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A COMPREHENSIVE REVIEW ON NOVEL PEGYLATED SELF-NANO EMULSIFYING FORMULATIONS (SNEFS) FOR ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

Self-Nano Emulsifying Formulations for Oral Drug Delivery Systems (SNEDDS)are the most prevailing and commercially available oil-based approach for drugs that exhibit low dissolution rate and inadequate absorption. SNEDDS for oral drug delivery are highly in quest due to their innumerable benefits like better portability, improved stability, and higher drug loading, coupled with ease and economy of their production. SNEDDS is a proven method for increasing the solubility and bioavailability of lipophilic compounds. Encapsulating a drug in SNEDDS can lead to increased solubilization, stability in the gastro-intestinal tract, and absorption resulting in enhanced bioavailability. Supersaturated, mucus-permeating, and targeted SNEDDSs can be developed for increasing efficacy and patient compliance. This paper presents an overview of the SNEDDSs for the oral administration of both lipophilic and hydrophilic compounds, their mechanism, formulation excipients and potentials of SNEDDSs, recent advancements, advantages and disadvantages of SNEDDSs formulations.

Keywords: Self-Nano Emulsifying Drug Delivery Systems (SNEDDSs), Oral Delivery, Poorly water soluble drugs, Solubilization, Advancements in SNEDDSs

INTRODUCTION:-

Drug Solubility:-

For attaining desired pharmacological activity, the dissolution of drug in solvent media is a major factor for the formation of a homogeneous system. For facilitating absorption at the desired site of action and low solubility which limits drug bioavailability, the drug must be in solution form. Drugs having poor solubility can also leads to higher doses for achieving therapeutic plasma concentrations post-administration. With 40%-50% of novel chemical compounds suffering from low solubility, it remains a challenge for scientists for formulating these drugs into a form that could facilitate maximum bioavailability.[1,2]

The Biopharmaceutics Classification System (BCS) classifies drugs into different classes based on solubility and intestinal permeability of the drug depending on intestinal drug absorption data provided by the United States Food and Drug Administration (USFDA) (Fig. 1). Drugs with low solubility and high permeability were categorized as class II. The rate limiting step for such drugs is drug dissolution from formulation and its solubility in gastric fluids but not the rate of absorption. Hence, the increase in solubility also increases drug bioavailability.[3,4]

Solubility Enhancement Techniques:-

The solubility enhancement follows two strategies; the first one is being the development of formulations for increasing the speed to the first in-human study without providing any functional link to these formulations used in clinical trials that can be commercialized and the second approach involves the development of formulations.

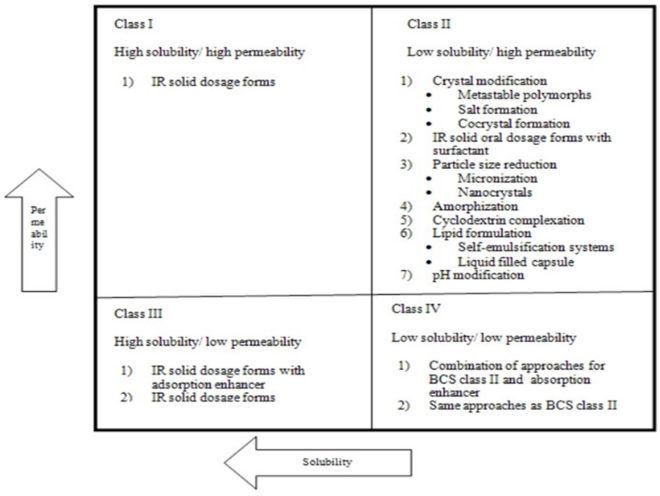

Fig. 1: BCS classification

Various solubility enhancement techniques that mainly involve physical, chemical, or administrative modification of drugs are given in Fig. 2.

