Whitepaper

An Insoluble Problem? Overcoming Oral Drug Solubility Challenges With Functional Polymers

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Almost half of currently marketed drug products, and around 90 percent of those in clinical development are associated with poor drug solubility or permeability. This article is part one of a two-part series on solubility enhancement. Here we discuss the basics of solubility enhancement and the formulation and manufacture of products that enhance solubility. We also address common questions on the topic.

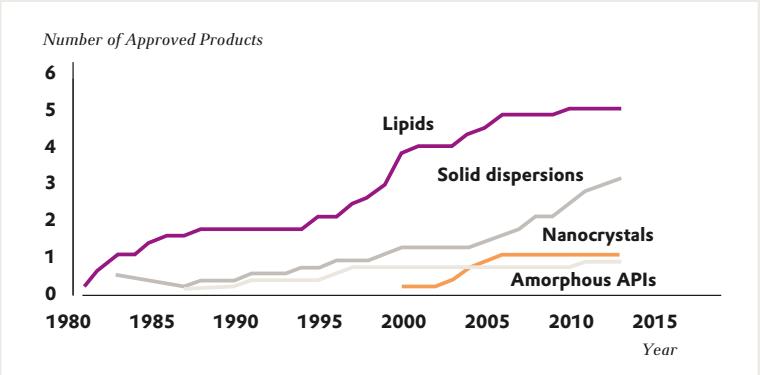
Introduction to solubility enhancement

The biopharmaceutical classification system classifies drugs according to their permeability and solubility. Drugs with poor solubility and/or permeability are class II or IV type drugs, and these require special formulation technologies for solubility enhancement. In the past 25 years the number of poorly water-soluble drug candidates has increased to the extent that as many as 70 – 80% of small molecule drug candidates may be classified as poorly water-soluble today.[1] Solubility enhancement technologies are therefore gaining increasing importance and are needed to unlock the potential of drug candidates and enable their release on the market.

When examining technologies used for solubility enhancement since the 1980s, lipids are the first choice for formulators.[2] However, the application of solid dispersions by polymeric carriers is growing rapidly due to their versatility and effectiveness with a variety of different APIs.

There are three key factors that need to be controlled when designing a drug product for solubility enhancement: the polymeric carrier; the manufacturing process; and the match to the desired API. By controlling these three factors bioavailability, drug release profile and manufacturability of your final drug product can be controlled.

Figure 1. Bioavailability enhancement – Analysis of the Historical Use of Solubilization Technologies, DDD 2014 Marshall Crew Agere Pharmaceuticals



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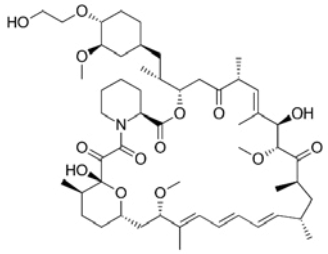
Lipinski's Rule of Five: Everolimus, Ivacaftor and Etravirine

When working on solubility enhancement, Lipinski's Rule of Five is an important guide. This rule says that if there are more than five H-bond donors in a drug molecule, or more than 10 H-bond acceptors, or if the molecular weight is larger than 500 Da, or the LogP is larger than five, then there is a higher chance of problematic solubility and bioavailability.[3]

Everolimus is a good example. When examining the parameters, we can see that the drug has 13 H-bond acceptors and a molecular weight of almost 1 kDa. This is a poorly soluble API that requires special techniques for solubility enhancement.[4]

Figure 2. Everolimus

Everolimus

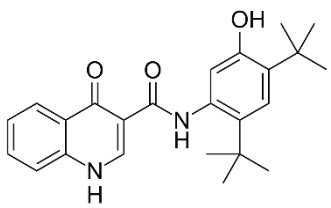


- 3 H-bond donors
- **13 H-bond acceptors**
- **Log P 5.0**
- **MW 958 g/mol**
- Solubility 0.0016 mg/ml
- T_m 80°C
- **Lipinsky Rule of Five**

But solubility and bioavailability of the drug is not everything. There are other parameters that need to be considered and controlled, such as manufacturability. Ivacaftor, for example, is also a poorly soluble drug that has a high melting point. This means it is important to choose a solvent-based manufacturing process like spray drying rather than a melt-based process.

