers	43
NARINGENIN	DENV, HCV	SNEDDS, Nanoparticles, Nano-suspension	44

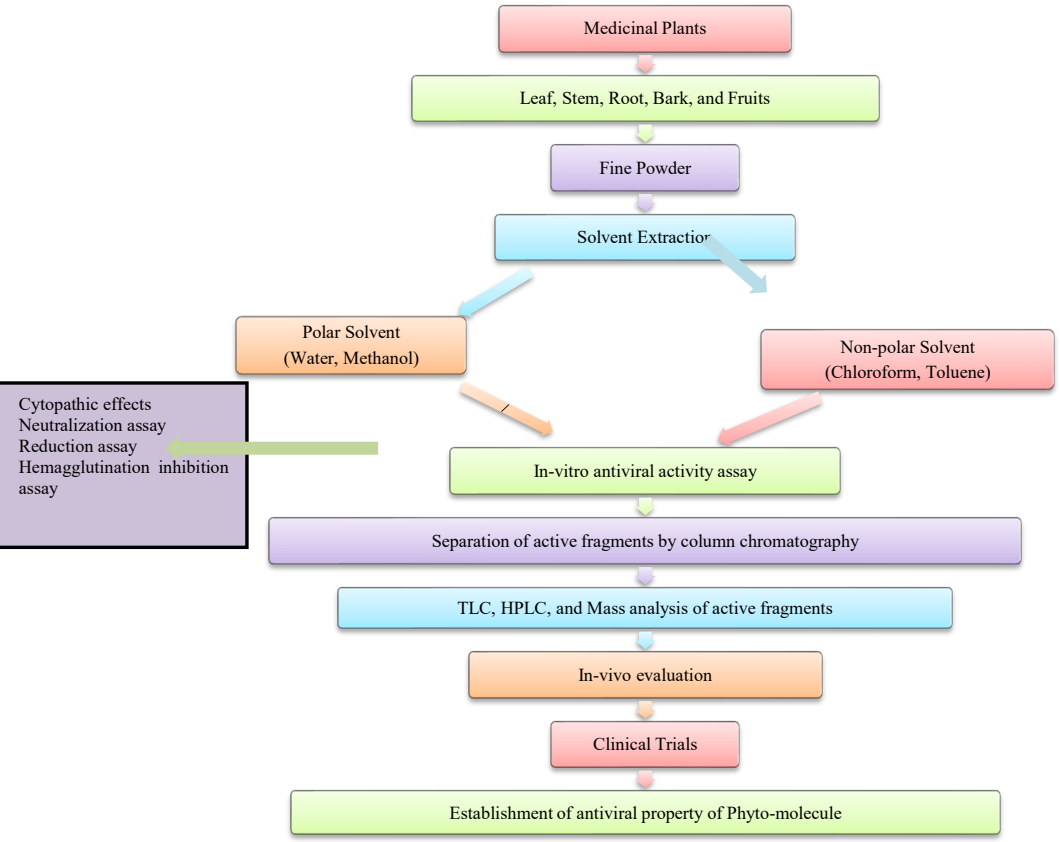

FIGURE 3. Pathway of formation of phytochemical used in treating antiviral infections from plant extracts.

6 MATERIALS

Selection Of Oil Phase

Oils show varying degrees of saturation when they contain medium and long-chain triglycerides. The highest drug absorption was shown by SNEDDS containing oil with lowest solubilization. The best indicator for in-vivo studies was not always high solubilization in oil phase. Natural oils (like castor oil, soyabean oil, ginger oil, coconut oil, etc.) exhibited relatively less drug loading and poor emulsification. The drugs were added to glass vials and placed for 5 minutes. The glass vial was shaken for 72 Hrs. in an isothermal shaker bath for 37ºc ± 2 ºC. Mixture must be centrifuged at 500-600 rpm for separation of the supernatant [45]

