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Review Article

REVIEW STUDY ON ANALYSIS OF THE SOLUBILITY OF BIOPHARMACEUTICAL CLASSIFICATION SYSTEM CLASS II DRUGS IN A SELF-EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

By dissolving drug molecules in these solutions, a unit dosage form for oral administration can be generated for oral administration. Self-emulsifying drug delivery system (SEDDS) is utilized to address the inadequate bioavailability of poorly soluble and highly permeable drugs, according to the literature. These methods can disseminate and deliver hydrophobic medications as a unit dose form for oral administration in this fashion. SEDDS formulations self-emulsify (micro/nano) after being discharged into the intestinal lumen and coming into contact with the gastrointestinal (GI) fluid. Several factors must be considered to make the oral drug administration difficult, including poor water solubility and limited permeability. Self-emulsifying drug delivery can increase the solubility of biopharmaceutical classification system (BCS) II medicines. The SEDDS is a drug delivery system that enhances the solubility of lipophilic medications. It has risen in popularity over time. Under moderate agitation and subsequent dilution, GI fluids are categorized as hydrophilic liquid mixes that are isotropic. This research looks at a variety of uses as well as recent advancements in SEDDS composition, evaluation, dosage forms, and novel techniques to convert liquid SEDDS to solids. Final Thoughts Determining whether or not it is feasible to construct a BCS Category 2 medication formulation based on SEDDS represents a significant contribution of this effort. Medicines with solubility issues and low and variable bioavailability will benefit from the connected technologies.

Keywords: Biopharmaceutical classification system Class II, Enhanced solubility, Self-emulsifying drug delivery system, Bioavailability, First Pass Metabolism, Lipid-based formulation.

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INTRODUCTION

Self-emulsifying drug delivery system (SEDDS) is utilized to address inadequate bioavailability of poorly soluble and highly permeable drugs, according to the literature. These methods can disseminate and deliver hydrophobic medications as a unit dose form for oral administration in this fashion. SEDDS formulations self-emulsify (micro/Nano) after being discharged into the intestinal lumen and coming into contact with the gastrointestinal (GI) fluid. This solubilizes the medication, allowing it to be absorbed through lymphatic channels, bypassing the hepatic first-pass action [1]. Poor water solubility and restricted permeability are well-known obstacles to oral medication administration. Other difficulties include a narrow therapeutic window, first-pass metabolism, and inter-and intra-individual medication response heterogeneity. Nanoparticles based on lipids have a strong drug loading ability. A drug delivery system's (DDS) lipid makeup determines whether the drug will be released immediately or later. Several medicinal compounds with the required pharmacological activity have been created to advances combinatorial chemistry and high-throughput screening techniques. Oral administration is the most prevalent method of drug administration. Oral administration is preferred to ensure patient compliance. The oral route has become increasingly popular in recent decades because of its ease of administration, patient acceptance, precise dosing precision, cost-effective manufacturing procedure, and generally increased shelf life of the product. An experimental model, the biopharmaceutical classification system (BCS), measures permeability and solubility. According to the system's initial design, post-approval alterations and generic drugs would be regulated purely based on *in vitro* data [2-4]. Most medications are administered orally; hence, the system was designed to allow waivers (permission to skip *in vivo* bioequivalence studies) for drugs that meet specified solubility and permeability requirements and swiftly dissolve in the human body. Meanwhile, the pharmaceutical sector is increasingly exploiting the BCS to design new medications. In the absence of adequate formulation strategies, this system can indicate medications that should not be tried on humans for safety reasons. A drug's oral absorption (Ab) can be affected by three factors: dissolution (Dn), solubility, and intestinal permeability. Regarding drug product development, the FDA has a strong role to play. For drug products, Dn standards can be applied. In this way, the number of *in vivo* studies can be reduced by performing *in vitro – in vivo* correlation (IVIVC). As a result, you'll be able to save time throughout product development [5-7].

CLASS LIMITS IN BCS USED

1. When a drug substance's highest dose strength is solubilized in 250 ml water over a pH range of 1–7, it is considered significantly solubilized
2. It is termed extremely permeable because of the mass balance or because it differs from intravenous dosing when 90% of the dose is absorbed
3. The USP apparatus I or II is judged to be promptly dissolving the drug product when its volume (900 ml) dissolves the drug ingredient within 85% of the labeled amount
4. For pharmacological compounds, the BCS defines three dimensionless numbers. The terms "Dn" and "Ab" are used interchangeably (An). The most fundamental view of GI drug Ab is represented by these numbers, which are a combination of physicochemical and physiological characteristics
5. Drug substances are defined by BCS as having three dimensionless numbers. These values are referred to as "Dn" and "Ab" (Dn/Ab) (An). As a result of these physicochemical and physiological characteristics, these numbers give the most basic view of GI drug Ab
6. The Ab number (An) is calculated by multiplying the permeability (Peff) and the intestinal radius by the residence duration (Tsi)
7. Bergstrom and others (BCS Contains Six Classes) the BCS of (Bergstrom *et al*.) modifiers classified drugs based on their solubility and permeability. Low, medium, or high solubility and permeability

were categorized. An entirely new classification has been developed as the result of calculations on solubility and permeability when it comes to drug development; they indicated that these models might be used to detect Ab patterns so that pharmacokinetic parameters can optimize early on in the process

8. If the molecules are transported from a solid to a liquid, this mass transfer occurs. Chemically and physically, the solubility of a medicinal material makes it possible for it to be synthesized and combined with other chemicals in a homogenous manner. The human fasting intestinal solubility parameter (e.g., Fa SSIF) can be used to quantify the degree of human Ab. "Soluble-limited absorbable dosages" refers to Class II drugs that have been shown to have an equilibrium between their permeability and solubility, according to this theory. When it comes to valuation (Fig. 1) [8-10].

