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A Comprehensive Review on Self-Micro Emulsifying Drug Delivery Systems (SMEDDS)

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ABSTRACT

The pharmaceutical industry faces a major challenge with orally administered drugs like poor aqueous solubility, resulting in poor dissolution, low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality. Approximately 35–40% of recently launched drugs have low aqueous solubility. A challenge in developing the best oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products is that about 40% of new medication ideas possess limited solubility in water. These challenges have been rectified using a variety of techniques, such as altering the solubility or maintaining the medicine dissolved during the gastrointestinal transit time. Lipid solutions, emulsions, and emulsion pre-concentrates have received a lot of interest because they may be created as physically stable formulations suited for encapsulating such poorly soluble pharmaceuticals. Recently, self-micro emulsifying drug delivery systems (SMEDDS) in particular have been getting more attention. This is predominantly because these systems are physically stable, simple to manufacture, and capable of being filled in soft gelatin capsules. Once they reach the gastrointestinal tract, these systems will produce a micro-emulsion containing a drug with a major surface area. Self-micro emulsifying drug delivery system (SMEDDS) has emerged as a vital strategy to formulate poor water-soluble compounds for bioavailability enhancement. Due to the intestinal lymphatic system and pharmaceutical partitioning into the aqueous phase of intestinal fluids, the emulsions will further increase drug absorption. The oral bioavailability of such medications as well as an overview of SMEDDS, a significant technology for the formulation of lipophilic agents, both are discussed in this review.

INTRODUCTION

The simplest and most practical method of non-invasive delivery is via the oral route. However, drug molecules with poor water solubility may be hampered by oral drug administration. A significant challenge to the current drug delivery system is presented by the about 40% of novel drug substances that have low water solubility, which results in poor oral bioavailability, substantial intra- and inter-subject variability, and a lack of dosage proportionality [1]. The Biopharmaceutical Classification System assigns these medications, which have a low water solubility and a high permeability, to class II drugs. More than 70% of human dosage forms are administered orally, which is attributed to its acceptance and convenience as a method of administering drug molecules to patients since it is associated with good patient compliance on the one hand and cost-effective and flexible dose formulation on the other [2,3]. Aqueous solubility, which is necessary for pharmaceutical molecules to be accessible for systemic absorption given that GIT fluid is aqueous in nature, is one of the most crucial needs. The drug molecules must next cross the biological membrane after becoming solubilized to enter the systemic circulation [4].

The Food and Drug Administration (FDA) classifies drug molecules into four groups according to how soluble they are in water and how permeable they are to biological membranes. The Biopharmaceutical Classification System (BCS) is the name of this classification scheme [5,6]. The low aqueous solubility of Class II drug compounds is the key factor affecting their bioavailability. The rate-limiting stage in this class is the dissolving process, therefore choosing the right drug delivery method and additives is essential to get over this significant barrier and increase the proportion of the drug that will enter the systemic circulation [7]. With varying degrees of success, several approaches were developed to solve the problem; among these strategies, the solid self-emulsifying drug delivery system (SSEDDS) has undergone significant testing. Out of all the techniques that are now accessible, SEDDS that use a lipid-based methodology has been shown to increase drug dissolving rates and aid in the development of soluble drug phases. These mixtures are simple to pour into both soft and hard gelatin capsules. [8,9]. The self-emulsifying formulation is an isotropic combination of the medication, lipids, surfactants, and co-solvent that, upon agitation in the gastrointestinal (GI) tract, produces a superfine emulsion [10]. Based on the size of the globules developed during dispersion, the SEDDS are divided into two types: SMEDDS and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) [11].

The SEDDS form micro-emulsions known as SMEDDS. It produces optically clear emulsion and is thermodynamically stable. The size of the droplets in a micro-emulsion determines how they differ significantly from conventional emulsions. Typically, the size of the droplets of micro-emulsion created by the SMEDDS is between 2 and 100 nm, whereas that of the droplets of ordinary emulsion ranges between 0.2 and 10 m. The overall surface area for absorption and dispersion is substantially greater than that of a solid dosage form because of the tiny particle size, making it easier to enter the gastrointestinal system and be absorbed. The bioavailability of drugs is therefore improved [12].