Selection Of Surfactant and Co-Surfactant

The second important component in SNEDDS was surfactant, because of their amphiphilic properties, it was found at the oil-water interface. Surfactants were classified on basis of the Hydrophilic-Lipophilic Balance (HLB) scale. Surfactant was characterized as ionic and non-ionic. The lower toxicity is characterized by use of non-ionic surfactants andcan form a stable emulsion. The non-ionic surfactant with an HLB value >12 was recommended. The ability of emulsification of the surfactant, HLB value, and solubility of the drug was most important parameters considered while selecting a surfactant [46]. Surfactants wereselected based on their emulsification ability towards a particular drug. Co-surfactant was selected based on

the ability to form emulsion on the basis of surfactant and drug molecules. A low interfacial tension was provided by use of single surfactant; thus, another surfactant is added as a co-surfactant. The divergent types of surfactants which was used for formulation shown in FIGURE 4[45]. They enhance drug solubility that promotes nano-emulsion stability and homogeneity. Commonly used co-solvents include propylene glycol, and polyethylene glycol (PEG). The amount of co-emulsifier should keep at a low level because of their polarity. The mixture was then diluted with deionized warm water to form an emulsion. The formed emulsion was allowed for 2 hours to stabilize[21].

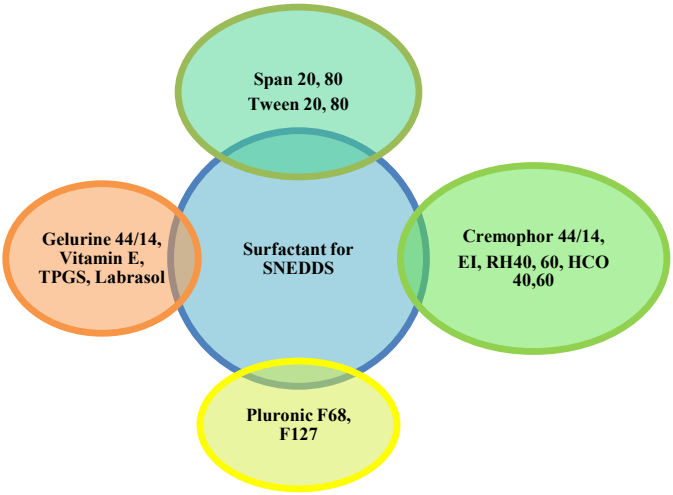

FIGURE 4. Different types of surfactants were used for formulation of SNEDDS.

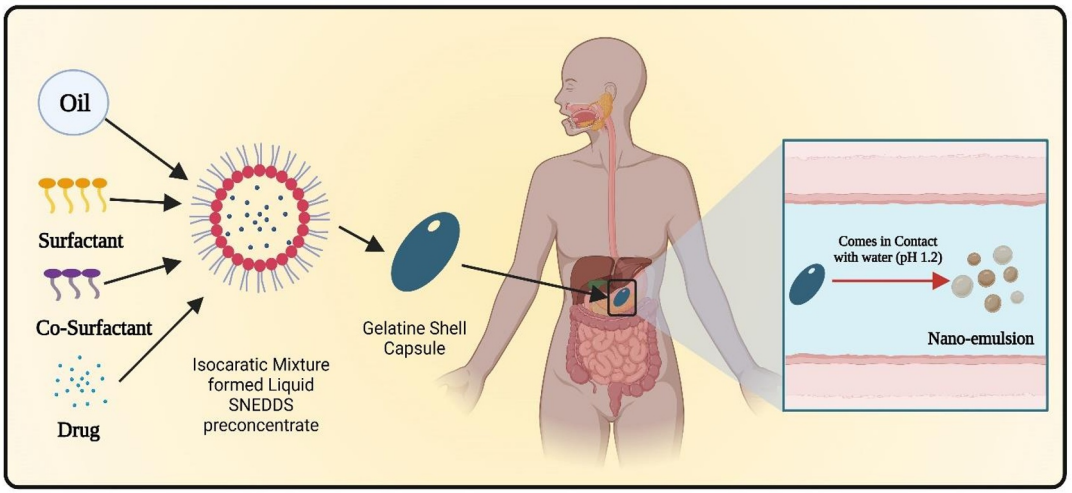

FIGURE 5. Mechanism of action of SNEDDS while giving through oral route

8 MECHANISMS OF ACTION OF SNEDDS

SNEDDS comprise of Oil, Surfactant, co-surfactant, and Drug in capsulated form with size less than 200nm. After administration of SNEDDS forms Oil-in-Water nano-emulsion immediately due to gentle agitation rising from gastric environment. These nanoparticles dispersed the oil phase offers a bigger interfacial surface to disperse in GI fluids. This can enhance solubility and permeability of drug by changing its transport property. There was quick digestion and rapid

absorption of drug occur in GI tract. SNEDDS also hold superior drug loading efficiency as compared to other lipid-based formulations as shown in

