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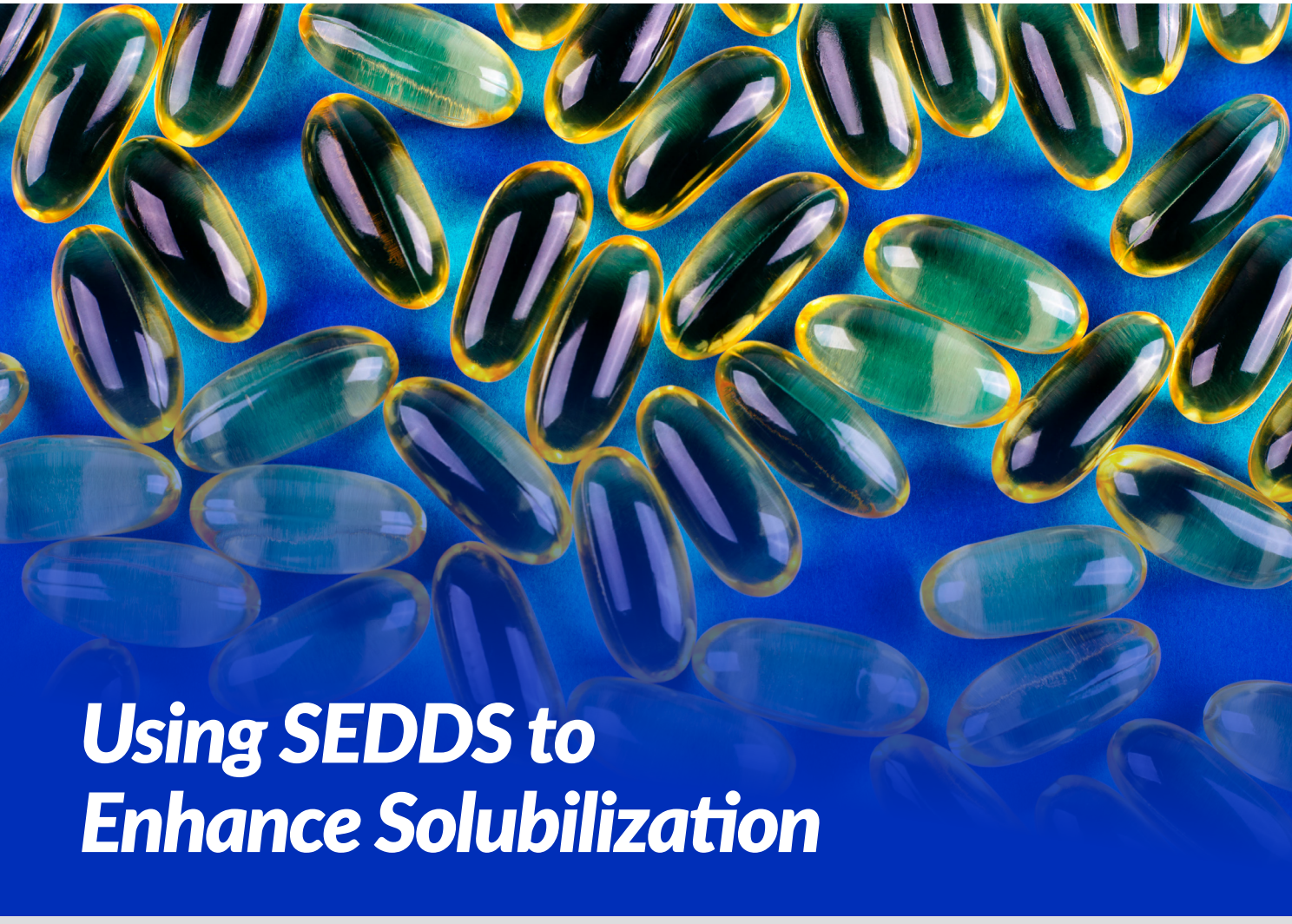

Using SEDDS to Enhance Solubilization

How Excipient Type Influences Self-Emulsifying Drug Delivery

Expert Discussion: SEDDS and Their Potential in the Market

Lipids for Self-Emulsifying Drug Delivery Systems

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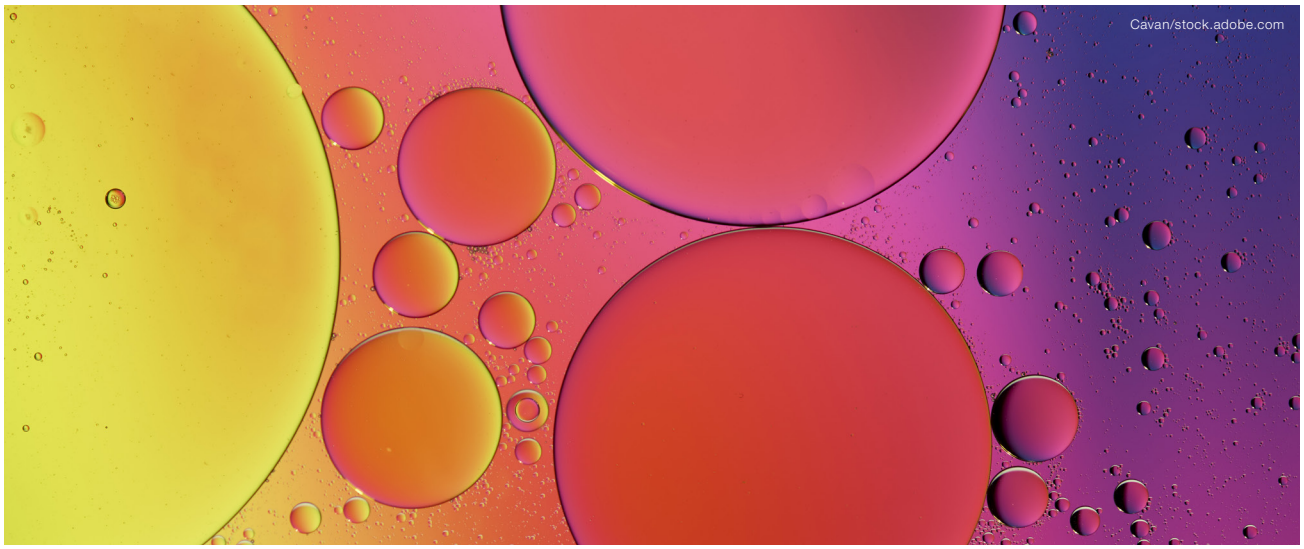


How Excipient Type Influences Self-Emulsifying Drug Delivery

Frank Romanski

Identifying the most stable SEDDS formulations and excipients for lipid-based drug delivery systems.

High-throughput platforms can be used to develop tertiary phase diagrams, which can be leveraged to identify the most stable SEDDS formulations and excipients for lipid-based drug delivery systems.