Mechanism of self-emulsification

The mechanism by which self-emulsification happens is not yet fully understood. Taking everything into consideration, it has been suggested that self-emulsification occurs when the energy needed to grow the surface region of the dispersion to a higher level than the threshold of dispersion is the entropy change. A straightforward emulsion preparation's free energy is a direct working of the energy necessary to create the most recent surface between the water and oil phases. The system's free energy is completed when the two phases of the emulsion eventually separate to reduce the interfacial area.[13]

When the energy required to expand the surface area of the dispersion is larger than the entropy change that favours dispersion, self-emulsification happens [40,79]. The following equation may be used to determine how much energy is needed to form a fresh surface between the water and oil phases in a conventional emulsion:

$$\Delta G = \sum N_i \pi r_i^2 S$$

Where,

ΔG is the free energy associated with the process (ignoring the free energy of mixing),

N is the number of droplets of radius

r represents the radius of the droplet

S represents the interfacial energy.

The above equation demonstrates that the interface that forms spontaneously between oil and water is thermodynamically stable. The self-emulsification of an emulsion, or the

spontaneous formation of an emulsion, occurs when the amount of free energy required to develop the emulsion is either very low, positive, or negative. [79]

Advantages of SMEDDS

SMEDDS formulation provides several benefits, including:

1. Reducing disruption from GIT and gut wall interaction.

2. Give peptides to the GIT that are susceptible to enzymatic hydrolysis.

3. When a polymer is consolidated, a drug has a prolonged release.

4. SMEDDS can be manufactured safely and easily.

5. More predictable transient absorption characteristics of medicines.

6. A specific drug focuses on a specific GI tract absorption site that replaces ingestion.

7. Protection against drugs from potentially dangerous digestive illnesses.

8. The novel technique will boost the lipophilic medication's capacity to dissolve in water and thus increase its accessibility.

9. It shows that there are significant intra- and inter-subject variations in absorption that affect the plasma profile of solid or liquid dosage forms [6].

Factors affecting SMEDDS:

1. Nature and dose of the API: generally, drugs having a low therapeutic dose are preferred for the formulation of SMEDDS. If a drug does not have very high solubility in at least one of the components of SMEDDS, especially the lipophilic phase, it is not appropriate for SMEDDS. The most challenging drugs to deliver through SMEDDS are those with poor solubility in water and lipids, often with log p values of around 2. The medication's solubility in the oil phase has a significant impact on SMEDDS's capacity to sustain the drug in the solubilized state. [12]

2. Concentration of Surfactant or Co-surfactant: There may be a danger of precipitation if the surfactant or co-surfactant is performing a larger role in the solubilisation of the drug since the dilution of SMEDDS will reduce the solvent capacity of the surfactant or co-surfactant.14

3. Polarity of the Lipophilic phase: One of the variables influencing how drugs are released from micro-emulsions is the polarity of the lipid phase. The chain length and level of unsaturation of the fatty acid, the HLB, and the molecular weight of the micronized medication all influence the polarity of the droplet. The maximum polarity will improve the high degree of release of the drug into the aqueous phase. [14]

SELECTION OF APPROPRIATE DRUG CANDIDATES FOR SNEDDS FORMULATION

Solubilizing the medication in the GI system is one of the challenges a formulator has while creating an oral dosage form. Drug absorption is accelerated and broadened by SNEDDS. Drugs in BCS Class II that have poor water solubility and bioavailability are treated using the SMEDDS technique [15]. By avoiding the absorptive barrier of decreased water solubility and transitioning to the bile-salt mixed micellar phase, where absorption occurs quickly, the administration of these medicines as lipids increases their bioavailability [16]. The properties of the medication, such as its water solubility and log P, are insufficient since they cannot be used to anticipate the effects in vivo effects [17]. The amount of free energy required for the formation of an emulsion in the SNEDDS formulation might be small, positive, or even negative. As a result, emulsification occurs without warning. The interfacial structure must show no resistance to surface shearing so that emulsification can occur. Water's ease of penetration into various liquid crystalline or gel phases on the droplet surface may be the cause of emulsification's simplicity. [18-22]

Formulation design

Formulation of SMEDDS involves the following steps.