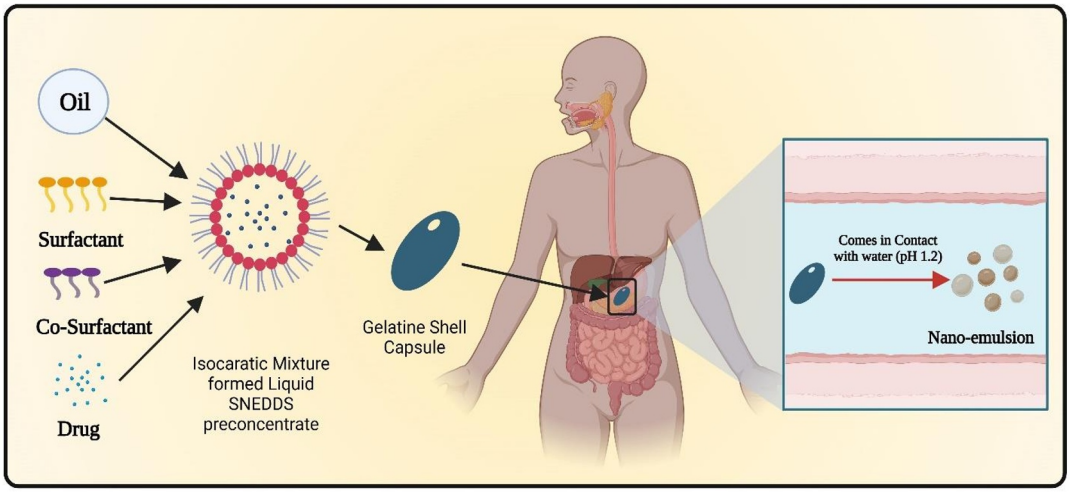

FIGURE *5*[47].

9 DELIVERIES OF PHYTOCHEMICALS USING SNEDDS TO TREAT VIRAL DISEASES

Pharmaceutical nanotechnology in the field of natural medicine was useful and promising to treat several diseases which cause severe effects on human health. The new strategies for the delivery of poorly water-soluble phytochemicals allow improved pharmacokinetic and clinical outcomes [47]The SNEDSS allow greater solubility and oral bioavailability (<10%) of myricetin. The four formulations were prepared F04 (Capryol 90/Cremophor RH 40/PEG 400 in a 4:3:3 ratio), F08 (Capryol 90/Cremophor RH 40/1,2-propanediol 4:3:3), F13 (Capryol 90/Cremophor EL/Transcutol HP 4:3:3), and F15 (Capryol 90/Cremophor RH 40/Transcutol HP 2:7:1), and solubility of myricetin in different excipients was studied. Three of the above four chosen formulations show accepted cell viability (>90%), while fourth formulation was slightly toxic, mostly because of high non-ionic surfactant concentration (70%). In vitro drugrelease testing shows that myricetin has dissolution of 51% after one hour, whereas drug release for all SNEDDS formulations was over 90% after one minute [48]

10 METHOD OF PREPARATION FOR SNEDDS

The preparation method of SNEDDS includes active pharmaceutical ingredients, excipients, polymers, and emulsifiers. They mainly divided into 2 methods:

High-energy-emulsification
Low-energy-emulsification

By combining this both techniques, such as HEE and LEE, reverse SNEDDS was prepared which was highly viscous system[49]. The both methods are further divided as :

High Energy Emulsification Method[50]

A. High Pressure Homogenization (HPH)- The preparing SNEDDS require compel homogenization. This scattered in 2 phases (oil-mixture and aqueous-phase) and mixing speed through trivial cove chops at load of 500-5000psi is required.
B. Ultrasonication- This was a more convenient method for lowering drop size. The energy-range was given by sonotrodes which was also known as Sonicator-probe. The endpoint of sonicatorreaches the liquid medium; container produces mechanical throb.

C. Micro-fluidization- The original addition methodology, that employee's custom of manoeuvre called micro-fluidizer. This deals with constant number of an era to get hold of beloved range to shaped even or homogenous Nano-emulsion system.

