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REVIEW ON NOVEL DRUG DELIVERY SYSTEM.

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Abstract :-

The main objective of this article, is to improve the oral bioavailability of the drug substances in animals or humans. The self-emulsifying drug delivery system (SEDDS) is the one of the best proven method for poorly soluble drug substances by improving its solubility and bioavailability. The SEDDS is the mixture of oils, surfactant, cosurfactant, which are further emulsified with the help of aqueous media by following the various conditions like gently stirring and digestive motility that would be come across in the gastrointestinal tract. The conventional development of these formulations depend on actual observation to approach drug and excipient compatibility, as well as to select and optimize the formulation composition. The ability of SEDDS formulations to improve oral bioavailability has been allocated to a number of mechanisms, especially through increased apparent solubility of highly lipophilic drugs, as well as reduced metabolism or efflux. SEDDS is considered as a best platform for oral delivery of hydrophobic drug in order to overcome their poor and asymmetrical bioavailability challenges.

It could be orally administered under gastrointestinal peristalsis and continuously dispersed to form an oil-in-water microemulsion with typical particle sizes lower than 100nm. The microemulsion forms a hydration layer that easily cross the gastrointestinal wall, which increasing the solubility of poorly soluble drugs and significantly improving bioavailability. The conventional approach to SEDDS development is an empirical process depend on iterative trial-and-error to screen, optimize, and evaluate the formulation. One of the most pertinent questions lies with the selection of appropriate excipients and mixtures thereof. Typically, this begins with the quantification of the drug solubility in excipients, followed by screening excipient mixtures based on their emulsification properties, through visual evaluation.

In fact, these are integral considerations of theoretical frameworks such as Lipinski's Rule of five, the Biopharmaceutical Classification System (BCS) and the expanded Developability Classification System (DCS), which provide ways to differentiate promising drugs for oral administration. Indeed, in the 20 years since the rule of five was first proposed, new chemical entities approved by the FDA have been shown to increase in molecule weight & calculated water-octanol partition coefficient (clogP).

Keywords: SEDDS, NDDS, AUC, Nanoparticles, Liposomes, Drug efficacy.

Introduction :-

The drug can be absorbe in the GI tract if it is dissolve in hydrous intestinal medium. Especially, the study on lipid formulation has play a very important role in the formulation of oral dosage form, especially for self-emulsifying drug delivery system (SEDDS). In the fasting and feeding states, after oral administration, the SEDDS tends to produce a reproducible drug concentration-time curve (AUC)and also plays a very important role to improve oral bioavailability. SEDDS has attracted increasing attention because of its ability to conquer the mucous layer due to its small droplet size, charge, droplet surface, shape deformation(5). Among them, the SEDDS has garnered attention during recent years as it improves oral bioavailability, reduces drug dose, and increasing drug protection from unsuitable environment in the gastrointestinal tract(17).

Furthermore, SEDDS can be prepared in a simpler and more cost-efficient manner which is significant advantageous compared with other nanocarriers such as liposomes and nanoparticles(5). Cepharanthine (CEP) is a bis-benzylisoquinoline alkaloid isolated from plants of Stephania genus in 1934(6). In 1937 application of cepharanthine reduced the average mortality rate among patients with severe pulmonary tuberculosis from 41 to 22% at the Yokohama Sanatorium in Japan(7). Nonetheless, the initial successful clinical application of CEP in the treatment of tuberculosis has encouraged its utilization in other pathological indications such as anti-inflammation, analgesia, anti-viruse and anti-tumor activity(8,9,10,11).

In December 2019, the emergency of the 2019 novel coronavirus disease (labeled COVID-19), caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2),has posed an unprecedented challenge to global public health. In a large drug screen of 2406 clinically approved drugs, CEP was recently identified as the most effective drug against SARS-CoV-2-related pangolin coronavirus. CEP has become a drugs of choice for treating COVID-19(12,13,14).

Poor bioavailability is a major challenge to formulate an oral dosage form. Poor aqueous solubility is one of the important primary factors of bioavailability because a drug cannot be absorbed through the gastrointestinal tract unless it is in solution state(15).

The absolute bioavailability of CEP by oral route was only 5.65+_0.35% in rats(18). Therefore, it is urgent to explore effective means to boast oral bioavailability to meet the clinical needs of CEP.The several clinically approved drugs depend on delivery in SEDDS formulations including cyclosporine A (e.g., Sandimmune, Neoral), tipranavir (e.g., Aptivus), and fenofibrate (e.g.,Lipofen), Among others (25,26).

