High throughput screening for the discovery of self-emulsifying drug delivery systems (SEDDS)

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Introduction

The modern solubilization challenge is that APIs that cannot be dissolved, cannot be absorbed and ultimately cannot treat patients. Poorly water-soluble drugs are typically divided into two macro categories, “brick dust” molecules, exhibiting a strong crystal lattice structure or “grease ball” molecules, exhibiting notably low melting point but very high hydrophobicity. Lipid-based drug delivery systems, specifically those made from Self-Emulsifying Drug Delivery Systems (SEDDS) have been shown to be an excellent formulation for the improvement of bioavailability of poorly water-soluble drugs in both categories.

However, the formulation of these systems is traditionally difficult due to the temperature and ingredient sensitivity of the formulations. In order to identify robust, „off-the-shelf“ proven SEDDS formulations, an advanced, High Throughput Robotic system was utilized to systematically identify SEDDS formulations in order to create a tertiary phase diagram for a series of commonly used pharmaceutical ingredients. These were then subsequently tested for dispersibility and feasibility for use in soft and hard capsule systems.

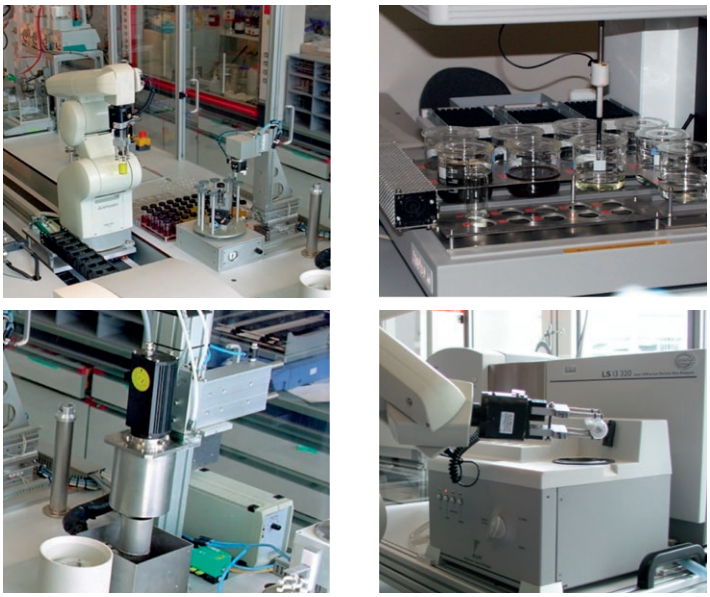

Figure 1: BASF designed high throughput robotic system (HTS).

Methods

A BASF designed high throughput robotic system (HTS) was utilized to screen and identify tertiary phase diagrams capable of forming stable microemulsions. Samples were heated, dispersed, mixed and analyzed in a precisely defined order and time. The resulting formulations were tested for viscosity, turbidity, conductivity and image analysis in order to determine true microemulsion regions, defined as low viscosity (≤700 cPs), isotropic and optically clear systems. An image of the setup is shown in Figure 1.

Ingredients were dosed by combining surfactant, cosurfactant, pH 7.0 buffered water and oil phases. Homogenization, utilizing 1 min shaking was used as a first pass mechanism for mixing the systems. If the systems remained inhomogeneous after 1 minute, a 20 second homogenization was utilized using the Ultra Turrax T-25 homogenizer at 60°C; samples were rested then for 24 hours and tested. Homogeneous samples were noted, while clearly phase-separate systems were also noted.

Aqueous phases were made with purified water, oil phases with medium chain triglycerides (Kollisolv® MCT 70), primary surfactant was Kolliphor® RH 40, with smaller levels of co-surfactant glyceryl monooleate. These arget excipients were previously identified using high throughput chemistry. Five ratios of surfactant and co-surfactant were explored to identify the most effective ratio. These ratios were isolated by the desired HLB value. Kolliphor® RH 40 (RH 40) was used as the primary surfactant, while co-surfactant Glyceryl Monooleate (GMO) was used to modulate the HLB value. Each HLB value served as a surfactant combination “block”.