Low Energy emulsification Method [50]

A. Phase inversion emulsification method- This method was employed by transition of phase by applying increased in temperature route in emulsification.
B. Continuous Emulsification- The emulsification was always formed in which, organic resolution consisting of grease & lipophilic-emulsifiers filled with miscible emulsifiers. The string Oil-in-Water was prepared.

In-Vitro Assessment of Self-emulsification

When SNEDDS encounter water, the energy gets released [51]. The energy released was larger than required energy to show surface area between two immiscible phases. The dilution method was used for self-emulsification. Based on physical nature, they were grading as A to E [52].

Grade A: These system forms nano-emulsion in less than one minute. These show a clear and dark blue appearance in color.

Grade B: The dark blue to white color is formed and rapidly forms an emulsion.

Grade C: Milky emulsion was formed in less than two minutes.

Grade D: It hasa slightly oily appearance and appears greyish white in color.

Grade E: The large oil globules are present in emulsion surface andshow poor emulsification properties.

Different dosage forms of SNEDDS

- Self-emulsifying sustained release microspheres
- Dry emulsions
- Self-emulsifying tablets
- Self-emulsifying capsules
- Self-emulsifying implants

11 CONSTRUCTION OF TERNARY PHASE DIAGRAM

A ternary diagram of Lubricant, Emulsifier, Co-Emulsifier was plotted; each of the three shows at the tip of the triangle. It plays an important role in studying the phase behavior of formed formulation. A ternary mixture with different compositions of Lubricant, Emulsifier, Co-Emulsifier was prepared. One edge of the triangle represented each selection for identification of the region of SNEDDS. The concentration of oil varied from 25-75%(w/w), the surfactant concentration ranges from 30 to 75%(w/w) and the co-surfactant concentration was between 0 to 30%(w/w) [23]. For any mixture, the total concentration of Lubricant, Emulsifier, Co-Emulsifier should always be 100%. For example, in a particular experiment, the first mixture of surfactants was 75%, 25% of oily phase, and 0% of co-surfactant[53]. In further experiments, the co-emulsifier was increased/ decreased by 10% for each, the lubricant was kept at constant and the concentration of surfactant was adjusted to make 100% total composition[11]. The potential to generate an emulsion inside the self-emulsification zone increases, the amount of co-emulsifier in SNEDDS also increases. The maximum ratio of Smax was 45 to 75%. As Smax ratio increases, it shows effectiveness of SNEDDS (mixture of emulsifier and co-emulsifier) was more than 60% [47]. As concentration was exceeded to 70% it caused an increase in droplet size. The increase in water content can easily passes the oil droplet, were easily undergoes the "self-emulsification" process [54]. The Ternary Phase Diagram of Oil, Surfactant, and Co-Surfactant was shown in FIGURE 6. In this figure the concentration of surfactant and co-surfactant was shown. The oil, PEG 600, and Tween 20 was used in this figure.