One of the most pertinent questions lies with the selection of appropriate excipients & mixtures therefore. Typically, this begins with quantification of the drug solubility in excipients, followed by screening excipient mixtures based on their emulsification properties through visual assessment(27).

The LFCS (Lipid-based formulation classification system) defines four categories of oral lipid-based formulations according to their compositions are as follows :

1) Type I- Oils without surfactants
2) Type II- Oils and water insoluble surfactants
3) Type III- Oils, surfactants, and cosolvents
4) Type IV- Water-soluble surfactants and cosolvents

which essentially range from a pure mixture of oils to a combination of exclusively surfactants and cosolvents (28).

Advantages

1. High drug solubilization capacity. 2. Good thermodynamic stability. 3. Protect the drug from enzymatic hydrolysis. 4. Improvement in oral bioavailability. 5. Improve drug loading capacity. 6. Reduce the intrasubject and intersubject variability and food effects. 7. Useful for drug targeting toward specific absorption window. 8. Control of delivery profile.

Disadvantages1. Lack of in vitro model for assessment of the formulations. 2. Chemical instabilities of drugs and high surfactant concentrations. 3. Moreover, volatile co solvents in the conventional self-emulsifying formulation s are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drugs. 4. These formulations potentially are dependent on digestion prior to release the drug.

List of SEDDS available in the market:

API	Excipients	BCS Class	SEDDS Use	Dosage form	Ref.
Nevirapine	Oleic acid, Tween 20, PEG 600	II	HIV Infection	Capsules	Ramprasad chintalapudi et al. (2015)
Diclofenac sodium	Tween 80, Polyethylene glycol, Propylene glycol, Lactose, Talc, Coconut Oil	II	(NSAID) Anti-inflammatory	Capsules	Chris Alalor et al. (2021)
Rosuvastatin	Tween, Oleic acid, PEG 400	II	Regulate cholesterol level in blood (Cardio-vascular disease)	Capsules	Ravinder verma et al. (2018)
Loratadine	Labrafac-CM10, Tween 80, Polyethylene glycol 400, Liquid paraffin, Span 20, Capriole,	II	Anti-cancer	Capsules	Vishal kumar pal (2011)
Docetaxel	Vitamin E TPGS, Capryol 90, Gelucire-44/14, Transcutol HP, Ethyl acetate, Methyl-ter-butyl ether (Vitamin E TPGS, Capryol 90, Gelucire-44/14, Transcutol HP, Ethyl acetate,	IV	Anti-tumor	Capsules	Guru R. Valicherla et al. (2016)

	Methyl-ter-butyl ether (TBNE)				
Cepharanthine	Isopropyl palmitate (IPP), Cremophor RH40, Macrogol 200 (PEG 400)	IV	Anti-inflammation, Analgesia, Anti-virus, Anti-tumor	Capsules	Pan Gao et al. (2021)
Ketoconazole	IPM, Tween 80, PEG 400	II	Anti-fungal (candidiasis)	Lipstick form	Bhupendra G. Prajapati et al. (2023)
Ticagrelor	Clove oil, Tween 80, PEG 400	IV	Antiplatelet	Capsules	Anam aziz et al. (2024)
Paclitaxel	Ethyl oleate, Tween 80, Carbitol, PEG 400	IV	Anti-cancer	Capsules	Hea-Young Cho et al. (2016)
Raloxifene	Capryol 90, Tween 80, Polyethylene glycol	II	Estrogen antagonist and agonist in the breast and bone tissues respectively	Capsules	Alam Zeb et al. (2023)
Simvastatin	Tween 60, Microcrystalline cellulose, Colloidal silicon dioxide, Starch maize, Magnesium stearate	II	Decrease low-density lipoprotein cholesterol in the blood	Tablet	Bashir MA et al. (2023)

Characterization of drug (CEP) SEDDS:-

1) Transmission Electron Microscopy
2) Particle Size & Zeta Potential (Z)

Stability Experiment :-

- Long –Term Stability
- Physical Stability After Dilution
- Physical Stability With Different Dispersion Media

Statistical Analysis :-

The form of mean + SD was applied to express the results. Statistical significance of data from different presentation was compared by one-way ANOVA.