1. Selection of active pharmaceutical ingredient (API) for self-micro-emulsifying drug delivery system (SMEDDS).
2. Screening of surfactant for emulsifying ability.
3. Selection of excipients for self-micro-emulsifying drug delivery system (SMEDDS).
4. The solubility of a drug in oils, surfactants, and co-surfactant.
5. Construction of pseudo ternary phase diagram.
6. Preparation of self-micro-emulsifying drug delivery system (SMEDDS).

7. Factor that affects to self-micro-emulsifying drug delivery system.

8. Characterization and evaluation of SMEDDS.

Composition of Self-Emulsifying Drug Delivery System:

Active Pharmaceutical Ingredient (API)

Before developing a SMEDDS formulation, the primary factors to be considered are the drug's dosage and lipophilicity. BCS class II pharmaceuticals such as itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefenamic acid, naproxen, and carbamazepine are favoured because SEDDS are used to improve the solubility of poorly water-soluble medications. [23-24]

A variety of physicochemical properties of the API, such as pKa, log P, atomic structure and weight, presence of the ionisable group, and quantity, have a substantial impact on how well SMEDDS work [25]. Low therapeutic dosage medications are considered typical drug applicants for SMEDDS. Keeping the active medicinal component soluble within the G.I.T. constant is one of the main challenges in developing oral preparation. The principal absorptive site of the gut is where medications that are supplied at extremely large doses are not acceptable for SMEDDS unless they have excellent solubilisation in at least one of the excipients of SMEDDS, ideally in the lipophilic phase. The drug must be physically and chemically stable throughout production, and the drug discharge rate design must continue to be stable during the SMEDDS's self-life [26].

Excipients used in SEDDS

The choice of excipients is extremely important when pharmaceutical acceptability and toxicity concerns are taken into account. Therefore, there is a lot of limitation on which excipients may be utilised. The concentration and type of the oil/surfactant ratio, the surfactant/co-surfactant ratio, and the temperature at which self-emulsification takes place are all particular to the self-emulsification process. So, while choosing excipients for SMEDDS, this complete component must be taken into account.

Oils

Depending on the molecular structure of the triglyceride, oils can enhance the fraction of lipophilic drug carried via the intestinal lymphatic system, solubilize the necessary dosage of

lipophilic medication, facilitate self-emulsification, and solubilize the appropriate amount of lipophilic drug. [27]. The systemic circulation is directly reached by portal blood carrying medium chain triglycerides (MCT) with carbon atoms between 6 and 12. While intestinal lymphatics are used to transport long-chain triglycerides (LCT) with carbon atoms higher than 12. The development of self-emulsifying formulations has utilised both long and medium-chain triglyceride (LCT and MCT) oils with varying saturation levels. The regular MCT oils in the SMEDDS are being gradually and successfully replaced by novel semi-synthetic MCTs, which can be described as amphiphilic compounds with surfactant properties. MCT is more soluble and has higher mobility in the lipid/water interfaces than LCT, which is associated with more rapid hydrolysis of MCT.

In general, compared to MCT, a larger concentration of cremophor RH40 is needed when utilising LCT to create micro-emulsions. Due to their low capacity to dissolve significant doses of lipophilic medicines, edible oils are not usually used. Since these excipients create effective emulsification systems with a large variety of surfactants authorised for oral administration and display enhanced drug solubility qualities, modified or hydrolyzed vegetable oils have been frequently employed [28]. They have beneficial physiological and formulation properties, and the breakdown products they produce are similar to the organic by-products of intestine digestion. Therefore, the choice of oil represents a compromise between the ability to solubilize and the capacity to promote the development of micro-emulsion. The solubility of the substance in the oil and the surfactant work together to increase drug solubility in SMEDDS (s).

Surfactants

In addition to the oily drug carrier vehicle, the self-emulsifying features of the formulation need the inclusion of rather high levels of surfactant. The intestinal membrane's permeability may be increased or its attraction to lipids may be enhanced by the surfactants. The lipid bilayer's structural order is disrupted by surfactants when they partition into the cell membrane, increasing the permeability and enhancing penetration. [29] Thus, the passive transcellular pathway is used by most medications to enter the body. Additionally, they speed up the drug's disintegration to further their effects on absorption.