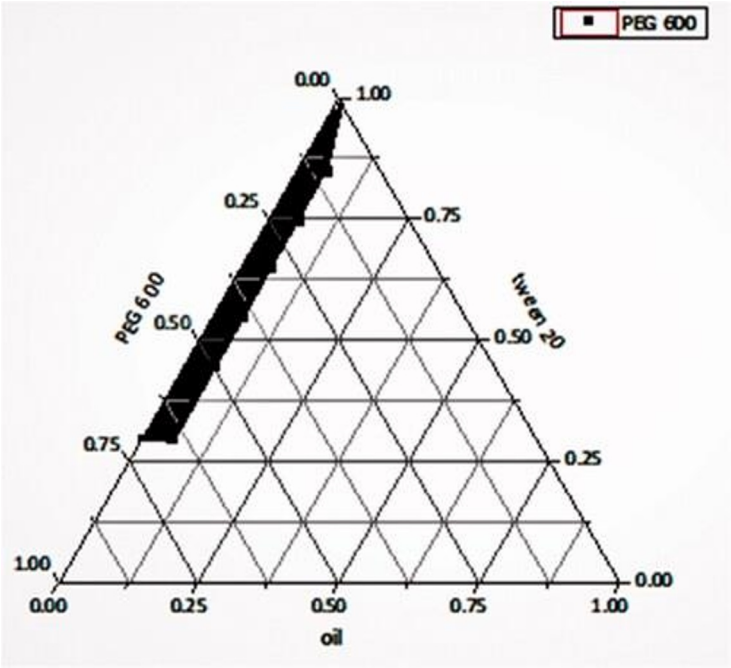

FIGURE 6. Ternary phase diagram of oil, surfactant, and co-surfactant

12 CHARACTERIZATIONS OF SNEDDS

Droplet Size

It investigated the effect of dispersion medium, and volume required for droplet size. The droplet size was formed between the range of 12 to 95mm. The SNEDDS formulation was diluted 10, 20, 30, up-to 1000 times with water, at 3 different pH buffers 1.2, 3.0, and 6.6, and it get compared with each other. The Phase Contrast Microscope (PCM) was used to determine the average droplet size of the formulation. The Mie equation of light scattering was used to determine sensitivity range between 10nm to 5um. The USP apparatus II Paddle method was used to determine emulsification time [54]

Refractive Index (RI)

RIwas generally used to determine the presence of transparent formulation. The Refractometer is employed to measure the RI. It also determines the thermodynamic stability of formulation [49].

Zeta potential

The information of colloidal stability was provided by using zeta potential. The oral absorption of drugs encapsulated in SNEDDS can affect the charge on particle. The flip-flop mechanism was used to determine change in zeta potential of SNEDDS formulation. The Surface potential of drug-free SNEDDDS ranged from -14.5 to -36.9mV showing good physical stability. The surface charge was used to determine the stability of nano-emulsion. The Malvern Zeta Sizer Nano Series ZS90 is used to determine zeta potential of the formulation [55]. As more zeta potential will show more stability as dispersion will oppose aggregation in the formulation [56,57].

Robustness

At different dilutions it was important that uniform emulsion was formed. The drug gets precipitated at higher dilutions and dilution also affects drug release. The dilution was formed by diluting it 10,50,100 up-to 1000 times with distilled water to form robustness of dilution. In an acceptable size range, all emulsions were found i. e. <200nm providing their robustness to dilution. The drug shows no precipitation or no phase separation even after 24Hrs when drug was diluted up-to 1000 times where reconstituted emulsion shows stability. The SNEDDS shows robustness to dilution when it was diluted with different dissolution media such as water, and 3 different buffers. The phase separation was observed by diluting sample and stored it for 12Hrs [56,57].

XRD

The XRD findings were good compared to DSC results. The drugs show characteristic x-ray diffraction peaks between 3 to 30 ºC. The drugs were analyzed within 60min and 2hr after sampling XRD to elucidate the solid state of the drug present in pellets. Scintillation detector and DIFRACplus software were used for signal processing. Drug experiments carried out using blank pellets obtained from the lipolysis of drug-free concentrate [7,58].

DSC

DSC analysis was conducted on Polymer 214 which is equipped with a cooling system and operates with universal analysis 214 software that is NETZSCH. Drug nitrogen was used to cleanse the sample cell at a flow rate of 80mL/min. The DSC instrument was calibrated for heat flow and temperature using the indium standard of high purity [59] .Pure drugs show keen endothermic peaks at temperatures which conform crystalline state of the drug. For DSC 5± 0.5mg samples of the drug Lubricant, Emulsifier, Co-Emulsifier and unloaded and loaded drug formulation were placed in aluminum crucibles and heated from 50-400ºC at 5 ºC/min heating rate under the steam of nitrogen gas flow at a rate 40mL/min using DSC [56,57]

FTIR

FTIR was performed for drug and excipient interaction. The IR spectrum was characterized by absorption peaks at different wavelengths. The spectra of different solid SNEDDS show that there was no shift of drug peaks in tested solid SNEDDS formulations. The peak shows very low (<2%) drug concentration within solid SNEDDS. The spectra of drug Lubricant, Emulsifier, Co-Emulsifier, and loaded and un-loaded drug formulations were calculated by FTIR spectrophotometer with a wavelength range of 400-4000cm^{-1}, and each sample was tested at 10times within a wavelength range [56].

TGA

For TGC 10 ± 0.5mg samples of the drug, oil, surfactant, co-surfactant, and unloaded and loaded drug formulation were placed in aluminum crucibles and heated from 50-400 ºC at 10 ºC/min heating rate under the steam of nitrogen gas flow at rate 40mL/min. The heating temperature was considered as a function of percentage weight loss [45].