In recent years, there has been significant interest in the integration of artificial intelligence (AI) and machine learning (ML) in pharmaceutical sciences, including drug formulation. These tools have been used in a variety of advanced applications, from the accelerated design of polymeric long-acting injectables to engineering peptides for sustained delivery to the eye, and the development of ionizable lipids for lipid nanoparticle delivery of mRNA (29,30,31,). In the context of oral lipid-based formulations, ML and computational techniques have played a role in early- stage development, notably based on small molecule drug solubility screening (32). Preliminary ML modeling has been used to predict drug supersaturation in lipid-based formulations and increases in the apparent solubility of drug upon dispersion of SEDDS (33,34).

Benefits of SEDDS as compared to conventional emulsion

1. Prolonged gastric residence

Polymers like HPMS and microcrystalline cellulose are responsible for the extension of overall transit and gastric emptying time. It causes helpful interactions with epithelial cells of stomach by incorporation of floating excipients which leads to enabling of formulations to be buoyant with the gastric media. This prolongs the total disintegration period as well as the time available for absorption (Setthacheewakul et al., Citation2011).

2. Improved intestinal solubility

There are varieties of methods, such as stabilizing supersaturated drug states and regulating digestible lipids' lipolysis, solidification of SEDDS can increase intestine solubility. Polymeric nanoparticles can be utilized as polymeric precipitator inhibitors (PPIs) for retaining the supersaturated state of solubilized molecules of drug. It also alters the functioning of digestive enzymes by altering in the chemistry and nanostructure of surface of the carrier material. As a result, the precipitation inhibitory action and solubilizing mechanism of lipolysis products increase encapsulated medicinal molecules' intestinal solubility (Joyce et al., Citation2015).

3. Improved drug permeability

Mucoadhesive polymers and chitosan, well-known solid-state intestinal permeation boosters are used to manufacture SEDDS to improve medication permeability through the intestinal epithelium. For improvement of permeability, there has been little research on solid-SEDDS. Studies have shown that attachment of silicates with liquid-SEDDS improves intestinal drug permeation, indicating the ability for solid-SEDDS to have potential to deliver class IV drug compounds (Joyce et al., Citation2019).

4. Lipid-based oral delivery

According to current parameters, the therapeutic effectiveness of an oral route of administration is increasing. Aqueous solubility, dissolution, and permeability are some of these parameters (Feeney et al., Citation2016). As per Biopharmaceutical Classification System (BCS), drugs are identified as class II (low solubility, high permeability) or class IV (low solubility, poor permeability). To address all of these challenges, new technologies in the form of innovative dosage forms have been created. It is largely directed at pathogens or diseased cells. Lipid-based formulations increase medication solubilization during GI transit and provide a lipophilic microenvironment to facilitate drug delivery to intestinal absorptive regions (Mohsin et al., Citation2009).

5. Biopharmaceutical issues

It is worth noting that lipids such as triglycerides can influence the oral bioavailability of drug by changing biopharmaceutical features such as improving dissolution rate and enhancing solubility in the intestinal fluid, chemical protection of the drug and enzymatic deterioration in oil droplets, and promoting lymphatic transport of highly lipophilic drugs by forming lipoproteins. The pattern of drug absorption and blood/lymph circulation are influenced by degree of saturation, chain length of, and volume of the lipid.

6. Specificity

Self-emulsification depends on the ratio of oil/surfactants, its nature of pair, concentration of surfactants, and self-emulsification temperature. Self-emulsifying system (SES), is usually fulfilled through limited and specific combinations of pharmaceutical excipients. The specific physicochemical compatibility of the drug determines the success of the incorporation of the drug into a SEDDS. That is why study of phase diagram and preformulation solubility is needed to prepare suitable formulation design (Tang et al., Citation2008).

7. Excipient selection

Self-emulsification is very definite to the nature of the combination of surfactant and oil, the concentration of surfactant and ratio of oil and surfactant as well as the temperature of the occurrence of self-emulsification. The findings support that only extremely precise pharmaceutical excipient combinations led the SESs to be efficient (Shah et al., Citation1994).

Applications

- Improvement in solubility and bioavailability
- Protection against Biodegradation
- Ease of manufactured and scale-up
- Reduction in inter-subject and intra-subject variability and food effects
- Prevention of enzymatic hydrolysis in GIT
- Increased drug loading capacity

Characterization of SEDDS

1. Visual evaluation

Visual observation helps in the assessment of self-emulsification. The existence of a clear, isotropic, transparent solution after water dilution of SEDDS suggests microemulsion production, whereas an opaque, milky white appearance indicates macroemulsion evolution. A lack of precipitation and/or phase separation suggests that the formulation is stable.

