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PARTAKING OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEMS (SNEDSS) IN THE VOYAGE OF DRUG DISCOVERY

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ABSTRACT

In the current decade of pharmaceutical research, to address various ailments and to combat the pathological conditions, appropriate drug has to be designed and discovered for targeting the specific receptor. Despite a drug with superior potency and efficacy, lack of solubility and bioavailability can hamper the therapeutic application of the drug compound. Hence to rule out the case and for effective utilization of drug, various drug delivery systems based on micro and nano-biotechnology have been evolved with advanced strategies and novel approaches. Among them, nano emulsion approaches like self-nano emulsifying drug delivery system (SNEDSS) have been shown to exhibit promising interventions in the bioavailability of the drug. Hence in this review, design of SNEDD and its characterization, methods and compounds involved in fabrication were included along with its proven therapeutic applications in several animal models and human patients.

Keywords: SNEDSS, bioavailability, drug delivery, nanobiotechnology, pharmaceutical

INTRODUCTION

As per the Biopharmaceutical Classification System (BCS), majority of the commercialised and designed drugs are under the class II with less soluble in nature, high permeable and class IV with highly soluble and low permeable. The solubility and permeability of the drug is highly correlated with its bioavailability. As most of the drugs are having poor solubility, there poses a need for the design and fabrication of novel carrier systems for addressing ailments in various clinical setup. The incorporation of nanoparticle approaches may also be advantageous in optimising the drug release, prolonging biological half-lives, and improving pharmacological efficacy. Hence to overcome the hurdle, among various liposome-based drug delivery systems, self-nano emulsifying drug delivery systems (SNEDDS) recently gained much contemplation in the avenue of pharmaceutical research.

SNEDDS are isotropic identical mixtures of a bioactive agent in a blend of lipids of either natural or synthetic origin, surfactants, and additional solvents **(Cherniakov *et al.*, 2015)**. Upon agitation in aqueous phases like gastrointestinal fluid, this mixture forms nano emulsions in two phases as oil in aqueous form. The oil portion of the emulsion determines the drug solubility and also the size of the droplet after emulsification. Addition of surfactants in SNEDSS should be promptly chosen based on the route of drug delivery as certain compounds can irritate the mucosal lining of gastrointestinal tract **(Jain *et al.*, 2013)**. The stability and function of SNEDSS should be validated in different aqueous formulations like water and other electrolyte solutions which should mimic the pH of normal intestinal fluid, as the drug carrier will reach the aqueous phase of gastrointestinal tract to elicit its action **(Uppuluri, 2015)**.

Fabrication of SNEDSS

The common sources of lipid employed in SNEDSS preparation are fatty acids of different chain length. This includes medium chain triglycerides such as caprylic acid, ethyl oleate, propylene fatty acid esters such as PG monocaprylate and dicaprylate and glyceryl monooleate. Similarly, surfactants utilised in the synthesis are derivatives of sorbitan esters, polysorbates, polyoxyethylene castor oil, poloxyethylene stearate, sucrose esters, polyoxyethylene-vitamin E and polyglycolyzed glycerides. Solubilizers are amphiphilic in nature with examples as propylene glycol, PEG and glycol ethers **(Makadia *et al.*, 2013)**.

The methods involved in synthesis of SNEDSS are broadly categorised into two groups as

1. High energy emulsification

2. Low energy emulsification

The former involves different techniques like high pressurised homogenisation, micro fluidization method and ultrasonication whereas the latter contains approaches like spontaneous emulsification and phase inversion emulsification.

Facets of SNEDSS

Bioavailability of the drug loaded into SNEDSS is highly influenced by the size of the fabricated droplet **(Tarr and Yalkowsky, 1989)**. The stability and integrity of SNEDSS can be maintained by the zeta potential in its maximal range **(Muller *et al.,* 2001)**. Venkatesh and Mallesh, 2013 reported that appropriate concentration of surfactant improves the potential of self-emulsification system of atorvastatin. Presence of lipid content in SNEDSS trigger the release of biliary fluid from hepatic duct and bile in turn creates micellar mix to increase the solubility in intestine. This micelle contains the non-polar group in interior side with polar chains facing the outer aqueous fluid of intestine. Hence, co-administration of less soluble drug with lipid formulations leads to trapping of drug within the micelle colloidal groups **(Cherniakov *et al.,* 2015)**.

Characterization of SNEDSS

The parameters need to be considered for evaluating the SNEDSS are its zeta potential, conductivity test by conductometer, pH value by pH meter, droplet size estimation by electron microscopy and others such as stability, viscosity, refractive index, percentage transmittance, filter paper test and dye test **(Akiladevi *et al.,* 2020)**.