Changes to the BCS system Changing the BCS: (Butler and Dress man 4940) With the BCS system, medicines are now categorized based on oral Ab parameters. Le system revise reflects quality by design (QbD), which gives an improved categorization scheme. Solubility-limited Ab dose will be employed if permeability and solubility are compensatory, according to the new method's assumptions: The target particle size of a medication can be used to analyze the development risk and critical quality attributes (CQA) of pharmaceuticals with slow dissolving and Ab rates. There are a lot of differences between BCS and this modified system, which has two subclasses and focuses more on degree than oral Ab rate there are several benefits to the Development Capability Rating System. By alerting formulators to poorly soluble medicines early, this DCS can help formulators prevent adverse effects and achieve full oral Ab. Drug foods are soluble 6. If you're curious about drug solubility, some options available to the pharmaceutical industry may be employed to improve the solubility of BCS Class II medicines. To categorize these tactics, we can use the following methods: In the case of Table 1 [11-13].

Systems for Dispersion of Solids Dispersion of Solids (SD) because it has the potential to improve the bioavailability, low cost, and industrial feasibility of medicine that is difficult to dissolve in water. One or more active components in an inert carrier are dispersed using the melts solvent method or melts solvent method to form a SD [14-16].

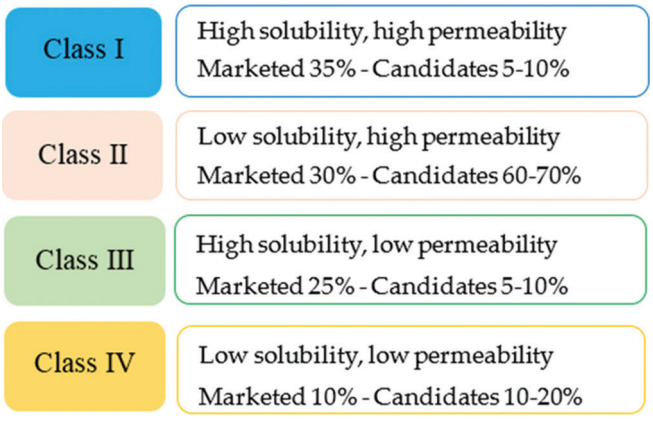

Fig. 1: Biopharmaceutical classification system classification

SD HAS ITS ADVANTAGES

1. It has the potential to improve the bioavailability, low cost, and industrial feasibility of medicines that are difficult or impossible to dissolve in water. Systems for SD Saturated Dispersion (SD) The melts solvent technique or melts solvent method is used to disperse one or more active components in an inert carrier into a SD utilizing the melts solvent technique [17]
2. Plusieurs advantages can be gained using SD. Porosity is increased Particles having a porous structure are produced through SD. Because of the carrier's properties, porosity is influenced. Compared to cross-linked polymers, linear polymer SDs contain bigger and more porous particles (Sharma and Jain 149). SD particles with a higher porosity improve the drug's solubility rate [18]
3. It's also possible for medicines that are weakly soluble in water to become more solubilized in water when they are amorphized (Pokharkar *et al*.) [20]
4. During Dn, no energy is required to disrupt the space lattice in an amorphous form (Taylor and Zografi 1691). In a supersaturated environment, SD dissolves into a metastable polymorphic form, which has superior solubility than the more stable crystalline form [12]
5. In contrast, drugs with high crystallization energy are often obtained by carefully selecting the carrier and that they have a specific interaction with it. The melting temperature difference between the drug and the carrier can be used to detect the amorphous composition of drugs with low crystallization energy. Pouton CW 11) (Vippagunta and others) [19-21].

CARRIER CHARACTERISTICS OF SD SHOULD CONSIDER THE FOLLOWING FACTORS WHILE CHOOSING A CARRIER FOR SD

- To increase wet ability and solubility, it should have a hydrophilic character. The glass transition temperature must be high to improve stability
- A minimal amount of water must be able to pass through it
- Drug and vehicle must be solubilized in common liquids when a drug is prepared using solvent evaporation technique
- Decrease the size of to make an effective main solid solution; the SD must be meltable to lower the freezing point. As a result, SD's commercialization is hampered by several issues, including crystallization of amorphous pharmaceuticals can occur during production mechanical stress or storage temperature and humidity stress, reducing their Dn rate
- Moisturizing the amorphous dosage form is also important since it might cause the medication to crystallize. This is frequently because the vehicles used in SD absorb water (Tiwari *et al*., 1338). Soft and sticky, the SD has poor fluidity and compression. As a result, the final product's physical and chemical characteristics are not reproducible. (Table 2) [22-24].

QbD approach

Assertion of Quality in Design The advent of the QbD idea has revolutionized the drug development process in recent years. From a univariate empirical knowledge, it has evolved into a scientific multivariate method that determines the systematic quality of a final product's formulation. For formulation development in this business,

Table 1: Dissolution enhancement methodologies

Methods that increase the solubility	Methods that increase the surface area	Newer technologies
Modifying the pH of microenvironment	Micronization	Lipid emulsions
Salt formation of weak acids and weak bases	Use of surfactants (to enhance effective surface area by improvement in wetting)	Microemulsions
Use of solvates and hydrates	Solvent deposition	Self-emulsifying drug delivery systems
Use of selected polymorphic forms	Solid dispersion	Nano sizing by precipitation
Complexation	Liquid-solid compacts	Cryogenic and super critical fluid technologies
Prodrug approach		Melt-granulation
Use of surfactants		Melt-extrusion
Sublimation technique		

Table 2: Methods of preparation and carriers used for solid dispersions (Tiwari *et al*. 1338; Chaves *et al*. 253)