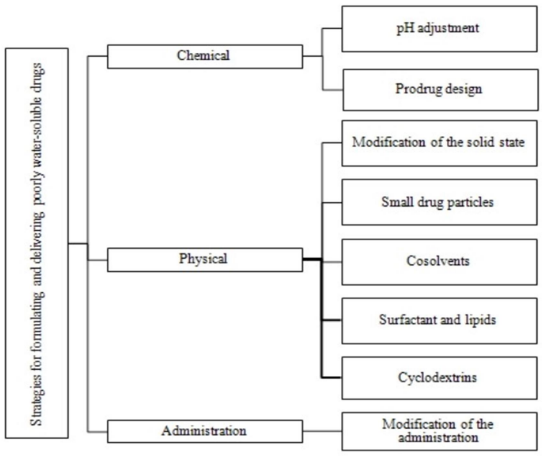

Fig. 2: Techniques employed for solubility enhancement of drugs

Various techniques adopted by the scientists include particle size reduction, Crystal Engineering, formation of salt form of drugs, drug complexing, conversion of amorphous form to crystalline form, supercritical fluid process, use of additives, etc., that alters physical and chemical characteristics of the drug. For increasing drug solubility, various formulation techniques like lipid nano-particles [(5)], liposomes [(6)] and self-emulsifying formulations were also adopted. Selection of method mainly depends on nature of drug, absorption site, and dosage of the drug.

Self-Nano Emulsifying Drug Delivery Systems (SNEDDS):-

Self-Nano Emulsifying Drug Delivery Systems (SNEDDSs) is belonging to lipid-based technique were proved to enhance drug dissolution rate and assisted the formulations of soluble drug phase. The main goal of these formulations is to maintain the drugs in solution within the GI tract. The self-emulsifying formulation is an isotropic blend of drug, lipids, surfactants and co-surfactants or co-solvents that creates superfine emulsion on agitation in the GI tract.[(7)]

SNEDDSs are oil-in-water nano-emulsions based on globule size of 200nm or below formed on dispersion process.[(8,9)] The spontaneous emulsification takes place when the entropy change affecting dispersion exceeds the energy required to enhance the surface area of the dispersion. SNEDDSs have shown some immense potential in overcoming the limitations related to the oral administration of several compounds. SNEDDSs is a competent, well designed, and

patient compliant technique for sparingly soluble drugs, as it increases solubility, dissolution patterns in the GI tract, increases permeability and absorption.[10]

SNEDDSs Mechanism of Action:-

Upon administration of SNEDDSs, followed by gentle agitation arising from gastric movement, forms oil-in-water nanoemulsion immediately and impulsively with particles of nanometric range(<200 nm). These nanoparticles comprising of drug which is previously dissolved in the oil phase provides a superior interfacial surface to facilitate dispersion into GI fluids. This increased interfacial area increases drug solubility and permeability by altering transport property. (Fig.3).

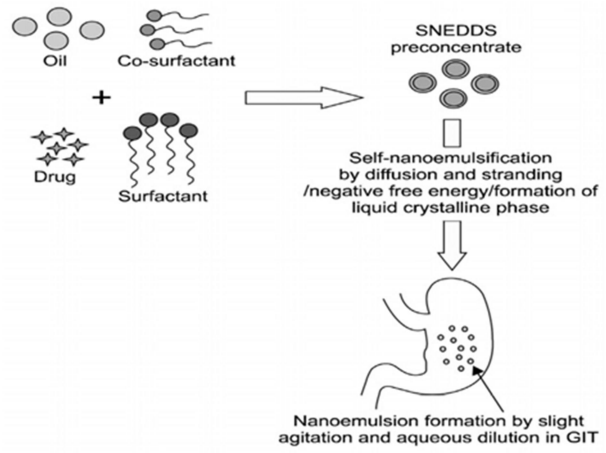

Fig. 3: SNEDDS mechanism of action

Droplets having nanosize experiences rapid digestion followed byrapid absorption of drug into the GI tract.[19] The dosage range of SNEDDSs is in between 25 mg to 2 grams. These are then effectively encapsulated as single dosage forms which provide greater stability, palatability, and patient acceptance. They also possess higher drug loading capacity when compared to other lipid-based formulations.[20]

Selection of appropriate Drug Candidates for SNEDDS Formulation:-

During formulation of an oral dosage form, a formulator faces more challenges are to solubilize the drug in the GI tract. SNEDDS improves the rate and scope of drug absorption. This approach is applied for BCS Class II drugs that suffer from inferior water solubility and bioavailability.[35] Administration of these drugs in form of lipid enhances their bioavailability by bypassing

the absorptive barrier of reduced water solubility and illustrate dissolution in GI by transferring to the bile-salt mixed micellar phase, through which absorption happens readily.[36] Water solubility, log P are not adequate properties of drug to identify the suitability of lipid-based formulation, as they do not predict the in vivo effects.[37]