Most published estimates state that greater than 70% of drugs in the small-molecule pipelines are considered poorly water soluble. Because the human body requires that a drug essentially be solubilized in an aqueous environment, this poor water solubility poses an enormous challenge to effective drug delivery. Drugs may be poorly water soluble for a number of reasons, such as molecules with strong crystal lattices and high melting points or, on the other end of the spectrum, drugs exhibiting extremely high hydrophobicity that simply do not interact physico-chemically with water. If these drugs are not solubilized, they cannot be absorbed and are thus not producing a therapeutic effect. As the “easy” molecules (i.e., both water soluble and readily absorbed) become more rare in

modern pharmaceutical pipelines, effective technological and formulation strategies need to be developed to effectively deliver the poorly water soluble molecules (i.e., APIs in BCS Class II and IV).

One key aspect for these formulations and technologies is that they need to be practical; formulations must be straightforward to manufacture, as well as pragmatic for the patient to consume. Thus, techniques such as amorphous solid dispersions (ASDs), which are made using hot melt extrusion and spray drying, and lipid-based drug delivery systems (LBDDS) are effectively used in the majority of the poorly water-soluble drugs brought to market. ASDs can be easily formulated into tablets, which are a widely accepted dosage form to be manufactured and ultimately consumed. LBDDS, with formulations that are often liquid or semi-solid, may be produced into hard or softgel capsules, which are also highly accepted from a patient compliance standpoint, and the knowledge base to manufacture these and scale them up exists within the industry. Despite the ease of manufacturing, however, the challenge remains of how to properly formulate LBDDS, and more specifically, self-emulsifying drug delivery systems (SEDDS), which are notoriously difficult to formulate from scratch.

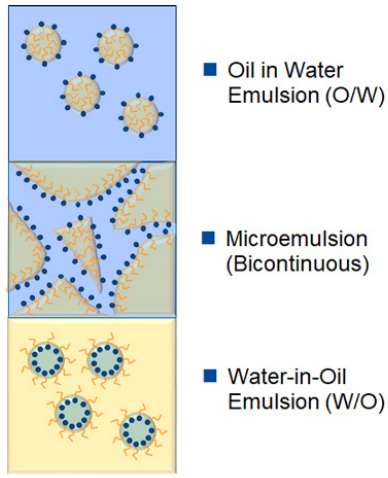
LBDDS delivery mechanism

LBDDS use the body's own mechanisms to effectively deliver drugs. As an example, when the body digests a fatty meal, the lipids and fats are dispersed through the gastrointestinal tract (GIT), where they are emulsified and subsequently absorbed. During the digestion process, lipophilic solubilized vitamins and nutrients are absorbed. LBDDS and more specifically, SEDDS, work using this same mechanism. The encapsulated formulation releases from the capsule in the stomach or intestine (which may be targeted through enteric or sustained release coatings); the oils are emulsified and stabilized by the surfactant phase to form small droplets, which consequently allow for rapid absorption of the drug into the body. Once dispersed, these are effectively an oil/water (O/W) emulsion. One could start with a predispersed O/W emulsion; however, a formulator cannot encapsulate an O/W emulsion effectively because it is inherently unstable from a thermodynamic perspective, and over a relatively short amount of time it will fully separate. To overcome this tendency and to formulate a truly stable system requires creating a microemulsion, which no longer has a defined oil and water phase, but rather a bicontinuous phase. Unlike traditional O/W or water/oil (W/O) emulsions, these are thermodynamically stable, clear, low viscosity, and exhibit a high capacity for drug solubilization. The stable region is drawn theoretically in **FIGURE 1**.

Microemulsion regions are also drawn using the classic fishtail diagram (see **FIGURE 2**), where the Winsor Type IV emulsions have the right blend of oil, water, and surfactant to maintain an equilibrium bicontinuous system.

HOW EXCIPIENT TYPE INFLUENCES SELF-EMULSIFYING DRUG DELIVERY

FIGURE 1: Microemulsions exhibit a stable region. All figures are courtesy of the author.



In these systems, there are no true droplets, but rather single digit nanoscale structures that coexist. The Y-axis on the diagram in FIGURE 2 may be the surfactant blend (hydrophilic surfactant and hydrophobic surfactant) or the temperature of the system.

It is these Winsor Type IV microemulsions that may be encapsulated effectively. Once these stable microemulsion systems inside of the capsules meet with the aqueous environment of the GIT, the system shifts to an O/W emulsion. Depending on the formulation, droplets can range from tens of nanometers to millimeters in diameter. These droplets encapsulate the poorly water-soluble drug and allow for absorption of the API as the oil is digested, forming micelles and other complex colloidal structures. In theory, this approach works well, but in reality, it can be challenging to isolate stable microemulsion regions within a given system in order to build formulations.

Formulating stable systems

SEDDS, which create tiny nano-scale droplets upon contact with the GIT, are highly effective, and a number of APIs have been recently approved that use this formulation approach (e.g., Rydapt, Neoral,

FIGURE 2: A fishtail diagram shows microemulsion regions; O is oil; W is water; S is surfactant.

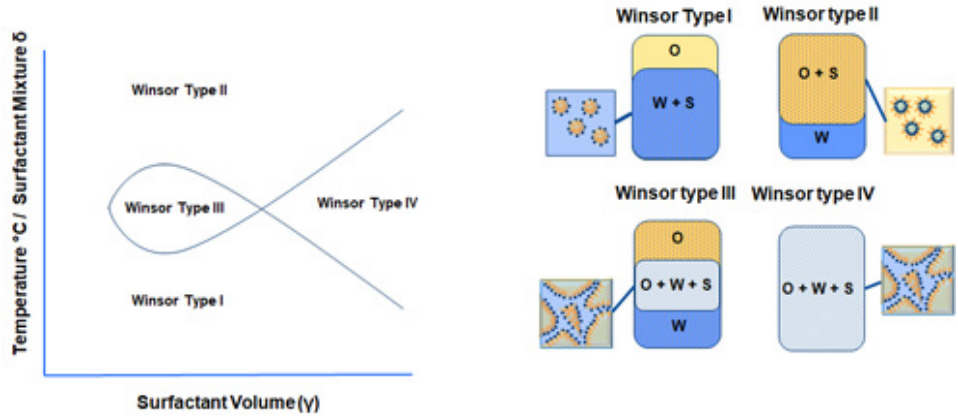
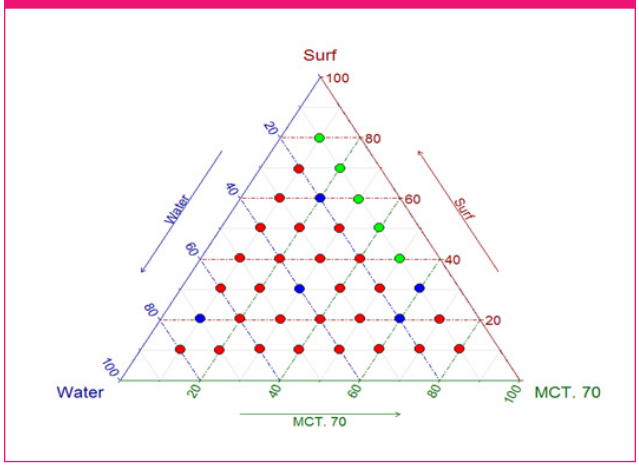


FIGURE 3: The stable regime in indicated by the green dots in the tertiary (oil, water, surfactant phase) diagram. The oil phase is a medium chain triglyceride (Kollisolv MCT 70, BASF).