Method of preparation		Carriers used
Advantages	Disadvantages	Polymeric materials: Eudragit systems (enteric acrylic acid-based polymers)
Solvent evaporation		
Ease in Preparation	Toxicity	
Feasible scale up	Residual amount	
Melting		Acids: Citric acid, succinic acid, and tartaric acid
Ease in preparation	Drug degradation for thermosensitive drugs	
Feasible scale-up	Low solubility in molten carrier	Sugars: Dextrose, sucrose, maltose, sorbitol, galactose, xylitol, inulin, chitosan, dextrin, and cyclodextrin
Antisolvent		Surfactants: Poloxamer, deoxycholic acid, tweens, spans, compritol 888 ATO, gel cure 44/14 and 50/13, sodium lauryl sulfate, phospholipid, polyoxyethylene stearate
Solvent-free	Low solubility in CO2 Limited scale-up	Miscellaneous: Urea, urethane, hydroxyalkyl xanthene, pentaerythritol

QbD has been mandatory since January 2012. As a result, the term "quality" may be used as an umbrella term with a preset goal of quality as well as a projected quality by defining needed and predetermined standards. When physical, chemical, physiological, pharmacological, and therapeutic characteristics are taken into account, safe and effective products are typically created (Singh B, Khurana L, 55) [25].

- An in-depth analysis of raw material and product design, method, and scale is typically required to achieve this goal. As a QbD technique, the Design of Experiments helps identify variables and their interactions (Lionberger *et al*., 268)
- CQA, Important Process Parameters, or IPP, assist in the identification of critical material attributes. The creation of pharmaceutical goods with the needed qualities, and quality is the result of this planning. Hence, QbD refers to establishing formulae and manufacturing processes to meet predefined product quality standards by designing and developing them (Lawrence 781) [26,27].
- Determine the cause of variability within the production process and build a relationship between the recipe and the process. As a result of this data, flexible and resilient production methods and products of the appropriate quality will be implemented over some time (Cui *et al*., 312). You may read about the QbD process in Fig. 2 [28].

Many studies have focused on improving the solubility of poorly water-soluble drugs by using lipid-based formulations, which have led to enhanced clinical efficacy, cost-effectiveness, and ease of preparation.

DDS BASED ON LIPIDIC MEDIUM

Solubility of weakly water-soluble drugs can be improved with lipid-based formulations leading to improved clinical efficacy, cost-effectiveness, and convenience of preparation [29].

There are three main criteria for choosing a drug: clinical efficacy, cost-effectiveness, and simplicity of preparation

Pharmaceutical delivery systems based on lipids

To improve the oral bioavailability of weakly water-soluble drugs, lipid-based DDSs are the most prevalent approach (LBDDS). A lipid-based waste disposal system there are several ways that LBDDS can improve lipophilic medications' Ab [30,31].

Enhanced Dn/solubilisation

There are lipids in the alimentary canal, which cause contractions of the gallbladder, as well as biliary and pancreatic secretions, such as Bile Salt and Cholesterol. A crude emulsion is formed by the use of these items in conjunction with stomach shear movement, which aids in the solubilization of the lipophilic medication. Furthermore, the presence of surfactants in the delivery system can increase the lipophilic compound's solubilization rate [32,33].

Improving permeability in the gut

Barrier function can be altered by several lipids, resulting in increased permeability. There is no limit to the Ab of BCS Class II compounds since they are permeable through the GI wall. When it comes to lipophilic drugs, this mechanism is not regarded as a significant contributor. If using a BCS Class II drug, though, this could be good. In addition, some lipids and surfactants that reduce efflux transporter activity inside the GI wall can be used to improve medicine Ab. In addition, the interaction between P-GP and CYP3A4 may inhibit metabolism [34,35].

Cellular lymphatic transport stimulation

It is also possible to increase the bioavailability of lipophilic medicines by stimulating intestinal lymphatic transport [36].

Gastric duration is lengthened

Lipids in the alimentary canal slow down gastric transit time. Decreased Ab causes a longer half-life of a lipophilic medication in the small intestine. This enhances the medication's solubility and, as a result, the Ab of the medicine [37].

DDS design based on lipids

There have been several DDS based on lipids developed over time. Within the design, there are usually two kinds of approaches to consider: formulations based on fat or lipids, and lipid carriers as particulate systems (lipid nanoparticles or liposomes). It is also possible to increase the bioavailability of lipophilic medicines by stimulating intestinal lymphatic transport. Lipospheres, Microporous Lipid Microspheres, and Nanostructure Lipid Carriers [38,39].

A formules based on liquid lipids

(Oil/water; water/oil, and bicontinuous structures) to stabilize the dispersed droplets, a surfactant is applied to an emulsion consisting of two immiscible phases. For the combination to be stable, it is crucial to use the proper surfactants and production conditions. Water, oil, and surfactant/cosurfactant are the minimal ingredients in a microemulsion, which produces a clear, thermodynamically stable system with droplet sizes of 10–140 nm. Depending on their lipophilicity, drugs will partition into aqueous and hydrophobic phases [40,41].