A total of 180 experiments were completed to cover the three-dimensional design space; these can be exemplified by Figure 2 and Figure 3:

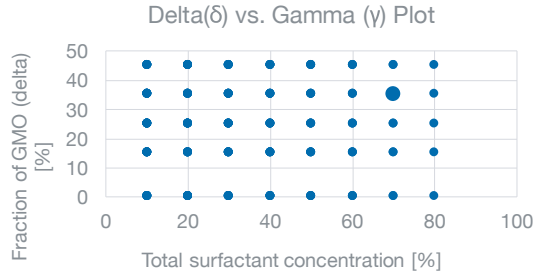

Figure 2: Surfactant concentration and composition experimental design plot

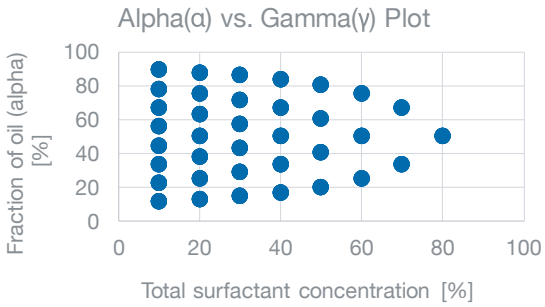

Figure 3: Surfactant concentration and oil phase fraction experimental design plot

Phase Volume ratio is the ratio of oil to the formulation, defined as:

$$\alpha = \frac{m\,(oil)}{m\,(water) + m\,(oil)}$$

Surfactant mixture ratio was defined as:

$$\delta = \frac{m\,(cosurfactanct)}{m\,(surfactant) + m\,(cosurfactant)}$$

Finally, the surfactant overall concentration was defined as:

$$\gamma = \frac{m\,(surfactant) + m\,(cosurfactant)}{m\,(all)}$$

Surfactant mixtures blocks were defined by Table 1:

Block	Delta	Surf. Fract. [%]		HLB
		RH 40	GMO	
1	0.0	100	0	15
2	0.15	85	15	13.3
3	0.25	75	25	12.2
4	0.35	65	35	11.1
5	0.45	55	45	9.96

Table 1: Surfactant mixtures utilized for optimal microemulsion discovery

All results were then subsequently plotted on tertiary phase diagrams. Successful microemulsion formulations, noted as isotropic with optical clarity, single phase, and low viscosity were noted and subsequently evaluated for consistency and stability; these are labeled green in the subsequent charts. Samples that retained stability after homogenization are labeled as blue, and while stable are not considered true bi-continuous microemulsions. Samples which were demonstrably unstable are labeled red.

Microemulsion formulations were dispersed in either 0.08 M HCl buffer or 6.8 pH Phosphate buffer to test for dispersibility and use as a SEDDS formulation. Droplet sizes were tested using dynamic light scattering (Malvern Zetasizer). Drug concentrations were determined via HPLC using two model compounds, Danazol and Nifedipin.

Results and Discussion

True microemulsions are formed when exact concentrations of water, oil, surfactant and co-surfactant are utilized within a given temperature range. These stable zones are typically described utilizing a classic "Fish Tail" diagram, shown in Figure 4.

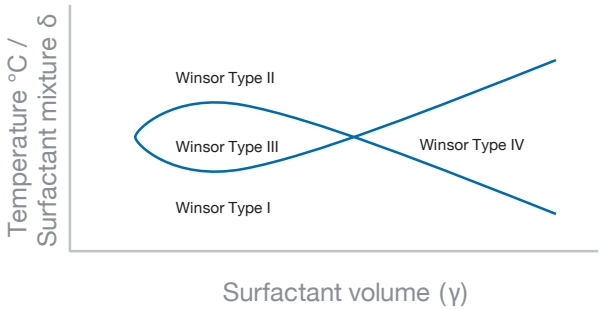

Figure 4: Fish tail diagram for microemulsion phases space

On the x-axis, the surfactant volume is shown, as with very high present surface area in a bi-continuous system, complementary high levels of surfactants are required. The y-axis can be plotted either as temperature or as the surfactant mixture; in this work, temperature remained constant and the surfactant mixture was varied. Winsor Type IV formulations are the target, where appropriate quantities of surfactant, oil, and aqueous phase form a bi-continuous, isotropic and low viscosity microemulsion. Once formed, they will remain thermodynamically stable unlike traditional O/W or W/O emulsions which coallesse over time. As described, five tertiary systems were constructed by varying concentrations of oil, water, surfactant, as well as surfactant blend. Blend concentrations are depicted in the five diagram blocks, the first, which did not contain a co-surfactant is shown in Figure 5.