2. Analysis of droplet size

The size of the droplet is determined by the surfactant's type and concentration. The microemulsion generated during dilution of SMEDDS with water has a very narrow droplet size distribution, which is critical for optimal drug release, *in vivo* absorption, and stability. Droplet size analysis is done using DLS methods.

3. Zeta potential measurement

The zeta potential reflects the emulsion's stability following dilution. If the zeta potential is larger, the formulation remains stable. When compared to particles with either surface charge, particles with a zwitterion charge exhibit greater biocompatibility and a longer blood residence period (Balakrishnan et al., Citation2009).

4. Emulsification time

The amount of time it takes to emulsify a formulation is determined by the oil/surfactant and oil phase ratio. This is determined using a basket dissolution equipment, which observes the development of a clear solution under agitation following drop wise formulation addition to a water-filled basket (Elnaggar et al., Citation2009).

5. Cloud point determination

The cloud point of a homogeneous solution is the temperature at which it drops its transparency. Above the cloud point, the surfactant normally loses its ability to form micelles. It is determined by progressively raising the temperature of the formulation and spectrophotometrically detecting the turbidity. The cloud point of the surfactant is the temperature at which the percentage transmittance decreases. To maintain self-emulsification, formulations should have a cloud point higher than 37.5 °C (Elnaggar et al., Citation2009).

6. Viscosity measurements

A rheometer, Brookfield viscometer having a cone and plate with rotating spindle is used to assess the viscosity of diluted SMEDDS formulations that are microemulsions (Betageri, Citation2019).

7. Liquefaction time

This analysis is performed to determine how long it takes for S-SEDDS to melt in a simulated GI environment without moving. The dosage form, which is threaded to the bulb of a thermometer, is covered in a transparent polyethylene film. The thermometer should then be placed in a round bottom flask with 250 mL of simulated stomach juice without pepsin and held at 37 °C. After that, the time it takes for the liquefaction to happen is noted.

8. Nuclear magnetic resonance (NMR) studies

These methods are utilized to investigate the dynamics and structure of microemulsions. Self-diffusion assessments utilizing several tracer approaches, most often radio labeling, provide information on the components' mobility and microenvironment. The magnetic gradient on the samples is used in the Fourier transform pulsed-gradient spin-echo (FT-PGSE) methods, which enables for the simultaneous and quick measurement of the self-diffusion coefficients of several components. The Stokes–Einstein equation may be used to compute the self-diffusion coefficient.

$D=KT/6\pi\eta r$

where T is the absolute temperature, η is the viscosity, K is the Boltzmann constant, and r is the radius of droplet.

9. Scattering techniques

The variation in the frequency of the scattering by the droplets due to Brownian motion is studied using DLS and PCS (Rahman et al., Citation2013).

10. Test of thermodynamic stability

Physical stability is essential for a formulation's performance, as precipitation of the chemical in the excipient matrix might have a detrimental influence. Excipient step separation can occur as a result of inadequate formulation physical stability, lowering bioavailability, and decreasing therapeutic effectiveness. Brittleness, softness, and delayed or partial drug release may arisefrom incompatibilities among the formulation and the gelatin shell of the capsule. The following cycles are used to carry out these investigations.

11. Turbidimetric test

Turbidity is a measurable characteristic that may be used to estimate droplet size and self-emulsification time. After a given amount of SEDDS is administered to a fixed amount of suitable medium under continual stirring at 50 rpm on a magnetic stirrer at optimal temperature, the turbidity is measured using a turbidity meter. As the time required for complete emulsification is too short, the rate of turbidity shift, or rate of emulsification, cannot

be measured. Turbidimetric analysis is used to track the growth of droplets following emulsification (Betageri, Citation2019).

12. Determination of self-emulsification time

Using a primitive nephelometer and a rotating paddle to assist emulsification, we investigated the efficiency of emulsification of several formulations of Tween 85/medium-chain triglyceride systems. The self-emulsification process was studied using light microscopy. The process of emulsification was precisely defined as the erosion of a thin cloud of microscopic particles off the surface of big droplets, rather than a steady decrease in droplet scale (Halim et al., Citation2021).

EvaluationParameters :- (35,36)

- Thermodynamic stability studies
- Centrifugation
- Dispersibility test
- Turbidimetric Evaluation
- Viscosity Determination
- Droplet Size Analysis Particle Size Measurements
- Refractive Index and Percent Transmittance

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