International Journal of Advanced Multidisciplinary Research
ISSN: 2393-8870
www.ijarm.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijamr Volume 11, Issue 11 -2024

Review Article

DOI: http://dx.doi.org/10.22192/ijamr.2024.11.11.001

A Review on Preparation and Evaluation of Self Emulsified Drug Delivery System

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Keywords

BCS class IV, SEDDS, Excipients selection and composition, microemulsion, nanoemulsion, evaluation methods.

Abstract

BCS class IV drugs are a hassle for formulation and development owing to their lower solubility and bioavailability. SEDDS is an advanced method of formulation exhibiting higher mucus and cell permeation activity; hence, it is of great importance nowadays in the formulation and development of pharmaceuticals. The excipients were selected based on a visual solubility study. It is formulated using a three-phase oil, water, surfactant, and cosurfactant mixture. The pseudo-ternary phase diagram helps to find the composition of the three phases that define the microemulsion region or nanoemulsion region. A wide category of formulations can be made of SEDDS, such as tablets, capsules, parenterals, dry emulsions, transdermal or mucoadhesive patches, etc. These are formulated by imposing various methods of solidification of liquid SEDDS: adsorption, atomization, lyophilization, melt granulation, melt extrusion, etc. Various evaluation methods are imposed to evaluate micro- or nanoemulsions, which include drug content, dispersibility tests, rheological properties, thermodynamic stability studies, robust dilution, particle size and droplet size analysis, self-emulsification time, drug release studies, etc. SEDDS is a very promising formulation system with enhanced bioavailability.

I. Introduction

Surfactant it is derived from the word surface active agent found in the year 1950. It is a compound which helps to reduce the interfacial tension between liquid- liquid, liquid- solid. These are ampihiphillic and amphipathic as posses both hydrophilic and lipophilic tail and head. It works on the mechanism of adsorption where formation of droplets is required depending on its diffusion coefficient. Mechanism can be kinetically limited by Some barriers like electrostatic repulsion or, steric interaction.

Surfactants may be included fluorocarbons, Siloxanes, polyether, polyethylene oxide, etc. It can be categorised into non-ionic, anionic, cationic, zwitter ions etc. Depending on charge on polar head. Anionic surfactants contains anionic functional group on its head like sulphate, sulphonate, phosphate, carboxylate etc. For example Ammonium lauryl Sulfate, sodium lauryl sulphate, docusate etc. Cationic surfactants are many ammonium ions at pH less than 10 are considered, for example benzalkonium chloride, Benzethonium chloride, Cetyl pyridinium chloride etc. Zwitteron or amphoteric surfactants in which the function functional group contains both positive and negative charges. For example Sphingomyelins, phospholipids, Phosphatidyl serines, Phosphatidyl cholines etc. Nonionic surfactants are the most preferable one hare the hydrocarbon chain are covalently bonded with oxygen which helps in hydrogen bonding. It is highly recommended because of its efficiency, toxicity, compatibility, and permissible in food. For examples Spans/ Sorbitan ester, Tweens/ Polysorbates. because of high HLB value surfactants Tween 20, Cremophore RH40, Tween 80, Accoonon MC8-2 are considered to be safe efficient and biocompatible. [1]

Medium chain alcohols of C3-8 with HLB value 10-14 are used as cosurfactants or cosolvents when added with surfactants to reduce interfacial tension in formulations. High concentration of surfactants required to prepare an highly dispersible or stable emulsion. Cosurfactants addition can able to reduce concentration of surfactant in formulations, its addition can reduce the interfacial tension to a negligible value and thus can able to make formulation into finely dispersible droplets, these plays an important role in solubility enhancement. Glycerol, ethanol, isopropanol, benzyl alcohol, dimethyl sulphoxide etc. are hydrophillic cosolvents helpful to facilitate the solubility of less soluble drugs in SEDDS formulation. these cosolvents are hydrophillic in nature with a decreasing order of Dimethylsulphoxide> Ethanol> Benzyl alcohol. [2] These are shortchain alcohols or amines when combined with surfactant alkyl chain it decreases the interfacial tension to a minute value which is helpful for production of micro or nanostructures. Oil is an important constituent in self emulsified drug delivery system which solubilise lipophillic drugs also facilitates in in self emulsification in GI tract thus increasing absorption via intestinal tract through intestinal lymphatic system.in SEDDS formulation both long chain as well as medium chain triglycerides used as oil phase. [3] long chain triglycerides (e.g: soyabean oil) are difficult to micro emulsify where as the triglycerides (ethyl oleate) with short chain or medium chain can better micro emulsify. [4]