For the development of SMEDDS, the selection of surfactant is also critical. HLB value and surfactant safety must be taken into account when choosing a surfactant for SMEDDS formulation. A surfactant's HLB contains crucial information on how it should be used when

creating SMEDDS. To permit quick and simple dispersion in the aqueous GI fluid as a very thin oil-in-water emulsion, the surfactant/emulsifier used in the formulation of SMEDDS should have a reasonably high HLB and hydrophilicity. This will result in good self-emulsifying performance. [30] It has frequently been demonstrated that using surfactant blends to attain the necessary HLB for emulsification offers better self-emulsifying capabilities than using a single surfactant with the same HLB. [31]

Numerous vegetable oil derivatives, such as Acrosyl (a castor oil derivative), continue to be discovered to provide the best self-emulsification46. Because they exhibit superior emulsion stability across a wider pH and ionic strength range and have lower toxicity than their ionic counterparts, non-ionic surfactants are often selected. However, they may hurt intestinal lumen permeability, which might make it easier for the co-administered medication to be absorbed. Membrane fluidity and permeability can alter as a result of hydrophobic surfactants penetrating the membrane. [32]

Surfactants help to facilitate the dispersion process by forming the interfacial layer and reducing the interfacial tension to a low value. When selecting a surfactant, it is important to take into consideration the HLB value and surfactant concentration.

The orally acceptable surfactants have a stronger hydrophilic-lipophilic balance and are non-ionic (HLB). Ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate are two common emulsifiers. [33] Natural emulsifiers are regarded as being less dangerous than their synthetic counterparts, however, surfactants have only partial self-emulsifying capabilities. In contrast to ionic surfactants, non-ionic surfactants are less harmful and increase intestinal lumen permeability.

Co-Surfactants/ Co-solvents

High surfactant concentrations (up to 50%) are often needed for the formulation of an effective SMEDDS, and the inclusion of co-surfactants promotes self-emulsification. Typically, co-surfactants with HLB values of 10 to 14 are combined with surfactants to lower the oil-water interfacial tension, fluidize the interfacial film's hydrocarbon region, boost drug loading into SMEDDS, and enable the spontaneous generation of micro-emulsions. [34] Therefore, amphiphilic solubilizers and/or surfactants (hydrophilic or lipophilic) are employed in this process. A growing self-micro-emulsification zone in the phase diagrams may be the consequence of the co-emulsifiers or solubilizers being added to SMEDDS. For

oral administration, organic solvents like ethanol, PEG, and PG work well as co-solvents because they make it possible to dissolve substantial amounts of either the hydrophilic surfactant or the medication in the lipid base. SMEDDS are created by a lipid mixture with increased ratios of surfactant and co-surfactant to oil. [35]

The development of an ideal SMEDDS necessitates rather high concentrations of surfactants (often more than 30% w/w), yet this produces GI discomfort. Therefore, co-surfactant is utilised to lower surfactant concentration. The co-role, surfactants in conjunction with the surfactant, is to reduce interfacial tension to a very tiny, momentary negative value. When this value is reached, the interface would enlarge to produce finely dispersed droplets and then absorb additional surfactants and surfactant/co-surfactants until their bulk condition is sufficiently diminished to restore interfacial tension to its original positive value. The "spontaneous emulsification" approach generates microemulsions. Although alcohol-free self-emulsifying microemulsions have also been described in the literature, large amounts of either the hydrophilic surfactant or the drug in the lipid base may help dissolve in the organic solvents, suitable for oral administration, such as ethanol, propylene glycol (PG), polyethene glycol (PEG), etc. and can act as co-surfactant in the self-emulsifying drug delivery systems 3. When used in capsule dosage forms, such systems may have some advantages over other formulations because alcohol and other volatile co-solvents in traditional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard-sealed gelatin capsules, precipitating the lipophilic drug. [36,37] On the other hand, the alcohol-free formulation may have a reduced capacity to dissolve lipophilic drugs. Therefore, competent judgement must be used while choosing the components. Table 1 provides a list of the surfactants utilised in commercial SMEDDS.

