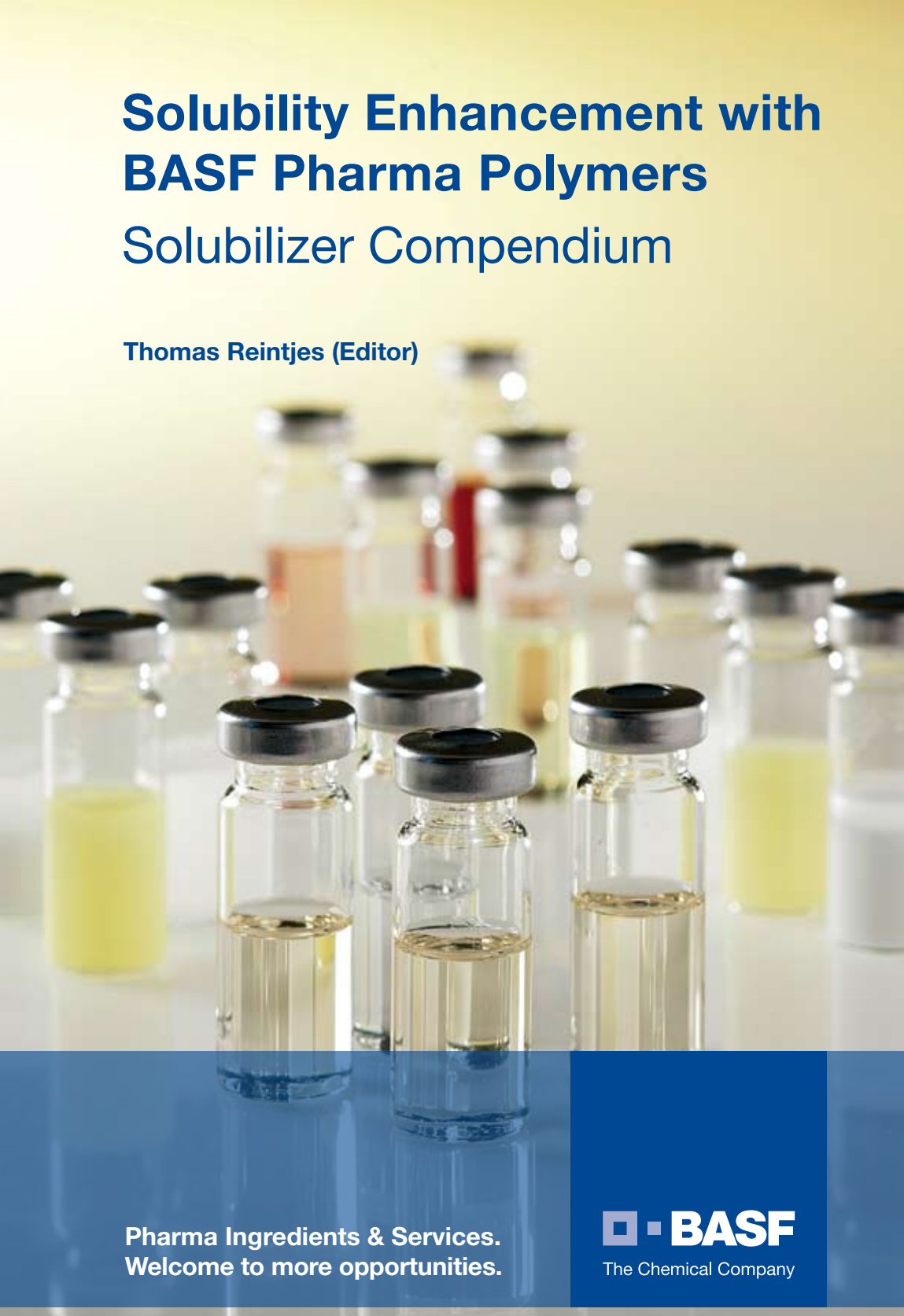
Solubility Enhancement with BASF Pharma Polymers

Solubilizer Compendium

Thomas Reintjes (Editor)



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October 2011
Thomas Reintjes (Editor)

Sebastian Koltzenburg

1 Formulation of problem drugs – and they are all problem drugs

1.1 Introduction

About 90 % of all compounds in today's pharmaceutical drug delivery pipelines are reported to be poorly soluble in water [1]. This poses enormous problems for the industry; for an active pharmaceutical ingredient cannot reach its molecular target in the body if the drug remains undissolved in the gastrointestinal tract (GIT) and is eventually excreted. The message is simple: drugs that don't dissolve will not heal you. Therefore, poor solubility is a critical factor if the molecule is to survive the pharmaceutical development process. Even those molecules that would have a highly beneficial effect on their physiological target would not be further developed if their bioavailability is limited by their solubility in water. Thus, solubilization technologies that overcome this issue by increasing the solubility of such drug candidates are becoming more and more important to the pharmaceutical industry by opening up pathways to prepare effective and marketable drugs from actives that would otherwise be useless. This chapter will explain the thermodynamics behind the problem of poor solubility and depict approaches to overcome it.

Since poor solubility and issues related to this are not specific to pharmaceuticals, this chapter will follow an out-of-the box approach and show where solutions established in other applications can help us overcome solubility problems in medicinal applications.

1.1.1 Classification of poorly soluble drugs: The Biopharmaceutical Classification System (BCS)

From a very rough perspective, drug candidates can suffer from two main problems (apart from an almost infinite number of further problems when it comes to details): solubility and permeability. These represent the basis used to classify drug candidates into four fundamental classes, a methodology known as the Biopharmaceutical Classification System (BCS), introduced by Amidon et al. [2]. Figure 1.1 illustrates this classification, complemented by an assessment of the percentage of new drug candidates in the four classes:

- **Class I:** In this class, we find drugs (or rather: drug candidates) with both high solubility and high permeability. They dissolve fast and quantitatively and are readily taken up by the intestine, eventually reaching their target in the body.
- **Class II:** These are drugs which would easily penetrate the relevant physiological barriers but suffer from poor solubility in the aqueous body fluids. Their share

of the modern drug delivery pipeline is continuously growing.

- **Class III:** Such actives are soluble in the GIT, but they are not taken up by the body. Like class II actives, they risk being excreted without exercising any physiological effect.
- **Class IV:** This is the nightmare for the medicinal chemist: drugs that neither dissolve nor penetrate physiological barriers.

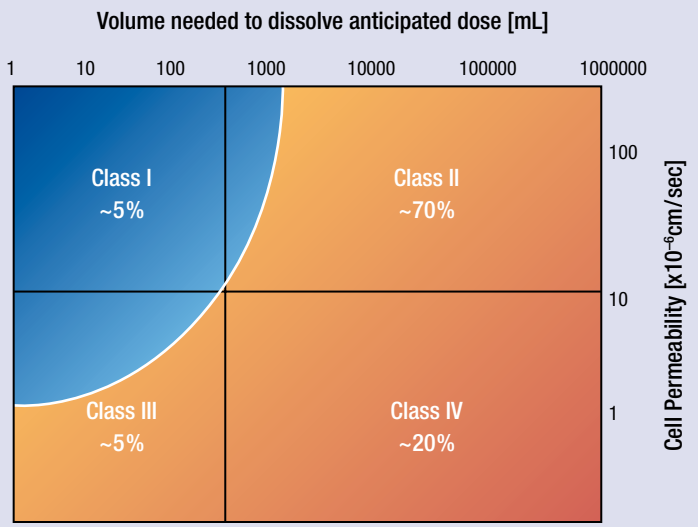

Figure 1.1 ▪ The Biopharmaceutical classification system and percentage of new chemical entities in the individual classes [1,2]; for further explanations see text.

All these drugs pose particular problems in the development cycle. Class I drugs do not normally have bioavailability problems (unless other problems such as fast metabolism or the like occur). However, in some cases, their pharmacokinetics can be compared to a military airplane: they appear extremely fast out of nowhere, and they disappear just as quickly. In other words: we observe a very fast increase in blood plasma levels, although, from a pharmacokinetic perspective, sometimes a slower but longer lasting action would be desirable. In such cases, one option is to work with a polymer-based formulation that deliberately retards drug dissolution and thus drives the kinetics in the direction of a slow release system.

Actives in class II represent the majority of new chemical entities in pharmaceutical development pipelines. However, if it proves possible to increase their solubility in the GIT, they can be formulated into marketable products. This book aims to give an overview of the tools that are currently available for this purpose. Class III drugs represent a real challenge. In the scientific literature, there are continuous discussions

about the use of penetration enhancers, and there are definitely mechanisms that increase the permeation of molecules through the gastrointestinal wall. However, the intestine is usually full of substances that the body does not want to penetrate into the portal vein – for good reasons – and unselective enhancement of penetration of this fundamental membrane implies the risk of significant side effects.

Class IV actives are usually outside of what is called the "drugable space". This space is indicated by the green line in Fig. 1.1. They combine the problems of class II and class III drugs, and often the best way to get out of such a situation is to send the candidate back to the pharmaceutical chemist and ask for chemical alternatives. If there are reasons to believe that this active will have an excellent performance at the target, e.g. based on in-silico modeling, prodrugs with enhanced dissolution and permeability that will be converted into active agents under physiological conditions are certainly an option to consider.

As mentioned above, class II actives represent the largest class of substances in today's drug delivery pipelines. In some cases, this is due to a large portion of hydrophobic moieties in the molecules. Evidently, molecules that consist of carbon and hydrogen only will be so non-polar that miscibility with water will be extremely low. Let us take a well-known example from the vitamin family, β-carotene (Fig. 1.2), to show that such effects are not specific to active pharmaceutical ingredients. This hydrocarbon has a water solubility clearly below 1 mg/L. Oral administration of crystalline β-carotene will not result in effective drug levels in the blood plasma. Such molecules can have quite significant solubility in hydrophobic solvents and are sometimes referred to as "grease balls".

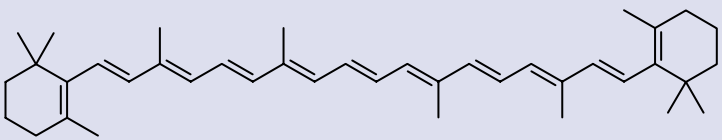

Figure 1.2 ▪ Chemical structure of β-carotene as an example of a very hydrophobic, poorly water-soluble molecule.

However, in some cases we can also observe poor water solubility with molecules that are composed of quite a significant number of polar moieties, such as itraconazole (Fig. 1.3). Such molecules usually have a high molar mass and dissolve neither in aqueous nor in non-polar solvents. To understand the reason behind this behavior, let us briefly consider the thermodynamics of the matter.

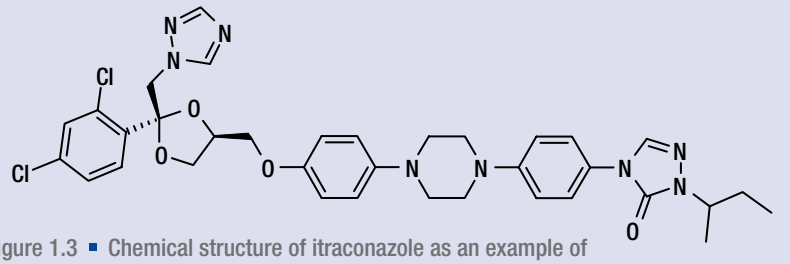

Figure 1.3 ▪ Chemical structure of itraconazole as an example of a polar but nevertheless poorly soluble molecule.

1.1.2 Poorly soluble drugs: The thermodynamics behind the problem

Without wanting to go too deeply into theory, let us consider the thermodynamic driving force behind dissolution processes. This driving force, characterized by Gibbs free energy ΔG, is composed of two fundamental contributions, enthalpy ΔH and entropy ΔS, according to equation 1.1, known as the Gibbs-Helmholtz equation.

$$\Delta G = \Delta H - T \cdot \Delta S \tag{1.1}$$

When two substances of equal molecular size (i. e. molecular volume) are mixed in a so-called regular mixture, this driving force is represented by

$$\Delta G = \underbrace{\varphi_1 \ln\varphi_1 + \varphi_2 \ln\varphi_2}_{\text{entropy term}} + \underbrace{\varphi_1 \cdot \varphi_2 \cdot \chi}_{\text{enthalpy term}} \tag{1.2}$$

where

φ_i = the volume fraction of component i (i. e. the volume of component i relative to the total volume). Index 1 refers to the solvent, index 2 to the solute.

χ = the interaction parameter between the two substances (see text).

The interaction parameter χ quantifies the interaction between the two compounds in the mixture. The larger (i. e. more positive) this parameter is, the higher (more positive) is the interaction enthalpy of the two compounds. Please recall that a positive enthalpy is indicative of an endothermal process that consumes heat (rather than releasing it), so this is an enthalpically unfavorable process. Many mixing processes are endothermal unless there are specific interactions between the components constituting the mixture, such as acid-base interactions.

If you look at the entropy contribution to the total Gibbs free energy in equation 1.2, it becomes clear that this term is always positive (since volume fractions in mixtures are always smaller than unity, the logarithm is negative, which compensates for the minus preceding the terms. Positive ΔS values characterize processes that are entropically favorable.

From these simple considerations, it becomes clear that entropy **always** favors mixing[1], whereas a typically positive mixing enthalpy often counteracts it. For a typical "grease ball", it becomes clear immediately that the interaction of a pure hydrocarbon with water is enthalpically so unfavorable that its contribution to the overall Gibbs free energy over-compensates for the favorable mixing entropy. As a result, "grease balls" are water-insoluble.

However, what is the problem with molecules such as itraconazole? The molecule comprises a significant number of polar rings that could interact quite well with water. To understand this, we must consider the molar volume of the compounds, which correlates (to a first approximation) to its molar mass. Please remember that equation (1.2) is valid only if the size of the solvent molecules matches that of the solute. If the molar volume of the compound to be dissolved exceeds the molar volume of the solvent, equation (1.2) needs to be modified and becomes

$$\Delta G = \underbrace{\varphi_1 \ln\varphi_1 + \frac{\varphi_2}{X_n} \ln\varphi_2}_{\text{entropy term}} + \underbrace{\varphi_1 \cdot \varphi_2 \cdot \chi}_{\text{enthalpy term}} \qquad (1.3)$$

X_n in this equation is the ratio of the two molar volumes (≥ 1).

As can be clearly seen in equation 1.3, this additional factor has a large impact on the mixing entropy. Since X_n is always greater than (or equal to) unity, the favorable mixing entropy is reduced in such cases, and, consequently, the mixing process is energetically less favorable. A favorable mixing entropy is easier to compensate for by the usually unfavorable mixing enthalpy.

This is a very typical situation encountered when working with large active ingredients in contact with water. Please note that the water molecule is one of the smallest molecules of all – it is basically **one** oxygen atom with ears – so this effect is particularly pronounced for aqueous solutions of large molecules.

Due to the high throughput of today's drug development pipelines, more and more complex molecules can be screened and identified as potential new drug candidates. Therefore, the number of high molar mass candidates is increasing steadily, thus increasing the proportion of class II actives. The three relatively simple thermodynamic equations thus explain why poor solubility is also a constantly increasing challenge to the pharmaceutical industry of the third millennium.

1.2 Approaches to overcome this issue

So, what can we do to solve this problem? From the formulation point of view, there are three main approaches:

- Surfactants
- Complex formation
- Nanotechnology.

[1] There are exceptions. But let's keep this simple.

The individual approaches differ in their applicability to “grease balls” vs. “brick dust”, as will be explained in detail in the following chapters.

1.2.1 Surfactants

Surfactants are amphiphilic molecules, i. e. molecules with a polar, hydrophilic moiety (the so-called the “head”) and an non-polar, hydrophobic part usually called the “tail”. The head group can be ionic or non-ionic, and the resulting structures are correspondingly referred to as ionic and non-ionic surfactants respectively. Typical representatives of these two classes are shown in Figure 1.4.

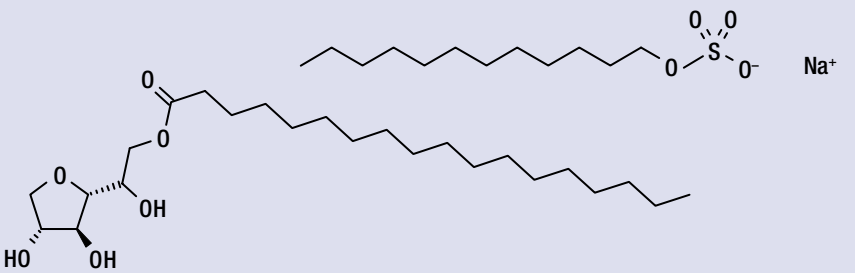

Figure 1.4 ▪ Chemical structures of sodium dodecyl sulfate (SDS), a typical ionic surfactant (top), and sorbitan monostearate (Span 60), a non-ionic surfactant.

Due to the relatively large hydrophobic part, these molecules are not very water-soluble either. In aqueous solution they exist as individual molecules only at very low concentrations. However, due to the existence of two (or sometimes more) unlike, incompatible molecule parts, they show unusual behavior when they reach their solubility limit. In contrast to “normal” (i. e. non-amphiphilic) substances that simply precipitate or form a new, relatively pure phase when they exceed their solubility limit, these substances agglomerate and form so-called supramolecular structures of well-defined size and shape. Due to the amphiphilic nature of the molecules, the hydrophobic parts gather and try to aggregate into a hydrophobic domain; however, the polar head groups do not have any reason to precipitate – they are happy in the aqueous phase, and they want to stay there. So, what is formed is an – often spherical – superstructure with a sort of core-shell structure. Here, the hydrophobic parts are in the core surrounded by the polar head groups, all of which keeps the whole structure well dispersed in the aqueous phase. Such structures are referred to as micelles (see Fig. 1.5), and the concentration at which they are formed is the so-called critical micelle concentration (CMC). Therefore, in contrast to conventional precipitation processes, we do not observe the formation of a macroscopic, separate phase. These micelles are usually extremely small; typical diameters are in the order of 5 nanometers. Thus, the system remains optically transparent and clear.