In SNEDDS formulation, the free energy is required for the formation of an emulsion is either little or positive or negative. Hence, emulsification happens impulsively. It is essential for the interfacial structure to illustrate no confrontation against surface shearing such that emulsification takes place. The purpose of emulsification may be due to the simplicity of water penetration into a variety of liquid crystalline or gel phases on the droplet surface.[38]

Excipients used in SNEDDS Formulation:-

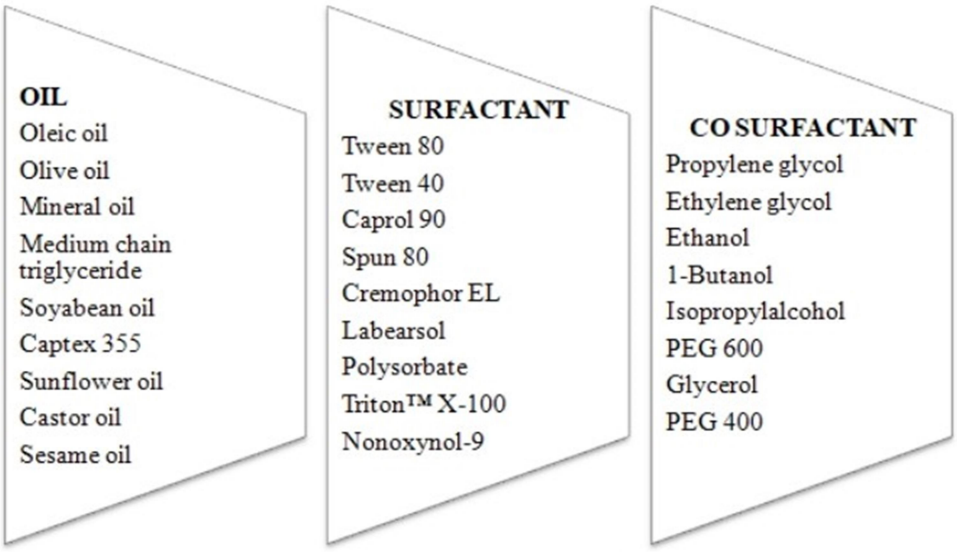

Fig. 5: List of oils, surfactants, and co-surfactants used in SNEDDS formulation

Oils:-

The purpose of using oils in SNEDDS formulation is to solubilize the lipophilic drug and ease self-emulsification, to augment the amount of drug passing through the intestinal lymphatic system, thus increasing absorption. The long-chain and medium-chain triglycerides (LCT & MCT) with varying saturations are employed. Hydrolyzed vegetable oils are used due to the formation of superior emulsification systems with more surfactants accepted for oral administration. New semisynthetic medium-chain compounds, known as amphiphilic compounds that possess surfactant

characteristics, are substituting the oils in SNEDDS.[23,24]

Surfactants:-

The orally acceptable surfactants are non-ionic that possess higher HLB value. Frequently employed emulsifiers, includes ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. Non-ionic surfactants have less toxicity as compared to ionic surfactants and direct to increased permeability through the intestinal lumen. The non-ionic surfactants with HLB > 12 are the most recommended, as they enable a spontaneous nano-emulsification with particle sizes less than 200 nm after aqueous dispersion. Thus, the amount of surfactant in SNEDDSs must be maintained at a low level as much as possible.[25,26]

Co-Surfactants:-

The SNEDDS formulations requires relatively higher concentrations (>30% w/w) of surfactants, which can be condensed by the addition of co-surfactant.[27] In SNEDDS, the co-surfactants with HLB values ranging between 10 and 14 are used. Hydrophilic co-surfactant is alcohol with medium-chain lengths, including hexanol, pentanol and octanol that reduce interface between oil and water that improves impulsive microemulsion formation. Commonly used co-solvents includes propylene glycol, ethanol, polyethylene glycol (PEG) and other newer co-solvents, such as transcutol®HP (Fig.5).[29,30]Apart from the previously presented components, in SNEDDS formulation, other ingredients such as antioxidants, viscosity enhancers and ingredients for modified drug release can be used.