Figure 3. Ivacaftor

Ivacaftor

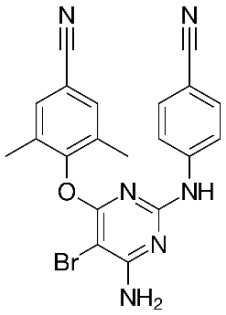


- 3 H-bond donors
- 4 H-bond acceptors
- Log P 5.0
- MW 392 g/mol
- Solubility 0.00005 mg/ml
- **T_m 292–295°C**
- **Technology solvent based**

A third example is Etravirine. This is also a poorly soluble drug with a relatively high melting point. At the same time, it also has a low glass transition temperature (T_g). This means there is a high tendency for the drug to recrystallize in the polymer matrix, which limits the stability of the product. The drug loading must not be too high to prevent recrystallization and lead to limited storage stability.

Figure 4. Etravirine

Etravirine

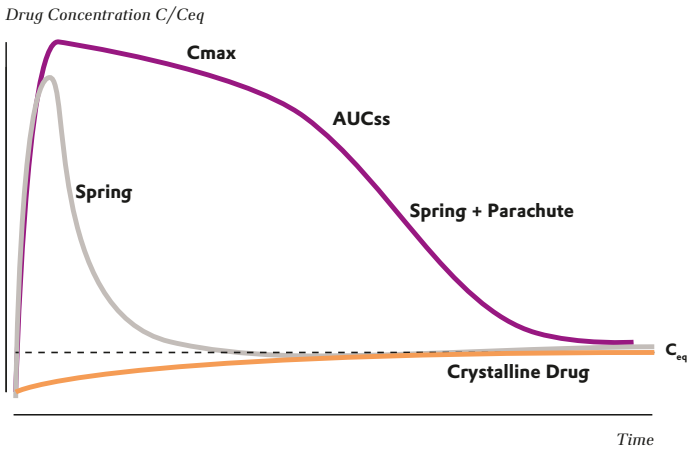


- 2 H-bond donors
- 6 H-bond acceptors
- Log P 3.7
- MW 435 g/mol
- Solubility 0.0169 mg/ml
- **Fragility T_m/T_g high**
- **Drug propensity to crystallize may limit drug loading (10–35 % w/w)**

Maximizing the benefits of amorphous solid dispersions (ASDs)

In an amorphous solid dispersion (ASD) an API molecule is dispersed in a polymer matrix. The system contains stored potential energy– which can be compared to that of a compressed spring. When the ASD is immersed into media, the energy is released, and the drug and the polymeric carrier are dissolved quickly to a supersaturated solution. This model is commonly referred to as a "spring and parachute".

Figure 5. The spring and parachute model[5]



At this point the drug must be stabilized and kept in solution for long enough to allow it to be absorbed by the body. The polymer in solution can stabilize the drug to prevent it from recrystallization. Polymers that can stabilize are suitable for solubility enhancement. These include polymethacrylates, cellulose derivatives like HPMC and HPMCAS, vinyl copolymers like PVA and PVP/VA64, and a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. The focus of this article is on polymethacrylate polymers.

The polymeric carriers

There are some general rules and parameters that should be considered when choosing the right carrier for a formulation. The most important parameter is the solubility of the API in the polymeric carrier. This will determine the loading capacity. Another important parameter is the molecular weight of the polymer.

In general, a higher molecular weight (M_w) is beneficial for solubility enhancement. This will allow better stabilization of the drug and of the drug molecules in the matrix. In supersaturated solutions a higher molecular weight prevents recrystallization, and the molecular weight also affects glass transition temperature (T_g) and melt viscosity. The latter two parameters typically increase with increasing molecular weight.