Novel Drug Delivery System (NDDS) is an important area of formulation and development where many approaches are included. In case of development of formulations based upon solubility and permeability enhancement, many promising methods are developed like Solid Lipid Nanoparticles, solid state emulsions, PLGA nanoparticles etc. Inspite of all those SEDDS is an advanced method of formulation exhibiting higher mucus and cell permeation activity hence is treating great importance now a days in Formulation and development of pharmaceuticals. [5] It is a biphasic isotropic system where lipophilic drugs may be solubilized in water using oils surfactants and cosurfactant. The SEDDS consists of oils (< 20% w/w) and high concentrations of surfactants and cosurfactants (approximately 30-60%). [6] Here the lipophillic drugs are micronized when dispersed in cosurfactants and thus facilitating reduced interfacial tension and solubilized in water this formulation facilitates faster and immediate action more effective in less dose to improve solubility and bioavailability. Peptides are delivered and absorbed without hydrolysis in GI tract. [7] Self double emulsifying drug delivery system is a type of W/O/W SEDDs in which surfactants mainly lipophillic surfactants are mixed with water in oil emulsion. this is having high stabilising capability also increase bioavailability. depending on droplet size SEDDS divided into SMEDDS or SNEDDS as mentioned in fig.1, which ranges from a few nanometer to several microns. Transparent SMEDDS have droplet size of 100 to 200 nm where as SNEDDS have droplet size less than 100

nms. [8] From few literatures it has been noticed that SNEDDS formulations have gastric acid tolerance and stability against enzymatic degradation as well, thus the drugs acid unstable also can be chosen for the formulation. [9]

In recent era the newly designed drugs, which are developed and synthesized are mainly less water soluble. SEDDS formulation helps to solubilise the less soluble drugs. It depends on the carriers, solvents in which surfactants, co-surfactants plays an important role. Oil helps to solubilise the lipophillic drugs. In this formulation it is a critical step to mix a drug with vehicles. The vehicle mixture is find out basing upon the solubility in surfactants, cosurfactants, oils. The ratio of these exipients can be confirmed from pseudoternary phase diagram. Self dispersing liquid formulation (SDLF) is one of the promising formulation to overcome low aqous solubility and bioavailability. Selfemulsification is the process in which, on administration of the formulation emulsifies into emulsions or microemulsions on addition into aqueous environment in GI tract where it disperse into fine, very fine droplets. [10] Advantages than coventional emulsion system includes, the SEDDS formulation gets frequently disperse into fine globules without any shear or stress. It is highly stable formulation no need to bother about instability issues also resistant to small temperature change. It can be converted to many types of formulation system and can also be packed in blister and strip packagings. It can be manufactured by basic instruments rather costly or any specialized instrument. [11]