Oil	Surfactant	Co-surfactant
Olive oil	Tween 80	Ethanol
Oleic oil	Labrador	Butanol
Corn oil	Labrafac	ethanol
Labrafil M 2125 CS	Tween 80	Transcutol HP
Mineral oil	Tween 40	Propylene glycol
Ceol 218	Tween 20	Ethylene glycol
Soyabean oil	Cremophor EL	polyethene glycol
Captex 355	Caprol 90	PEG 4000
Sunflower oil	Chromophore RH 40	Monitor 988
Cotton seed oil	PEG 400	Capmul MCM
Acryl K 140	PEG 200	Glycerol
Sesame oil	Sorbitol	Tetraglycol
Castor oil	Span 80	Plurol Oleique
Coconut oil	Span 20	Sorbitol
Miglyol 812 N	Kolliphor RH	
Captex 300	poloxamer 407	

Viscosity Enhancers: Incorporating extra substances like acetyl alcohol, tragacanth, beeswax, and stearic acids, among others, might change the viscosity of the emulsions.

Polymers: At physiological pH, a polymer matrix (inert) that is present in concentrations between 5 and 40% by weight but is not ionisable can form a matrix. Examples include ethyl cellulose, hydroxypropyl methylcellulose, etc.

Antioxidant Agents: The oily component of SMEDDS formulations is stabilised by lipophilic antioxidants (such as tocopherol, propyl gallate, and ascorbic palmitate).

Other components

Flavours, antioxidants, and pH adjusters are just a few examples of components. Unsaturated lipids, which make up the majority of lipid products, exhibit peroxide materialisation with oxidation, it is true. Free radicals can injure the medicine and cause toxicity, such as peroxyl (ROO), alkoxide (RO), and hydroxyl (OH). Lipid peroxides may also be created as a result of auto-oxidation, which rises with the lipid's degree of unsaturation. Due to the pH of the

solution or from the processing energy needed, such as ultrasonic radiation, the hydrolysis of the lipid occurs at a rapid rate. In this way, lipophilic antioxidants (such -tocopherol, propyl gallate, and BHT) may be necessary to preserve the oily content of the SMEDDS. [14]

CHARACTERIZATIONS AND EVALUATION OF SMEDDS

The various ways to characterize SMEDDS are compiled below;

Visual assessment

Visual evaluation is the main self-emulsification assessment technique. This might reveal important details regarding the mixture's ability to micro- and self-emulsify as well as its final dispersion. [38,39]

Equilibrium phase diagram

By employing equilibrium phase diagrams, it is possible to compare various surfactants and their interactions with co-solvents. One may quickly determine visually where one phase region's borders are. A ternary phase diagram can show how a three-component system behaves during phase transitions. To produce uniform pre-concentrates, self-emulsifying ability, and drug loading, the best concentrations of various excipients must be determined. [40] This is done using a phase diagram. When more than three components are employed, those that are closely connected are considered as one component and shown as such in the diagram at each corner of the phase diagram.

Turbidity measurement

Determining if the dispersion approaches equilibrium quickly and within a predictable period, this establishes the effectiveness of self-emulsification. Turbidity metres are employed in the execution of these measurements. [41,42]

Droplet size

To assess the droplet size of an emulsion, microscopic methods, photon correlation spectroscopy, or a Coulter Nanosizer is often utilised. Because it affects both the stability of the micro-emulsion and the pace and amount of drug release, droplet size is a crucial component of self-emulsification performance. [43] PCS (photon correlation spectroscopy) or SEM (scanning electron microscopy), which can detect sizes between 10-5000 nm, are used to determine the globule size of the microemulsion.

The polydispersity index (PDI)

The ratio of the standard deviation to the mean droplet size uniformity is known as the polydispersity; the higher the polydispersity, the less uniform the droplet size is. [44].

Refractive index and per cent transmission:

The transparency of preparations is revealed by the refractive index and % transmittance. The SMEDDS' refractive index (RI) is calculated using a refractometer and distinguished using water one. [45-48]

Differential scanning colourimetry

The evaluation of micro-emulsions created by the dilution of self-micro-emulsifying drug delivery systems (SMEDDS) in the designation of peaks equivalent to water often uses this method. [49,50]

NMR techniques.