To make the story complete, we should mention that a further increase in surfactant concentration will lead to the formation of additional, so-called liquid crystalline phases, as indicated in Fig. 1.5. These phases comprise, among others, tube-like and laminar arrangements of surfactant molecules as well as particular arrangements of micelles. However, a detailed discussion of these phases would go far beyond the scope of this chapter. For a more comprehensive review on surfactants, see e.g. reference [3].

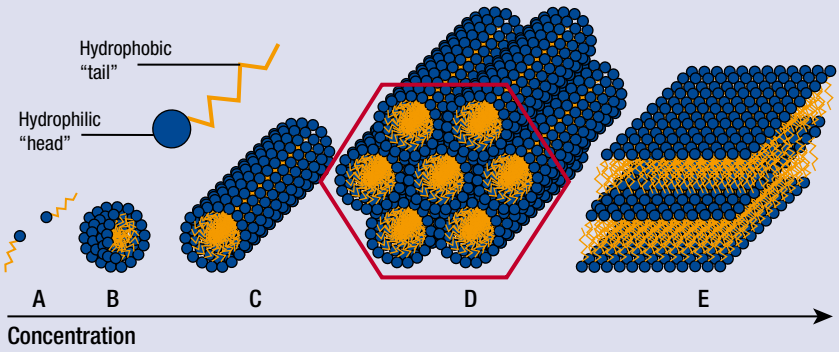

Figure 1.5 ▪ Schematic sketch of different surfactant phases formed from individual surfactant molecules at increasing concentration.

Usually, the CMC for most surfactants is very low. For non-ionic surfactants, it is in the order of 10^{-5} mol/L. For ionic surfactants, micelle formation is slightly more difficult due to the electrostatic repulsion between the ionic head groups; therefore, typical CMC values are in the order of 10^{-3} mol/L.

It is important to understand the driving force behind micelle formation. Often, people tend to argue that micelle formation is caused by the tendency of the hydrophobic "tails" to attract each other and thus to agglomerate. This point of view is misleading. In fact, the hydrophobic moieties do not care about their environment. They do not interact with their surrounding molecules anyway. In contrast, it is the water molecules with their well-known tendency to form extensive (and relatively strong) hydrogen bonds that expel the hydrophobic molecule parts. They strongly interact with their neighbors, and they are very selective as to which molecules they like and which they don't. And evidently, they don't like hydrophobes.

At first glance, one might tend to believe that – from the point of view of the Gibbs-Helmholtz equation – the driving force is enthalpy. However, like in the discussion of the poor solubility of large molecules, it is the entropy that makes the difference[2]. To understand this, we need to clearly understand that before micelle formation, i. e. in a state in which the surfactants were molecularly dissolved in the aqueous phase, the hydrophobic surfactant tails were naturally surrounded by water molecules. Although

[2]This coincides with my personal feeling that the impact of entropy is notoriously underestimated in discussions about solubilization and supramolecular effects in general.

there is an unfavorable interaction of these water molecules with the hydrophobic molecules, they are bound to them. Micelle formation releases these molecules, and the release of such a high number of small molecules is always favorable with respect to system entropy. The entropy of the system does not necessarily support this process. On the contrary, micelle formation can even be an endothermal (!) process[3] driven by entropic forces.

One key aspect of these micelles is the existence of a hydrophobic domain in their core. The situation can be characterized as an aqueous phase with hydrophobic, non-polar "holes" in it; and these domains can be used to solubilize non-polar molecules. The core of a micelle feels like a non-polar solvent; thus, if the solubility of the drug in non-polar solvents is high – which is particularly true for "grease balls" – they will dissolve in the core of the micellar phase. This has several important implications:

(a) The drug molecules do not separate from the aqueous phase (i. e. they do not precipitate), but they are still dispersed in the medium, which could be a gastro-intestinal fluid.

(b) In the micellar core, the drug is stable in the form of individual, dissolved molecules and **not** as a crystalline phase. This is extremely important if bioavailability issues are to be overcome, since it has been known for quite some time that breaking the crystallinity of active ingredients is a key step in rendering a given compound more bioavailable.

Nature also uses this highly effective principle in the form of surfactant-like biomolecules, e. g. bile salts.

Besides their solubilizing capacity, surfactants also act as dispersants. This means that they can stabilize small particles of insoluble substances (usually of a size around or below 1 µm) in a liquid, which is usually water. Again, the amphiphilic character of the surfactant is utilized: The hydrophobic tail moiety will adsorb onto the hydrophobic surface of the water-insoluble particle, whereas the hydrophilic head will point away from it into the aqueous phase. The use of ionic surfactants will lead to electrostatically charged particles, which will be repelled by other particles in the system because they are equally charged. This helps to disperse the particles in the aqueous phase. If non-ionic surfactants are used, the hydrophilic parts of the molecule form a sort of hydrophilic layer around the particle that also prevents particle-particle attraction and likewise stabilizes an aqueous dispersion.

Similar to the tendency of surfactants to adsorb onto surfaces, they also exhibit a high affinity to liquid-liquid interfaces (leading to the stabilization of emulsions, i. e. dispersions of small droplets of one liquid in another) and to liquid-gas interfaces. The latter effect leads to an accumulation of surfactant molecules at the surfaces of aqueous surfactant solutions. The hydrophilic parts of the molecule stay in the aqueous phase, whereas the hydrophobic tails point out of the water into the air. This may sound surprising.

[3] An alternative explanation proposes that the structure of the water molecules in vicinity of the hydrophobic tail is severely disturbed, and that they take on a structure similar to ice. Upon micelle formation, this structure is destroyed. The melting of ice is known to be an endothermal process leading to an increase of entropy due to increased mobility of the individual water molecules.

However, please remember that hydrophobic molecules or molecule moieties do not care about their molecular environment – just like air. In this sense, gases can be considered as hydrophobic media.

The accumulation of surfactant molecules leads to a decrease of the energy of the water-gas interface. Usually, when two media of different polarity meet (such as it is the case here), the interface has a relatively high energy level due to the incompatibility of the two media. Surfactant molecules have the ability to bridge this gap. Their polar head is in the polar fluid, whereas their non-polar tails are in the non-polar gas; thus, the high energy level of the interface is decreased. This impact of surfactants on the surface tension (the surface energy per unit area) can be used to determine the critical micelle concentration (CMC). Starting with pure water with an interfacial tension of 72 mN/m, the addition of surfactants leads to a steady decrease of surface tension until the surface is completely covered with surfactant molecules. Evidently, at this point, surface tension reaches a plateau (see Fig. 1.6). As no additional surfactant molecules can be positioned at the water-air interface, a further increase in surfactant concentration will force the surfactant molecules to agglomerate and to form micelles. Therefore, a measurement of the surface tension as a function of surfactant concentration according to Figure 1.6 can be used to determine the CMC of the surfactant. Alternatively, the CMC can be measured by direct measurement of the presence (or absence) of micelles at a given concentration, e. g. by light scattering[4].

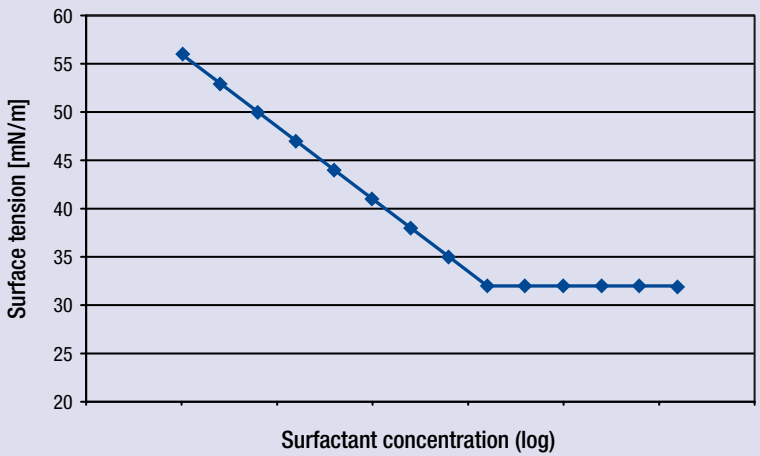

Figure 1.6 ▪ Schematic diagram of surface tension as a function of surfactant concentration.

Please note that the driving force ΔG for micelle formation depends on temperature, according to equation (1.1). The higher the driving force for micelle formation, the lower the CMC. Therefore, the CMC is also a function of temperature. As a consequence, the phase behavior of surfactants is both a function of concentration **and** temperature,

[4] Again, I must refer to specialized literature for a detailed discussion of methods to determine the CMC of surfactant solutions.

and in analogy to the critical micelle concentration at a given temperature, one can also define a critical micelle temperature at a given surfactant concentration. From all this, it becomes clear that surfactants are a fascinating (and very well investigated) class of molecules that exert a significant impact on the properties of pure water, going far beyond its usual properties. Micelles can act as "nano-sinks" for poorly soluble drugs, provided that they dissolve in the hydrophobic core of these micelles. Therefore, they present an attractive potential solution to overcome poor water solubility of BCS class II actives, and in particular for the "grease ball" fraction among them.

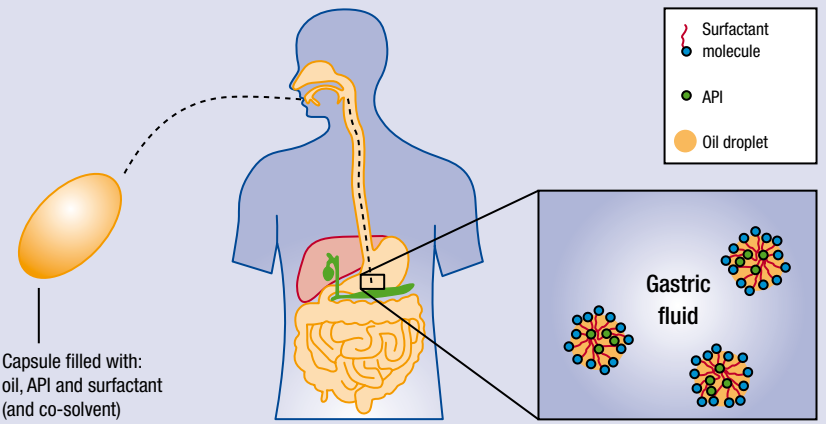

Figure 1.7 ▪ Principle of a self-emulsifying drug delivery system (SEDDS) (for explanations see text).

In the previous section, the use of surfactants to decrease the crystallinity of a drug and to improve its oral bioavailability was discussed. However, more than 80 % of all pharmaceutical dosage forms marketed today are solids, so the question arises as to how to prepare a formulation that forms emulsions in the GIT. So-called Self-Emulsifying Drug Delivery Systems (SEDDS) can achieve this.

SEDDS formulations consist of hard or soft gelatine capsules filled with a liquid. This liquid contains the active pharmaceutical ingredient, oil that dissolves the active and at least one surfactant. Optionally, other inactive ingredients such as co-solvents are added[5]. The system is homogeneous and isotropic. If this dosage form is swallowed, the gelatine capsule will dissolve in the stomach and the liquid comes into contact with the gastric fluid. Due to the presence of the surfactants and the agitation provided by the stomach, the oil phase will spontaneously emulsify in the gastric fluid and form an emulsion containing the lipophilic active (Fig. 1.7).

The advantages of SEDDS are obvious: The active is provided in a dissolved, non-crystalline state and it is finely dispersed in the GIT. Usually, emulsions produced

[5] Often, solubility of an active in a solvent mixture can be higher than its solubility in the pure solvent. Therefore, so-called co-solvents can be added to the formulation. Likewise, mixtures of surfactants can be superior to pure surfactants, in particular for the formulation of microemulsions. However, a detailed discussion of these effects would go far beyond the scope of this chapter.

from SEDDS develop a droplet size of 100 to 300 nm. More recently, so-called Self-Microemulsifying Drug Delivery Systems (SMEDDS) have been successfully introduced into the market. These systems are characterized by an even smaller droplet diameter produced under physiological conditions (below 100 nm).

The idea of dissolving an active ingredient in a suitable oil and emulsifying the oil phase in water has been used for quite some time in the field of crop protection formulations. Usually, these formulations can develop high bioavailability for the same reasons as pharmaceutical formulations (reduced crystallinity, fine dispersion of the drug), although for crop protection products the solvent content may be an issue due to VOC problems[6]. However, the successful development of a pharmaceutically acceptable SEDDS is far from being trivial. Many surfactants used in SEDDS are lipid-based, and these surfactants strongly interact with lipases in the GIT fluids. Naturally, this significantly affects the stability of the emulsion droplets over time. This is a serious obstacle to the development of in-vitro test assays for such formulations, and it makes it difficult to predict how the formulation will behave in-vivo. Moreover, the ratio of oil(s), lipid(s), co-solvent(s) relative to the active has to be tailored very carefully. The oral bioavailability of the active in the SEDDS depends on many parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge. All the factors impact the self-emulsification ability. Only selected combinations of these excipients result in the desired emulsification behavior.

Additionally, SEDDS are limited to lipophilic drugs. As discussed above, poor water solubility of a drug does not necessarily mean that the drug dissolves well in hydrophobic solvents. Therefore, an SEDDS formulation approach can only be applied if the drug readily dissolves in a pharmaceutically acceptable oil, such as olive oil, and if it is incorporated chemically in this solvent. As a consequence, many “grease ball” drugs are candidates for development in an SEDDS, but the typical “brick dust” fraction that dissolves neither in oil nor in water can not be administered this way.

Although much effort has been put into studies on SEDDS, only three actives have been successfully introduced into the market in this form. At present, there are four products on the market, namely Sandimmune® and Neoral® (cyclosporine A), Norvir® (ritonavir), and Fortovase® (saquinavir).

Sandimmune® and Neoral® are both marketed by Novartis. However, the formulations differ in that Sandimmune® is an SEDDS whereas Neoral® is an SMEDDS. Cyclosporin A is a cyclic peptide comprising 11 amino acids with a molar mass of about 1,200 g/mol. Water solubility is very low, but the drug exhibits fair solubility in oils. It can be formulated as a conventional SEDDS as is the case in Sandimmune®; however, strong inter-patient variability of the bioavailability of the emulsion formed from the SEDDS ranging from 10–60 % has been observed. Neoral® as a microemulsion preconcentrate based on corn oil,-mono-, di-, and triglycerides, polyoxyl 40-hydrogenated castor oil, DL-(α)-tocopherol and propylene glycol turned out to be less sensitive to such fluctuations. Furthermore, the AUC of this microemulsion-based approach

[6]VOC = volatile organic compound

turned out to be substantially higher, probably due to the smaller droplet size, leading to a better distribution of the drug in the GIT.

All in all, SEDDS and SMEDDS are promising but highly complex ways to overcome solubility issues with class II actives, at least for the "grease ball" fraction within this class. It needs to be assessed over time whether the undoubted benefits and the potentially high bioavailability of such formulations will compensate for the extra effort required for development.

1.2.2 Complex formation with polymers

One approach, which is more widely applicable and which also addresses the problem of the "brick dust" fraction of class II actives, is the use of polymeric solubilizers. Polymeric solubilizers are water-soluble polymers with the ability to form complexes with other molecules in the system. The idea as such is not new and has been applied in detergents for some time to avoid the unwanted transfer of dyes from colored clothes onto white ones. During the washing process, colored textiles often lose a certain fraction of their dyes that may be only loosely bound to the textile surface. These dyes may then re-deposit onto other textiles, and they usually select your most expensive favorite garments for doing so… So-called dye transfer inhibitors can prevent this by formation of a stable complex with the dye molecules; this stabilizes the dye in the dissolved form and therefore keeps it from depositing onto other textile surfaces. Such a complex is shown in Figure 1.8.

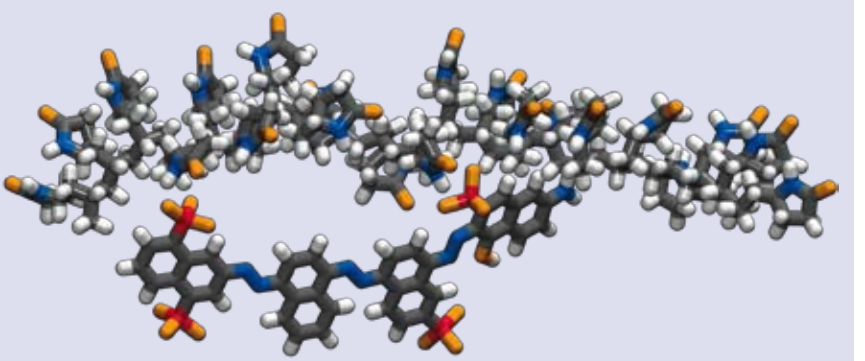

Figure 1.8 ▪ Complex formed by poly(vinylpyrrolidone) and a dye (direct blue 71).

Such interactions have been widely investigated and can be determined quantitatively (see Table 1.1).

Table 1.1 ▪ Binding constants, binding enthalpy and relative dye transfer inhibition performance of selected polymers with a given dye (direct red 80) [4].

PVCap: poly(vinyl caprolactam)
PVP: poly(vinyl pyrrolidone)
PVI: poly(vinyl imidazole)
PVIVP: poly(vinyl pyrrolidone-co-vinyl imidazole)

Polymer	Binding constants K_p [L/mol] (dye/polymer = 10^{-2})	Enthalpy of reaction ΔH_r [kJ/mol]	DTI-Performance [%]
PVCap	700	+11.0	0
PVP	1500	-13.2	39
PVI	5500	-29.3	79
PVIVP	60000	-26.2	84

In a very analogous fashion, water-soluble polymers can also stabilize active pharmaceutical ingredients in an aqueous phase, which increases their water solubility (Fig. 1.9).