This lipid based formulation was 1st introduced in the year 2000, by pouton & porter. this formulation is classified into 5 types, [12] Type-I: the drug is in solution of triglycerides and exhibits poor aqous dispersion, and need panceatic lipase in GIT to generate lipid digestion product and the drug tranfers into aqous colloidal phase. The suitable drug are highly lipophillic with logP > 4. Type-II: These are typically reffered to SEDDS drugs are in solution of a mixture of oil and lipophillic surfactants with HLB<12, they disperse into fine particles in aqous medium. It generates large interfacial area which allows efficient partitioning of drug between oil and aqous phase. Type-III: it includes hydrophillic surfactant with HLB> 12 and co-surfactant such as ethanol, propylene glycol, polyethylene glycol. These formulations disperse quickly and form fine micro dispersion and give a transparent dispersion. it is sub-categorised into IIIA and IIIB. IIIB achieves greater dispersion than IIIA. Type-IV: the formulation contains pure surfactants or mixture of surfactant and co-surfactant without natural oil and is the most lipophillic formulation. Very fine emulsion is formed can be dispersed quickly also high drug loading capacity. SDLF (Solid Dispertion Liquid Formulation) forms SEDDS when surfactants used is of HLB value less than 12 and SMEDDS (Self Micro Emulsifying Drug Delivery System when surfactants used are of HLB value more than 12. Both of these are safe and effective formulation. This is one of the best solution to the poor water solubility of drug under BCS class II and IV.

According to BCS (Biopharmaceutics classification) classification system, the drugs are classified under four categories class I, class II, class III, class IV. This classification is based upon aqous solubility and bioavailability/ permeability. Class-I includes highly water soluble and highly permeable drug, class II includes less aqous soluble and highly permeable drugs, class III adds the drugs highly soluble but less permeable, where as class IV includes less soluble and less permeable drugs. Nutraceutical Bioavailability Classification Scheme (NuBACS) is considered for nutraceuticals in industries, which describes about bioavailability of nutraceuticals. [13] These class IV drugs are highly notorious drugs, whose formulation are not very suitable. It is a challenging task to make suitable formulations of these class IV drugs. These drugs by going for drug design stage the structure can be modified to get a permeable drug, but it is so costly and time consuming process. Rather than modifying the structure, it can also be done to enhance it's solubility and made it permeable through membrane. There are many techniques available to enhance it's solubility and permeability like using lipid carriers, polymeric

nanocareers, crystal engineering technique, solid-liquid technology, selfemulsification etc. for solubility enhancement liposomes, solid liquid nanoparticles (SLNs), nanocapsules, micelles, dendrimeres etc. plays a major role to cross lipoprotein membrane. [14] To reach therapeutic concentration a poorly water soluble or less permeable drugs specially in case of orally administered drugs required to increase the dose. This increased dose may causes long term toxicity in gastric mucosa thus ionic liquefaction has also been employed to overcome the condition. [15]

Lipid based transformation of poorly soluble drugs is one of the good option to make bioavailable formulation. Drug absorption mainly depends upon solubility of drug in GI fluid and permeability through lipid bilayer membrane. When lipid based formulation ingested the nutritional triglycerides and formulation triglycerides are digested by gastric lipase and gets mixed mechanically in GI tract by propulsion, grinding and retropulsion and forms an emulsion of finely dispersed droplets which can be easily cross the lipid bilayer. It is an advanced and important approach where spontaneous formation of nano or micro emulsion depending on physiological or GI fluid environment. These formulations are named as SNEDDS Self nano emulsifying drug delivery system and SMEDDS Self micro emulsifying system. In SNEDDS formulation the size globule is less than 100nm when dispersed in water. It is also known as Nanoemulsion / miniemulsion / ultrafine emulsion/ submicron emulsion. It forms a thermodynamically stable, transparent, transluscent, non ionized formulation. It is one of the highly stable emulsion as it provides a large interfacial area between oil/ water phase, thus inhibits inversion or phase separation. [16]

As drugs under BCS class II and IV are less water soluble and less permeable compared to class I and III, thus are suitable candidates for SNEDDS formulations. There are three types of nanoemulsion can be formulated are, W/O nanoemulsion, in which water droplets dispersed in oil and oil acts as continuous phase. O/W: nanoemulsion- Oil droplets dispersed in water, where water acts as continuous phase.