Dispensing systems with SEDDS

Drug delivery methods that self-emulsify Many SEDDS are made of oil and surfactant, and are hence binary systems. Due to the size of the lipid droplets, their dispersions look turbid. In contrast, self-nanoemulsifying DDS (SMEDDS) contains oil, surfactant, and cosurfactant, as well as co-solvent and drug material, which will spontaneously form micro-emulsions (with particle sizes <100 nm) following dilution with an aqueous phase, mild stirring, and mild agitation, when combined. A SEDDS or a SMEDDS will be selected based on their solubility and dissolvability profiles during *in vitro* screening with a different

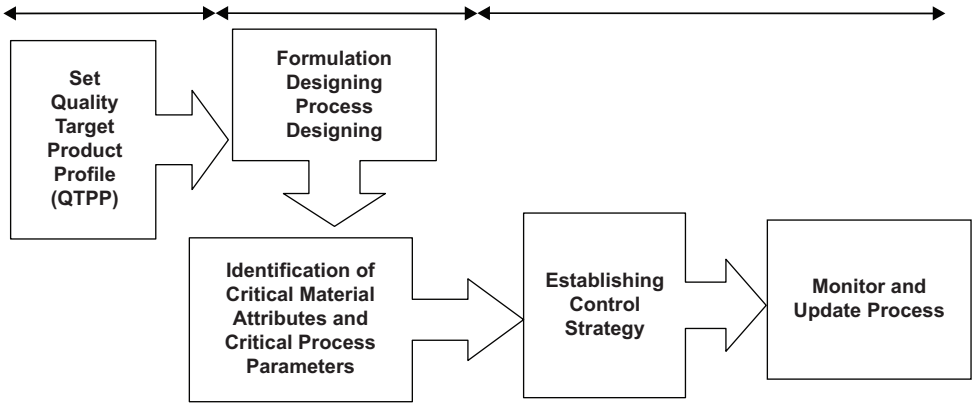

Fig. 2: Quick Look at quality by design (Chaves *et al*. 253)

Table 3: Example of BCS Class II drug

S.No	Class	Drug
1	Phenothiazine	
	a. Aliphatic side chain	Chlorpromazine
		Triflupromazine
	b. Piperidine side chain	Thioridazine
	c. Piperazine side chain	Trifluoperazine
		Fluphenazine
2	Butyrophenones	Haloperidol
		Trifluperidol
		Penfluridol
3	Thioxanthenes	Flupentixol
4	Other heterocyclics	Pimozide
		Loxapine
5	Atypical antipsychotics	Clozapine
		Risperidone
		Olanzapine
		Quetiapine
		Aripiprazole
		Ziprasidone

excipient. SMEDDS have demonstrated a high degree of solubilization and dimensional stability. As they improve intestinal permeability and minimize food effects, they will significantly boost oral bioavailability. There is an alternative to the LBDDS: a solid-in-oil suspension. To the best of our knowledge, no significant GI injuries or adverse effects have been recorded with Voltaren, a nonsteroidal anti-inflammatory (NSAID) [42-44].

Solid compositions based on lipids

There has been an increase in research in this field in the past few years. The enteric coating was used to coat microemulsions with cyclosporine to create solid-state micro-emulsions. In addition to dry emulsion capsules, implants, sustained/controlled-release tablets, beads, and nano-particle suppositories, this type of SEDDS is routinely used in several dosage forms (suppositories) [45].

PARTICULATE DRUGS CONTAINED IN LIPID

The liposome

Two layers of lip lipids surround an aqueous compartment. Lipid-soluble medications are often incorporated into the bilayer membrane's lipid domain. This is known as lipophilic drug incorporation. Researchers have proven that liposomes can be used to increase the oral bioavailability of poorly soluble drugs such as peptides and proteins despite their low stability in the alimentary canal, although several studies have shown that liposomal insulin is taken orally often lowers blood sugar levels. Oral vaccination methods can use them. When liposomal vincristine is used, the therapeutic index of vincristine is frequently considerably improved**.** A system for treating human cancer due to phospholipid's GRAS classification, liposomal compositions are typically regarded as safe. For the most part, they are employed in parenteral applications or as injectable dosage forms (such as Doxil®) [46,47].

Particles of solid lipid nano size (SLNs)

With particle sizes between 50 nm and 1000 nm, SLSs are particulate systems in oil-in-water emulsions, by substituting a solid lipid for the liquid oil. Because the lipid matrix is formed of physiologically well-tolerated fats, they are less toxicologically hazardous; they combine particle shape integrity with the capacity to physically hide sensitive substances. 3 years is all it takes for them to lose their potency, and industrial-scale production is simple. Sodium lauryl sulfates improve bioavailability after oral administration of piribedil (cyclosporine A) and vinpocetine (vinpocetine). An alternate delivery technique is the utilization of lipid particulate systems such as SLNs, microparticles, and lipospheres. This improves protein stability and prevents proteolysis, while also enabling a prolonged release of the molecules that have been added. Some well-known peptides including insulin, cyclosporine A and insulin, calcitonin, and somatostatin are being studied in solid lipid particles [48-50].

Squalene

A natural lipid of the Terpenoid family, Squalene is thought to be the precursor to cholesterol production. It is widely utilized in pharmaceutical formulations for illness management and therapy because of its considerable nutritional advantages as well as for its biocompatibility, inertness, and other beneficial characteristics. Aside from that, squalene is a protective agent, has been proven to reduce chemotherapy-induced adverse effects, and displays chemopreventive properties. Even though it is only a modest tumor cell growth inhibitor, its potentiating action makes it useful in the treatment of cancer, either directly or indirectly. It is also being researched for its potential application in vaccine delivery because it boosts the immune response to a variety of related antigens. To increase the efficacy and efficiency of oral administration of medicinal chemicals, this triterpene has been employed for many years. Squalene is a great excipient for pharmaceutical applications, including the administration of vaccines and medicines, to summarize [51,52].