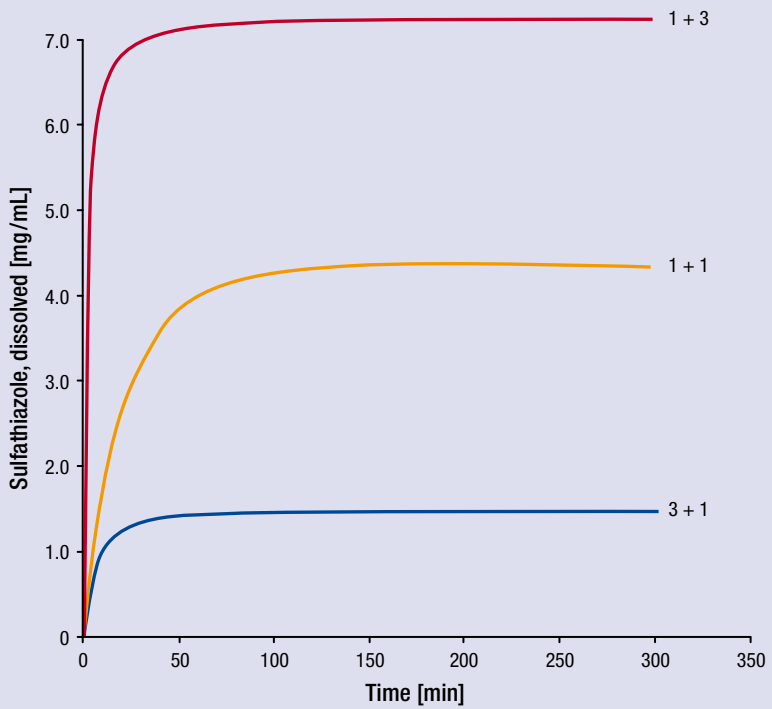

Figure 1.9 ▪ In-vitro measurement of the solubility of sulfathiazole for different drug: PVP ratios [5].

Poly(vinylpyrrolidone) or simply PVP, also known as Kollidon®, is a well-known example of a pharmaceutically acceptable polymer that solubilizes poorly water-soluble actives. In a way similar to surfactants, the molecules solubilized by such polymers are present in the aqueous phase as individual, non-crystalline molecules with a usually high bioavailability. The mode of action of PVP relies on the large dipole moment of the polymer side groups that strongly interact with any other dipole present in the system. However, for some drugs, such a dipole-dipole interaction, this is not sufficient to enable complex formation with the drug, in particular if the drug does not have any polar molecules. In such cases, amphiphilic polymers with hydrophobic "pockets" to attract the non-polar drug can be used. One example of such solubilizing polymers that was introduced only recently is a graft copolymer referred to as Soluplus® (see chapter 5).

Due to the presence of both hydrophilic and hydrophobic groups, the polymer can both interact with the poorly soluble drug and still be water-soluble. Again, complex formation is driven by entropy due to the release of water molecules previously bound to the polymer; however, molecular interactions between the polymer and the active resulting in a favorable enthalpy term are usually required for good performance.

The use of polymers such as PVP or Soluplus® brings about two important advantages for the formulation of poorly soluble drugs. This is because the polymer can fulfill two functions: It can act as a matrix material for the tablet and often forms so-called solid solutions with the drug (see chapter 2), and it enhances oral bioavailability once the tablet has been administered. Solubilizers such as Soluplus® present a major advantage on the way towards new technologies to bring such difficult-to-formulate drugs effectively to the patient. Details will be discussed in the following chapters, in particular chapter 5.

1.2.3 Nanotechnology: The kinetic approach

The idea of solubilizing a poorly soluble drug by influencing thermodynamic properties such as solubility or binding constants basically relies on increasing its concentration in the GI tract. Precisely speaking, solubilization increases the concentration of bioavailable (= solubilized) species in the GI tract. This is due to the generally accepted view that coarse, crystalline particles usually do not permeate through the gut wall. An increased concentration of such molecular species will increase the driving force to permeate through the intestinal wall according to Fick's laws of diffusion. However, increasing the concentration of a species above its equilibrium concentration always carries the risk of recrystallization of this species under physiological conditions.

Assuming that the transport of the dissolved species out of the gut and into the rest of the body is fast enough[7], oversaturation can – in principle – be avoided. Remember that the dissolution process is always an equilibrium process between the dissolved and the undissolved species. As long as the solubility limit is not reached,

[7] This assumption is valid for most class II actives. Otherwise, they would be in class IV.

molecules dissolve as individual molecules out of the solid form and into the liquid phase. Whenever we decrease the concentration of drug molecules in the liquid phase, e. g. the GIT fluid, some fraction of the solid drug will dissolve until the solubility limit is reached again. If we continuously remove the dissolved drug from the fluid – e. g. by allowing it to diffuse through the intestine wall – eventually the whole amount of drug that has been administered will dissolve and be taken up quantitatively.

Unfortunately, most class II actives are characterized by both low equilibrium solubility and a low dissolution rate at which this is established. This is due to the high stability of the drug in the crystalline form. Intuitively, it can be understood that dissolution will not be a fast process if the drug molecules are energetically "happy" where they are.

Therefore, to make complete dissolution possible within the time frame of digestion (which is approximately 24 hours), this requires that the dissolution process is fast, i. e. that the equilibrium between the solid and the dissolved states of the drug is established at a high rate. If this can be achieved, the absorption of the dissolved form leading to its removal from this equilibrium will (in principle) make it possible that even drugs with a low equilibrium solubility will eventually dissolve.

As a consequence, increasing the dissolution rate rather than the absolute equilibrium solubility is an effective way to increase the uptake of a poorly soluble drug into the body and, thus, to increase its bioavailability[8]. This is where nanotechnological drug formulations come into play[9].

If a poorly soluble drug is presented to the body in the form of nanoparticles, two important impacts on its solubility can be observed: Firstly, if the particles are very small (i. e. < 100 nm), solubility is a function of particle size according to the Kelvin equation (eq. 1.4):

$$S(r) = S_\infty \cdot \exp\left(\frac{2\gamma \cdot V_M}{r \cdot RT}\right) \qquad (1.4)$$

In this equation, S(r) is the solubility as a function of the radius r, S_∞ is the solubility of a coarse, crystalline particle with flat, even surfaces, γ is the interfacial tension between drug and solvent, V_M is the molar volume of the drug, R is the gas constant and T is the temperature. This equation clearly shows that solubility increases enormously when the particle size decreases. The effect becomes drastic at particle sizes below approx. 100 nm, depending on the drug, as shown in Fig. 1.10.

[8] Please note that these two approaches, namely increasing the equilibrium solubility and the dissolution rate, do not exclude each other. Ideally, they are combined.

[9] A comprehensive review on organic nanoparticles, including their impact on oral bioavailability, can be found in reference [6].

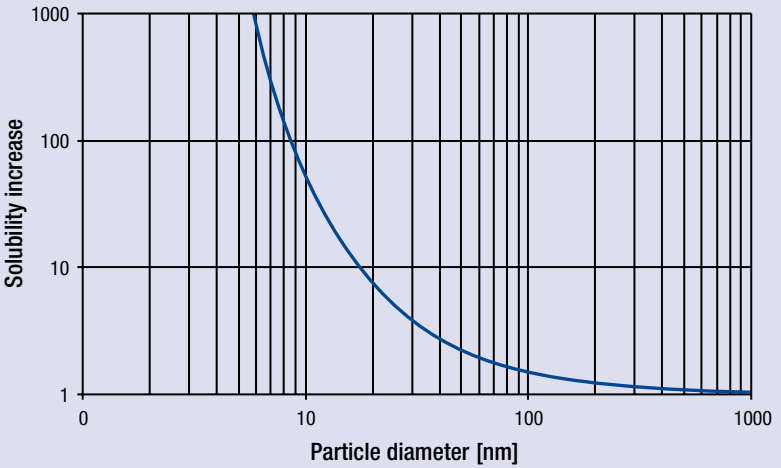

Figure 1.10: ■ Solubility increase (solubility according to eq. 1.4 divided by the solubility of the crystalline material) as a function of particle radius for typical organic compounds.

Secondly, there is an additional effect contributing to the high bioavailability of nanoparticular drug formulations. This is related to the surface area that naturally increases strongly as the drug particles decrease in size. This is expressed by the Noyes-Whitney equation (eq. 1.5):

$$\frac{dc}{dt} = \frac{D \cdot A}{h} (c(r) - c) \qquad (1.5)$$

This equation describes how fast the concentration in a given medium c increases with time t as a function of the diffusion coefficient of the drug D, its surface area A, the thickness of the diffusion layer around the particle h (i. e. the distance the drug needs to diffuse out of the region of high drug concentration c(r) immediately close to the particle surface into the bulk medium where the concentration of the drug is c), and the difference between drug solubility and drug concentration in the medium. In other words, drug particles will dissolve fast when:

(a) The solubility of the drug is higher than the concentration in the solvent – this can be achieved by setting the particles size according to equation 1.4.

(b) The drug particles have a high surface area.

As an example, Fig. 1.11 shows the oral bioavailability of a nanotechnological formulation of ß-carotene. As can be clearly seen, bioavailability is greatly accelerated compared to the coarse crystalline material.

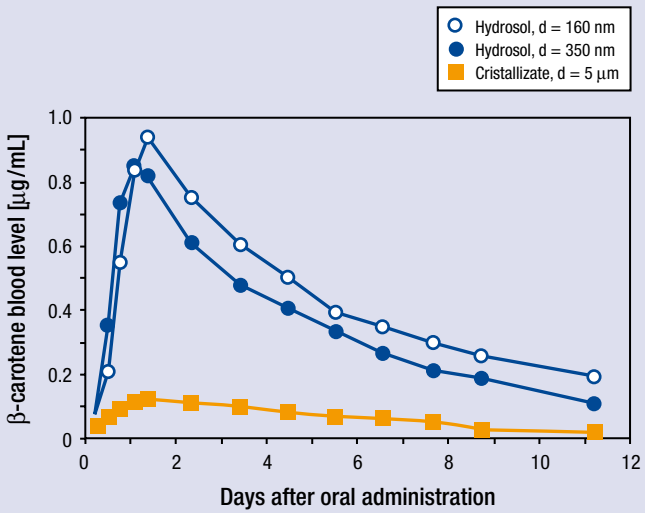

Figure 1.11 ▪ Graph of the β-carotene blood level as a function of time after single oral administration of β-carotene to calves with minimal β-carotene status. Comparison of nanodispersed formulations with a microdispersed crystallizate as described by Horn and Rieger in [6].

Naturally, nanoparticles have a higher specific surface area than coarse crystals. Therefore, small particle sizes will increase both drug solubility (eq. 1.4) **and** drug dissolution rate (eq. 1.5). Both effects potentially increase bioavailability.

Moreover, oral uptake of nanoparticles is enhanced even when particle sizes are so large (i. e. significantly above 100 nm) that the effects cannot be explained by eqs. (1.4) or (1.5). Additional effects such as increased adhesion to the intestinal wall have been discussed to account for these findings.

All in all, nanotechnology has been intensively discussed as a new route to increase solubility and, thus, bioavailability of poorly soluble drugs. First products have already been successfully introduced into the market. The first solid-dose formulation with this technology was the immunosuppressant Rapamune® (sirolimus). Emend® (antiemetic, aprepitant) was approved by the FDA in March 2003. TriCor® (fenofibrate) was approved by the FDA in 2004, and more nanomedicinal products are likely to follow.

1.3 Summary and outlook

Summing it all up, poor solubility is a major issue for today's pharmaceutical industry, leading to a high attrition rate in the development of new drugs. Therefore, effective ways to increase solubility of new chemical entities, in particular those classified as BCS class II, are invaluable tools for extending the drugable space and bringing these new molecules to the market.

Consequently, a lot of effort has been put into this field. Most approaches can be classified as being based on one or more of the following principles:

- Solubilization through surfactants
- Solubilizing polymers, and/or
- Nanotechnology.

For all these fields, the first products have already been launched. More will follow.

The following chapters will give additional details on formulation requirements for poorly soluble actives and in particular present concrete examples of excipients that will help pharmaceutical formulators to dissolve their drugs – and solve their problems!

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Matthias Karl, Michael Schönherr

2 Preparation of solid solutions and dispersions

2.1 Solid solutions and dispersions

2.1.1 Introduction and general aspects

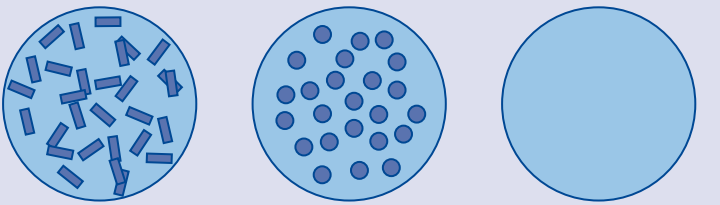
In this area, pharmaceutical research focuses on improving the **oral** bioavailability of poorly water-soluble drugs by enhancing the solubility and drug release of the APIs. This challenge is currently becoming more and more important as the percentage of poorly water-soluble new chemical entities in drug development is constantly increasing (detailed information on this topic is given in chapter 1) [7].

Approaches to overcome poor solubility of the drug substance include salt formation, solvation and particle size reduction. Other methods such as the solubilization of drugs in solvents, complexation (e. g. cyclodextrin) and the use of surfactants and cosolvents have also been used to improve the dissolution properties of poorly water-soluble drugs. However, although there are substantial limitations associated with each of these techniques, the formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for such drugs [8].

2.1.2 Types of solid dispersions

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.

Of the various types of solid dispersions, three are relevant for pharmaceutical applications since the polymers used are usually amorphous. Principally, the drug can be either dissolved or dispersed whilst in an amorphous or crystalline state. A thermodynamically stable formulation (Figure 2.1) is achieved when the drug is completely dissolved below its saturation solubility in the polymer, resulting in a solid solution (formulation is illustrated on the right). When the drug concentration exceeds its saturation solubility, the whole system is only kinetically controlled (formulation in the center) since the drug may crystallize or precipitate out of the polymer during storage. This is because the amorphous drug is dispersed in an amorphous polymer and as the drug may crystallize, hence changing its dissolution and biopharmaceutical properties. The system on the left is quite stable. In this case, the polymer contains crystalline drug – because only Ostwald ripening can occur – and this leads to the formation of larger crystals. However, this is not very pronounced due to the low diffusivity of the drug in a solid polymer [9].



Drug	Crystalline	Amorphous	Molecularly dissolved
Polymer	Amorphous	Amorphous	Amorphous
Thermo-dynamic stability	Almost stable	Unstable (kinetically controlled)	Stable (drug below saturation solubility)

Figure 2.1 ▪ Relevant types of solid dispersions

Various preparation techniques for solid dispersions deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, where both matrix and drug are generally poorly miscible. During many of the preparation methods, de-mixing and the formation of different phases can be observed. Phase separations like crystallization or the formation of amorphous drug clusters are difficult to control and should therefore be avoided. Generally, phase separation can be prevented by maintaining low molecular mobility of the matrix and the drug during preparation. Additionally, phase separation is prevented by maintaining the driving force for phase separation at a low level, for example by keeping the mixture at an elevated temperature, thereby retaining sufficient miscibility for as long as possible [8].

2.1.3 Manufacturing of solid dispersions

The melt method (e. g. hot-melt extrusion, spray congealing and melt granulation), solvent procedure (e. g. spray drying, solvent casting and freeze drying) and other technologies (e. g. milling) are the usual manufacturing methods for solid dispersions. The most popular techniques are hot-melt extrusion and spray drying, which are described in detail in subsequent chapters.

The film casting technique is very suitable for predicting the solubility of a certain API in a polymer matrix. This can be carried out prior to HME or spray drying experiments since it is much less time- and material consuming. In the film casting procedure, an appropriate solvent that dissolves the API and the polymer (or polymer-plasticizer) should be selected. When the substances are dissolved after stirring, the solution can be cast on a glass plate, resulting in a thin film. A scraper that produces a film of 120 µm

thickness is recommended as casting device. The thin film (thickness of the dry film < 120 µm) enables fast drying and avoids the recrystallization of the poorly soluble drug that can occur when high drug concentrations are used over a longer period, as happens in case of thick films. Drying should be performed for 30 minutes under ambient conditions (flue) and then in a vacuum drying cabinet (50 °C, 10 mbar for 30 minutes) to ensure fast and complete drying of the film. To analyze the extent of solubilization capacity of the polymer or of the polymer-plasticizer combination for a specific drug, increasing amounts of API should be used (25, 33 and 50 %). The higher the clearly dissolved drug concentration, the greater the solubilization capacity. A solid solution results in clear and smooth films. Drug crystals can easily be recognized as can amorphous precipitation (opaque films). Visual inspection of the films was performed 7 days after open storage at 23 °C / 54 % r. h. The film casting procedure is shown in Figure 2.2 [9].

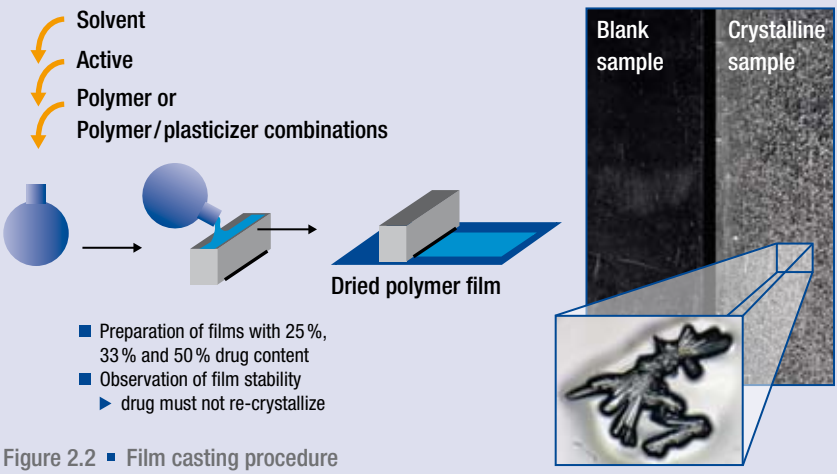


Figure 2.2 ▪ Film casting procedure

2.1.4 Analytical investigation of solid dispersions

Different molecular structures (crystalline, amorphous and molecularly dissolved) of the drug in the matrix can be encountered in solid dispersions.

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to obtain a complete picture.

Generally, Powder X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) techniques are important methods for determining the physical state of the incorporated drug. The XRD technique is illustrated in Figure 2.3. Sharper diffraction peaks indicate more crystalline material.