Avodart, Norvir). However, what is yet to be comprehensively studied is the effect of excipients on the formulations. Although it is generally accepted that an oil-phase, primary surfactant, and secondary surfactant are required to effectively formulate these products, scientists must often work with existing formulations. Otherwise, they must start from scratch, which can require hundreds if not thousands of experiments.

With the aim of reducing the amount of experimentation and the time required to evaluate the applicability of SEDDS for different formulations, the author and his colleagues developed an approach that may be useful in future work. Their research, summarized in this article, used a high-throughput robotic system to establish tertiary phase diagrams (FIGURE 3) to determine stable regimes within these surfactant, oil, and water phase diagrams. Then different formulations using different surfactants, oils and aqueous phases were evaluated within this stable range to determine their applicability.

Within the stable region indicated by the green dots in FIGURE 3, a series of formulations were crafted to comprehensively study the effect of excipients on the formulations by varying the oil phase, aqueous phase, and surfactant/blend phase. An aqueous phase was studied because, in most encapsulations (particularly with softgels), moisture ultimately enters the system and reaches an equilibrium with the non-ionic surfactants, sometimes at concentrations greater than 5% w/w. The approach of formulating with an aqueous phase of 10% (either as water, ethanol, or others) builds robustness into the formulation and enhances the ability to maintain stability in the future. This phase may be either water or ethanol; ethanol allows for higher levels of drug solubility and better miscibility between the phases but may pose additional formulation challenges, such as the handling of flammable solvents during manufacturing.

Next, the oil phase, which is primarily responsible for solubilization of the drug and is the primary ingredient that is digested, was designed to be varied based on the solubility of the drug, rate of digestion (e.g., medium chain triglycerides digest faster than long chain), and the concentration, which further affects the digestion rate.

TABLE 1: Stable formulations (F1 to F10) for self-emulsifying drug delivery were designed to aid formulation of lipid-based drug delivery systems for poorly water soluble APIs.

	Medium chain triglyceride (Kollisolv MCT 70, BASF) (%) (w/w)	Soybean oil (%) (w/w)	Maisine 35-1 (%) (w/w)	Corn oil (%) (w/w)	Glycerol monocapryl-caprate (%) (w/w)	Polyoxyl 40 hydrogenated castor oil (Kolliphor RH40, BASF) (%) (w/w)	Poloxamer 124 (Kollisolv P124, BASF) (%) (w/w)	Polyoxyl 35 castor oil (Kolliphor EL, BASF) (%) (w/w)	Glyceryl Monooleate (%) (w/w)	Water (%) (w/w)	Ethanol (%) (w/w)
F1	-	27.5	27.5	-	-	35	-	-	-	-	10
F2	10	-	-	-	-	68	-	-	12	10	-
F3	40	-	-	-	-	42.5	-	-	7.5	10	-
F4	10	-	-	-	-	-	-	68	12	10	-
F5	40	-	-	-	-	-	-	42.5	7.5	10	-
F6	10	-	-	-	-	-	68	-	12	-	10
F7	-	10	-	-	-	68	-	-	12	10	-
F8	-	-	-	10	-	68	-	-	12	10	-
F9	10	-	-	-	12	68	-	-	-	10	-
F10	40	-	-	-	7.5	42.5	-	-	-	10	-

Finally, the surfactant phase was designed. This phase is primarily responsible for the stability of the system as a microemulsion as well as the size and stability of the droplets after the microemulsion "breaks" to form an O/W emulsion. Typically, and in the case of these examples, one would use a hydrophilic and a hydrophobic surfactant to balance the phases and enable the formation of a true microemulsion; this case was also tested by high-throughput screening. The results of these efforts were 10 stable formulations that can be used at multiple temperatures, aqueous/moisture levels, and different applications, as shown in TABLE I (see next page).

Formulation test results

Formulations were tested using model drug compounds and studied for stability, robustness, dispersibility, and digestibility using in vitro models (1). These were further corroborated by observing in vivo absorption using a rat model.

Each of the formulations listed in TABLE I exhibits unique properties. The use of ethanol, in the case of F1 and F6, allows for higher drug solubility and rapid dispersibility in aqueous media. Those using potent concentrations of surfactant, such as a non-ionic oil-in-water solubilizer and emulsifying agent (Kolliphor RH 40, BASF) used in formulas F2 and F3, exhibit very small droplet sizes upon release (10s of nanometers) and highly stable micellar systems once the oil is digested, although it is important to note that they generally require a few minutes to fully disperse from the capsules. Similarly, those made with a non-ionic oil-in-water emulsifier and solubilizer (Kolliphor EL, BASF) used in formulas F4 and F5, exhibit small droplet dispersions, but a slightly faster digestion due to the faster digestibility of the surfactant. Formula F6 uses a liquid poloxamer surfactant (Kollisolv P124, BASF), which allows for rapid dispersion, but sacrifices stability of the oil droplets. By using other oils, such as soybean and corn oil (formulas F7 and F8, respectively), digestion rates may be varied (MCT being the fastest typically, soybean the slowest), and the solubility of the API may be tailored. Finally, co-surfactants, while a minor component, are key to maintaining the microemulsion.

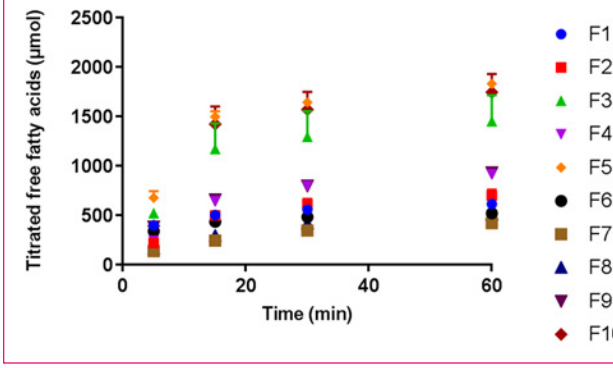
Several formulations are shown using glyceryl monooleate (formulas F2, F3, F4, F5, F6, F7, F8) and glyceryl monocaprylocaprate (formulas F9 and F10), offering different droplet sizes and digestion rates.

Best practices for testing formulations with an API

In order to test one of these formulations, it is generally recommended that the API be first saturated into the oil phase, which can be done by stirring overnight and filtering and testing API content by ultraviolet (UV) spectroscopy or high-performance liquid chromatography. Oil phases (oil + hydrophobic surfactant) and water phases (aqueous + hydrophilic surfactant) should be heated to approximately 60 °C and lightly mixed by hand; the microemulsions self-assemble. The resulting mircoemulsion may then cool and be dispensed into soft- or hard-shell capsules. Generally, the oil phase will be preloaded with API for formulation. It is recommended that approximately 80% of saturation in the total formulation be used for the final formulation to maintain API stability.

