Deep Eutectic Solvents as Formulation Technology

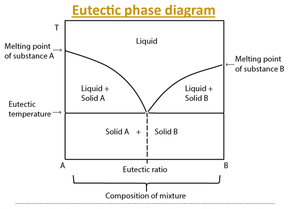
Increasing oral bioavailability

The majority of APIs in development have properties that cause significant issues when creating a formulation for oral administration: a **high melting point** and/or **low solubility**. A high melting point makes it impossible to use hot melt extrusion to create a solid dispersion, while a low solubility in appropriate solvents makes a variety of formulation techniques difficult and costly to use, such as spray drying or emulsification. SeraNovo has devised a novel formulation technology, opening up the way to the market for these notorious APIs. This factsheet explains the concept of our technology and our approach to increasing oral bioavailability.

Eutectic mixtures

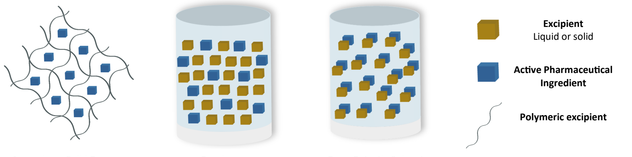
A mixture of two or more solid components exerting a melting point that is lower than each of the two constituents is called a eutectic mixture. Effectively one component prevents the other from crystallizing, keeping the mixture a liquid. This effect usually arises from specific hydrogen bonding between the two entities, causing a specific molar ratio to be optimal for the eutectic composition (see figure on the right for a eutectic phase diagram). These interactions can be so effective that certain "Brick Dust APIs" with melting points >300°C can be a liquid at room temperature with beneficial characteristics such as a low volatility and a high loading capacity. As the interactions between the two components mainly consist of hydrogen bonds, they are broken up easily when the mixture is exposed to water leading to a fast dissolution of the formulation in the stomach. The picture below shows a schematic representation in comparison with well-known systems.

Eutectic phase diagram



The eutectic phase diagram shows the melting point depression of two substances when mixed, A and B, reaching a minimum at a specific molar ratio called the Eutectic ratio. At ratios deviating from the eutectic ratio and below the melting temperature parts will remain solid.

Schematic representation of three formulation technologies



Amorphous Solid Dispersion
API dispersed in a polymer matrix

Cosolvency
API dissolved in solvent

Deep Eutectic Solvent
API *is* the solvent

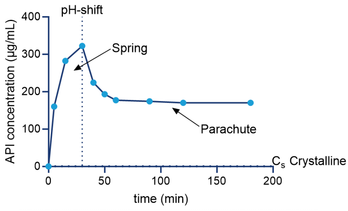
Approved Excipients

The eutectic mixture is created by using a variety of non-toxic and safe constituents which are either pharmaceutically acceptable or GRAS (Generally Recognized As Safe by the FDA). SeraNovo has a library of hundreds of constituents that satisfy safety criteria and can make endless unique combinations, optimised to fit your API perfectly in terms of performance and stability. Our library includes many types of solid and liquid excipients, such as polymers, sugars, organic acids, nutritional compounds, metabolites and food additives.

Spring and Parachute

An API has a high melting point when it is energetically favoured to maintain its crystal lattice. A lot of energy is required to break the crystal lattice, thus leading to a very slow dissolution when such a crystal is exposed to gastric fluids. However, in a eutectic mixture this crystal lattice has already been broken apart. So, when the eutectic mixture encounters gastric fluids, the water molecules quickly disintegrate the hydrogen bond network of the eutectic mixture. This causes a very rapid dissolution, usually far above the equilibrium solubility. This is called the "Spring". The API is now in solution far above its equilibrium solubility, prone to recrystallization. This is where polymeric constituents play their part: they prevent fast recrystallization of the API in intestinal fluids. This is called the "Parachute". The Parachute ensures a high concentration is maintained in the absorptive environment of the intestines. The dissolution graph on the right shows this mechanism using one of our formulations of a very poorly soluble, basic API.

pH-shift Dissolution Graph



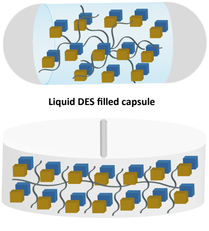
Shown is the concentration over time profile of a poorly soluble, basic API in a dissolution test, with a pH-shift at t=30 minutes which also includes a 2x dilution. The theoretical maximum concentrations are noted with the dotted lines on the right with the corresponding pH value.

Two variants, Liquid DES and Glass DES

SeraNovo's proprietary platform technology provides you with the option of a liquid formulation, a solid formulation (also called a "Glass") or both. The Glass formulations are dehydrated eutectic mixtures, liquifying upon contact with water. This provides enhanced stability as well as a higher drug load whilst keeping the production costs low in relation to conventional solid formulation production costs (e.g. spray drying). The table below highlights the various advantages compared to a conventional formulation technology, the Amorphous Solid Dispersion. The figure shows a schematic representation of what two finished DES dosage forms could look like.

	Physical Stability	Production cost	API Loading capacity	Capsule compatibility	Bioavailability	API compatibility
Deep Eutectic Solvent Technology	●	$$$$$	≤ 400 mg per size 00 capsule	Hard Gelatin Soft Gelatin HPMC	●	Broadly applicable
Amorphous Solid Dispersion	◐	$$$$$	≤ 400 mg per size 00 capsule	Hard Gelatin HPMC	◐	Unsuitable for high melting point, insoluble APIs

Finished dosage form



Liquid DES filled capsule

Glass DES tablet

Schematic representation of what the finished dosage form of a Liquid DES formulation and a Glass DES tablet could look like.

Frequently Asked Questions:

Q: What are the major benefits of SeraNovo's technology compared to competing technology?
A: Significant bioavailability enhancement compared to competing technologies with simpler and cheaper production.
Q: What is the regulatory framework around these 'new solvents'? Does each new solvent have to be registered as a new excipient?
A: The solvent breaks up in contact with water, leaving a solution of the individual excipients which are already accepted by the FDA, no additional registration required.
Q: How do you scale up the formulations?
A: SeraNovo has designed its technology to be easily scalable, for example for a Liquid formulation the machine used is available in sizes ranging from 3 Litres to >10.000 Litres.
Q: Can the Glass formulations be pressed into tablets?
A: Yes, however capsules are recommended for early studies for dose versatility and time saving.
Q: Does SeraNovo have IP on this technology?
A: Yes, SeraNovo is the sole owner of several patents in various stages of application.
Q: What development timelines are expected?
A: Typical timelines for feasibility studies are 1-2 months and 2-3 months for formulation development. Timelines may vary depending on stability studies and any specific customer requirements.

Technology Advantages:

- Suitable for high melting point, low solubility APIs
- Superior bioavailability
- Simple production scale-up
- Short development time

Interested? Contact us!
info@seranovo.com

Contact

SeraNovo
Solving the Insoluble