DDS THAT SELF-EMULSIFIES

Consider the oral method: 30–40% (35–40%) of the most recent medications are water-insoluble Taking these drugs orally often results in issues such as low Ab, high inter-, and intra-subject variability, and an inability to dose proportionally. The improved oral bioavailability of lipophilic medications is being pursued to increase their therapeutic efficacy. However, it was proven that SDs (suspension), co-precipitation, salt formation, emulsion, micelle usage, and co-grinding may all be employed to overcome these problems to achieve a satisfactory outcome. To deliver medicine, emulsions are utilized as a vehicle owing to their propensity to boost the oral bioavailability of poorly absorbed drugs According to the definition of SEDDS, they are isotropic blends of oils, solid. and liquid surfactants (or a combination

of the two), as well as hydrophilic solvent and co-solvent/surfactant combinations. If the aqueous medium is gently stirred and diluted with water, they can generate fine oil in water (O/W) emulsions or microemulsions, for example. in the digestive system (SMEDDS). For self-emulsification, therefore, digestion motility of the stomach and intestinal system provides the necessary agitation. As a result, SMEDDS creates transparent micro-emulsions with droplet sizes of as little as 50 nm. In addition, they provide a wider interfacial area for the partitioning of medication between oil and water compared to simple oily solutions. With Dn rate-limited Ab, these systems may improve the pace and amount of lipophilic medicinal molecules being absorbed. Have been demonstrated to boost the oral bioavailability of lipophilic medicines such cyclosporine and ontazolast as well as progesterone and halofantrine. Using a colloidal microemulsion to deliver lipophilic medicines has two major advantages: Ease of dispersion and small particle size. Most lipid formulations on the market today are complicated blends of lipid and surfactant. Examples of co-solvents/co-surfactants include drug solubility inside the formulation (and therefore increase drug payload) and dispersion of dosage form following exposure of the capsule fill to GI contents. Emulsions, on the other hand, are sensitive and metastable dispersed forms. In addition to being transparent and low-viscosity, they are also thermodynamically stable. The distinction between micelles (approx. 10–140 nm) and emulsion droplets (approx. 100–600 nm) is not clearly defined in microemulsions, which are very labile. Normal emulsion droplets, on the other hand, remain solitary until they merge or Ostwald ripen, whichever occurs first [53,54].

ADVANTAGES OF SMEDDS

Stability is improved

In contrast to traditional composition, SMEDDS has tiny particle sizes. Assistive technology: Aqueous SMEDDS dispersions have significantly lower particle sizes (l00–250 nm) than vesicular and emulsion phases, which have much higher particle sizes (>250 nm). Intestinal aqueous physical phenomena and the Ab brush border membrane can transport drugs more efficiently with smaller particles [55].

Less dependence on lipolysis

Triglyceride components in SMEDDS are smaller, which makes them less dependent on lipolysis and other variables that influence lipolysis speed and extent. The lessened dependency on lipolysis allows for a faster beginning of therapeutic activity and improved bio performance characteristics [56].

Independence from bile content in the diet

Because SMEDDS have a higher solubilization capacity than salt micelles, they are less dependent on endogenous bile, patient illness conditions, and meal fat content. Due to these benefits, a meal-dosage limitation can overcome meal dependency [57,58].

SMEDDS

Formulations feature superior solubilization compared to standard formulations. In addition, it is usual to modify the surfactant mixture of a medicinal medicine to better match the therapeutic agent's polarity distribution [59].

Faster Dn and release

The bioavailability of some weakly water-soluble medications is severely hampered by Dn, which is the speed-limiting stage of Ab. Dilution-resistance of SMEDDS ensures that during Ab, the medicinal substance remains solubilized. Additionally, the dilution rate of lipid solubilized drugs is not limited by entrapment inside the emulsion carriers, which helps to prevent liabilities associated with the drug's poor partitioning to water, such as large-droplet area. Partitioning can be accomplished fast as a result [60,61].

Consistency in execution

A major benefit for therapeutic drugs with a limited therapeutic index is that SMEDDS dispersions are thermodynamically stable during the period crucial to Ab and can be replicated predictably [62].

Efficacious releasing

Examples include permeability enhancers and enzyme inhibitors that retain the therapeutic agent or Ab promoter solubilized for transport to Ab sites but still easily accessible for Ab, resulting in a more effective transport and release of the drug. As a result, the stomach empties faster. SMEDDS are less sensitive to stomach emptying delays than standard formulations including triglycerides, which produce larger droplets on dispersion. This leads to quicker Ab and avoids undesired retention inside the GI tract (GIT) the small size. Since the SMEDDS dispersions are tiny, the medicinal drug may be transported more quickly through the aquatic physical phenomena. Manufacture and proportions are basic.

- Production and proportion of simple SMEDDS have two main advantages over other drug delivery methods, such as SDs. This explains the SMEDDS's interest in the industry. Several years ago, emulsifiable concentrates of herbicides and pesticides were formulated to take advantage of the phenomena of self-emulsification. Users, such as a farmer or a family gardener, dilute crop spray concentrates using these formulations. This allows hydrophobic chemicals to be delivered efficiently. SMEDDS, on the other hand, do not use excipient that is suitable for oral administration to humans. For a variety of reasons, self-micro emulsifying drug delivery devices are not widely adopted (SMEDDS). While some of the answers are based on the norms and practices of pharmaceutical research labs, others are based on real-life situations [63]
- Pharmaceutical companies, who heavily depend on tablet-making technology, opt for tablet formulation early on, often before enough data on the drug's bioavailability is available. It is difficult to go back to oily formulation after adopting the solid dosage form route. Outsourcing the packaging of an oily substance can be necessary. Since oily formulations have a low solvent capacity, unless the medication is exceptionally hydrophobic/lipophilic (log p>4), the use of oily formulations is generally restricted to highly powerful molecules
- However, there are not enough data to predict the chemical stability of SMEDDSs at this time (SMEDDS)
- There is a definite toxicological danger associated with high surfactant concentrations. When developing a novel chemical entity, formulators prefer to use tried-and-true materials to avoid complications that may surface later on in the development process. When it comes to hydrophobic pharmaceuticals, Cyclosporine A is a good example of a SMEDDS. Until more human bioavailability studies are conducted, and until more information is known about the long-term toxicity of SMEDDS, the full potential of SMEDDS will not be fulfilled. (SMEDDS) [64].