A higher T_g is beneficial for storage stability to prevent recrystallization in the final drug product. The heat capacity is also an important parameter because it's very important for thermal processing of the polymer by hot-melt extrusion. There are further processing parameters that must be considered for manufacture of a drug product. These include hygroscopicity and mechanical properties such as compressibility. These are properties that need to be kept in mind when choosing the right polymeric carrier for a formulation.

The use of EUDRAGIT® poly(meth)acrylate polymers for solubility enhancement

The polymers listed in Table 1 are particularly suitable for solubility enhancement. All these polymers are manufactured in a controlled manner by free radical polymerization, which enables narrow specification windows and low batch-to-batch variability. The polymers are monographed in relevant pharmacopeia in different regions.

Table 1. EUDRAGIT® Poly(meth)acrylate polymers most suitable for solubility enhancement

Polymer	Physical properties	Chemical/ IUPAC name	Ph.Eur.	USP/NF	JPE	M_w (g/mol)	T_g (°C)
EUDRAGIT® E 100	granules	Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1	Basic Butylated Methacrylate Copolymer	polymer conforms to Amino Methacrylate Copolymer - NF	Aminoalkyl Methacrylate Copolymer E	~ 47 000	45
EUDRAGIT® E PO	powder	Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1	Basic Butylated Methacrylate Copolymer	polymer conforms to Amino Methacrylate Copolymer - NF	Aminoalkyl Methacrylate Copolymer E	~ 47 000	45
EUDRAGIT® L 100-55	powder	Poly(methacrylic acid-co-ethyl acrylate) 1:1	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Type A	Methacrylic Acid Copolymer, Type C - NF	Dried Methacrylic Acid Copolymer LD	~ 320 000	70~96*
EUDRAGIT® L 100	powder	Poly(methacrylic acid-co-methyl methacrylate) 1:1	Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	Methacrylic Acid Copolymer, Type A - NF	Methacrylic Acid Copolymer L	~ 125 000	>130
EUDRAGIT® FS 100	powder	Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1	-	-	-	~ 280 000	43

* T_g was determined using different DSC methods

The two products we would like to focus on in this article are EUDRAGIT® E and EUDRAGIT® L because they are particularly suitable for solubility enhancement.

EUDRAGIT® E – a cationic polymer

This product is a copolymer of dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. The polymer is soluble in gastric juices up to pH 5 and swells beyond pH 5. Historically, the polymer has mainly been used for immediate release applications, as a protective coating, for moisture protection or taste masking. EUDRAGIT® E is also a matrix former and a potent carrier for solubility enhancement, especially because of the ability to interact with a wide range of different APIs.

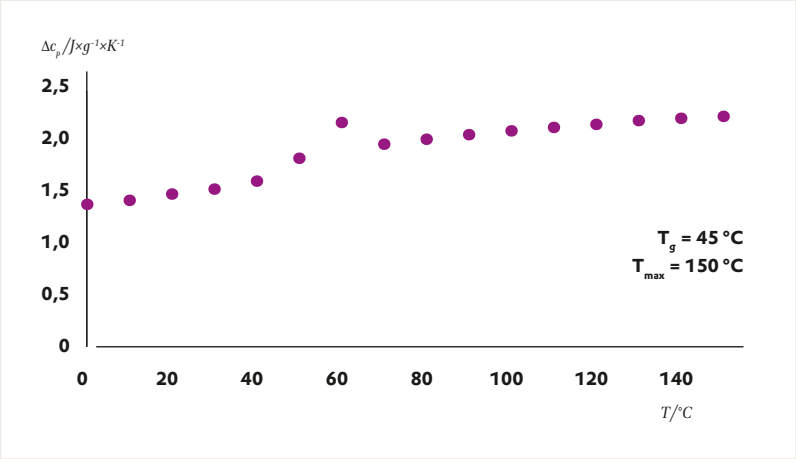
The amino functionality of EUDRAGIT® E is protonated under physiological conditions. The cationic charge can interact with anionic functionalities in the drug molecules, for example, with carboxylic acids. At the same time, the amine also acts as an electron donor, which enables interaction with electron acceptor functional groups, like aromatic functionalities, in the API. Hydrophobic interactions are also possible.