After adding self-micro-emulsification systems to the prepared micro-emulsion, the NMR method was used to determine the micro-emulsion structure. [38]

Electron microscopic studies

Freeze-fracture electron microscopy is used to examine the surface characteristics of micro-emulsion. [51]

Small angle x-ray and neutron scattering methods:

This sort of method is useful for estimating the structures that result from the dilution of SMEDDS. Evaluation of the fluid crystalline structures produced by the dilution of SMEDDS is important because these regulate the stability of drug preparation, self-emulsion, and drug discharge quantity. examination of X-ray scattering on preparations with different water content ratios. [52-55]

Zeta potential measurement

The zeta potential analyzer or zeta meter system is often used to determine zeta potential. It is used to determine the droplets' charge. The zeta potential analyser's evaluation of the consistency of the emulsion after suitable dilution displays. [56-60] A higher zeta potential

indicates that the formulation is more consistent. Due to the free unsaturated fats yet positive when cationic lipids, the zeta meter system value is often negative.

Determination of emulsification time

This method is used to estimate how long emulsification will take. In this experiment, the effectiveness of emulsifying different surfactant and lipid compositions is measured in a crude nephelometer with a revolving paddle. [61]

Stability

(a) Temperature stability:

The shelf life as a function of time and storage temperature is determined by visual perception of the SMEDDS system at various time intervals. To assess the temperature soundness of tests, preparations are diluted with distilled water and stored at a varied range of temperatures (room temperature, 2-8°C or lower). Additionally, any evidence of phase separation, flocculation, or precipitation is often observed. [62,63]

(b) Centrifugation: The improved SMEDDS system is diluted with distilled water to evaluate the metastable system. Micro-emulsions are now centrifuged for 15 minutes at 0°C at 1000 rpm to check for any changes in the homogeneity of small-scale emulsions. [64-66]

Particle size distribution

The measurement of the micro emulsion's particle size distribution using dynamic light scattering methods. The Brownian diffusion velocity and, by extension, the dispersed droplet velocity is measured using the variation in scattered light intensity. [67] Cryogenic transmission electron microscopy can be used to further confirm particle size distributions (cryo-TEM). The benefit of being able to see the particle sizes and shapes is provided by cryo-TEM.

Conductivity measurements

The point at which the system transitions from having an oil continuous phase to a water-continuous phase may be identified by conductivity measurements. It also assists in the observation of phase inversion or percolation processes. [68]

In vitro release.

To evaluate the in-vitro drug discharge, the USP dissolution testing mechanical assembly type II (paddle type) should be used [69-71]. A suitable dissolving media is used in the dissolution test at a temperature of 37±5 °C.

In-vivo studies.

Several models are used to carry out in vivo experiments. Animal ethical committees must give their approval for any in vivo animal experiments, and the study is required to abide by those rules. With three groups of six animals each, the study was separated into three groups for control. [72-74]

Bioavailability study in the rat

The SMEDDS formulation including medication and the free standard drug solution is used to randomly segregate male rodents into two groups [75]. The rats are kept for 72 hours before the analysis so they may become acquainted with the lab environment and have free access to water. A comparable dosage was administered to the two groups [76]. Blood samples are taken at various intervals of time. The samples are centrifuged for 5–10 minutes at 10,000 rpm. HPLC is a tool that may be used to measure medication concentration. [77,78]

CONCLUSION

Self-micro emulsifying drug delivery systems are designed to increase the oral bioavailability of drugs that are poorly soluble and have limited bioavailability. It is the most effective way to boost a drug's solubility and bioavailability when taken orally. The aqueous medium is diluted after the oil, surfactant, and co-surfactant combination has been gently stirred. It creates a transparent oil/water microemulsion. To assist the researchers in selecting the best component for their research, numerous SMEDDS preparation components are examined in this review. SMEDDS are evaluated using a variety of assessment parameters, including the size of particles, degree of crystallinity, and charge in the formulations. Additionally, included in this review are numerous in vivo and in vitro models for characterising SMEDDS. This review paper will provide as a starting point for researchers studying SMEDDS, its advantages, mechanism of SMEDDS, methods for improving bioavailability, and drug solubility in water.

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CONFLICT OF INTEREST

The authors declare e that they have no conflict of interest, financial, or otherwise.

AUTHOR CONTRIBUTIONS

All authors contributed equally.

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