CONSTRAINTS WITH SMEDDS

- Drugs that are chemically unstable and have high stability concentrations aren't suited for them
- Large quantities of surfactant in formulations irritate the GIT (30–60%)
- Soft or firm gelatine capsules with a self-emulsifying formulation that contains volatile co-solvents cause the lipophilic medication to precipitate.

LIST OF COMPONENTS USED IN THE PRODUCTION OF SEDDS

a. Oil phase
b. Surfactants.

It's a surfactant/solvent combination. Oil/surfactant pairings, surfactant concentrations, and oil/surfactant ratio have all been found to affect self-emulsification. This is further supported by the fact that only very specific combinations of pharmacological excipients can lead to efficient self-emulsifying systems (see below).

Oils

The oil is a highly important excipient in SEDDS formulations since it can improve the proportion of lipophilic medication delivered through the lymphatic system, hence enhancing Ab from the alimentary canal. Various saturation levels of long and medium-chain triglyceride oils can be used in self-emulsifying compositions. SEDDS might be treated using edible oils, as they would be the logical and preferable lipid excipient. We don't use SEDDS very often since they have a hard time dissolving large quantities of lipophilic medicines effectively. This excipient creates good emulsification systems with a vast variety of surfactants permitted for oral administration and demonstrates superior drug solubility qualities. Their breakdown products are similar to the natural end products of intestinal digestion. Novel semi-synthetic medium-chain derivatives, which are characterized as amphiphilic molecules with surfactant features have gradually and successfully replaced conventional medium-chain triglycerides.

Surfactants

For self-emulsifying systems, nonionic surfactants with a high hydrophilic/lipophilic balance (HLB) are typically recommended HLB. Polyoxyethylene 20 oleate and other polyglycolyzed-ethoxylic acids are typically used to achieve the desired result (Tween 80). The safety of a surfactant could be a deciding factor in choosing which one to use. Natural emulsifiers are preferred over synthetic surfactants. In contrast, this excipient potential to self-emulsify is limited. However, even though non-ionic surfactants are less damaging than ionic surfactants, they will cause reversible changes in the intestinal lumen's permeability typically, the surfactant content in SEDDS ranges from 30 to 60% by weight, depending on the type of SEDDS. Because too much surfactant might induce GI pain, it's important to get the concentration of surfactant appropriate. For the formulation of SEDDS to form o/w droplets or spread fast in aqueous media (good self-emulsifying performance), a high HLB and hydrophilicity surfactant is required. Anti-precipitation measures should be taken to keep drugs solubilized for as long as possible at the site of Ab. Hydrophobic pharmaceutical compounds can be dissolved or solubilized by water-soluble surfactants, which are amphiphilic and can dissolve or solubilize vast amounts of them. SMEDDS are generated in lipid mixtures containing high ratios of cosurfactant and surfactant to oil. The relationship between droplet size and surfactant concentration may be seen. An increase in the surfactant level, for example, could result in smaller droplets from a saturated C8-C10 polyglycolic glycerine mixture (Labrafac CM-10). There may be some stabilization of oil droplets as a result of surfactant molecules localized at the interface. Surfactant concentrations, on the other hand, might sometimes increase the size of the average droplet. Surfactant concentrations increase oil droplet penetration into the aqueous phase [65].

Cosurfactants

When it comes to lowering the surface tension between surfaces, a cosurfactant plays a key role. Surfactant absorbs additional surfactant until the bulk condition is lowered sufficiently to make the interfacial surface tension positive once again after reaching this threshold. In this process, referred to as "instant emulsification", the microemulsion is created. Co-surfactant use is vital not only for microemulsion generation but also for microemulsion solubilization. Aside from the chemical composition of the oil, salinity and temperature should also be considered.

Co-solvents

Sufficient Co-solvent must be employed in high concentrations to achieve optimal SEDDS. There is a vast variety of organic solvents that can be taken orally. Such substances include propanediol and dimethyl ether poly(ethylene glycol). They can also be employed as cosurfactants in micro-emulsion systems. Alcohols and other volatile co-solvents evaporate into or into the shell of soft gelatine capsules or hard-sealed gelatine capsules in traditional SEDDS, resulting in drug precipitation. They have a limited lipophilic drug dissolving potential because they are alcohol-free formulations [36].

MECHANISM OF SELF EMULSIFICATION

He argues that dispersion is favored more by entropy change than it is by extending the area of dispersion. Free energy is considered to have a self-emulsifying process. It has been suggested that the energy required to build a replacement surface between oil and water phases is directly proportional to free energy in the classic emulsion and can be expressed by the equation: G=Nr2.

Droplets of radius r are counted as N.

As soon as the two phases of the emulsion are separated in time, emulsifying agents are added to stabilize the emulsion. A monolayer of droplets is formed by the agent, which minimizes the interfacial energy and prevents coalescence. Free energy required to create an aqueous emulsion in self-emulsifying systems is either very low and positive or negative. As an alternative to energy input, emulsification involves the shrinkage of local interfacial areas, which leads to instability (Fig. 3).

To create a SEDDS, it is important to consider the following. Oils, surfactants, and co-solvents can dissolve the medicine. The choice of oils, surfactants, and co-solvents helped with solubility and phase diagram preparation. Dn of drugs in a solvent and surfactant mixture to produce SEDDS formulation. Since the drug interferes with self-emulsification to some extent, the ideal oil-surfactant ratio must be included in the SEDDS [67,68].