Color code:
Unstable systems
Stable multiphase systems
Microemulsions

Homogeneous solutions available post shear

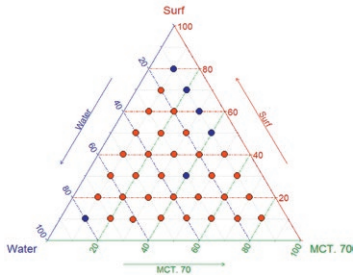

Figure 5: Block I tertiary phase diagram – surfactant ratio RH 40:GMO as 100:0

The use of a co-surfactant was clearly needed in order to create true microemulsions. It is important to note that the region in the upper right corner, where large concentrations of Oil and Surfactant are present with 10% water were stable post-homogenization. Utilizing a surfactant ratio of 85:15, RH 40 to GMO, a theoretical HLB blend of 13.3, is shown in Figure 6.

Color code:
Unstable systems
Stable multiphase systems
Microemulsions

Clear isotropic microemulsions were successfully produced with:
(10% W, 40-80% S, Balance O)

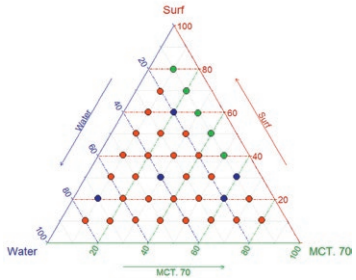

Figure 6: Block II tertiary phase diagram – surfactant ratio RH 40:GMO as 85:15

In Block II, it is clear that the upper right region with 10% water and varied ratios of oil and surfactant was able to successfully produce microemulsions. These, labeled in green vary by a surfactant ratio of 40 to 80% w/w. By increasing the level of co-surfactant to 75:25, reducing the HLB to 12.2, the next diagram was produced as Block III, shown in Figure 7.

Color code:
Unstable systems
Stable multiphase systems
Microemulsions

Broader range of homogeneous formulations are available with shear input

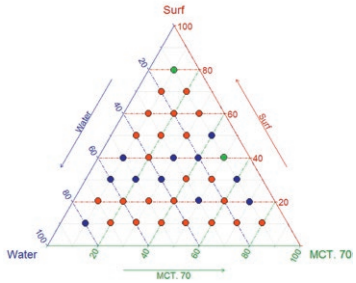

Figure 7: Block III tertiary phase diagram – surfactant ratio RH 40:GMO as 75:25

What is clear from Block III, as well as Block IV and V which are not shown for brevity is that higher levels of co-surfactant were not necessary and also reduced the microemulsion region on the diagram. In Block III, only two points labeled F and G were microemulsions, while between them clear phase separation was evident. Consequently, only Block II, with the 85:15 surfactant ratio was utilized for subsequent testing.

It is important to note the droplet distribution once in contact with the body or aqueous testing media. True microemulsions once in contact with extraneous water will shift to an O/W emulsion with fine oil droplets rapidly dispersed. An example of the previously depicted formulations is shown in Figure 8, where oil droplet particle size distribution was tested by dynamic light scattering in acidic stomach conditions (HCl buffer, 0.08 M) and intestinal conditions (pH 6.8 Phosphate Buffer).