Testing of these formulations can be challenging, because in a standard dissolution bath with UV filter it is often too difficult to parse the API concentration

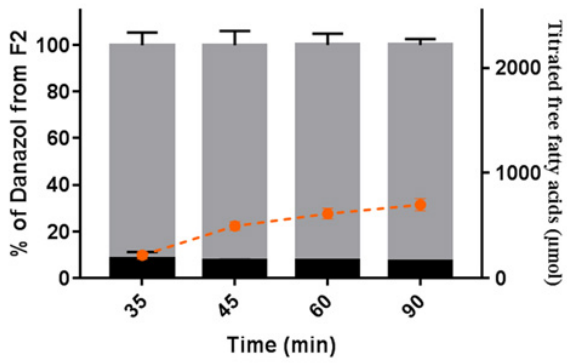
FIGURE 4: Digestion rates of the formulations (F1 to F10).



from the droplets, micelles, and other phases in the bath. Therefore, it is recommended that formulators test these using lipolysis, membrane-based absorption models (macroFlux, Pion) or cell-based methods, such as Caco-2. Using a lipolysis mode and the model drug Danazol (synthetic steroid, MP 224.2°C, 337.46 g/mol, LogP = 3.62), the varied digestion rates of the 10 formulations can be clearly noted, as shown in FIGURE 4.

Those formulations with a higher oil content, particularly those with medium chain triglycerides (Kollisolv MCT 70, BASF) exhibit the fastest digestion over one hour in intestinal media. Comparing the digestibility as well as the solubility of the API, one can compare formulations more succinctly.
As an example, formulation F2, with high concentrations of Polyoxyl 40 hydrogenated castor oil (Kolliphor RH 40, BASF), disperses into nanoscale droplets and is digested slowly. Formulation F3, with the same ingredients but a much higher oil concentration, exhibits a much faster digestion rate and higher API

FIGURE 5: Digestion over 90 minutes with formulation F2 (left) and F3 (right). The orange line is the titrated free fatty acid (digestion rate); the grey bar is solubilized and available API; and the black bar is precipitated, unavailable API.



capacity but sacrifices the size of the resulting oil droplets. Over a 90-minute digestion, these differences can be seen as graphed in FIGURE 5: the orange line is the titrated free fatty acid (digestion rate); the grey is solubilized and available API; and the black, precipitated unavailable API.

In summary, the formation of microemulsions is a challenge that can be overcome using modern methods such as robotic high throughput screening. These identified regions can then be utilized to craft functional pharmaceutical formulations capable of varied API loading, digestion rates, and dispersibility. The ten new formulations described in TABLE I are available for formulators to place "on the shelf" as more challenging APIs come through the pipeline.

Reference

1. S.D.S Jorgensen, et. al. Eur. J. Pharmaceutics and Biopharmaceutics124, 116-124 (2018).

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Expert Discussion: SEDDS and Their Potential in the Market

Expert opinion from Lindsay Johnson, PhD; Nitin Swarnakar, PhD; and Anirudh Acharya

Q&A with experts in SEDDS formulation, market potential, and lipid product management.

Self-emulsifying drug delivery systems (SEDDS) have many benefits. They can increase the solubility and bioavailability of ingredients, they're easy for consumers to take, and the main delivery systems—soft gelatin capsules or solid-state carriers—are relatively fast manufacturing approaches that allow for quick scale-ups. BASF not only offers this technology, but experts work with customers to design the best SEDDS solution, based on the company's 10 ready-to-use SEDDS compositions.

Here, *Pharmaceutical Technology* asked BASF experts about the challenges, potential, and future of SEDDS formulations.

PHARMACEUTICAL TECHNOLOGY: **What are the main drivers to select SEDDS as a strategy to bring a formulation to market?**

JOHNSON: High lipophilicity and poor aqueous solubility are the endemic problems of new drug molecules. SEDDS are a mechanism to improve oral bioavailability of a poorly water-soluble drug, especially for more

lipophilic, oily compounds that are very challenging otherwise. Formulating using a SEDDS approach brings multiple solubilization advantages that are unique, segmented and differentiated from other solubilization strategies such as amorphous solid dispersions.

You mention other solubilization strategies. How do SEDDS compare to other solubility-enhancing techniques?

JOHNSON: SEDDS, especially as liquid formulations, offer many handles for formulation design through choice and ratio of surfactants, co-surfactants, oils, and solvents. Other solubility enhancement techniques do not always offer as many degrees of freedom. For example, amorphous solid dispersions are more limited in excipient choice, as excipient selection is limited to those stable against the physical manufacturing and processing conditions, and resistant to the destabilizing effects of plasticization. The manufacturing of SEDDS, especially as liquids that are then filled into capsules, eliminates nearly all the harsh thermal and shear stresses compared to amorphous solid dispersions made from extrusion, for example, and thus can be used for more thermally labile drugs. Compared to amorphous solid dispersions made from spray drying, SEDDS do not use sacrificial solvents or require as many downstream processing steps.

"The manufacturing of SEDDS, especially as liquids that are then filled into capsules, eliminates nearly all the harsh thermal and shear stresses compared to amorphous solid dispersions made from extrusion, for example, and thus can be used for more thermally labile drugs."

– Lindsay Johnson, PhD

SEDDs, as liquids typically filled into gelatin capsules, also have the same favorable attributes as standard, simple softgel formulations, which include dosing with high accuracy and repeatability, low- and ultra-low-dose administration, fewer CMC [Chemistry, Manufacturing and Controls] hurdles than other dosage forms, rapid onset of action at the desired GIT location, and relatively direct scale up. Also, SEDDS do not lose the advantages of other oral dosage forms, like opportunities for taste- and odor-masking, and protection from air and light.

You describe many advantages for SEDDS. What, if any, limitations are there for the widespread adoption of SEDDS formulations and how can those be overcome?

SWARNAKAR: Current global formulation development trends suggests that lipid-based formulations, including SEDDS, have tremendous potential in the field of oral delivery. However, the development of

new, commercial SEDDS formulations is challenging due to the complex nature of the formulation.

The main limitation of SEDDS is the initial step of finding the magical combination of oils, surfactant, and co-surfactant composition that creates a stable system. The nature of each component significantly affects the final functional properties of the SEDDS such as droplet size, digestibility of the droplets, and API absorption, and these behaviors dictate the final efficacy and behavior of the system. This is time-consuming and requires many ternary and quaternary phase diagram studies.

How can we overcome this limitation? By using pre-designed formulations that allow for a simple drop-in of the active. BASF has designed 10 ready-to-use SEDDS compositions and categorized them based on digestibility and overall HLB (Hydrophilic–Lipophilic Balance) value. In addition, we have evaluated and categorized them based on the performance, indicating target profile attributes like emulsion droplet size and its rate and extent of digestibility in the GIT

"The main limitation of SEDDS is the initial step of finding the magical combination of oils, surfactant, and co-surfactant composition that creates a stable system."

– Nitin Kumar Swarnakar, PhD

tract. In nutshell, our robust understanding of these 10 systems allows us to directly recommend a starting point based on the solubility of active ingredient and desired delivery profile.

What excipient considerations are unique to SEDDS?