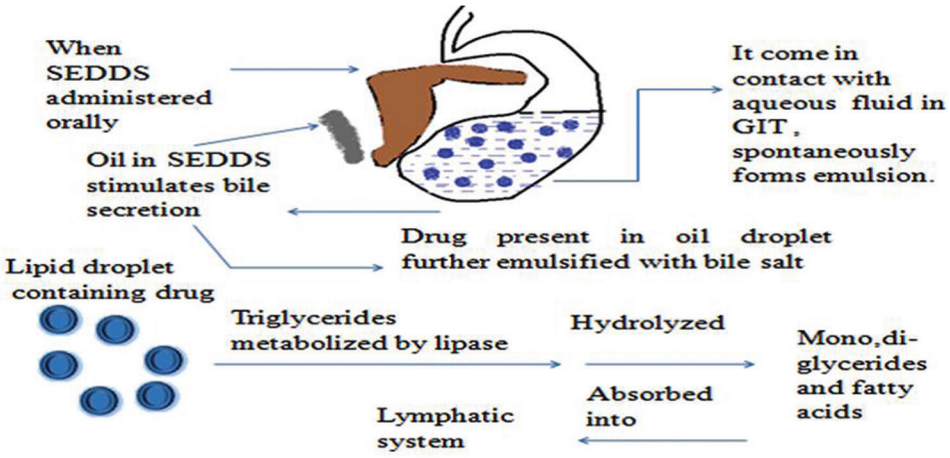

Fig. 3: Mechanism of emulsification

CHARACTERIZATION OF SEDDS

Differential scanning calorimetric

A scanning differential for calorimetric SMEDDS differential scanning calorimetric measurements can be performed using the DSC 60. Aluminum pans are used to collect liquids and solids for testing and analysis. The use of DSC is critical for the detection of chemical interactions.

Infrared spectroscopy using Fourier transforms

Infrared Fourier transforms spectroscopy. SMEDDS, you are likely to be using Fourier transform infrared (FT-IR). A suitable container should be used as soon as the sample is taken. To determine chemical interactions, the FT-IR technique should be utilized.

Macroscopic evaluation

Microemulsion formulation is introduced to 100 ml of water in an Erlenmeyer flask. Color, transparency, and phase separation of the optimized microemulsion formulation did not change at 37°C.

Visual assessment

An Erlenmeyer flask filled with water is filled with the formulation and gently swirled to determine its self-emulsification ability. Based on whether or not they occurred successfully or not, the likelihood of emulsion formation is rated as either positive or negative. To locate the vast self-emulsion zone, phase diagrams might be employed.

The self-emulsification time must be determined

The emulsification time of SMEDDS is determined under the USP XXII dissolving device. Drop by drop, each mixture is added to 37°C filtered water. Conventional chrome steel dissolving paddle revolving at 50 rpm is commonly used to gently stir the solution. Estimating emulsification time is done by looking at it.

Study of solubility

There is an unknown amount of selected vehicles in every cap vial containing more than medication products. In an ice bath, they are heated to 40°C to enhance solubilization after they have been sealed up. To integrate the systems, vortex mixers are utilized. To shake the suspensions, they are placed in a shaker at 25°C for 48 h. Centrifuge each vial at 3000 rpm for 5 min to remove the extra insoluble LOV. The concentration of the medication is then determined.

Transmittance test

The U.V. Spectrophotometer is used to measure the transmittance of the improved microemulsion formulation about dilution. For each sample, three replicate experiments are done to determine the sample's transmittance at 650 nm.

Measurement of the size of the droplet

Specific to this, it is used as a means of evaluating stability. Zetasizer uses photon-correlation spectroscopy to measure the size of the droplet (PSC). All measurements are taken at a scattering angle of 90° and a temperature of 25°. To screen the microemulsion, a 0.22 m filter is utilized. A similar amount of water was used to dilute it. Adding more water makes the mixture acceptable for measuring. Usually, 100–200 times diluted.

Measurement of zeta potentials

Zetasizer is used to determine the micro emulsion's zeta potential. To test samples, zeta cells are used. A methanol solution is used to clean the cuvettes before each experiment, followed by a rinse using the sample to be analyzed.

Stability

A visual assessment of the SMEDDS system at different intervals is used to estimate its shelf life based on time and storage temperature. Their temperature stability is tested by diluting them with filtered water and storing them in a refrigerator at three different temperatures (between 2°C and 8°C). Meta-stable systems can be estimated by diluting optimized SMEDDS formulation with purified water. Testing the homogeneity of microemulsions is done by centrifuging them for 15 min, at 1000 pm, and at 0°C [69-71].

Release *in vitro* test

Use of purified distilled water/Dn medium (USP 24 t) for quantitative *in vitro* release testing. When dialysis bags are empty, SMEDDS are inserted in the bags to match the discharge profile with a conventional dosage form. We take samples at predetermined intervals, filter them through a 0.45 membrane filter, dilute them appropriately, and then spectrophotometrically analyze them for a result. Just as soon as the test sample is removed, a fresh dissolving medium is added. Beer Lambert's equation is used to calculate the percentage of medication dissolved at different time intervals.

THE FOLLOWING ARE THE SEVERAL TYPES OF SEDDS DOSAGE

1. Microemulsion droplets are formed when liquid suspoemulsion (SE) capsules are given. Once in the GIT, these droplets scatter until they arrive at the Ab site. Because of the irreversible phase separation in the microemulsion, there is no way to increase medication Ab. This was solved by adding sodium dodecyl sulfate salt to the SE formulation
2. A prolonged or controlled release that is self-emulsifying Preparing SE tablets has been made easier using the combination of lipids and surfactant, which has shown significant promise. As a result, SE pills are quite useful in preventing harmful effects
3. A self-emulsifying, extended, or controlled release. As a multiple unit dose form, pellets have various advantages over conventional solid dosage forms. These advantages include flexibility in production, a reduction in intra- and inter-subject variability in plasma profile, and a reduction in GI discomfort without compromising drug Ab
4. Using excipient in self-emulsifying SDs could assist overcome these obstacles.

Topical delivery

There are some reasons why topical administration of medicine is preferable to other ways. One of them is that it avoids first-pass drug processing in the liver and its associated adverse consequences.