Bicontineous nanoemulsion: in this case both water and oil are contineous phase as droplets are dispersed both in oil and water. Surfactants are soluble in both oil and water. SNEDDS is capable to dissolve large quantity of APIs. It provides ultra low interfacial area. Many formulations including liquids, sprays, foams, cream, ointments etc. nanoemulsion is difficult to prepare as expensive instruments like high pressure homoginiser, ultrasonic equipments are required. This can be of liquid SNEDDs and solid SNEDDs. This nanosclae was first introduced by Richard Feynman a nobel laureate during 1965. [17] The liquid SNEDDs is the formulation in which API is dissolved in oil/ co-surfactant/ surfactant mixture. oil, surfactant and co-surfactant mixture is selected from ternary phase diagram. in composition of SEDDS formulation oil acts as hydrophobic sink, surfactant as emulsifying agent and cosurfactant to enhance solubilisation. [18] Whereas the solid SNEDDs formulation in which the liquid SNEDDs is triturated in mortar and pestle and the dump mass is sieved through sieve no. 120 and dried at ambient temperature. [16]

The mechanism of SEDDS emulsification is not very clear but from various literatures it is suggested that, the dispersion of system favours due to entropy change. The free energy of formulation is directly related to the energy required to create a new interface between two phases.

It can be described in terms of ΔG, N_i, r_i, σ that is,

$$\Delta G = \sum N_i \, 4 \, \Pi \, r_i^{\,2} \, \sigma$$

Where,
ΔG = represents free energy
N_i = represents radus of droplets
$r_i^{\,2}$ = Number of droplets
σ = Interfacial energy

Naturally the two phases try to separate and reduce interfacial energy and the free energy hence, to make it stable emulsifying agents play an important role forming monolayer around

emulsion droplets. In SEDDS formulation spontaneous emulsion takes place as the free energy becomes negligible. [19]

II. Material and Method

It is quite important to choose a suitable drug formulation. As it is a lipid based formulation the drug must be lipophillic which belongs to the water insoluble drug most commonly BCS class IV drug. solubility, permeability, dissolution rate are important factors to achieve therapeutic efficacy. A compound should have aqous solubility as well as lipophillic nature to cross the membrane of gastro intestinal tract. [20]

A. Selection of excipients:

Drug and excipients should be collected from any Pharmaceutical industry or any recognized laboratory should be of analytical grade.[21] The excipients selected based upon visual solubility study. The solubility of the selected drug is tested by mixing an recurrent amount of drug to a fixed volume of solvent or excipient in increasing dielectric constant and decreasing HLB value. [22] Solubility of API in different excipients is studied by dissolving in different oils , surfactants, and cosurfactants using cyclomixure and placed in a biological shaker at 37°C followed by centrifugation and furthere the solubility can be quantified spectrometrically. [23] A few examples of excepients are mentioned in table 1 for few specific drugs.

B. Pseudoternary Phase Diagram

Construction of pseudoternary phase diagram is a primary step and the foundation of SEDDS formulation. To solubilise the poorly soluble drugs or to enhance solubility we should make a composition of exipients or vehicles in which the drug shows high loading capacity. To support the enhancement of solubility and optimize or screen out the area of composition of vehicles which is most suitable for SMEDDS or SNEDDS formulation. The software based techniques of pseudo ternary phase diagram are most suitable and helpful.

This is a critical process to develop SEDDS in which the selection of Oil, surfactant, co-surfactant mainly based upon highest solubility of API and formation of a stable emulsion and emulsification capability. 5µl oil mixed with 10% aqous surfactant solution and is mixed repeatedly with the help of cyclo-mixer until turbidity appears. Co-surfactants finalized and optimized from phasediagram. [24] A ternary phase diagram can be made by either dilution method or by titration method. In dilution method the formulation of nanoemulsion is observed by diluting the mixure with double distilled water. The formation of nanosized globules determined by spectroscopy method. Otherwise can be done by titrating with distilled water. [25] Titration method is the common method and can be carried out by selecting all three vehicles S_{mix} is selected which is the mixture of surfactant and cosurfactant, it's selection is based upon titration of various compositions against distilled water upto which it gives the clear solution. In the next step Smix and oil composition is titrated with water until it gives a clear solution. By putting the titration values in software we can get a pseudoternary phase diagram which shows the area in which the SEDDS formulation can be prepared. [24] Softwares available… chemix software [26], Origin 9.0 software (OriginLab, Massachusetts, USA) [27], SigmaPlot 13.0 software [28].