JOHNSON: The first consideration for any drug product is to ensure that the excipient's chemical and quality attributes meet pharmacopoeial status. However, while pharmacopoeia monographs describe overall quality parameters, some can be very flexible and wide-ranging. This is especially true for lipid-based excipients, which are what most SEDDS compositions are composed of. For example, glyceryl monooleate has a monoglyceride content ranging from 40% to 90%. This range can lead to very wide variance in performance in a final formulation. Another example can be in the surfactants. Namesake polysorbates can vary significantly in fatty acid composition and degree of esterification, attributes that will significantly affect surfactant behavior. This means that there will be limitations in switching from supplier-to-supplier or being second-sourced, so it is important for any formulator to build their SEDDS formulation

off of a portfolio from a reliable supplier. It is very difficult, actually, to swap out suppliers once a formulator has designed a SEDDS formulation that works well for a target API — because going from supplier to supplier with a different excipient composition will influence how that API is delivered.

ACHARYA: That applies to many common excipients to SEDDS within our portfolio – Kollisolv® MCT 70, Kolliphor® RH 40, Kolliphor® EL, our polysorbates Kolliphor® PS 20, 60, and 80, and others. When working with these types of excipients, you want to make sure that you're partnering with an excipient supplier who understands not only their excipient structure, but also the chemistries and the interactions, and has strict control on manufacturing processes. This is what BASF prides itself on. We can be a key partner in addressing a lot of the challenges around lipid and solution engineering, so that you ultimately have an optimal product.

What are the API dosing considerations when formulating SEDDS?

SWARNAKAR: As with any oral dosage form, you want to ensure patient compliance acceptability. An initial screening investigation into drug solubility in the SEDDS formulation is a key starting point for determining if a specific formulation will work 'in the real world'. If a drug's solubility in the formulation is limited and would thus require large or multiple capsules to deliver the targeted, therapeutic dose, the formulator may wish to use a different SEDDS composition. We have done a lot of work in this area, and have developed methods for predicting an API's solubility within our 10 SEDDS systems.

JOHNSON: One of the added advantages of SEDDS is the freedom to include excipients specifically to impact bioavailability through absorption. For example, common ingredients like polysorbates and low-molecular-weight polyethylene glycols in SEDDS formulations are known P-gP inhibitors, and can be used as a part of the formulation in order to support transport through the GIT membrane.

How do SEDDS formulations perform compared to conventional formulation approaches?

JOHNSON: One of the key differences for SEDDS from conventional formulation approaches, or even solubility-enhancing techniques, is the direct dispersion of colloidal structures formed upon delivery. This removes any dissolution mechanism – of drug or excipient – as a rate-limiting step for absorption. There is no requirement of tablet hydration, disintegration, deaggregation, or dissolution, and there is no particle-size dependency.

SWARNAKAR: Of course, with any system, the most important consideration is the final delivery of the drug in humans. However, because SEDDS are such complex systems during dissolution, compared to conventional formulation methods, there have been few successful models that reliably correlate *in vitro* data to *in vivo* results. Thus, current development of optimal, well-performing SEDDS formulations are mostly empirical and demand many animal studies, which are expensive and time consuming.

BASF has, in partnership with Professor Anette Muellertz, established a correlation of *in vitro* results with *in vivo* performance for our 10 SEDDS formulations using a GIT membrane-mimic system. This correlation helps minimize costly preclinical studies, and gives credible direction to early preformulation work.

Will adoption of SEDDS increase?

JOHNSON: We are already seeing commercial SEDDS formulations in the market, although this language is not always referenced in the insert. I do believe this approach will increase in adoption over the coming years.

In my view, the key limitations of softgels, whether filled with SEDDS or a simple formulation, is education and access to equipment. Softgel and SEDDS formulation is not as robustly taught in academics as tableting, and commercial equipment is isolated to large-scale manufacturers. Once lab-scale gelatin capsule equipment is more accessible, this technology will expand.

"In my view, the key limitations of softgels, whether filled with SEDDS or a simple formulation, is education and access to equipment. Softgel and SEDDS formulation is not as robustly taught in academics as tableting, and commercial equipment is isolated to large-scale manufacturers."

– Lindsay Johnson, PhD

Furthermore, as more vegetarian options for soft capsules have come to market in the last year or two, softgels can now access a more global population, where before this dosage form was off limits for individuals and markets sensitive to animal products. This will also encourage adoption in this direction.

SWARNAKAR: Another mechanism to increase the adoption of SEDDS is through different final dosage forms. Conventionally, SEDDS are delivered as liquid in softgels, though recently there are expanding options for converting the liquid SEDDS into solid SEDDS that can be pressed or filled into capsules. Using suitable inert materials and various processes, like freeze drying or spray drying, the liquid SEDDS can be adsorbed onto a solid or converted into a solid, that then delivers the same colloidal structures upon dissolution.

What special considerations are there for manufacturing excipients for SEDDS formulations?

ACHARYA: BASF is one of the very few pharma excipient suppliers, or possibly the only one, who has dedicated technical, regulatory and quality support. Our teams are really all-encompassing and comprehensive, and very few, if any, other suppliers can offer this to customers.

"For lipid-based excipients, BASF offers pharmaceutical grade, high-quality excipients, that minimize quality attribute variations, often with tighter restrictions that pharmacopeial requirements."

– Anirudh Acharya

Apart from considerations already mentioned, a formulator also wants to make sure that, especially for lipid-based formulations, an excipient supplier is going to communicate under strict change control protocols. This is exceptionally important in lipid-based formulations because the variability in the raw materials can be quite great, even if a final product is still monograph compliant. For lipid-based excipients, BASF offers pharmaceutical grade, high-quality excipients, that minimize quality attribute variations, often with tighter restrictions that pharmacopeial requirements.

Customers can enjoy long-term reliability of supply with us, which may not always be the case with other suppliers. For our raw materials, we are either backwards-integrated, or we are able to confidently secure global supply agreements. Furthermore, we have massive capacities and plants, which means we can rapidly scale up to support customers with their own expanding demands.

How do you see the growth in SEDDS formulations driving the market development for lipid-based pharmaceutical excipients in the next few years?

ACHARYA: From a global business perspective, we know that an increasing number of active pharmaceutical ingredients are non-water-soluble or difficult to solubilize. We see SEDDS formulations as a key door-opener for those drugs. In the next five to 10 years out, this will just become more and more relevant. As the number of low-water-soluble actives increases, using SEDDS formulations to address solubility and bioavailability challenges will continue to develop this market. We are already seeing major players come to market with commercial SEDDS formulations, and this will expand with others.

How does sustainability play a role in these formulations?

JOHNSON: Any time that you are able to improve bioavailability of an active through increased solubility, you are lowering the patient burden and increasing the efficacy

of the formulation. This means fewer doses, fewer side effects to mitigate, and, usually, improved patient compliance and treatment efficacy. Furthermore, SEDDS do not require harsh solvents or large-scale thermal energy, and thus are environmentally conscious and energy efficient.

ACHARYA: We also see a drive in the market for sustainably sourced excipients, and are pioneers in this space with a fully certified RSPO (Roundtable on Sustainable Palm Oil) lipid portfolio. This will continue to increase in importance, as we increasingly see our customers being sensitive to sustainability. We are well ahead of the curve and we're also enabling our customers to be a lot more sustainable and making them future ready. Perhaps in the future, formulation decision trees may even include an evaluation of the footprint of the dosage form and ingredients.