The amine and the hydrophilic and hydrophobic functionalities of the polymer enable micelle formation, which prevents the drug from recrystallization in the supersaturated solution. This contributes to the parachute mechanism that keeps the API dissolved long enough for being absorbed by the body.

Thermal processing of EUDRAGIT® E

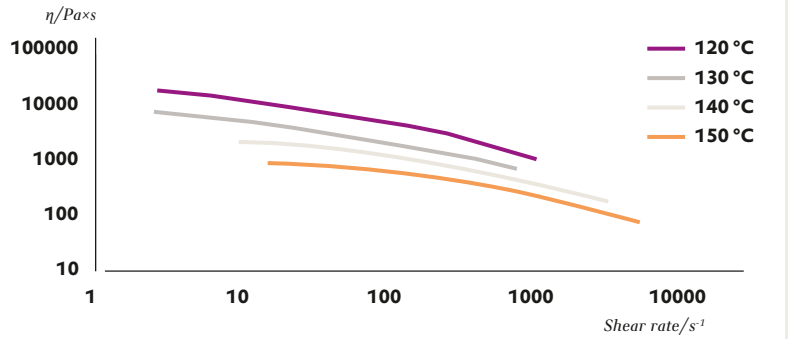
Figure 6 shows the heat capacity of EUDRAGIT® E as a function of temperature, which is a key thermal characteristic of the polymer. Heat capacity increases with increasing temperature, and a spike beyond T_g indicates increase of flexibility of the polymer. The polymer can be processed beyond that temperature. The degradation temperature is 150 °C, so the operation window for thermally processing EUDRAGIT® E is set.

Figure 6. Specific heat capacities of EUDRAGIT® E (determined by DSC)



Viscosity of EUDRAGIT® E

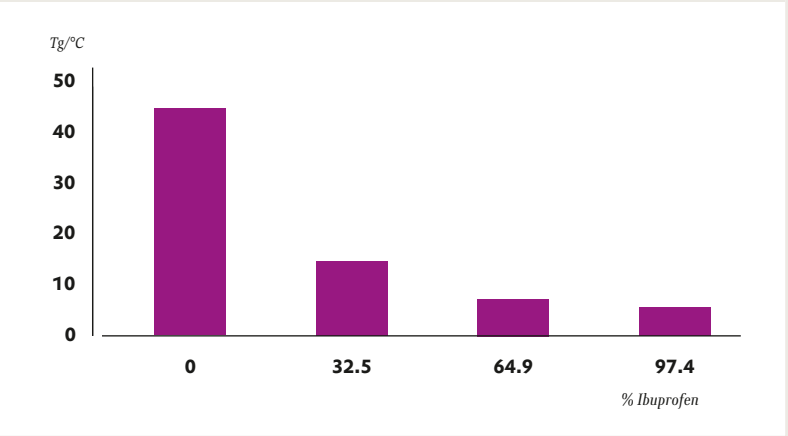
Figure 7. Viscosity of EUDRAGIT® E as function of shear rate at different temperatures (determined by high pressure capillary rheometer)



In figure 7 the viscosity of EUDRAGIT® E is shown as a function of shear rate. The viscosity decreases with increase of shear rate and temperature. This data is helpful for finding the right operational conditions in an extruder.

The interaction of different ingredients in the formulations must also be considered. Ibuprofen, for example, is a very strong plasticizer for EUDRAGIT® E. Figure 8 shows that T_g decreases with increasing concentration of ibuprofen.

Figure 8. T_g of EUDRAGIT® E 100-ibuprofen mixtures (determined by DSC)



EUDRAGIT® L – anionic polymers

Historically, EUDRAGIT® L products have been used for enteric coatings and extended-release matrix formulations. There are two types of EUDRAGIT® L: L 100 and L 100-55. EUDRAGIT® L 100 starts to dissolve beyond pH 6 and EUDRAGIT® L 100-55 starts to dissolve beyond pH 5.5.