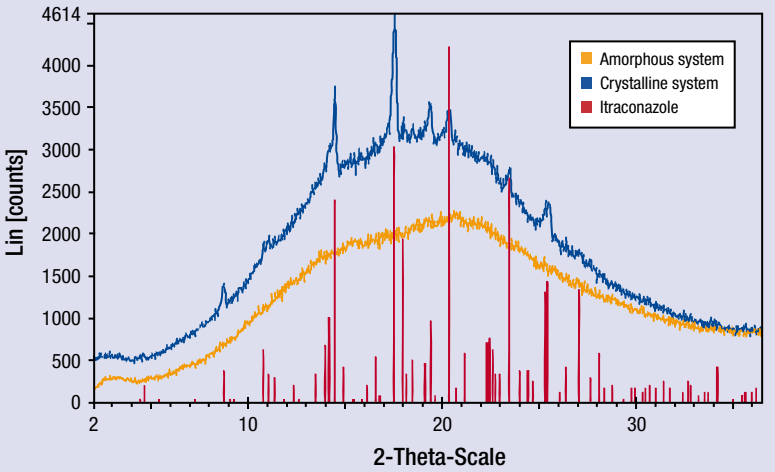


Figure 2.3 ▪ XRD examples of extrudates of Kollidon® VA 64 with the active pharmaceutical ingredient (API) itraconazole

In DSC, solid dispersions are heated at a constant heating rate and the amount of energy required is determined. With DSC, the temperatures at which thermal events (e. g. glass transition, (re)crystallization, melting or degradation) occur can be detected and determined.

Both techniques provide information concerning the crystallinity or amorphicity of the API and the matrix. However, they can usually not distinguish between molecularly dispersed drug and amorphous drug material. An innovative method is the use of 13 C solid state NMR to meet this need [10].

Currently, additional techniques are available to detect the crystals in solid dispersions: infrared spectroscopy (IR), dissolution calorimetry – which measures the energy of dissolution of the sample – vapor sorption and macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline samples [7].

The solid dispersion appears to be a suitable formulation for increasing the dissolution and absorption rates of poorly soluble drugs. However, the result of aging or storage under various conditions and the effects on the drug release characteristics and chemical stabilities of the formulations still have to be shown [11].

The biopharmaceutical properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the polymer matrix. The stability and dissolution behavior could be different for solid dispersions that incorporate the drug in different states [8].

2.2 Hot-melt extrusion

2.2.1 Introduction to hot-melt extrusion

Interest in hot-melt extrusion (HME) techniques for pharmaceutical applications has grown significantly in recent years. Hot-melt extrusion is an established manufacturing process that has been used in the plastics and food industries since the 1930s. In the 1980s, BASF SE was the first to apply the melt extrusion process based on polymers with a high glass transition temperature (such as polyvinylpyrrolidones) to pharmaceuticals [7]. Later on, Soliqs, the drug delivery business unit of Abbott GmbH & Co KG, commercialized the technology and subsequently launched several drugs [12]. A number of research groups have demonstrated HME processes as being viable techniques for the preparation of pharmaceutical drug delivery systems, including granules [13, 14], pellets [15, 16], sustained release tablets [17-21], transdermal and transmucosal drug delivery systems [22-30] and implants [31-34]. The HME technique is an attractive alternative to traditional processing methods [35]. Examples for solving pharmaceutical challenges using HME are given in Table 2.1.

Table 2.1 ▪ Advantages of hot-melt extrusion

Problem	Solution by HME
Poor (low / unreliable) bioavailability due to poor API solubility	Use of Hot-Melt Extrusion to prepare solid solution / dispersion or SEDDS (enhanced dissolution)
Poor API stability during processing caused by hydrolysis	Use of Hot-Melt Extrusion as alternative to wet agglomeration (no hydrolytic stress)
Unreliable sustained release action	Use of Hot-Melt Extrusion to prepare sustained release dosage form (single / multiple units)
Poor stability or tolerability of API in the stomach	Use of Hot-Melt Extrusion to prepare enteric dosage forms (single / multiple units)
Poor taste of the API	Use of Hot-Melt Extrusion to prepare taste-masked dosage forms
Manufacturing of films	Use of Hot-Melt Extrusion to prepare oral strips or dermal patches

Hot-melt extrusion technology is a popular technique in the pharmaceutical industry. It is of particular interest for dispersing APIs in a matrix at the molecular level, thus forming solid solutions. This technique is currently becoming more and more important as the percentage of poorly soluble new chemical entities in drug development is constantly increasing [7]. For BCS class II compounds in particular, improved absorption and therapeutic efficacy can be realized by enhancing API solubility [12]. An

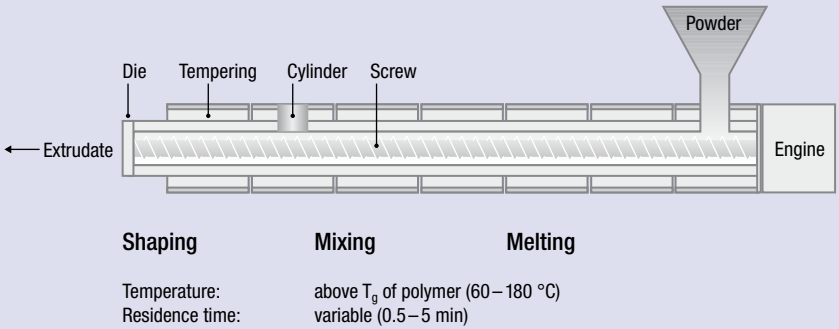
additional benefit of the HME technique is a robust and continuous manufacturing process which can be run in practically any pharmaceutical plant. However, as with other breakthrough innovations, numerous obstacles had to be overcome before the technology and resulting dosage forms could be commercially exploited. Compared with other pharmaceutical technologies such as granulation and compression, hot-melt extrusion is still an emerging technology and its potential has not yet been fully exploited. The technology itself can be described as a process in which a material melts or softens under elevated temperature and pressure and is forced through an orifice by screws. A prerequisite of the polymer to be used in hot-melt extrusion is appropriate thermoplastic behavior. However, the number of such polymers approved for pharmaceutical use is limited.

2.2.2 The hot-melt extrusion process

Extruders for pharmaceutical use have been designed and adapted for mixing drugs with carriers in various dosage forms. The significant difference between extruders for thermoplastics and pharmaceutical applications is the equipment used, where, for pharmaceuticals, the contact surface must meet regulatory requirements. Those parts of extruders used in pharmaceuticals that have contact with product must not be reactive nor may they release components into the product. Extruder equipment is specially configured to fulfill all cleaning and validation standards applicable to the pharmaceutical industry.

In principle, an extruder consists of barrels enclosing single-, twin- or multi-screws which transport and subsequently force the melt through a die, thus giving it a particular shape. The barrel can be heated to the desired temperature. Due to the external heat and shear provided by the screws, the polymer is plasticized and hence its viscosity reduced. Since the extruder is fed at one side and the extruded material exits from the other side, it is a typical continuous process; this makes it even more attractive for pharmaceutical applications [36]. The hot-melt extrusion process comprises the steps melting, mixing and shaping (see Figure 2.4).

The purpose of the feeding section is to transfer the materials from the feeder to the barrel. The polymer mixture typically begins to soften in the melting zone. The melt moves in a circulatory manner in a helical path by means of transverse flow, drag flow, pressure flow and leakages [35]. Thermoplastic polymers primarily exist in a molten state when entering the shaping section. The function of this zone is to reduce the pulsation flow and ensure a uniform delivery rate through the die. At the end of the barrel, the attached die determines the shape of the extrudates.



Modified according to: M. Thommes, Systematische Untersuchungen zur Eignung von kappa-Carrageenan als Pelletierhilfsstoff in der Feuchtextrusion / Sphäronisation, Ph. D. Thesis, University of Düsseldorf, 2006.

Figure 2.4 ▪ Principle of hot-melt extrusion

The complete extrusion set-up consists of three distinct parts:

- Screws with a conveying and kneading system for material transport and mixing
- A die system for forming the extrudates
- Downstream auxiliary equipment (cooling, pelletizing and collecting)

The components of the extruder are:

- The feed hopper (gravimetric or volumetric feeding)
- Temperature-controlled barrels (heating and / or cooling)
- Die (different die configurations are available)

Additional equipment:

- Process analytical technology (e. g. spectroscopic systems)
- Vacuum pumps for degassing extrudates
- Pelletizer equipment
- Calendering equipment

In-process control parameters can be e. g.:

- Zone and die temperatures
- Screw speed
- Torque or power consumption
- Pressure
- Melt viscosity
- Feed rate

Extruders are available as single- or multi-screw versions. Twin-screw extruders utilize two screws usually arranged side by side. The use of two screws allows a number of different configurations to be obtained and imposes different conditions on all zones of the extruder. In the twin-screw extruder, the screws can either rotate in the same (co-rotating) or in the opposite (counter-rotating) direction [35].

Co-rotating extruders are the most important types for industrial applications. They can be operated at high screw speeds and high output and provide good mixing and conveying characteristics as well as more flexibility in screw design. The co-rotating and counter-rotating twin-screw extruders can be classified as either non-intermeshing or intermeshing. In most cases, co-rotating intermeshing twin-screw extruders are used. The main advantages of single- and twin-screw extruders are listed below.

Advantages of twin-screw compared to single-screw extruders [35]:

- Easier material feeding
- High kneading potential
- High dispersing capacity
- Less tendency to overheat (important for sensitive APIs)
- Shorter and constant residence times

Advantages of single-screw compared to twin-screw extruders:

- Mechanical simplicity
- Low cost of investment

The major advantages of the twin-screw extruders are in their conveying and transport mechanisms and in their mixing abilities compared to the single-screw extruders. This is why applications are continuing to expand within the pharmaceutical field.

Conveying and kneading elements

Most extruders have a modular design to facilitate different screw configurations. The configuration of the screw has a significant impact on the extrusion process and can be designed to achieve either a high or a low shear. In the extrusion process the screws are specified in terms of the L/D ratio (length of the screw divided by the screw diameter) [37, 38]. The configuration of the screws can be varied by the number and arrangement of conveying and kneading elements [39].

The design of the kneading elements has an influence on the mixing behavior within the extrusion process. The advance angle also determines the conveying ability of the element ranging from forwards (30° and 60°) to neutral (90°) to reverse (30°) mode. Neutral elements (90°) push material neither forwards nor backwards. Irrespective of the reverse-flighted element, the ability for mixing and shearing of the material increases the higher the advance angle. Reverse-flighted kneading blocks have a retaining character and are usually used when substantial mechanical stress has to be exerted upon the material [14].

Process variables of twin-screw extrusion

Process variables in twin-screw extrusion can be divided into step- and continuous changes. Continuous changes include modifications during the running process and step changes require off-line modifications (Table 2.2).

Table 2.2 ▪ Variables in twin-screw extrusion

Step changes:	Continuous changes:
■ Screw design	■ Screw speed
■ Die design	■ Feed rate
■ Barrel layout	■ Barrel temperature

Screw speed, feed rate and barrel temperature are the most relevant process parameters in twin-screw extrusion. These parameters in particular influence the system parameters mechanical energy, residence time and the temperature of the material.

On increasing feed rate and screw speed, the residence time of the material decreases and the torque of the machine increases for the feed rate used; it is also constant for the screw speed in question. At higher temperatures, the torque decreases due to a lowering of the melt viscosity of the polymer (Figure 2.5).

Figure 2.5 ▪ Effect of feed rate, screw speed and temperature on HME

Extrudability is mainly determined by the glass transition (T_g) or melting temperature (T_m) and melt viscosity [40]. Materials of high molecular weight generate a high melt viscosity and are difficult to extrude. A high glass transition or melting temperature requires high processing temperatures, which can affect sensitive drugs. As a general rule, extrusion processes can be run at temperatures 20–40 °C above the glass transition temperature. Most polymers demonstrate thixotropic behavior, which means that the viscosity reduces as a function of increasing shear stress.

2.2.3 Polymers for hot-melt extrusion

The polymer used in HME must exhibit thermoplastic characteristics in order to enable the hot-melt extrusion process to be carried out and it must be thermally stable at the extrusion temperatures employed. Other relevant characteristics are: suitable T_g or T_m (50–180 °C), low hygroscopicity and no toxicity since larger amounts of polymer are used (Figure 2.6). Polymers with a high solubilization capacity are particularly suitable because large quantities of drugs can be dissolved [41].

- **Thermoplastic behavior** → **deformability is essential**
- **Suitable T_g** → **50 – 180 °C**
- **High thermal stability** → **50 – 180 °C**
- **Low hygroscopicity** → **prevents crystallization**
- **No toxicity** → **application of large amounts**
- **High or no solubilization capability** → **thermodynamically stable formulation**

Figure 2.6 ▪ Basic requirements for polymers used in HME

Some features like lipophilicity, hydrogen bonding acceptors or donors [42] and amide groups are basic prerequisites for a high solubilization capacity; the same applies to organic solvents. This explains why povidone (Kollidon®), copovidone (Kollidon® VA 64) and Soluplus® are highly suitable for hot-melt extrusion. Kollidon® VA 64 and Soluplus® in particular are much more lipophilic than many other water-soluble polymers containing hydroxyl groups and, therefore, are best suited to the lipophilicity of poorly soluble drugs. In addition, the solubility parameter (see Extrusion Compendium [41] pages 53–55) can be used to determine whether actives and polymers are compatible [43, 44]. Regarding the topics solubilization/extrusion and bioavailability enhancement of poorly soluble drugs, some examples of Soluplus® formulations are described in chapter 5.

The solubilization capacity of a certain excipient can also be determined using hot-melt extrusion [41]. Figure 2.7 clearly illustrates how the appearance of a Soluplus® extrudate changes with increasing amounts of API: While the extrudates containing 25 % fenofibrate appear almost transparent, they change to more and whiter extrudates when the concentration of drug is increased in 5 % steps. This white color is attributed to undissolved, crystalline drug and indicates that the solubility of fenofibrate in Soluplus® is around 25–30 %. However, it is advisable to perform some solvent casting trials with a certain API/excipient ratio, as previously described, to obtain a first impression of the API solubility within the polymer matrix.

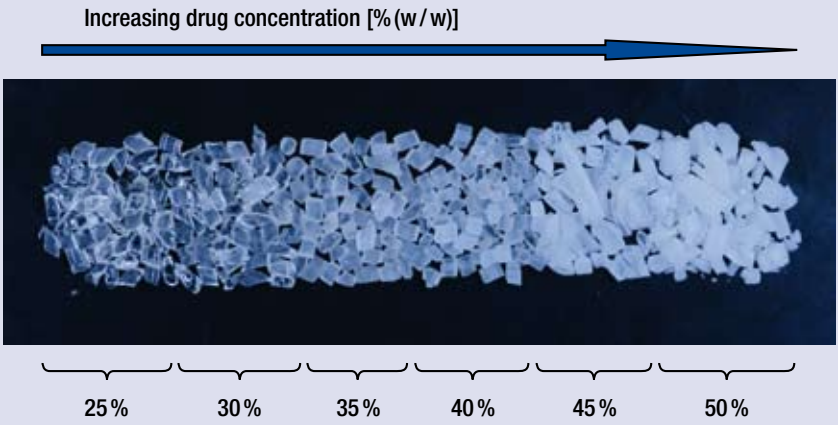


Figure 2.7 ▪ Appearance of Soluplus® with increasing drug concentration of fenofibrate

2.3 Spray drying as a preparation technique for solid solutions

2.3.1. Introduction

In spray drying, liquids are converted into powdered solids. The process functions by atomizing the liquid and vaporizing off the solvent used. The heat required for the process is provided by a drying gas; this gives off its heat and takes up the solvent vapor. The drying gas also becomes colder and moister during the drying process.

The widespread use of spray drying has led to the development of numerous different types of processes. Below, a standard configuration, as shown in Figure 2.8, is described.

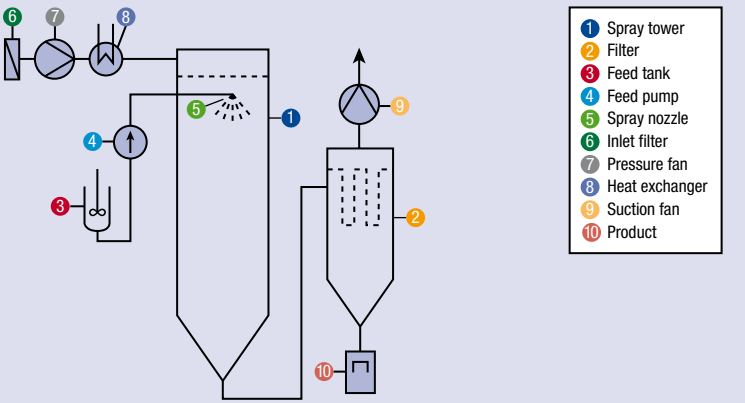


Figure 2.8 ▪ Standard spraying tower

In this chapter, we will concentrate on the core process of spray drying using a pressure nozzle. Further information on the technique can be obtained for example from Master's "Spray Drying Handbook" [45] and Lefebre's "Atomization and Sprays" [46].

In the manufacture of solid solutions, spray drying offers a number of advantages:

- It is a widespread technique and is readily available.
- In one process step, it is possible to manufacture a powder for producing tablets starting from a liquid.
- It is a gentle process with respect to temperature as the individual process steps require seconds only and the maximum product temperature is only as high as the gas exit temperature of the spray drier (approx. 50–100 °C).
- Due to the short drying times involved, amorphous solids with good solubility properties are frequently formed.

2.3.2 Spray drying: theory and practice

In general, a spray drying process involves the following steps:

I. Manufacture and atomization of the liquid.
II. Drying and formation of particle morphology within the spray tower.
III. Filtration, post drying, cooling and packaging of the powder.

Below, we will have a closer look at these steps as illustrated in Figure 2.8.

I. Manufacture and atomization of the liquid

For the spray drying process, one decisive factor is whether water or organic solvent is used. The active ingredients and excipients normally used in the manufacture of solid solutions are mostly more readily soluble in organic solvents than in water. However, spray drying with organic solvents requires an explosion-proof spray tower. This in turn involves high investment and also requires higher operating costs due to the necessary use of inert gas (e. g. nitrogen). The residual solvent content in the spray powder after drying must be so low that there is no risk of explosion in the gas space above the powder. Often, it is required that the solvent concentration should be a maximum of 40 % of the lower explosion limit.