Formulation of SNEDDS:-

From the pseudo ternary phase diagram, the concentration of oil and surfactant/co-surfactant could be determined and then the formulations can be prepared. The drug and the oil-surfactant mixture can be mixed together by using vortex mixer at ambient temperature.[31]

SNEDDS can be prepared by using Buchi 190 nozzle-type mini-spray dryer. Carriers are used to prepare solid-SNEDDS by suspending in 100 ml of solvent. Hydrophobic carriers can be suspended in 100ml of ethanol and hydrophilic carriers can be suspended in 100ml of water. To these solutions, the liquid SNEDDS can be added with continuous mixing at room temperature to obtain good emulsions.

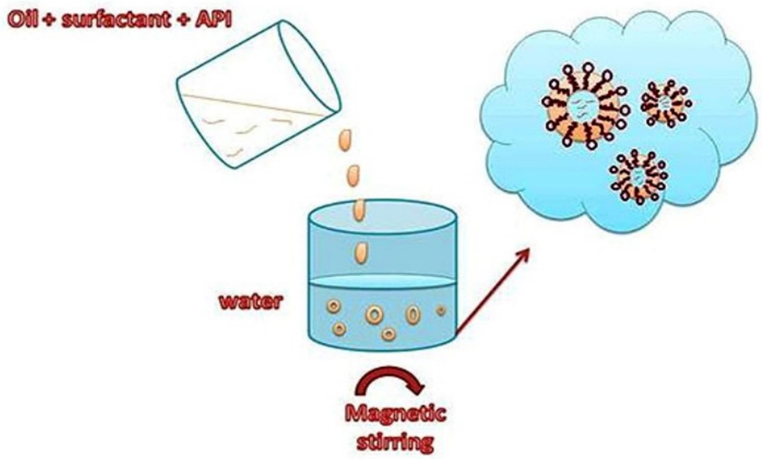

Fig 2: Formulation of SNEDDS

Using peristaltic pump, the solution can be delivered through the nozzle (0.7 mm diameter) at a flow rate of 5ml/min and it will be spray-dried at an inlet temperatures of 100 and 60 f C and outlet temperature of 80 and 60 f C. The direction of the airflow and the direction of the sprayed product should be the same. Silicon Dioxide is the mostly used solid carrier which gives efficient increase in the dissolution and oral bioavailability of the drug.[31,32]

Characterization of SNEDDS:-

Various parameters like droplet size and polydispersity index, colloidal stability and self-nano emulsification time of the SNEDDS as a function of extent of dilution and variation in the pH/electrolyte content of aqueous phase needs to be studied to characterize the final SNEDDS. To get an idea about the colloidal stability, the zeta potential of the SNEDDS should be evaluated. The nanoemulsion droplets morphology can be studied by transmission electron microscopy. Various dissolution media have to be adopted to study the in-vitro dissolution profile of SNEDDS. The chemical stability of drug in SNEDDS should be evaluated by carrying out long-term storage stability studies.[34]

Novel Pegylated Self-Nano Emulsifying Formulations for Oral Drug Delivery System:-

The novel pegylated self-nano emulsifying formulations for oral drug delivery system [1,34] are listed below:-

1) Supersaturated SNEDDS (s-SNEDDS)
2) Solid SNEDDS
3) Controlled-Release Solid SNEDDS
4) Mucus Permeation SNEDDS

5) Bioactive SNEDDS
6) Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS)
7) Targeted SNEDDS
8) SNEDDS for the Oral Delivery of Herbal Drugs
9) SNEDDS for the Oral Delivery of Hydrophilic Macromolecules

1) Supersaturated SNEDDS:-

The extent of drug solubility in excipients used for SNEDDS formulation determines the dosage of drug loading. The solubilizing ability of SNEDDS is reduced due to a reduction in lipid contentresults in drug precipitation.[(1)]The presence of large amounts of hydrophilic surfactants also improves drug precipitation. To overcome this drawback, s-SNEDDS comprising hydrophilic precipitation inhibitors were studied. S-SNEDDSs are thermodynamically stable SNEDDSs containing a polymer (such as polyvinyl pyrrolidone (PVP) or hydroxyl propyl methyl cellulose) that should inhibit the nucleation process, and subsequent drug precipitation, thus temporarily maintaining supersaturated solution of the drug in the GI tract.[(39,40)] S-SNEDDS increases the stability, concentration v/s time profile, and drug release rate, the scope of absorption, drug bioavailability, half-life and feat of hydrophobic and less lipophilic drugs.[(41)]Recently, s-SNEDDS for Simvastatin, Ezetimibe, Silybin Halofandrine, trans-resveratrol, hydrocortisone and Paclitaxel, were reported to exhibit comparatively higher bioavailability.