Oculars and pulmonary delivery

The oculars and the pulmonary delivery: When it comes to the treatment of sickness, medications are mostly administered topically.

Parenteral delivery

Since so little drug is transported to the target place when administered parenterally, this can be a serious concern in the industry.

Perspectives on biopharmaceuticals

i. Fats and/or meals can boost the bioavailability of water-soluble medications that are weakly soluble in water. Different mechanisms, such as, can increase the bioavailability of lipids. Alterations (reductions) in GI transit, although the mechanisms are not fully known
ii. Increased solubility of luminal drugs
iii. Intestinal lymphatic stimulation
iv. In the biochemical barriers, there are changes
v. Modifications in alimentary canal barrier function
vi. The polarity of the lipid phase in a micro-discharge emulsion affects the rate of discharge.

Formulation

Processes for turning water into solids. These solidification methods are listed below.

1. The capsule can be filled with liquid and semisolid self-emulating compositions. "Oral SE formulations in liquid or semisolid form can be encapsulated using the capsule feeling technique because it is the simplest and most common method. As a semisolid formulation, it's a four-step process: Heating the semisolid excipient to a minimum of 20°C above its freezing point

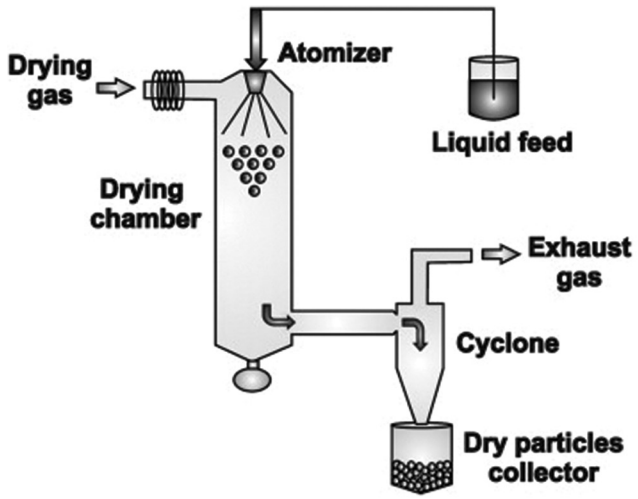

Fig. 4: Spray drying

2. Use of active ingredients (with stirring)
3. This is followed by the molt filling the capsules and cooling to the proper temperature. A two-step method is required for liquid formulations
4. Completing the capsules by filling them with formulation, then either banding or micro spraying the capsule's body and cap.

Solubilization of the mixture

As a result, the mixture must first be dissolved before it can be sprayed. Droplets are created by spraying the liquid mixture that has already been solubilized. Once the volatile phase (e.g., emulsion water) is evaporated, it is time to construct the tablet design. The drying chamber is built based on the particular drying properties of the products and powders (Fig. 4).

By adsorption on solid carriers, liquid SE formulations can be transformed into free-flowing powders. The liquid is added to carriers and then mixed with a mixer. A binder that has been warmed or melted at low temperatures is added to the powder to achieve agglomeration.

Spheronization of melt extrusion/extrusion

As a result of accurately controlling temperature, product flow, and pressure, you may extrude items with uniform shapes and densities [72,73].

APPLICATIONS

1. Adding medications to SEDDS improve solubility and bioavailability by bypassing Class-2 drugs' low solubility/high permeability dissolving phase. Although ketoprofen, a NSAID that is moderately hydrophobic (log p 0.979), maybe a viable choice for sustained-release formulations, its long-term usage is associated with a substantial risk of GI discomfort. As a result of its poor solubility, ketoprofen can also be released partially from sustained-release formulations
2. Increasing the solubility of the medicine and lowering GI pain boosted bioavailability. With the use of a gelling agent, Ketoprofen could not be released. As soon as the SEDDS lipid matrix comes into contact with water, it forms an O/W emulsion. Medicine will be administered in dissolved form to the mucosal surface of the stomach, making it quickly absorbable. Area under the curve (bioavailability) and Cmax of several drugs increase when provided in a SEDDS
3. A SEDDS capacity to slow down degradation and boost Ab could be particularly advantageous for medications whose low solubility and breakdown throughout the alimentary canal contribute to a lower oral bioavailability. As a result of acidic PH in the stomach or enzymatic breakdown, many medications are destroyed in the physiological system. Since SEDDS operate as a barrier between the degradation environment and the drug, such medicines are frequently well-protected when delivered in liquid crystal form. Aspirin is a good example.

Controlling the drug's release

To achieve prolonged release, boost bioavailability, and reduce GI discomfort, ketoprofen matrix pellets, sustained-release microparticles, floating oral ketoprofen systems, and transdermal ketoprofen systems have been developed. Preparation and stabilization by nanocrystailization method. SEDDS formulations of Ketoprofen often address this problem. This formulation improved bioavailability by increasing medication solubility and reducing GI discomfort. The addition of a gelling agent to SEDDS also helped to keep Ketoprofen from being released. Flurbiprofen Davies, 1995, Naproxen Davies and Anderson, 1997; Faassen and Vromans, 2004, Ketoprofen Faassen and Vromans, 2004, Rifampicin (Agrawal and Panchagnula, 2005; Becker *et al*., 2009; Panchagnula and Agrawal, 2004), and carbamazepine Agrawal and Panchagn (Table 3) [74,75].

CONCLUSIONS

The current review study on BCS is an experimental model for evaluating porousness and solubility under controlled conditions. If *in vitro* data were not enough, it was designed to help regulate post-approval modifications and generic drugs, by awarding approvals based almost exclusively on *in vitro* evidence. SEDDS-like medication formulations in BCS category II can be constructed with the help of this investigation. Medicines with solubility difficulties and low or variable bioavailability will be supported by the connected technologies.

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