When using organic solvents, higher throughputs can be achieved due to the substantially lower heat of evaporation required in comparison to water. In many cases higher solid concentrations in the liquid can be achieved as the viscosity in organic solvents is lower. These influences can be of considerable advantage if organic solvents are preferred to water. Thus, when developing formulations, the advantages and disadvantages of organic solvents compared to water should be taken into account at an early stage. It can thus be beneficial to develop alternative formulations in parallel until concrete data have been gathered on the performance and economics of the planned manufacturing process.

The solid content of the liquid should be as high as possible (≥ 20 %). This is because, on the one hand, it improves the economics of the process as a spray drying plant is based on liquid evaporation and low solid content means that the plant can be smaller

and the cost of cleaning and service also lower. On the other hand, liquids with low concentrations of solid generally produce fine powders of low bulk density and poor flow properties, both of which tend to have a negative effect on subsequent process steps.

The solid content also determines the viscosity and hence the ability of the liquid to be atomized. The process of atomization creates the large liquid surface area that is necessary for the heat- and mass transfer required for the liquid to be dried within a few seconds in the spray tower. Atomization should be carried out to produce a spray with a controlled and dense drop size distribution. As large drops require longer to dry than small drops, these determine the dimensions of the spray tower. Drops that are too large and still moist and sticky can reach the walls of the spray tower where they can form coatings. It is thus of importance that the atomization system is properly dimensioned and that it operates smoothly.

Hollow cone pressure nozzles are frequently used for atomization, as illustrated by the example of a Schlick nozzle in Figure 2.9. In such a case, the viscosity should not be higher than 50–100 mPa*s. Such hollow cone pressure nozzles are normally used for the pressure range of 20–200 bar. The maximum throughput per nozzle is approx. 500 kg liquid per hour. For higher throughputs, several nozzles can be employed. The size of the drops can be set via the atomization pressure.

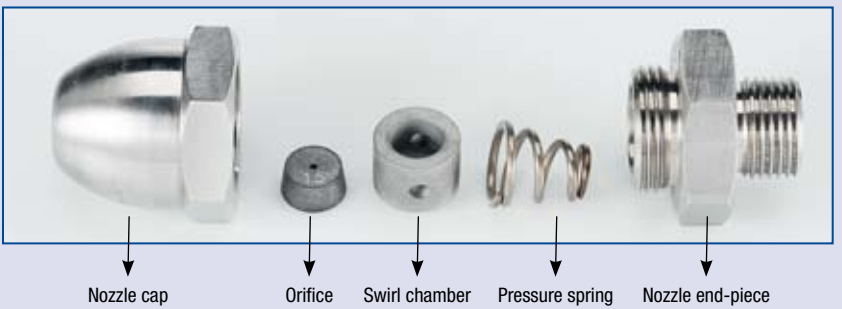


Figure 2.9 ▪ Hollow cone pressure nozzle (Schlick)

The spray pattern of a pressure nozzle is illustrated in Figure 2.10.

II. Drying and formation of particle morphology within the spray tower

For a liquid to be suitable for spray drying and hence for the manufacture of a solid solution, two parameters must be taken into account: the drying kinetics and the achievable moisture equilibrium.

Under **suitable drying kinetics,** a thin liquid film can be converted into a manageable solid within a few seconds. For this to be achieved, a minimum process temperature is required dependent on the boiling point of the solvent and the affinity of the solid to the solvent. At such a temperature (roughly, one corresponding to the outlet temperature of the spray drier), the solid should not be sticky.

Figure 2.10 ▪ Spray pattern of a pressure nozzle

In most cases, the drying kinetics would be assessed by drying small amounts in a laboratory scale spray tower. Due to the smaller dimensions of such an apparatus, the powder produced should be very fine (approx. 10–20 µm). For this reason, the samples obtained are not representative in their powder properties with respect to the product to be obtained later; however, it provides an indication of expected behavior within the spray tower, e. g. the tendency to form coatings on the walls of the tower.

The **moisture equilibrium** is characterized by the sorptive behavior of solvent with respect to the solid. For each amount of humidity in the gas phase there should be a moist equilibrium on the part of the solid; this is characterized by the sorption isotherm. In this way, depending on the humidity in the exhaust of the spray tower, there will be a minimal residual moisture in the powder. However, the residual moisture that is practically achievable is higher than the equilibrium value due to the short process time and can only be determined in scale-up experiments.

In the case of spray drying plants operated with air in the open mode, the humidity of the exhaust air is not only dependent on the amount of water vaporized in the spray tower, but also by the humidity of the inlet air. This dependence has a stronger effect on the residual moisture of the powder the more hygroscopic the solid is. In order to reduce the effect of inlet moisture on the residual moisture of the product, the inlet air is usually dehumidified to a maximum dew point of approx. 10 °C.

One of the most interesting questions regarding the development of a spray dried powder is what powder properties can be achieved and how these can be influenced by the formulation and the process. The key to understanding this is to be found in the **particle morphology**. Many of the application properties of the spray powder such

as flow-, dust-, dissolution- and tableting behavior can be explained by physical properties such as particle size distribution, bulk density and REM imaging, all of which illustrate the particle structure. Figure 2.11 shows, on the left, a compact particle that has resulted from a slaked lime suspension and, on the right, particles that have been produced by spray drying a polymer solution of hollow beads.

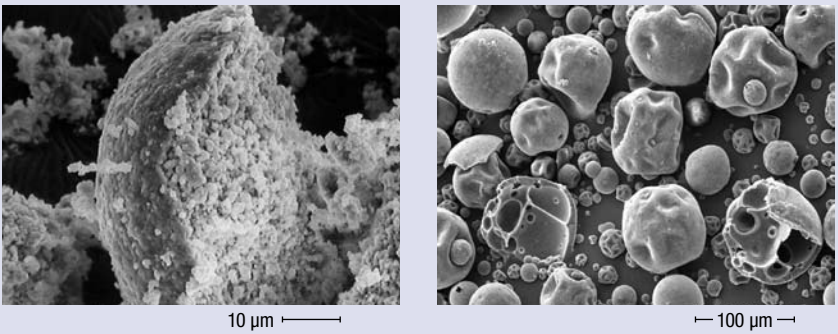


Figure 2.11 ▪ Forms of spray dried particles

The Büttiker model shown in Figure 2.12 assumes hollow bead formation due to the proportion of dissolved components. Pure suspensions of solid particles in the liquid shrink ideally and give rise to compact particles which in turn result in a powder of high bulk density. With increasing proportion of dissolved solid, the greater the chance of producing hollow bead formation.

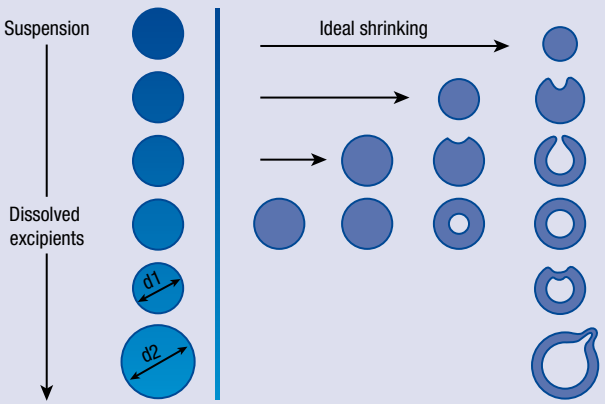


Figure 2.12 ▪ Influence of dissolved solid on particle morphology during spray drying (Büttiker model)

Apart from the composition of the liquid, the properties of the spray powder are determined principally by the process conditions in the spray tower. Some of these conditions are determined by the **construction of the spray drier.** Variants of spray driers are shown in Figure 2.13. Variant a) is a co-current flow nozzle tower. Here, the drying gas and the spray are led through the tower in co-current mode. In this way, the effluent liquid comes into contact with the warm air and shows a high drying speed during the first few seconds of the process. This drying speed can be increased by inserting a rotary atomizer as shown in variant b). The rotational atomizer, due to its circumferential speed of over 100 m/s, creates excellent heat- and mass transfer within its immediate atomization area. Variant c) also involves a nozzle tower. In this case, however, it is operated in counter-current mode. Here, the spray first comes into contact with the cool exhaust gas; it thus has a significantly lower initial drying speed than variant a) due to the lower temperature increment.

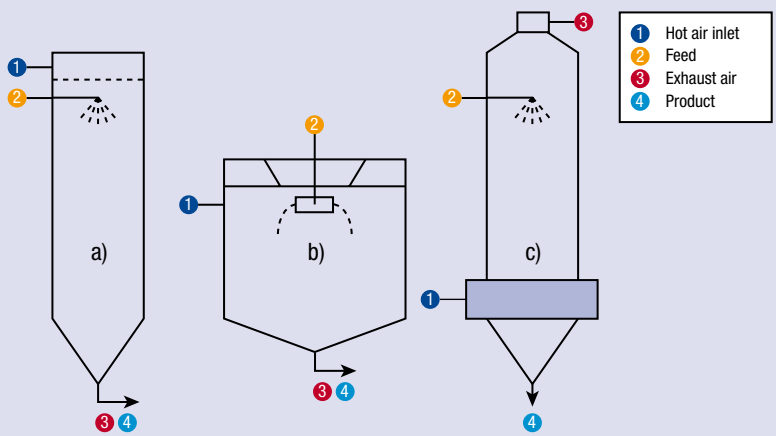


Figure 2.13 ▪ Variants of spray driers: a) co-current nozzle tower, b) disc tower, c) counter-current nozzle tower. See text above for explanation.

The bulk density of spray powder is strongly dependent on the initial drying speed in the spraying tower due to the formation of hollow beads. Thus, it is obvious that the lowest bulk density can be attained with variant b) whilst the highest can be attained with variant c). Apart from these primary effects there are, however, some secondary effects that do not occur directly in the spray tower but which also have to be taken into account. For example, large hollow beads with very thin shells are more likely to rupture than smaller beads with thicker shells; they are also more likely to be destroyed during the process, which of course alters the properties of the powder.

In addition to atomization, the most important **process parameters** in spray drying are the inlet- and outlet air temperatures and the gas speed in the spray tower.

III. Filtration, post drying, cooling and packaging of the powder

After drying in the spraying tower, the powder must be separated from the drying gas. Cyclones, bag filters and absolute filters can be used for this purpose. Cyclones are simple and economically priced devices; they are also easy to clean. Their disadvantage is that they have a limited degree of filtration; very small particles are simply not filtered out. Typical filtration rates are around 99 %, i. e. 1% of the solid is lost in the exhaust. The particles remain in the cyclone for a few seconds only. Bag filters form a filter cake on the filter material; this is then cleaned up with compressed air. Very high degrees of filtration can be achieved with such filters; the dust remaining is usually less than 1 to 10 mg / m^3. The particle residence time in the bag filter is dependent on the cleaning cycles and can be up to several minutes. The bag filter can also be used for post drying of the particles. The disadvantages of bag filters are the high purchase price, the complex cleaning process and the fiber impurities caused by the filter material.

If very clean exhaust air is required, as is the case with biologically active substances, only an absolute filter can achieve this. These are usually in the form of filter cassettes graded according to the degree of cleanliness required and filled with appropriate filter material. They are normally connected in series and disposed of after use.

Typical filter systems can be e. g.: bag filter + absolute filter or cyclone + bag filter + absolute filter.

In some cases, post drying and / or cooling of the powder is necessary once it has left the spray tower. Fluid-bed driers are frequently used for this purpose; they often combine drying and cooling. However, contact driers or coolers can also be used. This becomes meaningful e. g. when starting with continuous spray drying and then changing to batch processing. In such a case, a mixer can be inserted to define the batch size. When packaging, the selection of suitable containers is of particular importance. The package must be resistant to humidity and the inherent weight of the powder must not lead to the formation of lumps.

2.3.3 Preparation of solid solutions using spray drying

Spray driers as described above can be used for the preparation of solid solutions from active ingredients. In this case, the liquid is a mixture of solvent (water, organic solvent or a mixture of both), active ingredient and suitable excipients. The excipients help to improve the dissolution of the active ingredient or to stabilize it within the spray powder; they also prevent recrystallization during storage subsequent to spray drying. Should the active ingredient be poorly soluble, this can be improved by wet milling, a process that aids dispersion. If the solubility is still not adequate for economic production, it can be further improved (e. g. by briefly overheating the liquid according to BASF submission PF 56790 GD "Herstellung von festen Lösungen schwerlöslicher Wirkstoffe durch Kurzzeitüberhitzung und schnelle Trocknung" – Manufacture of solid solutions of poorly soluble active substances by briefly overheating and rapid drying). The process principle is illustrated in Figure 2.14.

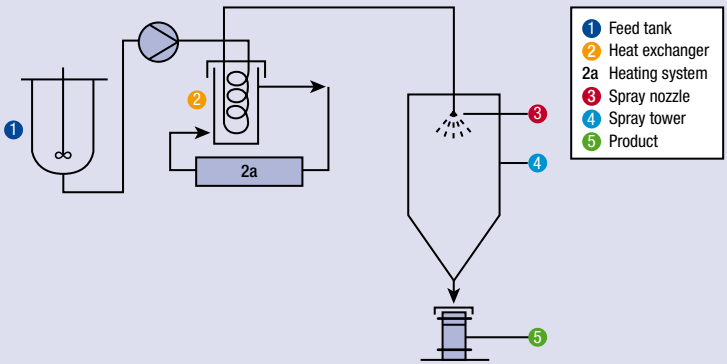


Figure 2.14 ▪ Manufacture of a solid solution by briefly overheating and subsequent spray drying

The mixture of water, active ingredient and excipients is subjected to wet milling and placed in feed tank 1. The active ingredient, depending on its solubility, may not be completely dissolved. On its way to the spray nozzle (3), the liquid passes through a heat exchanger (2) which, aided by a heating system (2a), is brought to a temperature above the boiling point of the liquid at ambient pressure. For example, the liquid can be exposed to a temperature of 150 °C for 15 seconds at a pressure of 100 bar. During this time the finely milled active ingredient can be fully dissolved in the aqueous polymer solution. The solution prepared in this way is then dried in the spray tower (4) and the powder-formed solid solution of the active ingredient is collected in the collection vessel (5).

The residual moisture of the spray powder, which should not be greater than 5 % (m/m), has an influence on the storage stability of the formulation and should thus be determined by appropriate experiments.

The process involved is illustrated below using the example of the spray drying of theophylline with Kollidon® 30:

Pure theophylline is a crystalline active ingredient with a melting point of approx. 270 °C (see Figure 2.15).

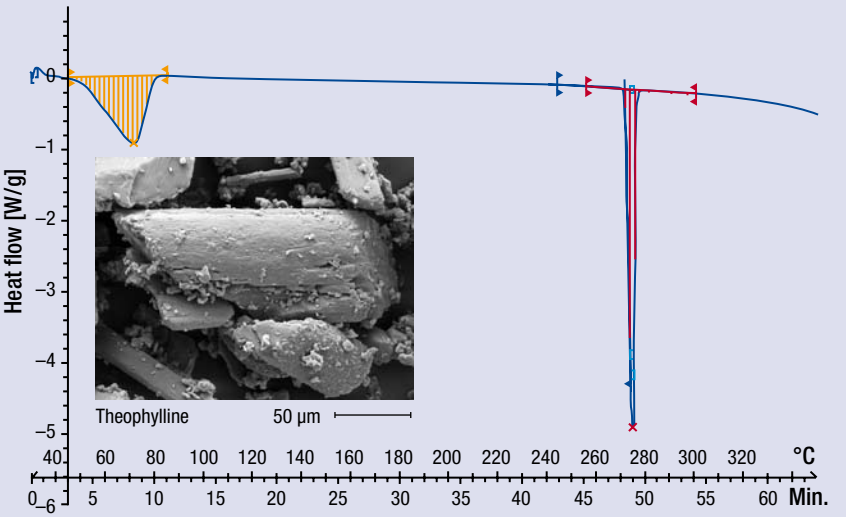


Figure 2.15 ■ REM image and DSC of pure theophylline

Pure Kollidon® 30 on the other hand is an amorphous polymeric excipient which forms hollow beads during spray drying. Apart from the vaporization of residual water in the area of 100 °C, no further energy aspects can be observed in the course of DSC (see Figure 2.16).

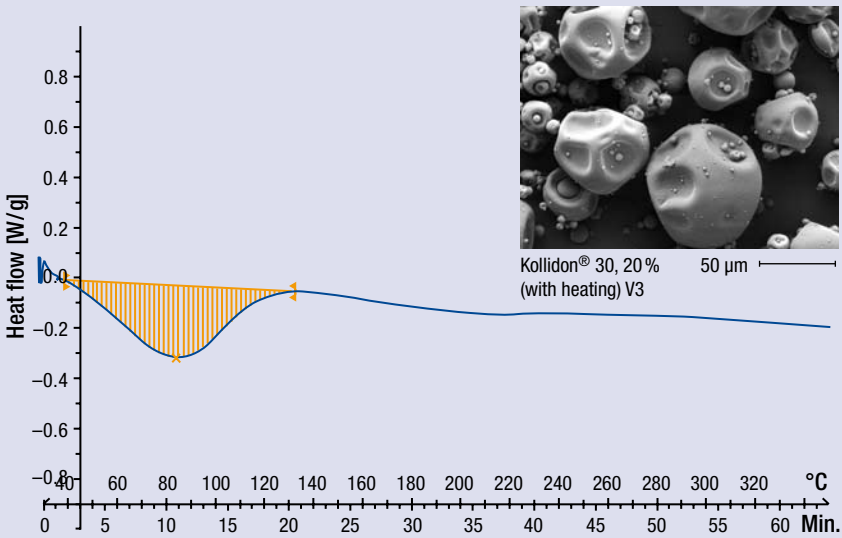


Figure 2.16 ■ REM image and DSC of pure Kollidon® 30line

In a pilot plant spray drying apparatus as shown in Figure 2.14, a mixture of Kollidon® 30 and theophylline were spray dried together. The mixture, comprising 10 % theophylline, 20 % Kollidon® 30 and 70 % water, was milled prior to spray drying in a stirred mixer mill and the particle size of the theophylline reduced to smaller than 5 µm. This suspension was then fed into the heat exchanger using a 3-stage piston membrane pump at a mass flow of 50 kg/h. The heat exchanger was heated with steam at 13 bar so that, after overheating, a temperature of 150 °C set in. The liquid was then atomized in a spray tower using a hollow cone pressure nozzle (bore diameter 0.6 mm) at a pressure of 100 bar. The spray tower was operated with nitrogen at an inlet temperature of 140 °C and an outlet temperature of approx. 100 °C. The spray dried powder was subsequently filtered using a tube filter.