PHARMACEUTICAL TECHNOLOGY: **Any final considerations for formulators considering this approach for the first time?**

JOHNSON: Contact us for a recommendation on where to start! We have 10 formulations ready to use for with your API, and experts ready to guide your development.

Lindsay Johnson, PhD
Global Technical Marketing Manager
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Lindsay Johnson is the Global Technical Marketing Manager for the Solubilization Platform at BASF Pharma Solutions. She is responsible for solubility-enhancing excipients and technologies used in solid and liquid oral dosage forms, as well as parenteral formulations. She received her PhD from University of Minnesota.

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Nitin Swarnakar is the North America Application Lab Manager for BASF Pharma Solutions. He leads strategic customer and innovation projects that enable BASF products for pharmaceutical uses. He received his PhD from National institute of Pharmaceutical Education & Research (NIPER)-Mohali, India.

Anirudh Acharya
Global Product Manager
BASF

Anirudh Acharya is the Global Product Manager for the lipid-based pharmaceutical excipients portfolio at BASF Pharma Solutions. He oversees all key operational and strategic aspects of the business globally, with innovation acting as a vital pillar to ensure the portfolio meets customers' evolving needs. Anirudh holds a Master's degree in Chemical Engineering from the University of Erlangen-Nuremberg, Germany.

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Lipids for Self-Emulsifying Drug Delivery Systems

Cynthia A. Challener

SEDDS and SMEDDS improve solubility and permeability while expanding efficacy and applicability.

With the majority of APIs under development considered poorly soluble and/or poorly permeable, formulators have been forced to develop new solutions for overcoming these key issues. Lipid-based drug delivery is one of only a few methods effective for increasing both the solubility and permeability of APIs.

Formulations that are designed to spontaneously emulsify upon contact with aqueous media, including self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS), are often preferred because they are relatively easy to formulate, can potentially decrease first-pass metabolism, minimize food effects (minimize the difference in API absorption in the fed and fasted states), and can protect APIs sensitive to degradation in aqueous environments. In addition, because the API is dissolved in a pre-concentrate and not subject to amorphous-to-crystal

transitions, which can occur over time with other technologies, SEDDS formulations are relatively more stable.

The key to successful SEDDS formulation is the choice of the right combination of lipid excipients for the particular API and route of administration.

Some basic SEDDS properties

Lipid-based formulations are generally classified into four categories, according to Philippe Caisse, scientific director pharmaceuticals at Gattefossé. Type I are composed 100% of lipids. Type II are SEDDS without water-soluble components that consist of 40–80% oils and 20–60% surfactants with low hydrophilic-lipophilic balance (HLB) values, have a turbid oil-in-water dispersion aspect, and are easily digested.

Type III lipid formulations are SEDDS/SMEDDS composed of <20–80% oils, 20–50% high-HLB surfactants, and 0–50% hydro cosolvents that have water-soluble components, form clear of bluish dispersions, and are less easily digested. Type IV systems are composed of 0–20% low-HLB surfactants, 30–80% high-HLB surfactants, and 0–50% hydro cosolvents and able to form clear micellar solutions but may not be digested. Typically, SEDDS are isotropic and kinetically stable (SMEDDS are thermodynamically stable) formulations of functional lipids containing one or APIs for systemic delivery, according to John K. Tillotson, pharmaceutical technical business director (Americas) for ABITEC. SEDDS compositions, adds Nitin Swarnakar, North America Application Laboratory manager within BASF Pharma Solutions, comprise precise combinations of oil, surfactant, and cosurfactants to yield low-viscosity, isotropic mixtures.

The nature and selection of each of these components will, Swarnakar says, significantly affect properties such as droplet size, speed of dispersion, digestibility of the droplets, and API absorption.For example, he notes that a less digestible mixture can be formulated by including a lipid with a long carbon chain or by increasing the concentration of a less digestible surfactant.“Depending on the goals of the formulation, an optimal composition can be targeted,” he states.

Several common lipids

As of 2019, there were at least 15 commercially available small-molecule drugs formulated as SEDDS (1,2). The relatively simple need to make a small-molecule API soluble to improve drug delivery—rendering it orally available or capable of getting across the lining of the gut—involves differences in lipid structure, according to Jamie Grabowski, vice president, portfolio and sourcing at Curia (formerly AMRI).
The most common classes of lipids employed are solubilizers, emulsifiers, surfactants, and potentially co-surfactants, Tillotson comments.Medium-chain triglycerides serve as solubilizers; mono- and di-glycerides as solubilizers and emulsifiers; and pegylated esters, polysorbates, and ethoxylated oils as surfactants and co-surfactants.

Surfactants can be water-insoluble (e.g., propylene glycol esters), water-dispersible (e.g., linoleyl polyoxyl-6 glycerides), or water-soluble (e.g., polyoxyl-based esters), according to Caisse. Diethylene glycol monoethyl ether is the most common hydrophilic cosolvent.

"These functional lipids are preferred based on their efficacy with regard to solubilization and emulsification capabilities," says Tillotson. For example, medium-chain triglycerides have a high solubilizing capacity for lipophilic drugs and are especially easy to emulsify using suitable surfactants, such as castor oil derivatives, according to Swarnakar.

A balancing act

SEDDS formulations start as isotropic mixtures that contain the API(s) dissolved in the functional oil, solubilizer, and surfactants. When the SEDDS formulation enters an aqueous environment, such as the GIT, the SEDDS forms API-containing droplets, with the API(s) contained in the hydrophobic interior and the emulsifiers, surfactants, and co-surfactants stabilizing the discontinuous oil phase inside the continuous aqueous phase.

For example, Tillotson notes that greater amounts of hydrophobic lipids tend to increase API solubility in the system for some APIs; in contrast, greater amounts of less hydrophobic lipids, such as emulsifiers and surfactants, tend to reduce globule size and generate micro-emulsions."The challenge is determining the optimum concentrations of each functional lipid in the pre-concentrate with regard to maximizing API solubilization and emulsion performance," he concludes.

Often SEDDS formulations may include three, four, or five excipients along with the API, according to Caisse. Formulating an optimal SEDDS may thus require numerous trials and formulation variations. He also notes that some all-in-one self-emulsifying excipient systems are available that can simplify the preparation of type II and Type III lipid-based formulations.

Multiple factors influence lipid selection

Generally, lipids with chain lengths of C8 to C18 are reported in the literature as being ideal for SEDDS formulations, according to Swarnakar. She adds that specific lipids are chosen based on the melting point and crystal lattice properties of the API in question.

Most poorly water-soluble drugs are lipophilic, and thus the solubility of the API in the lipid components of the system will be the first parameter considered, according to Caisse. For highly lipophilic drugs, oils or mixed mono, di-, and triglycerides are often used. For APIs with medium lipophilicity, low HLB (≤ 9) surfactants are often preferred, he says. For APIs with low hydrophilicity, high HLB (> 10) surfactants and hydrophilic solvents are often required.

Another very important consideration is the desired emulsion performance and characteristics of the SEDDS formulation, says Tillotson. "The ideal SEDDS formulation optimally balances the overall solubility

of the API(s) while realizing the desired emulsion characteristics, such as globule size and dispersibility. The goal is to develop a system that provides for maximal API loading, while also generating a rapidly-dispersing micro emulsion," he explains.