2) Solid SNEDDS:-

Despite the benefits provided by liquid SNEDDS, drawbacks such as drug/components precipitation when stored, interactions between the filling and capsule shell and formulation stability during storage are common issues faced by them. These limitations are overcome by the solidification of liquid SNEDDS. Solid SNEDDS possess enhanced solubility, bioavailability, easier manufacturing procedures, low cost, highly reproducible, higher stability and scalability. Solid SNEDDS are prepared by adsorption of L-SNEDDS on solid carriers, like aerosol, aeroperl, neusilin, coffee husk, and avicel, using various solidification techniques. Generally, these techniques are employed to develop solid SNEDDS include adsorption onto inert carriers, melt granulation, spray drying, extrusion-spheronisation.Characterization of solid SNEDDSs is done by Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA) which is mostly used to evaluate the thermal behavior of solid

SNEDDSs. X-ray Diffraction is used to determine the crystallization and polymorphism of drugs in solid SNEDDSs. FTIR is used to analyze the intermolecular interactions and drug carrier compatibilities. It provides information about functional groups and different chemical bonding between molecules.[1,17,34]

3) Controlled-Release Solid SNEDDS:-

The pharmacokinetic properties of established oral formulations are similar to that of SNEDDSs. They generate rapid absorption resulting in higher C_{max}, lower T_{max} that causes more fluctuations in plasma drug concentration, which needs to be closely monitored. Hence, this increases the need for the development of SNEDDS that possess sustained and controlled release properties without conciliation on bioavailability. The sustained release SNEDDS possess greater bioavailability, lower C_{max},extended mean residence time (MRT) and T_{max} and a notable decline in plasma drug instability. The controlled release of the drug was attained when reconstituted nano-size emulsions were released at zero order kinetics from the surface orifice of the tablet. For controlled release SNEDDS formulations, polymers like HPMC, MCC, poly PLGA, and hydrophobic gelucire.[1,17,34]

4) Mucus Permeation SNEDDS:-

Most SNEDDS formulations contains surfactants made of PEGylated groups to ensure self-emulsification process, so their relative high mucus-permeating abilities can be explained by those PEGylated groups located at the surface of the oil droplets making SNEDDS highly muco-inert.[34] The mucosal surfaces are roofed with an adhesive mucous layer that increases the barrier capacity of the mucosa. These mucous barriers are found in the nasal, ocular cavities, lungs, intestines and vagina. SNEDDS are considered superior mucous permeating nano carrier. The nano carriers are believed to cross the mucous layer due to their hydrophobic character without getting trapped on the layers. The particle size less than 50 nm is most favorable for mucous penetration, as the permeability of any formulation is dependent on size.[1]

The study shows that SNEDDS with particle size less than 12 nm showed maximum permeation of 70% than 450 nm with a permeation of 8%. The study also showed that modification in the charged surfaces, inclusion of mucolytic agents would also increases penetration. Themucoadhesive polymers used in these formulations includes HPMC cremophor RH 40 and triacetin.[12]

5) Bioactive SNEDDS:-

Bio macro-molecules, like lipid, protein, and polysaccharides are considered as modern therapeutic agents due to their higher specificity and lower toxicity effects. The low penetrating ability and larger particle size of biomolecules reduces their bioavailability, hence, is a challenge for incorporating them into formulations, which can be overcome by SNEDDS that are proved to enhance solubility, bioavailability, and penetration of molecules incorporated into it.

Sakloetsakun *et al*.[16] applied insulin/chitosan-TGA SNEDDS formulations for oral drug delivery. They formulated miglyol, cremophor EL, and thiolated chitosan-based SNEDDS for the administration of insulin orally. The formulation shows an increase in drug release compared to the marketed formulations. The in-vivo study also shows an increase in serum insulin than other oral insulin solution.