By using this spray drying process, a powder was obtained that was very similar in appearance to pure Kollidon® 30 and that, in spite of a proportion of 1 / 3 theophylline, showed no crystalline melting peak in DSC (Figure 2.17).

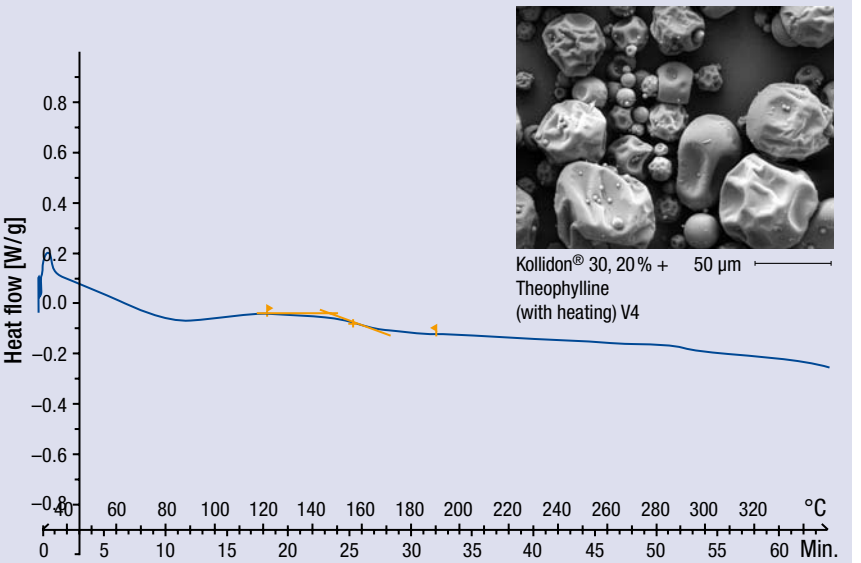


Figure 2.17 ▪ REM image and DSC of a spray dried mixture (1 / 3 theophylline, 2 / 3 Kollidon® 30)

The crystallinity of the pure theophylline (dark blue) is also shown in the x-ray structural analysis (XRD) (see Figure 2.18) while neither pure Kollidion 30 (red and yellow) nor the spray dried mixture (light blue) show crystalline structures. The combination of results from DSC and XRD clearly indicate the existence of a solid solution of theophylline in Kollidon® 30.

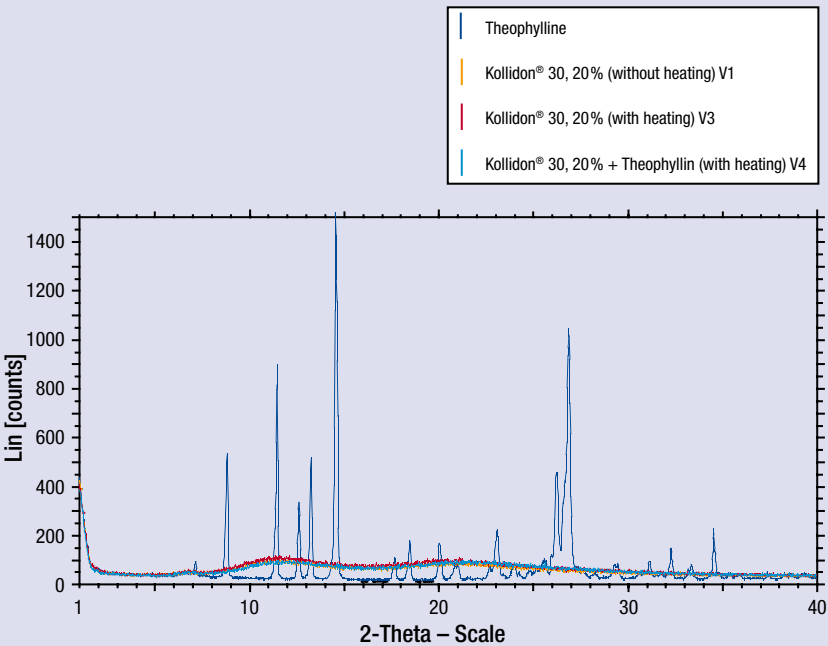


Figure 2.18 ■ X-ray structural analysis of theophylline, Kollidon® 30 and a solid solution of both

Even after lengthy storage the powder remained amorphous and no recrystallization of the theophylline occurred. This illustrates the high degree of suitability of the method for the manufacture of solid solutions.

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3 Investigation of solubilization efficacy using a high-throughput robot

3.1 Introduction

Pharmaceutical scientists are increasingly facing the challenge of formulating active pharmaceutical ingredients (APIs) that are poorly soluble in water. Such APIs are usually associated with low oral bioavailability. Four out of ten development candidates are discontinued due to insufficient “biopharmaceutical fitness” [47]. This trend is likely to continue: new APIs in pharmaceutical research are becoming more and more lipophilic and complex, given that combinatorial chemistry and pharmacological high-throughput screening (HTS) have become standard methods in the industry [48] and new drug targets are requiring more lipophilic API structures. Because of their problematic physico-chemical properties such as poor water solubility or low permeability, a large number of new chemical entities show poor bioavailability and consequently fail during the development phase [49-51]. Therefore, scientists around the world are currently trying to tackle the issue of bioavailability by developing novel strategies for increasing "biopharmaceutical fitness” during drug formulation. Such formulation strategies include pH adjustment, solid dispersions, particle size reduction, salts, co-solvents, SEDDS, micellar solutions and emulsions.

However, to date, scientists have still not been able to relate compound structures to the solubilizing activity of excipients. Thus, within the pharmaceutical industry, the solubilization effect is being examined more by the “trial and error” principle during early drug development. In conventional screening, this consumes large amounts of material, leads to long development times and consequently results in high development costs. The type and number of tested formulations is limited by the available time and the compounds on hand. However, the time required for experiments can be significantly reduced by applying HTS. The use of HTS provides absolutely reproducible and well-documented screening of the solubilization capacity of different solubilizers for various compounds [52, 53]. Moreover, it appears to be the only way of generating a sufficiently reliable database that allows the general structure-property relationships to be determined for deducing the solubilizing efficacy of solubilizer-compound combinations.

3.2 Kinetic and thermodynamic solubility

Many methods have been described on how to measure the solubility of compounds. Depending on the experimental set-up, the kinetic- or thermodynamic solubility of the compound in question can be measured.
For the determination of **kinetic (non-thermodynamic) solubility,** the compound is initially dissolved in an organic solvent (e.g. DMSO) and, in a second step, the

resulting stock solution is diluted in a well-stirred aqueous medium. Using the kinetic solubility approach, however, it is not possible to determine the possible influences of various polymorphic forms or the crystal lattice energy; this is because the compound has been pre-dissolved. Thus, the measured kinetic solubilities present the maximum solubility of the fastest precipitating modification of the compound. The kinetics of the compound therefore determine its "solubility" level.

The structure of this precipitating compound is unclear. It can be a crystal or amorphous form, a salt or co-crystal or even combinations of various possibilities [49]. Furthermore, as the process is time-dependant and supersaturation may occur, the obtained values lack reproducibility [54].

In addition, the kinetic method usually leads to a higher aqueous solubility compared to thermodynamic solubility. One reason for this is the presence of organic solvent, which acts as a co-solvent even at low concentrations (0.5–5 %) during measurement. Another reason for the higher aqueous solubility levels is the fact that the pre-dissolved compound is in a high energy state. This enhances the apparent solubility of the compound.

Figure 3.1 ▪ HTS robot at BASF for the determination of thermodynamic solubility

The determination of thermodynamic solubility (equilibrium solubility) is carried out by dosing a solid compound (in excess) into an aqueous medium. The measured solubility is the saturation solubility of the examined compound over the non-dissolved compound (equilibrium). Measurement of equilibrium solubility is commonly a single measurement after a defined time (24–72 h) for first assessments. Following these first screening experiments, it makes sense to verify the findings by determining the equilibrium solubility at different time points.

In contrast to the determination of kinetic solubility, the breakage of the crystal lattice plays an important role in thermodynamic solubility. Therefore, compounds in an amorphous state will have higher solubilities than compounds in the crystalline state. In solubility measurements, kinetic solubility is frequently determined using HTS [48]. The application of a compound dissolved in an organic liquid is faster and easier to handle. Furthermore, the quantity of compound required for a single test is lower (µg range) compared to a solid (mg range).

However, as the thermodynamic solubility measurement includes the dissolution step of the compound, this approach was used for setting up the HTS robot at BASF (Fig. 3.1).

3.3 Set-up of the Solu-HTS robot

3.3.1 Overview

The three-axes system moves either the needle or the dosing unit for powders to the different stations of preparation and analytics: Solid is weighed in the sample rack on the balance and solubilizer solutions are added to each sample. After incubation, the samples are diluted in the dilution rack and the amount of solubilized active ingredient determined by UV/VIS spectroscopy. The general set-up of the multi purpose HTS is shown in Fig. 3.2.

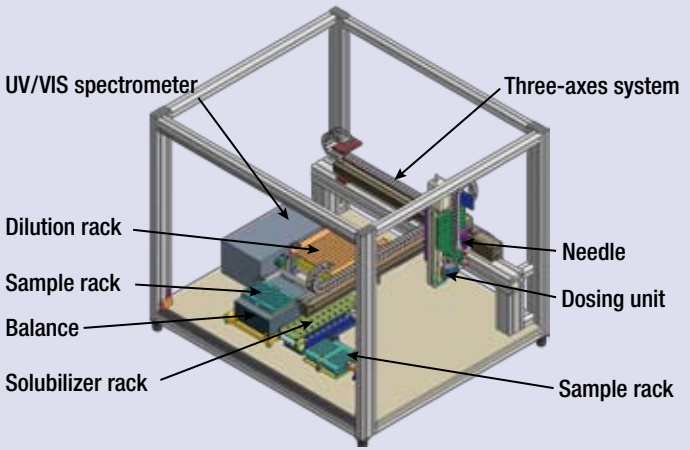


Figure 3.2 ▪ Set-up of the multi-purpose HTS Robot at BASF

The process can be divided into two parts:

- Sample preparation
- Sample analysis

Sample preparation is carried out by dosing solid active and liquid solubilizer solution into each well. For thermodynamic solubility, stirring bars are added and the samples incubated for 72 hours. Separation of the dissolved active and its solid form are performed by filtration and the amount of solubilized active determined via UV/VIS spectroscopy. The different processes performed by the robot are illustrated in Fig. 3.3.

Dosing	Dissolution	Filtration	Analysis	Data Processing
Solid actives Liquid solubilizer solution	Agitation Stirring		UV/VIS HPLC	Data elaboration Evaluation of results

Figure 3.3 ▪ Workflow of the multi-purpose HTS Robot

3.3.2 Preparation of samples

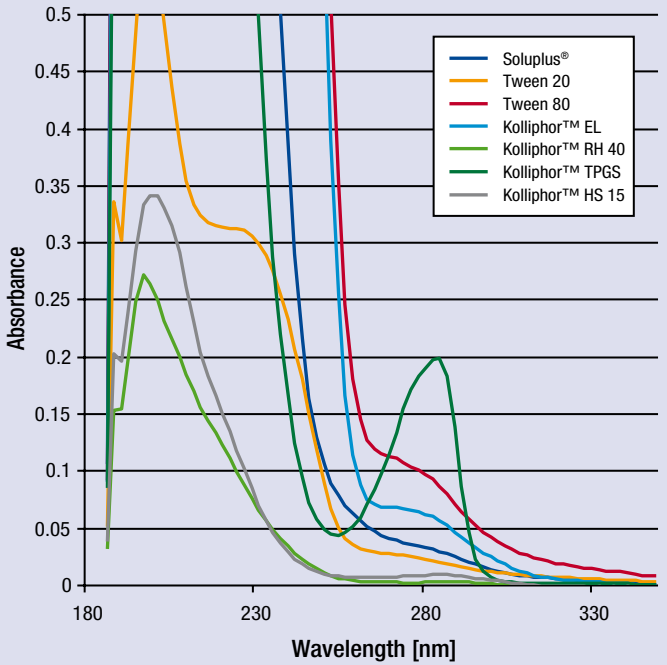
The set-up of the multi-purpose HTS robot allows for the dispensing of liquids and solids. Solubilizer solutions and API powders are dispensed into vials (Fig. 3.4). The amount of API to be added is set to 10 mg and the actual amount added is controlled using a balance (X404S DeltaRange, Mettler Toledo, Germany) and recorded. 0.5 mL of the solubilizer solution in phosphate buffer pH 7.0 is dispensed from a 1 % and 5 % (w/w) aqueous stock solution. Thermodynamic solubility measurement was used for setting up the HTS robot at BASF because it includes the dissolution step of the compound.

The 1.0 mL vials have standard dimensions and are placed on a standard tray to provide high operational freedom with regard to analytics such as UV/VIS spectroscopy or HPLC.

Figure 3.4 ▪ Preparation set-up showing the 3-axis robot arm and balance with vials

3.3.3 Analysis of dissolved API

After filtration of the saturated API solutions, each sample is analyzed by UV/VIS spectroscopy. For this purpose, the absorption spectra of pure active ingredient in terms of calibration curves as well as the absorption spectra of the pure solubilizers are measured during the same run (Fig. 3.5). Later, they are employed in the fitting procedure.



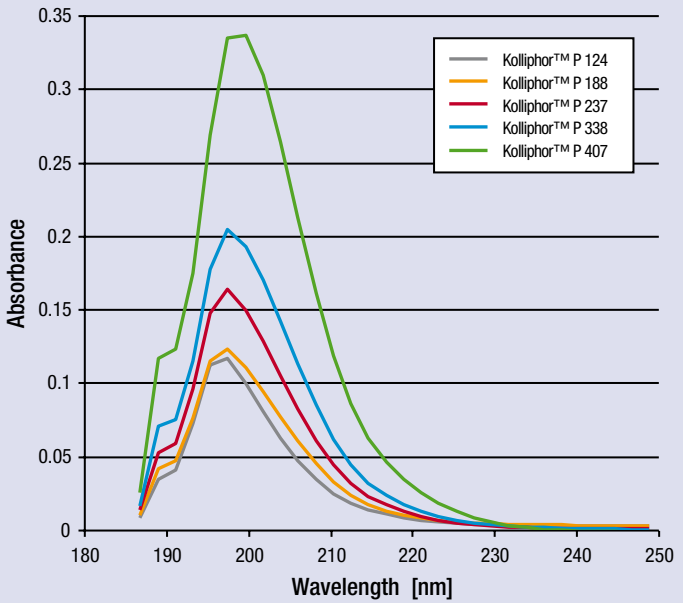


Figure 3.5 ▪ Absorption spectra of solubilizers

Soluplus®	> 260 nm	Kolliphor™ RH 40	> 210 nm
Tween 20	> 260 nm	Kolliphor™ TPGS	> 300 nm
Tween 80	> 270 nm	Kolliphor™ HS 15	> 210 nm
Kolliphor™ EL	> 270 nm	Kolliphor™ P grades	> 210 nm

The diode array monochromator covers a broad wavelength range (200–700 nm) and measures one full spectrum per second, usually over 100 seconds. The chromatogram (time/intensity graph) for the API-specific wavelength acts as a quality check for optimal performance of the robot. Overall, this leads to ~2 mill. data points per sample, which makes an automated data analysis a prerequisite. In the next step, the mean intensity value for each wavelength over 100 seconds and for each sample are generated and the active content calculated. This is performed by employing two different fitting procedures. The Peakfit method adds up the spectra of active and solubilizers and stores them in the database until the deviation from the measured spectrum is minimal (Fig. 3.6). With the area-over-baseline-method, a baseline is manually generated and the area over this baseline is compared to that of the pure API.

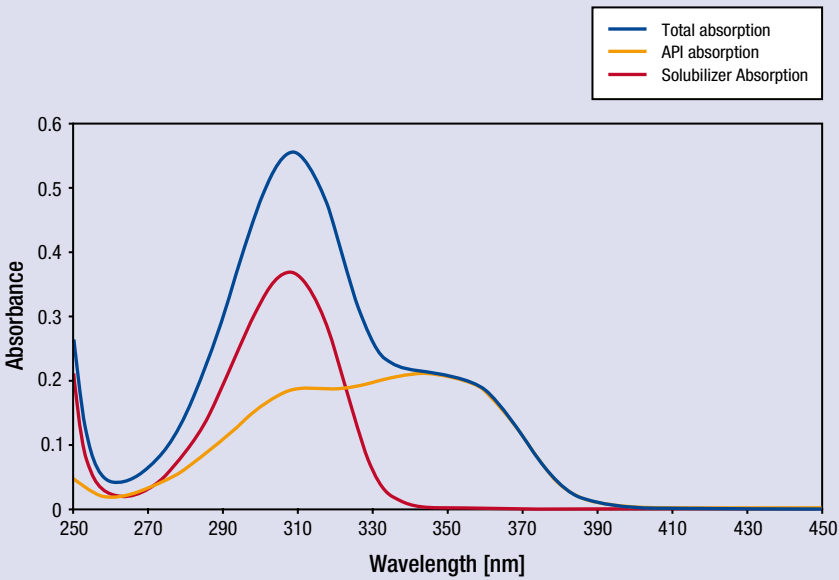


Figure 3.6 ▪ Absorption spectra of solubilizer, active and measured sample

3.4 Proof of concept: Manual vs. HTS experiments

The purpose of this study was to set up an HTS robot for the solubilization of poorly soluble APIs. Carbamazepine was used as a model API and the solubilization capacity of various solubilizers for this API was determined. Screenings obtained with the help of the robot benefit from automation, miniaturization and parallelization. It can be used to accelerate research projects and to scan various influencing parameters simultaneously. For proof of the concept, the results obtained were compared to the data from manual experiments in the lab.