Both EUDRAGIT® L types are effective carriers for solubility enhancement for a broad range of different APIs. One reason for this is the interaction of the carboxylic acid functional groups with functional groups of drug molecules. EUDRAGIT® L polymers exhibit relatively high T_g values. High T_g values reduce the mobility of API molecules in the polymer matrix and prevent recrystallization, thereby increasing storage stability of the final drug product. EUDRAGIT® polymers are very versatile: they can be used in spray drying, hot-melt extrusion and top-spray granulation.

Thermal processing of EUDRAGIT® L

Figure 9 shows the thermal heat capacity of EUDRAGIT® L 100 as a function of temperature. The T_g for EUDRAGIT® L 100 is beyond 130 °C and degradation starts in the same temperature range. This leads to a limited operation window for processing. Typically, a plasticizer is needed.

Figure 9. Specific heat capacity of EUDRAGIT® L 100 as a function of temperature (determined by DSC)

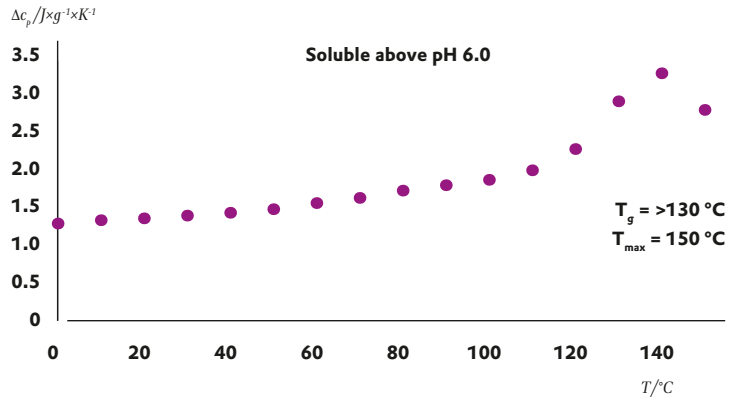


Figure 10 shows the heat capacity of EUDRAGIT® L 100-55 as a function of temperature. T_g of EUDRAGIT® L 100-55 is 70–96 °C (depending on DSC technique used). The maximum processing temperature is 140 °C.

For both types of EUDRAGIT® L pharmaceutically accepted plasticizers like triethyl citrate (TEC) can be used. Figure 11 shows the T_g as a function of plasticizer concentration.

Figure 10. Specific heat capacities of EUDRAGIT® L 100-55 as function of temperature (determined by DSC)

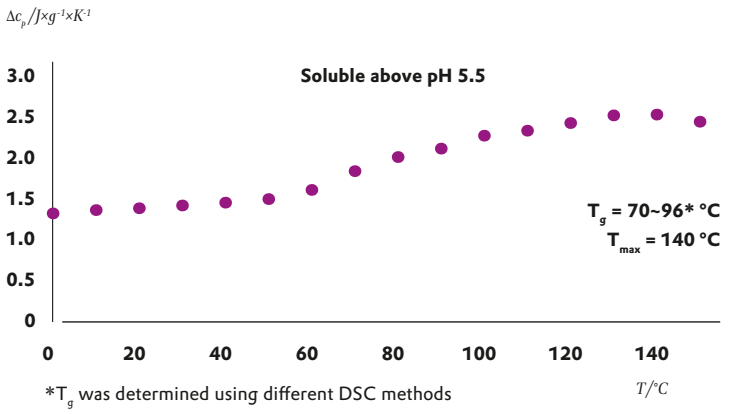


Figure 11. T_g of EUDRAGIT® L 100 and L 100-55 as a function of plasticizer concentration (determined by DSC)