Atorvastatin blended with SNEDSS formulation was evaluated for drug release study. It was found that atorvastatin formulated mixture showed enhanced oral absorption compared to control group which was evinced by the findings of intestinal permeability study **(Venkatesh and Mallesh, 2013)**.

Therapeutic applications of SNEDSS

Antimicrobial activity

Frankincense extract from oleoresin of *Bosswelia* plant was obtained and subjected for the formulation of frankincense-SNEDSS (Fr-SNEDSS) and was compared for its antimicrobial activity with frankincense extract alone. With the exception of *M. luteus* and *Candida albicans*, all investigated microorganisms yielded greater zones of inhibition from Fr-SNEDS than from Fr-extract **(El-Mancy *et al.,* 2021)**.

Antineoplastic activity

Fluvastatin, a HMG -CoA reductase inhibitor was proved to have antineoplastic effect in in vitro and in vivo animal models. Hence, to optimise the solubility and

permeability further, fluvastatin was incorporated in a SNEDSS based nanoparticle strategy (FLV-SNEDSS). The mixture of olive oil, Tween 80 and polyethylene glycol 200 were utilized for the fabrication of SNEDSS. The proliferative capability of MDA-MB-231 cells were significantly reduced by FLV-SNEDSS compared to pure fluvastatin alone. In Ehrlich ascites carcinoma (EAC) model, histopathological examination showed dysplastic modifications with changes in nucleoli. In EAC transplanted mice, treatment with FLV-SNEDSS notably restored the normal architecture of liver sinusoids. Its effect on liver was further confirmed by the substantial decline in enzymatic level of Aspartate transaminase (AST) **(Elimam *et al.*, 2022)**.

Antidiabetic activity

As the oral diabetic drugs are having compromised bioavailability, glimepiride (GMD) loaded SNEDSS was prepared in the form of transdermal patch. For the preparation of mixture, oleic acid, Tween 80 and DMSO were used to obtain drug inclusion at the maximum rate. GMD loaded SNEDSS were incorporated in hydroxypropyl methyl cellulose (HPMC) and chitosan biofilms for the effective design of transdermal patch. In diabetic wistar rats, GMD-HPMC patches exhibited higher reduction in glucose level after 4 hr of application whereas glimepiride tablets promoted same effect after 6hrs of administration **(Ahmed *et al.*, 2014)**.

Antihyperuric activity

Febuxostat (FEX), the recent drug discovered and approved by FDA for the use in gout against its ability in reducing the accumulation of uric acid inside the body which is the prime risk factor the occurrence of gout. Hence febuxostat loaded self-nano emulsifying lyophilized tablets (SNELTS) were synthesized by incorporation of fumed silica, xylitol, mannitol and lactose along with febuxostat encapsulated SNEDSS. Silica enhanced the absorption of the carrier, xylitol aided in the hardness nature of SNELTS and impart sweet taste to the final tablet formulation. The bioavailability and pharmacokinetic parameters were evaluated in human patients. Those who intake FEX-SNELTS exhibited notable improvement in the bioavialbility compared to the FEX alone **(Al-Amodi *et al.*,2020)**.

Mucoadhesive SNEDSS

In order to prevent pre-systemic metabolism of drugs, mucoadhesive SNEDDSs were engineered to enhance nanoparticle residence period at gastrointestinal epithelial surfaces. The selection of a suitable mucoadhesive polymer with regard to stability and lipophilic qualities is crucial. The traditional polymers, such as carboxymethyl cellulose

and chitosan, attached to one another through weak hydrogen bonds leading in a muco-adhesion that is commonly inadequate to facilitate a persistent distribution of drug at a particular target spot **(Buya *et al.,* 2020)**. Instead of conventional polymers, thiolated polymer based SNEDSS were designed, and they showed prolonged attachment in the gastrointestinal epithelial surface due to the stronger covalent interactions **(Leonavicuite *et al.,* 2017)**.

CONCLUSION

When compared to other lipid nanocarriers like solid lipid nanoparticles (SLNs), liposomes, or nanostructured lipid carriers (NLCs), SNEDDSs can be manufactured swiftly scaled up by blending the ingredients using standard equipment and then setting the resultant mixture into different solid based drug formulations such as in tablet or capsule form. Despite it showed many advancements in the drug delivery systems, efficient loading of drug and precipitation formation still remained a challenge. Hence with the help of various researches based on SNEDSS formulation, appropriate concentration of surfactant, lipid and co-surfactant should be added in the ideal ratio to minimise the underlying challenges.

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