3.4.1 Materials

Carbamazepine

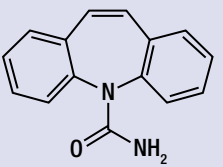


Table 3.1 ▪ Overview of solubilizers tested:

Name	Chemistry	Supplier
Kolliphor™ RH 40	Polyoxyl 40 hydrogenated castor oil Macrogolglycerol hydroxystearate Polyoxyl 35 castor oil	BASF SE
Kolliphor™ EL / ELP	Macrogolglycerol ricinoleate	BASF SE
Kolliphor™ HS 15	Macrogol 15 hydroxystearate	BASF SE
Kolliphor™ P 188	Poloxamer 188	BASF SE
Kolliphor™ P 407	Poloxamer 407	BASF SE
Tween 20	Polysorbate 20	Croda Plc
Tween 80	Polysorbate 80	Croda Plc
Kolliphor™ TPGS	D-α-Tocopheryl polyethylene glycol 1000 succinate	BASF SE

3.4.2 Determination of dissolved carbamazepine

Following incubation and a filtration step, a 1:10 dilution with a phosphate buffer/methanol 1:1 (v/v) mixture was carried out to avoid precipitation of the API. 0.1 mL of the diluted sample was then analyzed automatically using the incorporated UV spectrometer (DDT3200, Duratec, Germany) at a wavelength of 286 nm. In the case

of maximal absorbance being higher than 1.0, an appropriate second dilution step was automatically performed. In the manual trials, all steps were performed by a Ph. D. student. Evaluation of solubilized carbamazepine for the manually prepared samples was carried out using a Hewlett Packard HP8452A Diode Array UV/VIS spectrometer.

3.4.3 Results and discussion

The use of solubilizers resulted in an improvement in the saturation solubility of carbamazepine in all cases. The saturation solubility achieved for the different solubilizers tested ranged from approximately 190 ppm using Kolliphor™ P 188 to 610 ppm for Kolliphor™ TPGS at 1 % solubilizer concentration as detected by the UV/VIS spectrometer built into the HTS robot.

Kolliphor™ TPGS proved to be the most efficient solubilizer for carbamazepine and resulted in the highest saturation solubility.

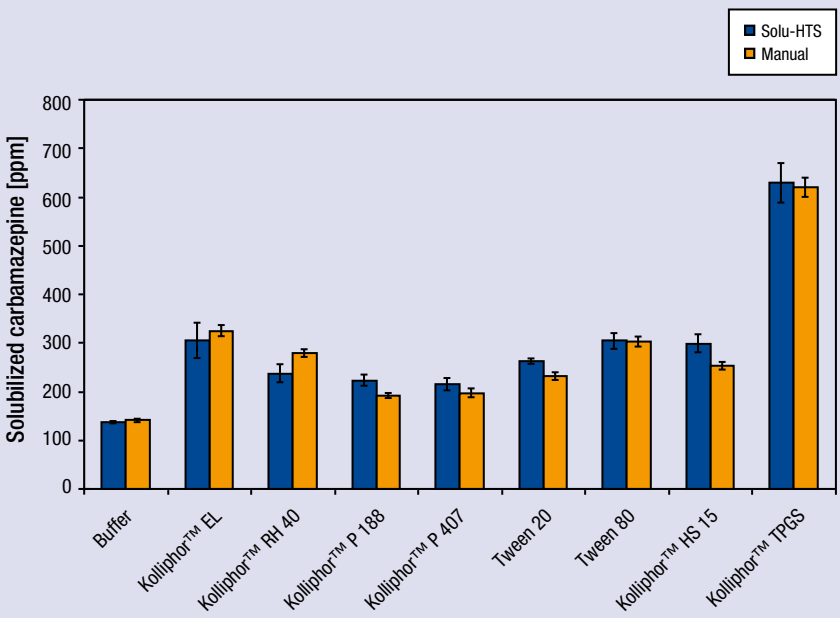


Figure 3.7 ▪ Comparison of the saturation solubility of carbamazepine obtained by two different methods – at a solubilizer concentration of 1 % (w/w)

The experiments showed that the use of an HTS robot for screening trials can help to save development time. The trials with the HTS robot took two days while the manually performed experiments by one operator took three times as long. As these were the first test trials using the robot, it can be expected that the analyzing speed in future trials can be increased due to optimization of the processes.

An additional benefit compared to manual work is perfect reproducibility of the dispensing steps and the automated documentation of parameters and results in a database. This data can be used in the evaluation step for data mining and statistical analysis to extract correlations and structure-property relationships.

3.5 Conclusion

The HTS robot was successfully used for the fast screening of different solubilizers with carbamazepine as a model API. The data obtained were comparable to the manually obtained results. The use of the HTS robot allowed for a large number of data and increased the information output significantly due to the built-in software. Therefore, this approach helps to reduce development time. The benefits are summarized in Table 3.2.

Table 3.2 ▪ Comparison of manual screening and screening with an HTS robot:

	Manual	HTS
Number of screened solubilizers*	Low	High
Amount of work	High	Low
Time requirement	High	Low
Repeatability	Medium	High
Documentation	Unknown	Full

*In a given time

It is to be expected that, using the HTS robot, a comprehensive database will be obtained, allowing for the correlation of the API structure and solubilization capacity of different solubilizers for specific APIs.

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Thomas Reintjes

4 Overview chart: BASF pharma polymers for solubility enhancement

4.1 General notes

The chart below gives an overview of the pharmaceutical excipients that are presented in detail in the next chapters. Besides their mode of action and state at room temperature (RT), at least one recommended application (dosage form or process) is given for each excipient. And while both mode of action and state are quite clear for most of the substances listed, a specific application is sometimes difficult to define. Some of the excipients have already been used for decades in various applications; others are quite new and little experience has been gathered to date. The same is true for the different applications: processes such as hot-melt extrusion (HME) for example are still relatively new to the pharmaceutical industry and thus not all the excipients have been extensively investigated for this specific process. Consequently, the recommendation of an excipient for a certain application should not exclude it from any other applications.

4.2 Chart legend

The mode of action is separated into:

Micellization M and complex formation C or a combination of both MC.

The second column divides the substances according to their state at room temperature into:

Solid S pasty P and liquid L.

The suitability of a certain substance for a specific application or process is expressed by:

++ if it is strongly recommended or by + if it is recommended but other substances are expected to perform even better. However, even if neither "strongly recommended", nor "recommended" is stated for a particular substance, it does not mean that this substance cannot be used for this specific process/application at all, but that possibly no convincing experiments have been performed to date.

4.3 Application chart

Substance	Mode of action	State (RT)	Recommended application						
			Topical formulation (ointment / gel)	Oral solution	Parenteral solution	Matrix in soft gel capsules	Matrix for HME	Plasticizer for HME	Matrix for spray drying
Soluplus®	MC	S					++		++
Kolliphor™ TPGS	M	S	+	+		++		+	
Kolliphor™ HS 15	M	P	+	+	++	+			
Kolliphor™ RH 40	M	P	+	++		++		+	
Kolliphor™ EL	M	L	++	+		+			
ELP	M	P	+	+	++	+			
Kollisolv™ P 124	M	L	+	+		++			
Kolliphor™ P 188	M	S	+	+				+	
micro	M	S	+	+				++	
Kolliphor™ P 237	M	S	+	+					
Kolliphor™ P 338	M	S	++	+					
Kolliphor™ P 407	M	S	++	+				+	
micro	M	S	+	+				++	
Kollidon® 12 PF	C	S		+	++		++		+
Kollidon® 17 PF	C	S		+	++				+
Kollidon® 25 / 30	C	S		++					++
Kollidon® VA 64 / Fine	C	S					++		+

Dejan Djuric

5 Soluplus®

5.1 Composition

Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, which was particularly developed for solid solutions. Due to its bifunctional character, it is able to act as a matrix polymer for solid solutions on the one hand, while being capable of solubilizing poorly soluble drugs in aqueous media on the other.

Soluplus® is a polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft copolymer (13 % PEG 6000 / 57 % vinyl caprolactam / 30 % vinyl acetate). It has a PEG 6000 backbone with one or two side chains consisting of vinyl acetate randomly copolymerized with vinyl caprolactam (Fig. 5.1).

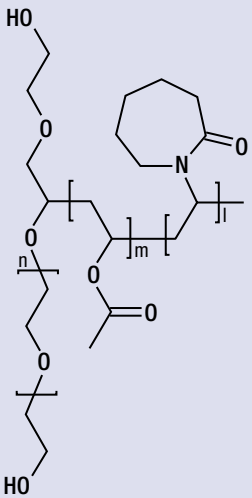


Figure 5.1 ▪ Chemical structure of Soluplus®

5.2 Properties

Soluplus® is available as free-flowing white to slightly yellowish granules with a faint characteristic odor and practically no taste. The spherically shaped granules (Fig. 5.2) have a mean particle size of approximately 340 µm (determined by laser diffraction); this ensures proper feeding of the extruder during processing.

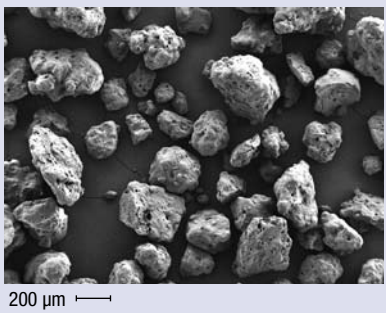


Figure 5.2 ▪ SEM picture of Soluplus® granules

The molecular weight of the polymer was determined by means of gel permeation chromatography (reference: polymethyl methacrylate) and has an average value of 118,000 g / mol (Fig. 5.3).

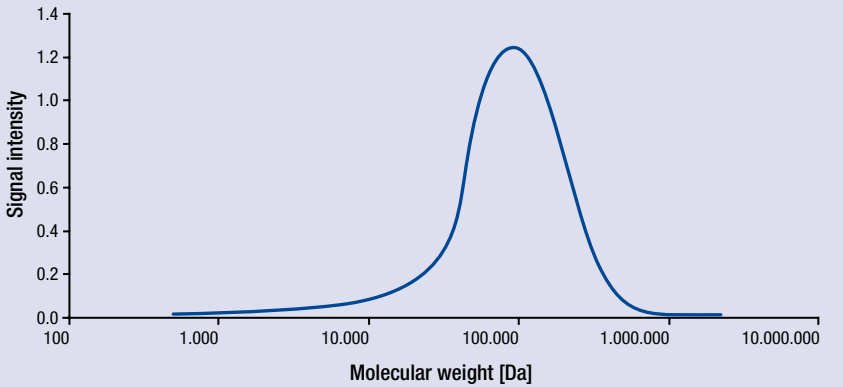


Figure 5.3 ▪ Molecular weight distribution of Soluplus®

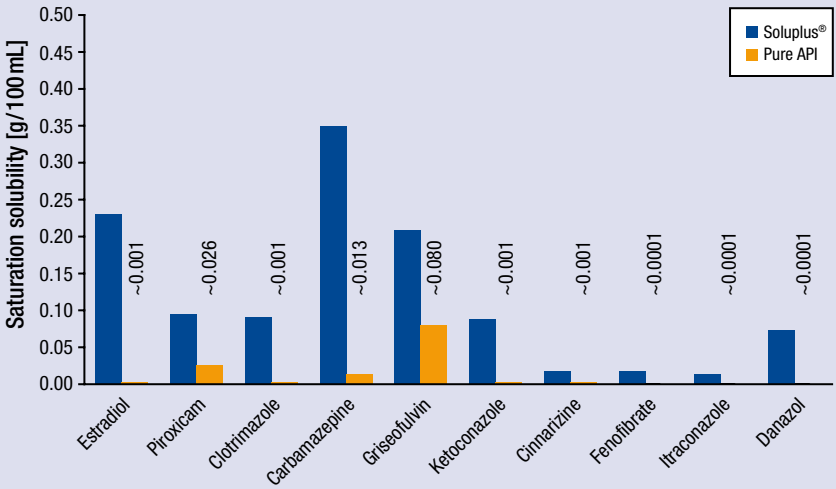
Since it was primarily developed for solid solutions, i. e. by means of hot-melt extrusion, the glass transition temperature (T_g) of the polymer was adjusted to approximately 70 °C in order to enable extrudability at lower temperatures compared to already known polymers. Moreover, the T_g is still high enough to provide sufficient rigidness for proper storage stability of the final solid solution.

Having an amphiphilic structure, Soluplus® also has a detectable critical micelle concentration (CMC = 7.6 mg / L) which is much lower than can be found with classical low-molecular weight surfactants.

5.3 Applications

Solubilization

Soluplus® can be used as a solubilizer in aqueous media for oral purposes. This can be realized for example when using it as a binder or in a simple suspension respectively. In order to confirm this, solubilization capacity was determined in duplicate by means of saturation solubility. A 10 % solution (w / w) of solubilizer in buffer media was oversaturated with active and stirred for 72 h at room temperature. The resulting suspension was filtered through a 0.45 µm filter. The amount of dissolved active was detected by UV spectroscopy (Hewlett Packard 8452A). Saturation solubility was expressed as a mean value in g / 100 mL as shown in Fig. 5.4.



10% solubilizer solution, saturation solubility in phosphate buffer pH 7.0 detected after 72 h stirring

Figure 5.4 ▪ Solubilization capacity of Soluplus® for poorly soluble actives

The use of Soluplus® resulted in increased solubility for all tested actives. The 10 % solubilizer solution enabled saturation solubilities ranging from 0.013 g/100 mL for itraconazole to 0.35 g/100 mL for carbamazepine. The saturation solubilities that were detected for the pure actives were all below 0.08 g/100 mL. With the use of Soluplus®, these values could be increased more than one hundredfold, e. g. in the case of estradiol, danazol or fenofibrate. A preference for solubilization of Soluplus® for discrete chemical structures could not be detected since a variety of different actives were solubilized successfully.

Extrusion and bioavailability enhancement

For formulation scientists, it has always been a challenge to overcome the issue of low bioavailability [55]. A popular technique for increasing the solubility and bioavailability is the formation of solid solutions prepared by hot-melt extrusion [56]. The effect of solubility enhancement can be shown by drug release studies; however, it can be verified more successfully by conducting bioavailability tests. Itraconazole as a poorly water-soluble drug was chosen to prove bioavailability enhancement when forming solid solutions with Soluplus®. A solid solution was prepared by hot-melt extrusion and administered to dogs. For comparison, in vitro drug release tests were performed as well.

Extrudates with 15 % itraconazole and 85 % Soluplus® were prepared using a 16 mm twin-screw extruder (Polylab, ThermoFisher, Germany) at 1 kg/h powder feed rate and 200 rpm screw speed at 150 °C.

XRD analysis revealed that no crystalline substance could be detected within the freshly extruded solid solution. In vitro dissolution testing of crystalline itraconazole led to ~4 % drug release of the tested 100 mg, which approximately equals the saturation solubility of the active in the applied 700 mL HCl (Fig. 5.6).

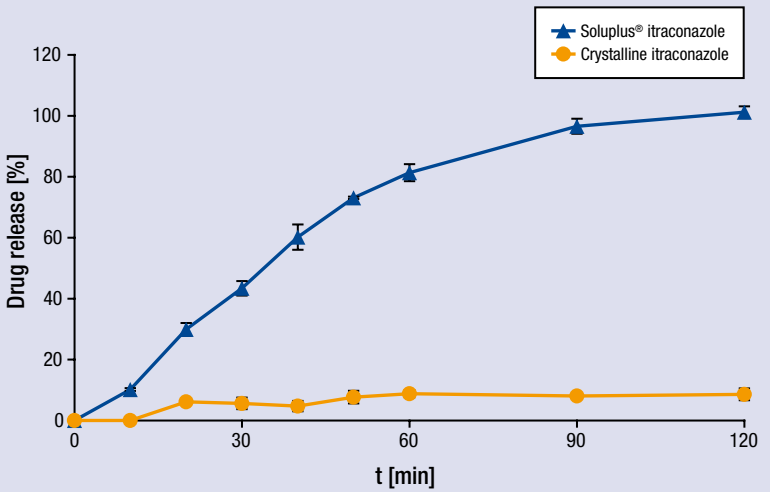


Figure 5.5 ▪ Drug release of itraconazole from extrudates with Soluplus® compared to crystalline substance

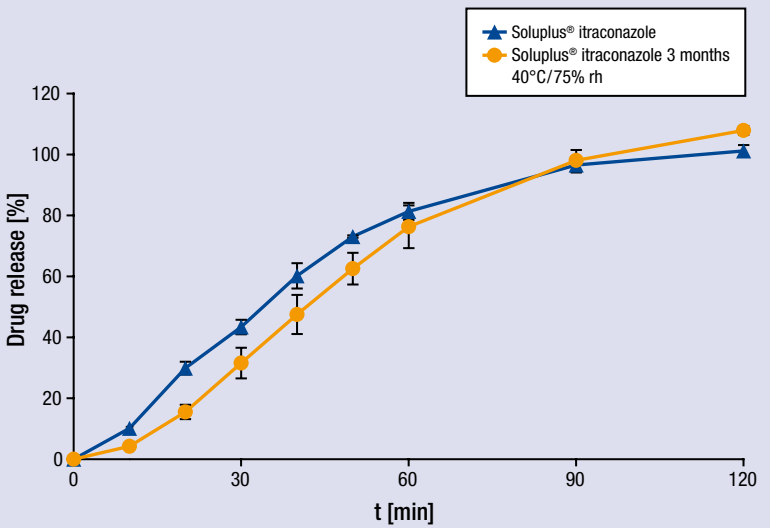


Figure 5.6 ▪ Drug release of itraconazole from fresh extrudates and after storage at 40 °C/75 % for 3 months

In comparison, the solid solution of Soluplus® and itraconazole showed complete drug release, itraconazole achieving oversaturation in the dissolution medium. After storage for 3 months under accelerated conditions in closed glass bottles, drug release was comparable and the extrudates were XRD-amorphous (Fig. 5.7).