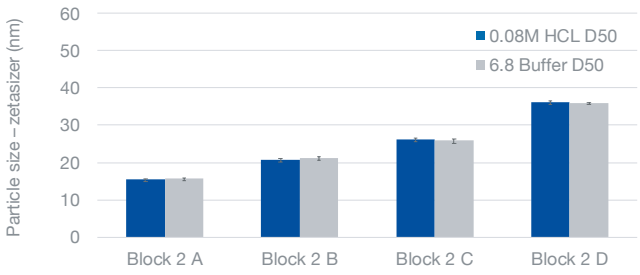

Figure 8: D_{50} oil droplet size post dispersion of microemulsions in acidic or phosphate buffer

The droplet sizes for D_{50} are notably small, with ranges from 15 to 35 nm at the D_{50} level. It is important to note that the distributions were relatively monodisperse, with D_{10} ranging from 10 to 20 nm and D_{90} from 20 to 60 nm, respective to A through D. What is also clear is that there was no effect of pH, which is due to the use of non-ionic surfactants. In a real formulation, these nanoscale oil droplets would be rapidly digested allowing for absorption of the poorly soluble API. In this range, it is clear that higher oil concentrations result in larger droplet sizes, where formulation D with 40% MCT oil has roughly double the median droplet sizes as formulation A with only 10% oil. On the other hand, higher surfactant concentrations allow for higher drug loading; this is shown in Figure 9, where common poorly water soluble drugs Danazol and Nifedipin are shown at stable drug loading concentrations.

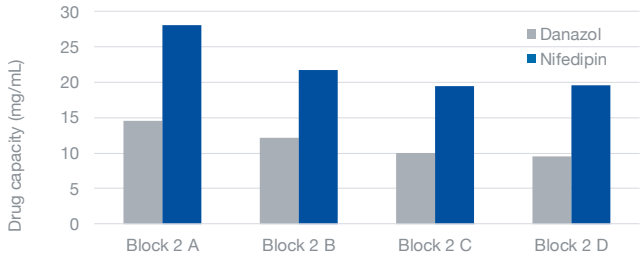

Figure 9: Drug capacity as a function of formulation for representative poorly soluble drugs Danazol and Nifedipin

It is important to note that drug loading did not have a significant effect on droplet size distribution, one such example is shown in Figure 10 for Nifedipin under stomach conditions.

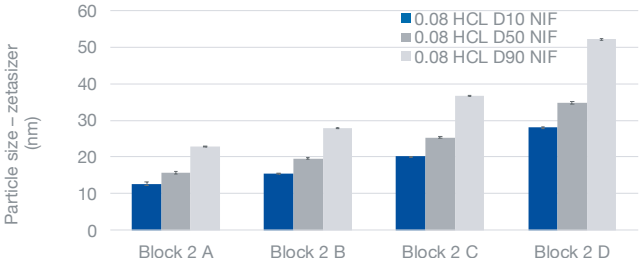

Figure 10: Example oil droplet size distribution for formulations saturated with representative poorly soluble drug Nifedipin

Conclusion

- SEDDS formulations start with a true microemulsion, which is challenging and manually cumbersome to identify; this challenge was addressed utilizing a high throughput robotic system in order to effectively identify regions of stable microemulsions to be used in SEDDS.
- It is important to utilize a cosurfactant and subsequently at the right ratio in order to create the most robust space for microemulsions in an oil-water-surfactant system.
- Produced microemulsions self-emulsify as SEDDS systems once dispersed into aqueous or biorelevant media into nanometer scale oil droplets.
- Oil droplet size was not affected by system pH due to the exclusive use of non-ionic surfactants.
- Larger droplets are evident with larger oil ratios in the SEDDS formulation, while higher drug loading is possible with larger surfactant ratios.
- This work will be used to further study the produced SEDDS formulations in mechanistic testing.

Solubilization

Poorly soluble drugs are one of the major challenges pharmaceutical manufacturers are facing. BASF offers a wide range of highly effective solubilization excipients, and has an unparalleled understanding of the corresponding process technologies. This makes us the leading partner in resolving bioavailability and solubility challenges by unlocking the full potential of your API.

This unique combination enables you to achieve effective solubilization and bioavailability in various dosage forms – from solid dispersions to lipid-based drug delivery systems. Moreover, we are a highly successful pioneer in the application of hot-melt extrusion technology in pharmaceutical production – helping you to achieve effectiveness.

Our service offer

We are providing in-depth expertise in all steps of the production of solid and liquid oral dosage forms.
The combination of our broad portfolio of functional excipients and our expert know-how enables you to create value-adding and unique formulations.

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