SEDDS formulations should also take into account the type of API being delivered, according to Tillotson. For example, Biopharmaceutics Classification System (BCS) Class II APIs are poorly soluble but readily permeable.Therefore, the focus in a BCS Class II carrying SEDDS is on lipids that provide the greatest solubility/carrier capacity for the API. In contrast, a BCS Class IV API is both poorly soluble and poorly permeable.In this case, the SEDDS needs to not only address API solubility in the functional lipids, but also, if possible, permeability issues.

For this reason, Tillotson says a BCS Class IV API-carrying SEDDS may include lipids that open tight junctions between enterocytes (functional lipids composed of C8 and C10 fatty acids) or lipids that inhibit the activity of P-glycoprotein (PGP) efflux pumps (certain mono- and di-glycerides and certain macrogolglycerides).

In addition to the nature of the API, lipids for SEDDS formulations are also selected depending on the delivery strategy, Swarnakar adds. With respect to the API, "like-dissolves-like" is the rule of thumb for choosing the lipid. "Generally, very hydrophobic drugs (log P > 5) can be solubilized in more lipophilic lipids with longer carbon chains," he says. Specifically, longer and fully saturated carbon chains are more stable and less digestible within the gastrointestinal tract (GT). "This less digestible nature can be beneficial to the absorption profile by providing a secondary, lymphatic route of absorption in addition to the standard portal vein absorption. This additional route of absorption can be used to enhance the bioavailability of specific APIs and increase API absorption times," observes Swarnakar.

Other factors related to the API in addition to low in vivo permeability may also be of importance, observes Caisse, such as heat sensitivity and a high first-pass metabolism. "Hence the design of a self-emulsifying formulation as an efficient delivery system for a given API is also related to the targeted strategy for its bioavailability enhancement or physical limits of its manufacturing process," he says.

The final dosage form should also be considered. Caisse notes that for soft-gel capsules and liquid- filled hard capsules, liquid/low-viscosity formulations are best, while for solid-filled hard capsules, semi-solid/solid excipients are preferred as the main components, although up to 20% liquid excipient is feasible.

Correlating in vitro and in vivo SEDDS performance

Despite the general understanding of how different lipids impact solubility and permeability, formulators have always struggled to predict the best SEDDS formulation prior

to costly in vivo and clinical work, according to Swarnakar. "Various reported in vitro methods, such as [United States Pharmacopeia] USP type 2 dissolutions, provide limited discrimination of SEDDS formulation behavior. The interference of turbidity and biphasic media make conventional in vitro screening methods inaccurate for SEDDS formulations," he explains.

"The ready-to-use compositions are categorized based on their compositional HLB values and performance-indicating target product profile attributes, including microemulsion droplet size and enzymatic digestibility."

To address this issue, BASF, in partnership with Professor Anette Müllertz at the University of Copenhagen, has recently established a robust in vitro-in vivo correlation of 10 ready-to-use SEDDS compositions using the MacroFlux device from Pion for determining the absorption potential of formulations and finished drug products in vitro. The ready-to-use compositions are categorized based on their compositional HLB values and performance-indicating target product profile attributes, including microemulsion droplet size and enzymatic digestibility.

"Through careful testing and consideration of the chemistries in these formulations, the formulator is able to pre-screen a range of formulations and select according to their preferred API absorption behavior," says Lindsay Johnson, global technical marketing manager–Pharma Solutions at BASF.She believes this tool will help formulators avoid costly pre-clinical studies and ensure continuity of product quality and performance during product development. "Overall, these tools will enable formulators to choose the best SEDDS formulation based on the API properties for preclinical and clinical trials and accelerate the product development timeline," she asserts.

Extending efficacy

New developments with SEDDS are focused on extending the efficacy of the dosage form beyond simple improvements in solubility. Areas of research, according to Tillotson, include chylomicron signaling for tissue targeting, long-chain lipid inclusion promoting lymphatic transport and reduced first pass metabolism, and employing lipids as a delivery system for more specific targeting such as conjugated antibody targeting with APIs.

Moving beyond capsules

Liquid SEDDS formulations for oral administration are generally loaded into liquid-filled soft-gelatin or hard-gelatin capsules. "An ongoing challenge is how to administer SEDDS on higher throughput dosage forms, such as tablets," says Tillotson.

There are many drivers for the development of solid or semi-solid SEDDs formulations in addition to the ability to easily incorporate

them into tablets. They may also offer improved stability and enable sustained-release or abuse-deterrent formulations. Liquid SEDDs, according to Caisse, are susceptible to degradation during long-term storage and suffer from in vivo precipitation issues and handling complexity.

Research is ongoing in this application at multiple institutions."The primary difficulty is generating tablets at industry tableting speeds with minimum or no sticking to the punches that also release the SEDDS formulation," he observes. Other solid SEDDS technologies are also being developed such as powder and granular SEDDS.

SEDDS compositions formulated as solids can be achieved, according to Swarnakar, using a variety of methods, including adsorption onto solid carriers, freeze drying, spray drying, and melt granulation. Caisse adds that wet granulation and extrusion/spheronization are other solidification techniques used for converting liquid SEDDS into solid SEDDS.

"The key to this strategy is to retain the solubilization and dissolution enhancing properties of the SEDDS formulations once they are absorbed on the solid carrier materials, Caisse observes."

Of these methods, Johnson notes that adsorption onto an inert solid carrier is most common. In this case, a liquid SEDDS solution is mixed onto various solidifying agents such as mannitol, lactose, or calcium carbonate.

The key to this strategy is to retain the solubilization and dissolution enhancing properties of the SEDDS formulations once they are absorbed on the solid carrier materials, Caisse observes.The resulting powders, he says, can be subsequently filled into capsules or formulated as solid dosage forms such as tablets, granules, or pellets in sachets.

The growing role of lipid nanoparticles
Progress has been dramatic in the past few years particularly with respect to the development of lipids that facilitate the absorption of large molecules—notably biologics, according to Grabowski. "Driving the development of these lipids for SEDDS is the need for drug products with expanded methods of administration, notably oral. This is a big challenge for biopharmaceutical companies that want to offer patients the choice of an oral drug instead of an injectable," he says.

Specifically, Grabowski notes that developers are moving away from relying on off-the-shelf lipids to get hydrophobic drug substances into solution or improve their stability. Instead, they are turning to complex cationic lipids that are actually helping with the functionality and efficacy of biologics by altering their bioavailability and

pharmacokinetics, both in SEDDS and lipid nanoparticles (LNPs) such as those used in the formulation of mRNA vaccines against the SARS-CoV-2 virus, he says.

Cationic lipids improve the solubility, oral absorption, bioavailability, and pharmacokinetics of biologic drug substances, according to Grabowski. In LNPs, which have a much more complex structure than SEDDS, they are used along with cholesterol, a minor lipid, and one other typically proprietary compound.

Lipid nanoparticles such as cubosomes, adds Tillotson, contain both hydrophilic and hydrophobic regions and are readily absorbed by cells through typical lipidomic pathways. "The amphiphilic nature of these lipid carriers allows for the incorporation of proteins, RNA and both hydrophilic and hydrophobic APIs.For this reason, lipid nanoparticles composed of high-purity, functional lipids are ideal carriers for biologics and small-molecule actives," he contends.