Different compositions should be selected from various micro or nanoemulsion regions of the Pseudo ternary phase diagrams. A few formulation systems should be selected based upon maximum solubility of the selected drug where it give micro or nanoemulsion spontaneously in gastric medium or in body fluid. The finalized formulation system is furthere characterised for it's nanoemulsion behaviour. Compatibility study of drug and excipients plays an important role in formulation thus is carried out using FTIR Spectroscopy. [29]

Table. 1 Details of excepient in various formulations:

Name of drug	Oil	Surfactant	Co-surfactant	Type of formulation	Method used
Paclitaxel [30]	Ethyl eoleate	Tween80: Carbitol, 90:10, w/w)	PEG 400	Solid SEDDS	Spray drying method
Ibuprofen [31]	Labrafac	Tween 80	PEG 200	SEDDS formulation	Mixing
Erlotinib [32]	Labrafil M2125CS	Labrasol	Transcutol HP	Solid SEDDS	Spray drying using dextran 40 and Aerosil 200 as solid carriers
Curcumin [26]	Ethyl Oleate	Capmul MCM	PEG 400	SMEDDS	Water titration method
Spironolactone [33]	castor oil	tween-80	PEG-600	Solid SEDDS formulation	Adsorption on solid carrier
Bisdemethoxycurcumin [27]	Ethyl oleate	Kolliphor EL	PEG 400	L-SEDDS	Pseudo Ternary Phase Diagram
Griseofulvin [34]	Captex 355	Tween 80	Labrasol	SEDDS	Adsorption onto colloidal silicon dioxide
Delafloxacin [36]	Lauroglycol-™-90	Tween 80	Transcutol HP	SNEDDS	Mixing
Vancomycin [5]	Capmul 808G EP/NF, Captex 8000	Cremophor EL and Cremophor RH 40	Transcutol HP and dimethyl sulfoxide DMSO	SEDDS	Mixing

III. Various SEDDs formulations:

SEDDs formulation can be formulated for topical as well as internal use. Also it's opthalmic preparations, pulmonary delivery, and parenteral formulations are been prepared. The formulation administered orally includes, Self emulsified sustained and controlled release tablets, Self emulsified sustained and controlled release pellets Self emulsified solid dispersion. Topical applications are most suited and effective. the main advantage of this formulation is it avoids first pass metabolism and related toxicity. [37]

A. Capsule SEDDS:

Capsule SEDDs are filled with liquid SEDDs, when ingested in GI tract it is frequently dispersed into fine micro or nano-droplets or emulsion with very small sized droplets. To avoid phase separation sodium dodecylsulphate is used.

B. Sustained and controlled release SEDDS:

It is highly recomended formulation as able to reduce adverse reactions. For example few medications like indomethacin sustained release SEDDs able to reduce GI bleeding favouring easy penetration through GI membrane.

C. Solid dispertion SEDDs:

The main problem of solid dispersion is it's instability which can be overcome by use of surfactant and cosurfactant, the SEDDs excipients. It is one of the widely used formulation and is prepared by hot melt granulation method.

Topical preparation: Most preferable and suitable formulation with enhanced dermal absorption and pharmacological effect. Also the formulation is quite safe, avoiding toxic effect related to first pass metabolism.

D. Parenteral SEDDs:

Use of SEDDs enhance the drug loading capacity of parenterals, so that required amount or effective dose can reach the target site.

E. Dry emulsion:

mainly O/W emulsion are spray dried and freeze dried with an adsorbant carrier. The formulation need to be dispersed in water before use. Medium chain triglycerides are used in this formulation. The advantage of this formulation is , it is free from the toxic effect of organic solvents also good stability is observed. This is furthere used in tablet or capsule formulations.