Karamanidou *et al*. formulated mucous permeating SNEDDS for oral delivery of insulin. The developed formulations have enhanced mucous permeability that was affected by ionic strength. Addition of Insulin/Dimyristol phosphatidyl glycerol (INS/DMPG) in SNEDDS prohibited an early burst release of insulin, hence considered a promising way for the oral delivery of insulin.[17]

6) Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS):-

Majority of anti-cancer agents and proteins cannot be administered orally as SNEDDS. Studies recommend that SDEDDS that comprises oil-water-oil emulsions are used for the delivery of peptide and protein drugs. SDEDDS are hydrophilic surfactants containing o/w emulsions that produce w/o/w emulsion on dilution with water followed by gentle agitation. SDEDDS preserve peptides and drugs from enzymatic inactivation in GIT with improved competence and diminished doses.[18]

7) Targeted SNEDDS:-

Drugs in clinical trials may fails to reach favorable outcomes because they cannot target a desired site of action. A successful strategy is established to overcome this issue by improving therapeutic efficacy and reducing toxicity can be achieved by targeted drug delivery. Nano-emulsions remain inside the body for long intervals evading mononuclear phagocytes. Cationic droplets were directed towards an anionic membrane barrier. These formulations are taken by liver, thus aiding targeting delivery.[1] PEGylation is the mechanism in which PEG is connected to a nano-droplet that forms a

barrier at the surface, where enzymatic degradation is initiated, thus, increasing stability. HPMC and thiolated chitosan can also be used for the retention of drugs in the GI tract. Furthermore, passive and active targeting is achievable by attaching suitable ligands (antibodies, nucleic acid or peptides) to target a specific site of action.(34) Batool *et al*. developed a papain-grafted S-protected hyaluronic acid-lithocholic acid co-block (P-G-S-P-H-L-AC) amphiphilic polymer as a muco-permeating stabilizer to target MCF-7 breast cancer epithelial cells. The P-G-S-P-H-L-AC amphiphilic polymer was incorporated into a SNEDDS loaded with tamoxifen. An ex vivo permeation study revealed 7.11-fold higher diffusion of tamoxifen by tamoxifen P-G-S-P-H-L-AC SNEDDS compared to free tamoxifen. Furthermore, the formulated SNEDDS was safe and compatible against macrophages. It could efficiently kill MCF-7 breast cancer cells compared to free drug.(42)

8) SNEDDS for the Oral Delivery of Herbal Drugs:-

SNEDDSs represent a very attractive drug delivery carrier for herbal medicines. Qian *et al*. developed SNEDDSs of myricetin to improve its solubility and oral absorption. These myricetin-SNEDDSs had high solubility, fast drug release characteristics (>80% in 1 min), improved permeability and low cytotoxicity compared with the free myricetin. The oral bio-availability of myricetin was improved 2.5- to 6.3-fold compared to myricetin alone in rats. To improve the aqueous solubility and oral absorption of bruceine D, Dou *et al*. developed a SNEDDS composed of Solutol® HS-15, MCT, and propylene glycol. Recently, Kazi *et al*. designed solid SNEDDSs consisting of curcumin and piperine by incorporating bioactive natural oils (avocado, apricot, black seed and Zanthoxylum rhetsa) in the formulations.The optimal liquid SNEDDSs were solidified using Aeroperl® or Neusilin®. SNEDDS consisting of 20% black seed oil, 20% Imwitor® 988, 10% Transcutol® HP, Pharmaceutics 2020, 12, 1194 32 of 55 50% Cremophor® RH40 and Neusilin® enhanced curcumin and piperine release (up to 60% and 77%, respectively). In addition, these formulations could efficiently deliver the black seed oil to the patient.(12)

9) SNEDDS for the Oral Delivery of Hydrophilic Macromolecules:-

The use of hydrophilic molecules like polysaccharides, peptides, proteins and genes has attracted growing interest presently owing to their high specificity, selectivity and reduced side effects.There are many

challenges towards the oral administration of these hydrophilic macromolecules due to GI barriers that limits their oral absorption . The low oral bio-availability of these drugs is a result of many factors, including poor diffusion related to hydrophilicity and large size, mucus barrier, gastric acidity, and enzymatic degradation. Advanced SNEDDS provides novel nano-emulsions with improved functional characteristics such as prolonged GI residence time, increased stability in GI fluids, improved mucus diffusion, improved permeation and enhanced cell uptake leading to increased oral bioavailability of encapsulated drugs. SNEDDSs are also considered to be an innovative alternative for oral delivery of gene among the non-viral vectors. Incorporation of nucleic acids (e.g., pDNA, siRNA, microRNA) into nano-emulsions formed upon SNEDDSs dispersion could protect them from enzymatic metabolism and enhance their cellular uptake.[12]

Potential of SNEDDS:-

The bioavailability enhancement ability of SNEDDS is explained by various in-vivo and in-vitro methods (Fig.6)[1]. The key discoveries that portray the potentials of SNEDDS are given below.