13 MARKETED FORMULATIONS

TABLE 3. Marketed formulations used to treat viral infections using SNEDDS.

Active Pharmaceutical Ingredients (API)	Brand Name	Dosage Form	Category	Reference
SAQUINAVIR	FORTOVASE	Soft Gelatin Capsule	HIV Antiviral	[60]
RITONAVIR	NORVIR	Soft Gelatin Capsule	HIV Antiviral	[61]
AMPRENAVIR	AGENARASE	Soft Gelatin Capsule	HIV Antiviral	[62]

CYCLOSPORIN A/I	NEORAL	Soft Gelatin Capsule	Immunosuppressant	[63]

ADVANTAGES

Based on composition and formulation, SNEDDS give some advantages compared to other lipid-based formulations-

- The physical/chemical stability will not get affected even in long term storage[16,21,22.]
- Filled into unit dosage forms, e.g., soft/hard gelatin capsule.
- Improves patient compliance and acceptability [16,21,22,58].
- No palatability-related issues were observed[16,21,64–68].
- They were easy for manufacturing and scale up[16,21,22].
- It minimizes irritation between the drug and the gut wall of the body[58,59,64–68].
- They show selective drug targeting in the therapeutic window[16,21,22,58].
- Rapid onset of action

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DISADVANTAGES

- It shows a lack of good in-vivo-in-vitro-correlations.
- Less drug loading due to leakage.
- The traditional dissolution method does not work [16,21,22].
- Volatile co-emulsifiers combine into the shells of the capsule causing the precipitation of hydrophobic drugs [16,21,22,58].
- Increase surfactant concentration irritates the GI tract [59,64–68].

FACTORS AFFECTING FOR SNEDDS FORMULATION

- The very high drug dose was not suitable for SNEDDS.
- The drugs which show low solubility in water, and lipids was difficult to formulate by SNEDDS [69].
- To keep drug in solubilized form for SNEDDS was greatly affected by its solubility in oil phase [70].
- The solvent capacity of surfactant and co-surfactant get lower by diluting for SNEDDS formulation [71,72].

FORMULATION CONSIDERATION

The various factors which affect formulation:

- The physiochemical nature and convergence of lubricant, emulsifier, co-emulsifier[73,74].
- The proportion of oil-to-surfactant mixture [75].
- The temperature and pH of watery phase [76].
- Physiochemical properties of API like pKa value.[77]
- Physiochemical properties of lubricant, emulsifier, co-emulsifier, and their concentration [78].
- Through which route we administered the formulation also plays role in selecting formulation ingredients [79,80].

APPLICATIONS

- It was used for target-specific delivery for transdermal, parenteral, intravenous, and ocular administration [16,21,22,58].
- It has a novel approach to stopping problems associated with first-pass metabolism and getting directly absorbed in the systemic circulation[16,21,22].
- The dissolution process gets bypassed when drug was formulated as SNEDDS, which also increases solubility and bioavailability of drug product [16,21,22].
- Solid SNEDDS will minimizes problems compared to liquid SNEDDS as they offer better compliance [16,21,22].
- SNEDDS was independent of pH solubility and increases bioavailability and Cmax of a drug [64–68].
- The pellets show sustained release, from drug release tests, with 90% pellets released in 10Hrs [16,21].

14 CONCLUSIONS

The dissolution and absorption rate of poorly aqueous-soluble drugs could be increase with the help of SNEDDS, the formulation approaches and excipients used for SNEDDS formulation was cost-effective and simple. The use of SNEDDS in different areas shows excellent physical stability and less complex manufacturing. The techniques and additives used to formulate SNEDDS were economic and simple. The critical parameters that impact GI absorption effectiveness include charge and size of oil droplet in emulsion produced. Around 40% of novel drugs are hydrophobic, it predicts that further drug products for pharmaceutical industry will be formed as SNEDDS in coming years. There were new techniques used to convert L-SNEDDS into powders and granules which are further processed into conventional 'powder-fill' capsules or into compressed tablets. The SNEDDS medicinal and economic potential has greatly influenced by the discovery of S-SNEDDS, S-SNEDDS were considered state-of-the-art delivery vehicles for poorly water-soluble pharmaceuticals, to improve drug loading, stability, ease of processing and storage.

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