***F. SEDDS tablet*:** These are formulated by adsorption on granular material followed by compression.

IV. Techniques used for Solid SEDDS formulation: [37]

S-SEDDS are most commonly formulated in gelatin capsules, now a days it also can be formulated in various other formulations. From liquid SEDDS we can make various solid dosage forms by various techniques like adsorption, lyophilization, spray drying, melt granulation etc. These techniques helps in formulation of solid SEDDS and these can be fur-there converted into tablet, capsule, powder, pellets, suppositories or any other solid dosage formulation.

A. Solidification by adsorption:

Bending liquid SEDDS with solid carriers which adsorbs liquid SEDDS and gives a powder form. The solid carriers might be microporous substances of inorganic or cross linked polymeric substances with large surface area like silica, magnesium trisilicate, neusilin, talc, carboxy methyl cellulose, sodium carboxy methyl cellulose etc. Nanoparticle adsorbants like silicone dioxide, carbon nanotubes, nanohorns, charcoal etc.

B. Atomization / Spray drying:

Liquid SEDDS converts into powder form by atomization technique. The specification of powder depends on the atomizer, temperature of drying chamber, air flow pattern etc. the liquid SEDDS introduced into the atomizer where the sprayed fine droplets dried in drying chamber by evapouration of volatile liquids or water. After obtaining the fine powders the various solid dosage forms can be formulated.

C. Lyophilization/ freeze drying:

This technique is an alternative method to form a dry emulsion in which temperature and mass transfer occurs. In this freeze drying techniques the drug and carrier are codissolved in a common solvent and is furthere frozen or sublimed. This is commonly applicable for manufacture of lyophilized molecular dispersion.

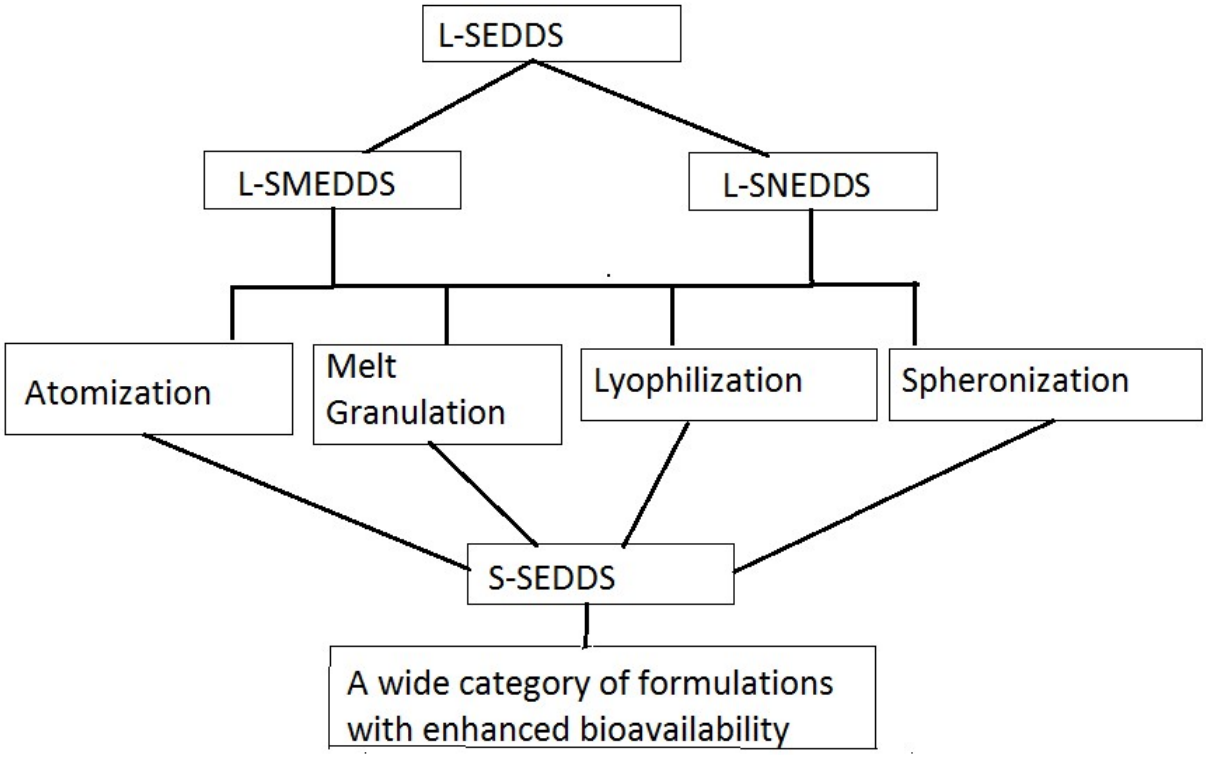
D. Melt granulation:

The lipid binders are used which melts at relatively low temperature and helps in obtaining agglomerates of liquid SEDDS.

E. Spheronization / melt extrusion:

Formation of spheroids upon converting raw materials into plastic characterastics and compressing forcefully into dies so that desired spheroids can be obtained. This technique involves mixing of APIS and excipients and blending with binders followed by extrusion into ropelike structure and furthere converted into spheroids of desired size and shape by spheronization.

Fig-1



V. Evaluation of SEDDS formulation:

After formulating a dosage form it is essential to carry out evaluation to evaluate the quality of formulation. It includes a number of tests like drug content, dispersibility test, rheological properties, thertmodynamic stability study, robustness to diluation, turbid metric evaluation, droplet size or particle size analysis, self emulsification time, invitro dissolution study etc. which are explained below.

A. Drug content:

It can be calculated from a pre weighed SEDDS by extracting with a suitable solvent and required to filtered and diluted. The drug content should be analysed spectrometrically with the help of a suitable analytical method like UV Spectrophotometer. [38]

B. Dispersibility test:

The test tells about the ability to emulsify into globules of varying sizes. This can be carried out by using a paddle type dissolution apparatus of USP standard. It is been carried out by mixing 1ml of formulation in 500ml distilled water maintain temperature 37 ± 0.5°C and the paddle is rotated for 50 rpm. Upon mixing with water it gives a dispersion of various globule size and appearance. This observation becomes helpful in invitro dissolution study depending upon the observations and results obtained from the

dispersibility test which is elaborated below basing upon formation of emulsion after dispersibility.

Grade A, which gives immediately with clear bluish appearance should be considered as nanoemulsion in GIT. Grade B forms rapidly with less clear bluish white appearance in GIT, is considered as nanoemulsion. Grade C forms in a few minutes and gives a milky appearance is considered as SEDDS in GIT. Grade D take more than 2 to 3 minutes and gives oily appearance is considered to be emulsion or emulgel. Grade E need long time and gives large globules on the surface which represents poor emulsion.

C. Rheological properties:

As SEDDS includes capsules, tablet formulations it is important to find it's rheological properties like viscocity, thixotropy, static yield, creep value etc. these parameters can be evaluated by using rational viscometer or digital instruments. Basing upon viscocity the emulsion system can be indicated like O/W if less viscus and W/O if more viscus.

D. Thermodynamic stability study:

Stability study plays an important role as the instability caused by precipitation of formulation or phase separation or incompatibility of formulation with gelatin capsule cell may cause brittleness or softness hampering release of drug or delaying disintegration of formulation. The following studies are carried out like heating cooling cycle, centrifugation, freeze thaw stress cycle.

E. Heating cooling cycle:

Here six cycles carried out with temperature ranging from temperature ranging from 4°C to 45°C. At each temperature a minimum time period of 48 hours should be kept. The formulations which passes the cycle proceeds towards centrifugation.

F. Centrifugation:

The formulation should be allowed to store between 21°C to 25°C stored not less than 48hrs and centrifuge for 30 minutes at 3500rpm speed. The formulation that passes the test considered for freeze thaw stress test. [39]

G. Freeze thaw stress cycle:

Formulation is kept for 48hrs time. In temperature should be ranging from 21°C to 25°c. the formulation that passes the test should be considered for self emulsification study or, dispersibility study.

H. Robust to dilution:

Dilution of formulation in different dissolution media and is observed for its stability after 12 to 24 hours of storage. If any precipitation or phase separation will not be observed it is considered to be robust to dilution.