1) Enhancing oral delivery of proteins.
2) Improved oral delivery of natural phytochemicals.
3) Protection against biodegradation.
4) Supersaturable SNEDDS
5) SNEDDS applied for enhancement of bioavailability of anti-hypertensive drugs.

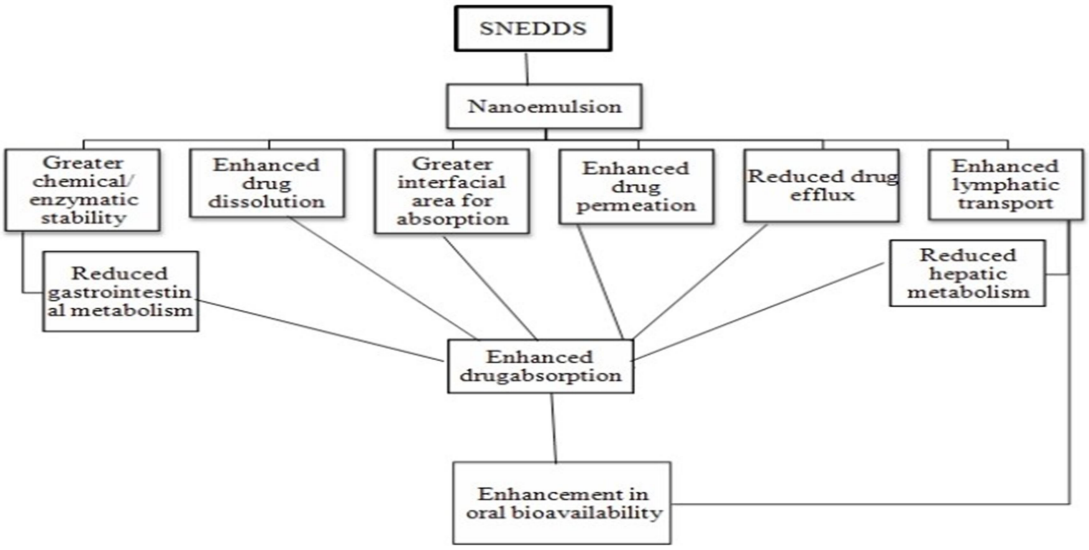

Fig. 6: Potential of SNEDDS

Future Perspective:-

The advancements in SNEDDS research in the recent past was explored intensively for enhancement of solubility and oral bioavailability of class II drugs.Previously, SNEDDSs formulations were used to overcome issues related to low aqueous solubility and oral bio-availability drugs. However, the scope of SNEDDSs is far beyond the solubility and dissolution issues. Presently, they have evolved into mucus-permeating, supersaturated, solid and targeted SNEDDSs to tackle issues related to classical SNEDDSs and to make new changes for several applications. Many anti-cancer, anti-diabetic, and anti-viral drug solubility, stability, and bio-availability characteristics were improved via SNEDDSs formulations. The commercialization of SNEDDS depends on the capacity of drug delivery scientists to attend to this aspect of SNEDDS.(1)

CONCLUSION:-

Ease of manufacture and scale-up is one of the most important advantages that make SNEDDS unique when compared with other novel drug delivery systems like solid dispersion, liposomes and nanoparticles. Very simple and economical manufacturing facilities such as simple mixer with an agitator and volumetric liquid filling equipment in large-scale manufacturing requires for SNEDDS. These SNEDDS are better formulation for drugs having poor solubility. This gives good absorption profile thus providing high bioavailability of such drugs when administered orally. In general, it is believed that nano-scale offers better transport properties and is a major driving factor for the augmented therapeutic efficacy of drugs. However, the role of nano-scale in improving the transport of drugs across biological membranes and therapeutic efficacy is debatable in the case of nano-emulsions. The amenability of converting SNEDDS into solid self-nano emulsifying systems enables development into solid dosage form. Thus, the solid self-nano emulsifying system can serve as platform technology for delivering poorly soluble drugs.(34)

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