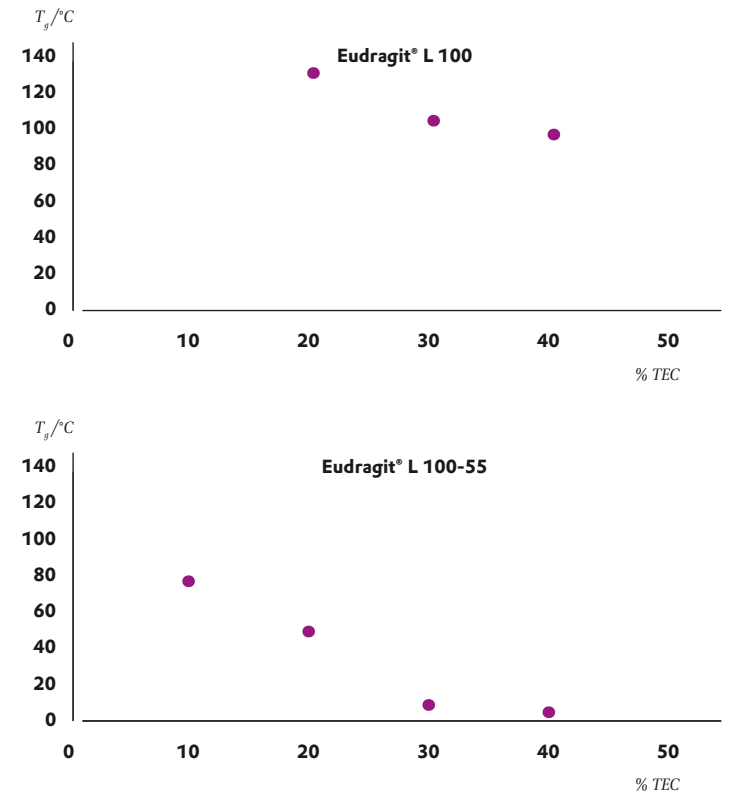


Figure 12. Viscosity of EUDRAGIT® L 100-55 at 150 °C with different plasticizer concentrations (determined by high pressure capillary rheometer)

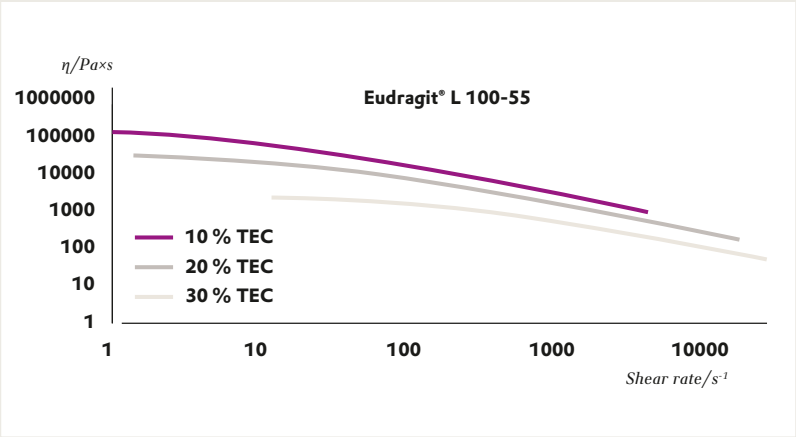


Figure 12 shows the progression of viscosity of EUDRAGIT® L 100-55 as a function of shear rate. Data was obtained at constant temperature of 150 °C using three different plasticizer concentrations. The viscosity can be controlled by adjusting plasticizer concentration and temperature.

CONCLUSION

The EUDRAGIT® polymers presented in this article are effective carriers for solubility enhancement. These thermoplastic polymers are suitable for different manufacturing techniques including hot melt extrusion. The polymers show good processability during hot melt extrusion at moderate torque. Evonik experts are more than happy to support with technical information for finding the right processing parameters.

Over the past two decades, Evonik has worked with customers to help choose the right polymer excipient, process technology and formulation solutions to overcome poor solubility of APIs. Find out more about Evonik's drug delivery solutions including specific product documentation on our platform onCare

For more information and project enquiries, contact us at healthcare@evonik.com

ABOUT THE AUTHOR

Dr Thomas Endres is an expert in polymeric excipients for oral and parenteral dosage forms and has extensive experience in the management of innovation and customer projects. Thomas studied macromolecular chemistry at the University of Marburg in Germany before completing his doctoral research at the Institute of Pharmaceutical Technology in Marburg. Thomas joined Evonik in 2012 and has held different roles in R&D in Germany, and as manager for biomaterials in the U.S.

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