I. Turbid metric evaluation:

Turbidity is the term which express the self emulsification time and droplet size. A fixed amount of formulation is kept in a dilution medium stirred continuously with 50 rpm at a fixed temperature on a magnetic stirrer and then the turbidity should be measured with turbidimeter.

J. Particle size or, droplet size analysis:

The size of particle is one of the most important parameter which can be measured by various techniques like X-ray, Neutron scattering technniques, dynamic light scattering techniques etc. DLS is based upon time variation to scatter light in brownian motion of dispersed particles with the help of stokes Einstein equation. laser light of a specific wavelength is passed through diluted sample and the intensity of scattered light passes through detector to detect the particle size in the formulation. [40] There are various equipments available for particle size analysis like master sizer, particle size analyzer, zeta sizer etc.

are having capability to measure sizes ranging from 10 to 5000nm. These instruments are working on the basis of various light scattering techniques like photon correlation spectroscopy, dynamic light scattering, laser diffraction techniques etc.

K. Self emulsification time:

To determine self emulsification time USP dissolution apparatus is used. A fixed amount of formulation should be added to a required amount of solution medium like 0.1 N HCl or 0.5% sodium lauryl sulphate. The time required to emulsify s.hould be noted as emulsification time.

L. Liquefaction time:

Time taken to melt in simulated gastric fluid without agitation. To carry out this method formulation is kept in a transparent polyethylene film is tied to bulb of thermometer. The setup should be kept in a RB flask in which simulated gastric fluid without pepsin is taken. The temperature of 37 ± 0.5°C should be maintained during the process.

M. RI (refractive index)/ percentage transmittance:

This is a parameter to determine transparency of SEDDS formulation. To find out RI refractometer is used, in which a drop of solution is kept on a slide and compared with water. (RI of water = 1.333). The %T should be calculated using UV-VIS spectrophotometer and water taken as blank. RI value close to water and %T value > 99% indicates transparent nature of formulation.

VI. Drug Release Study

A. In vitro drug release study:

Through this method the drug release is studied using dialysis membrane in dialysis medium of phosphate buffer of pH 6.8. 1ml of formulation with dialyzing medium is filled in membrane which tied to both ends with the help of thread. This system should be rotated in dialyzing medium at 100rpm in a magnetic stirrer or dissolution apparatus. At different time interval samples are withdrawn and analyzed for it's dilution. Also dialysis bag containing about 5ml of the suspension dipped into 100ml phosphate buffer of pH 7.4 and shaken in biological shaker at 100rpm maintaining temperature 37± 2 ◦C. In a specified time interval 2ml of sample were withdrawn and should be analysed by UV spectrophotometer. [41]

B. In-vitro drug release technique:

Quantitative drug release study is carried out using USP type II dissolution apparatus. Fluid medium taken is 500ml of gastric fluid with0.5% W/V sodium lauryl sulphate at 50 rpm and the study is carried out maintaining temperature 37±0.5 °C. Aliquots are analyzed at regular intervals by UV-VIS Spectrophotometry or any other techniques.

VII. Conclusion

SEDDS is a promising attempt towards formulating an effective formulation having high membrane permeability. It can me made using the composition of oil as vehicle, surfactant and cosurfactant from the pseudo ternary phase diagram which ever gives suitable nanoemulsion region. The SEDDS formulation in aqous environment upon gentle agitation gives nanoemulsions which are very fine nanosized particles and thus can easily cross membrane. As the LSEDDS can be taken for various types of formulations thus a wide range of opportunities are there in area of formulation and development. It seems to be one of the unique formulations which needs more research for its furthere development.

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DOI:10.22192/ijamr.2024.11.11.001	

How to cite this article:
Sunismita Sahu, Ranjit Mohapatra, Amiya Kanta Mishra. (2024). A Review on Preparation and Evaluation of Self Emulsified Drug Delivery System. Int. J. Adv. Multidiscip. Res. 11(11): 1-13.
DOI: http://dx.doi.org/10.22192/ijamr.2024.11.11.001