Increasing focus on lipid design

Across all research regarding lipid-based delivery, the main focus is on the purposeful design of lipids with specific structural and physiochemical properties. "Ultimately," asserts Grabowski, "the industry will stop using off-the-shelf compounds such as cholesterol for LNPs and switch to carefully designed lipids with improved and diverse structures that enable fine tuning of the intended pharmacological impacts."

"Lipid nanoparticles such as cubosomes, adds Tillotson, contain both hydrophilic and hydrophobic regions and are readily absorbed by cells through typical lipidomic pathways."

For instance, Grabowski notes that assessing the structures of cationic lipids through structure-activity relationships will help improve the pharmacokinetics of drug delivery. "It will become less about simply being able to form micelles and more about making lipids that allow the drug substance to get across the gut lining and improve pharmacokinetics. That's going to be the big issue," he asserts.

Similarly, Tillotson sees emerging research on lipid-based drug delivery as being focused on the design and manufacture of high-purity lipids for specific applications, such as incorporation into LNPs for the systemic delivery of biological therapeutics. He also notes that ongoing lipidomics research seeks to identify novel lipids and lipid metabolites that can be potentially employed in biomarker discovery programs for specific disease states.

Greater expectations for GMP lipid manufacture

In many advanced lipid-based formulations, including SEDDS/SMEDDS, the lipids are not inactive ingredients, but functional excipients that impact the efficacy of the drug product. Both drug manufacturers and

regulators are responding by treating these types of functional excipients more like APIs, according to Grabowski.

"Increasingly drug manufacturers want lipids used in their drug formulations to be made according to [current good manufacturing practice] CGMP requirements," Grabowski says. "While lipids may not need to be produced in a CGMP environment for early-phase research, if regulators potentially consider them to be additional 'APIs' because they affect the bioavailability of the drug substance or efficacy of the drug product, the lipid supplier will be expected to have the ability to produce GMP lipids." As an example, Grabowski notes that there is movement toward treating cationic lipids as APIs.

One of the biggest challenges with CGMP manufacturing of lipids, observes Tillotson, is maintaining both quality and consistency. "This goal is achieved by maintaining consistent raw material stocks and tight specifications on manufacturing unit operations," he says. That is important for SEDDS in particular, adds Johnson, because across one monographed chemistry, different manufacturer materials may ultimately perform differently in a final formulation. "For this reason, the sensitivity of formulations needs to be considered as the choice of supplier is weighed," she comments.

Another challenge for lipid manufacturing highlighted by Caisse is the need to find new ways to manufacture lipids with sustainable raw materials and more eco-friendly processes that leverage new classes of catalysts. Additionally, suppliers who start from certified sustainably sourced base raw materials, like palm kernel oil, coconut oil, corn oil, and others, can bring value and awareness to ethical and sustainable sourcing in the pharmaceutical industry, according to Johnson. For example, she observes that many of BASF's lipid-based pharmaceutical excipients come with an external certification for being responsibly sourced.

References

1. I. Pehlivanov, JIMAB 25(2), 2575–2582 (2019).
2. S.P. Kovvasu et al., Asian J Pharmaceutics 13 (2):73–84 (2019).

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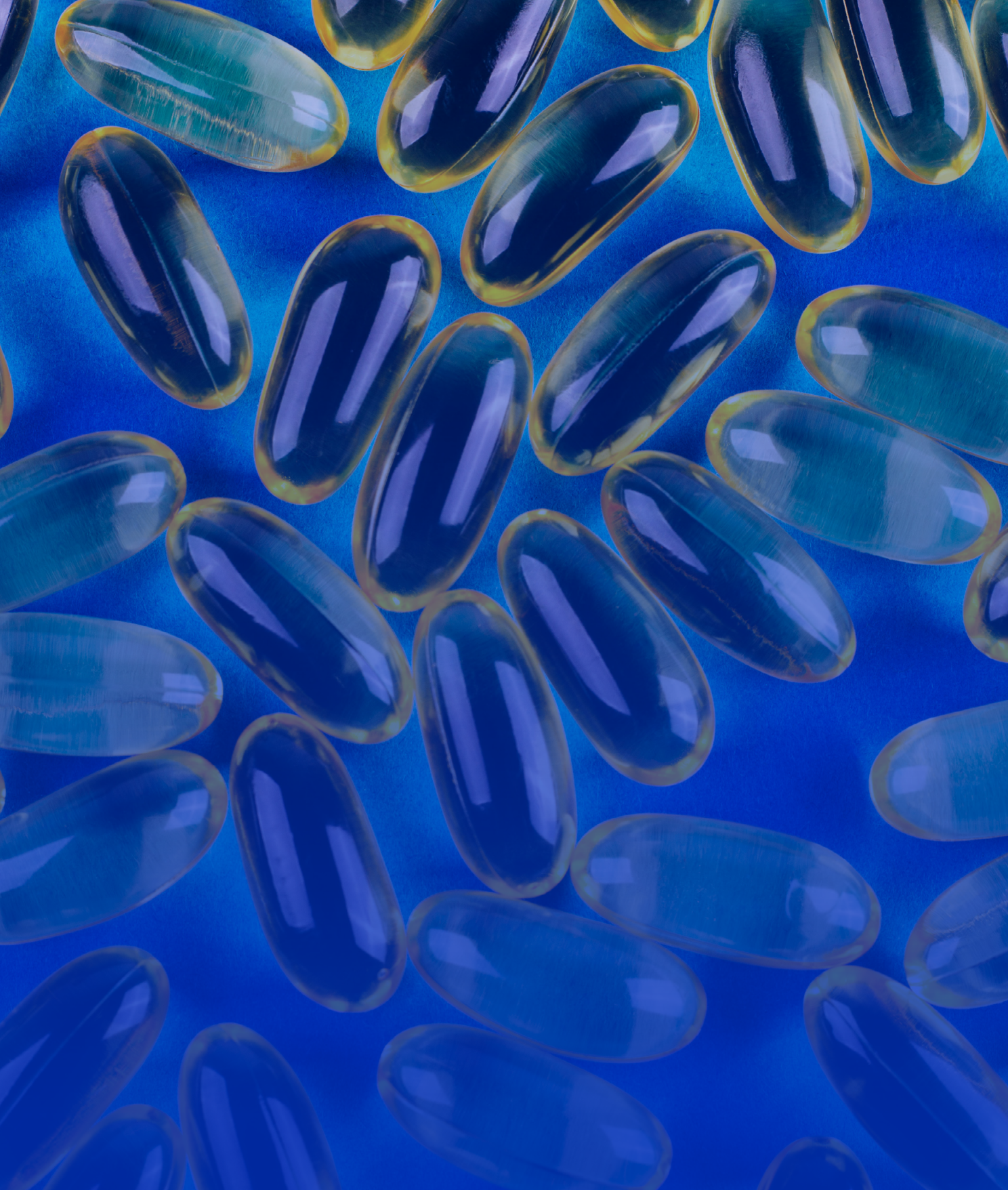

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