The in vivo tests were performed on beagles (n = 5) over 21 days (3 administrations at intervals of 7 days). 10 mg API/kg bodyweight and day were administered orally at fasted state. Blood sampling was performed before the administration of drug substances and then at 0.5, 1, 2, 4, 6, 8 and 24 h after administration. For the dog formulations, the extruded strands were milled with an analytical mill (A 10, IKA, Germany) for 15 seconds and then sieved through a 500 µm sieve. For comparison, crystalline itraconazole was also administered. The results are shown in Fig. 5.8.

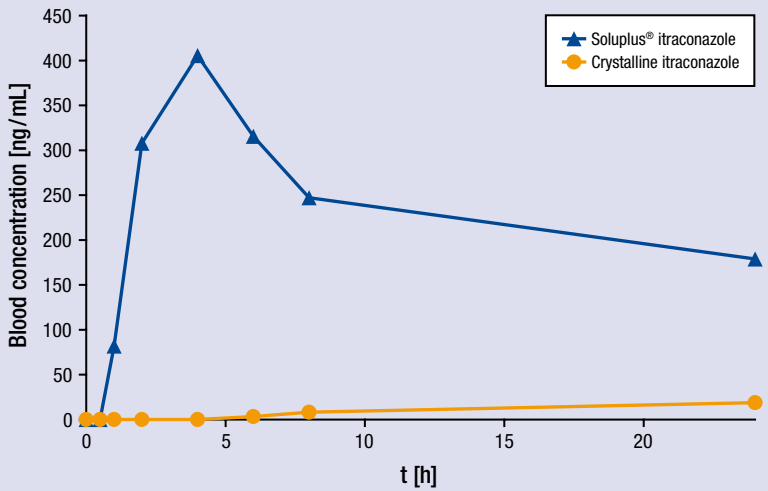


Figure 5.7 ▪ Blood concentration of itraconazole formulations in dogs (mean, n=5)

In contrast to the slight drug release in vitro, crystalline itraconazole was not absorbed by the dogs. The blood concentrations were below the detection limit. However, administration of solid solutions with itraconazole resulted in high blood concentration levels with a maximum blood concentration after 4 h.

Finally, with the use of Soluplus®, complete drug release of poorly soluble itraconazole could be realized in vitro as well as bioavailability enhancement in vivo.

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Jochen Dressler

6 Kolliphor™ TPGS

6.1 Composition

Kolliphor™ TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate) is a D-alpha vitamin E ester derived from natural vitamin E. TPGS is manufactured by esterification of natural d-α-tocopheryl succinate with polyethylene glycol 1000.

The resulting product is a mixture containing mainly monoester (Fig. 6.1), a certain amount of diester and residual free PEG 1000. The empirical formula of TPGS is $C_{33}O_5H_{54}(CH_2CH_2O)_{20–22}$ (molecular weight: ~ 1513 g / mol).

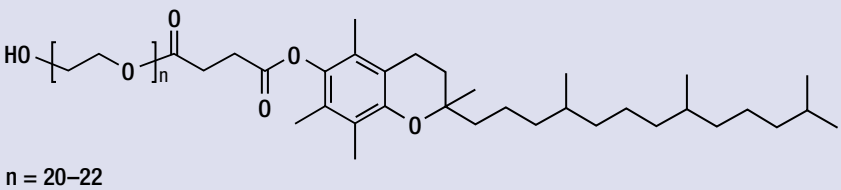

Figure 6.1 ▪ Chemical structure of Kolliphor™ TPGS

Table 6.1 ▪ Monograph listing, names and declaration

USP / NF Monograph Name	Vitamin E polyethylene glycol succinate
INCI Name	Tocophersolan
CAS Number	9002-96-4
EINECS Number	Polymer

6.2 Properties

Kolliphor™ TPGS is a non-ionic surfactant with amphiphilic character: The tocopheryl succinate moiety acts as the lipophilic part while the polyethylene glycol structure can be seen as the hydrophilic part. Further properties are summarized in Table 6.2.

Table 6.2 ▪ Overview of the physical and chemical properties of TPGS [57]

Molecular weight	approx. 1513 g/mol
Physical form	waxy solid
Specific gravity at 45 °C	approx. 1.06
Melting Point	37 – 41 °C
Appearance	white to light brown
Gardner color	max. 10
Vitamin E content	260 – 300 mg / g as d-alpha-tocopherol
Potency	387 – 447 I.U. / g
Solubility in water	miscible in all parts
HLB value	approx. 13
Stability	stable in air and in solutions between a pH range of 4.5 to 7.5
Critical micelle concentration (CMC)	approx. 0.02 wt% (determination of surface tension at 37 °C; [1])
Dynamic viscosity (5% sol. in water)	approx. 1.5 mPa*s at 22 °C [10]

Kolliphor™ TPGS can be dissolved in water and is preferably used in aqueous concentrations from 0.5 to 20%. TPGS mainly improves the bioavailability of poorly soluble drugs by enhancing drug solubility as well as by modulating P-glycoprotein-dependent drug efflux mechanisms [58, 59, 60]. Due to its amphiphilic character, TPGS exhibits emulsifying properties and allows the formulation of O/W emulsions. TPGS has been used as a water-soluble source of natural vitamin E with high bioavailability, especially for patients suffering from vitamin E malabsorption. Although TPGS lacks the free hydroxyl group of vitamin E, it can still be used successfully as an antioxidant. A summary of the different fields of application is given in Table 6.3.

Table 6.3 ▪ Typical fields of application of Kolliphor™ TPGS:

- Solubilizer for poorly soluble drugs
- Bioavailability enhancer for BCS Class II, III, IV drugs
- Stabilizer for amorphous drugs or nanocrystal suspensions
- Drug permeability enhancer by inhibition of P-glycoprotein
- Emulsion vehicle (SEDDS; SMEDDS)
- Thermal binder for hot-melt granulation and hot-melt extrusion
- Water-soluble source of vitamin E
- Antioxidant
- Reduction of tissue and skin sensitivity to certain drugs
- Carrier for dermal applications

Prior to application, TPGS is melted, preferably by heating the whole container up to 60 °C, and by gently mixing the molten mass to obtain a uniform melt which is then dosed for further processing. Kolliphor™ TPGS can be molten and cooled in cycles several times without affecting the quality. The product can be sterilized and is thermally stable up to 200 °C. Thermal decomposition is observed at 215 °C during DSC analysis. If TPGS is melted using a water bath heating assembly, it is recommended to ensure that TPGS has no contact with water vapor for any length of time, even if TPGS is not hygroscopic.

The viscosity of aqueous TPGS solutions rises with increasing concentration. Additionally, during the heating of highly concentrated TPGS solutions, further viscosity increases can be observed above 70 °C (Table 6.4). Temperature-dependent viscosity increase is a reversible phenomenon which is observed for aqueous concentrations above 10 %.

Table 6.4 ▪ Influence of heat and concentration on solution viscosity (Brookfield)

	Temperature [°C] / Viscosity [mPa*s]			
TPGS concentration wt %	20	60	70	80
10	< 10 mPa*s	< 10 mPa*s	< 10 mPa*s	50 mPa*s
20	< 10 mPa*s	10 mPa*s	530 mPa*s	5620 mPa*s

Kolliphor™ TPGS remains stable for several years under ambient storage conditions in closed containers . Aqueous solutions of TPGS are stable at a pH range between pH 4.5 and 7.5. Hydrolysis of the TPGS ester can occur under acidic conditions below pH 1.8 and under alkaline conditions above pH 10.

Kolliphor™ TPGS is compatible with many commonly used pharmaceutical excipients; some examples are given in Table 6.5.

Table 6.5 ▪ Examples of the compatibility of TPGS with common excipients:

TPGS is compatible with:	
Calcium carbonate	Cellulose derivatives (HPMC)
Fumed silica	Glycerin
Lactose	Magnesium stearate
Microcrystalline cellulose (MCC)	Polyethylene glycol, propylene glycol
Polysorbate 20	Polysorbate 60
Polysorbate 80	Polyvinylpyrrolidone
TPGS is incompatible with:	
Citric acid, sodium bicarbonate	Sodium lauryl sulfate (at high concentrations)

6.3 Applications

Kolliphor™ TPGS can be used to improve the solubility of poorly soluble drugs in tablets or capsules [61]. For tableting or filling hard capsules, hot-melt granulation can be performed using TPGS as a binder for granulation. Active ingredients can be admixed to the binder in the molten state if they are not heat-sensitive. The following application example is the formulation of vitamin E tablets (Table 6.6) that can be used as a dietary supplement if normal vitamin E cannot be absorbed by patients with vitamin E malabsorption [62].

Table 6.6 ▪ Examples of tablet formulation as a vitamin E supplement:

Substance name	Function	Amount [%]
Kolliphor™ TPGS	Active pharmaceutical ingredient API	15.68
Fujicalin SG	Filler / binder	54.05
Ethanol 96 %	Solvent	30.27
		Total 100

Fujicalin (highly porous dibasic calcium phosphate, anhydrous; Fuji Chemical Industry Co., Ltd) is granulated/wetted with a solution of Kolliphor™ TPGS in ethanol using a high shear mixer that can be operated with organic solvents. Granulation is carried out for 15 minutes at low speed to allow uniform incorporation of TPGS into the porous particles. The powder is gently dried under reduced atmospheric pressure or in a fluidized bed dryer to remove residual ethanol while the product temperature is maintained below 35 °C. The granules are compressed into tablets of 1.2 g. Due to the self-lubricating properties of TPGS, it might not be necessary to use additional lubricant. In this example, one tablet contains about 100 I.U. of natural vitamin E.

To enhance the solubility of poorly soluble drugs, it is recommended to melt the drug together with TPGS and eventually together with additional co-solvents such as polyethylene glycol 400. The melt can be liquid-filled into hard capsules where it solidifies, added to water to form an emulsion that can be further used for nasal and pulmonary applications [63] or spray dried together with additional excipients [64] (e.g. mannitol, lactose, hypromellose) to obtain a solid dispersion or solid solution. Instead of formulating a melt, TPGS and the active can also be dissolved in an appropriate organic solvent and – if necessary – a co-solvent (e.g. PEG 400 or propylene glycol) can be added. In this context it is recommended to dissolve the active in TPGS first before further diluting in the aqueous phase since this order is relevant for proper micelle formation and for good solubilization results.

Kolliphor™ TPGS has been widely investigated for the solubility enhancement of poorly soluble drugs. Using the Solu-HTS screening system, different concentrations of Kolliphor™ TPGS have been successfully tested as solubilizers for selected active ingredients. The solubility of carbamazepine, which is used as an anticonvulsant, can be markedly increased using TPGS (Fig. 6.2). This finding was also confirmed in dissolution studies [65].

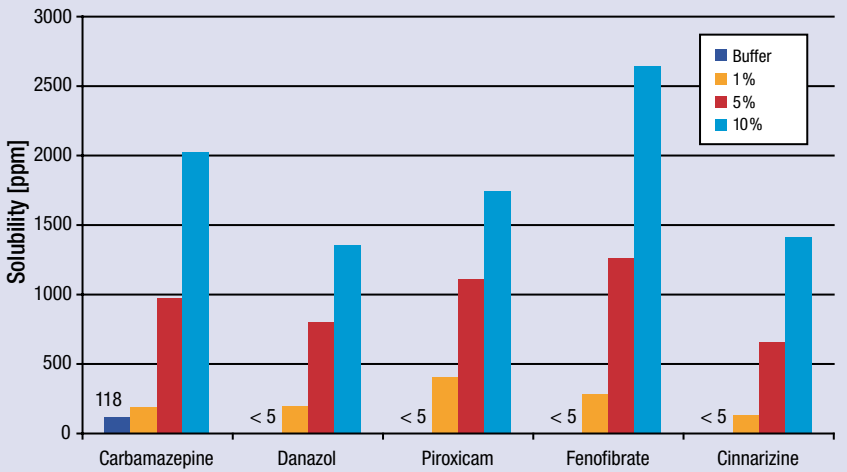

Figure 6.2 ▪ TPGS increases drug solubility in a concentration-dependent manner during Solu-HTS screening experiments

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7 Kolliphor™ HS 15

7.1 Composition

Kolliphor™ HS 15 is a non-ionic solubilizer and emulsifying agent. It is comprised of 15 moles of ethylene oxide and 1 mole of 12-hydroxy stearic acid. The ethoxylation reaction can take place on the carboxylic group or the hydroxyl group of the fatty acid, or on both functional groups. Thus, Kolliphor™ HS 15 is a mixture of polyglycol mono- and di-esters of 12-hydroxystearic acid derivatives (Fig. 7.1, A and B), and about 30 % of free polyethylene glycol.

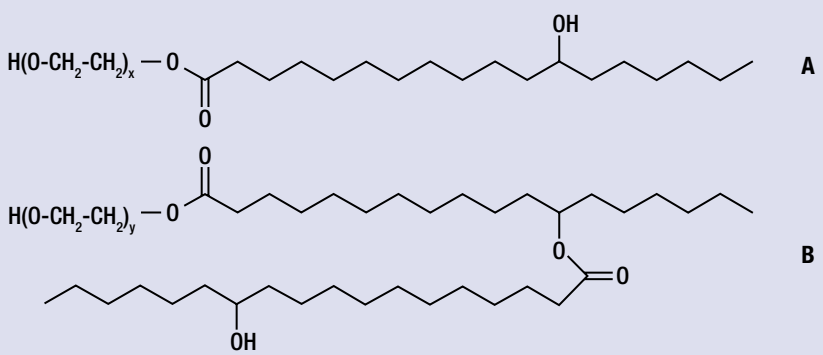

Figure 7.1 ▪ Chemical structures of the main components in Kolliphor™ HS 15

The synthesis of Kolliphor™ HS 15 is shown in Fig. 7.2: Reaction of hydrogenated fatty acid (I) with ethylene oxide (II) in the presence of an alkaline catalyst yields the polyethoxylated major components III and V. Other minor components such as free polyethylene glycol (VII) and (IV and VI) are also formed. The 12-C atoms of the fatty acid chains in Kolliphor™ HS 15 are non-chiral and the product is a racemic mixture. The stereo configuration of C-12 atoms does not affect the functionality of Kolliphor™ HS 15 as a solubilizer.

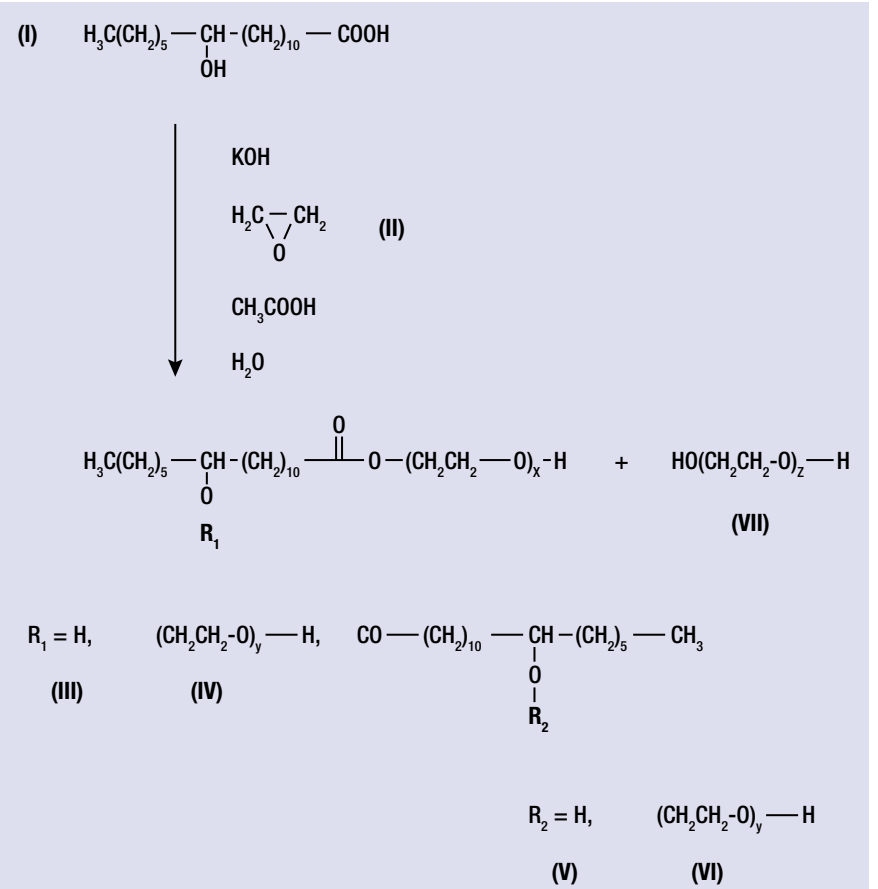

Figure 7.2 ▪ Reaction scheme for the synthesis of Kolliphor™ HS 15 (for explanations please see text).

No metallic catalysts are used in the manufacture of Kolliphor™ HS 15 and the manufacturing process does not require any purification steps except for the removal of water and volatile components under reduced pressure and at elevated temperatures.

Kolliphor™ HS 15 is also known by the chemical names, polyethylene glycol 15-hydroxy stearate and polyoxyl 15-hydroxystearate. The compendial names are: Macrogol 15 Hydroxystearate (Ph. Eur.) and Polyoxyl 15 Hydroxystearate (USP).

7.2 Properties

An overview of the different properties of Kolliphor™ HS 15 is given in Table 7.1; a summary of the complete specifications is available upon request.

Table 7.1 ▪ Properties of Kolliphor™ HS 15

Property	Observation
Appearance	Yellowish white paste, waxy
Melting point	~ 30 °C
Solubility	Freely soluble in water, ethanol, 2-propanol; insoluble in liquid paraffin
Viscosity (30 % solution)	20 mPas (20 °C)
pH	6 – 7
Hydrophilic lipophilic balance (HLB) [1,3]	14 – 16
Critical micelle concentration (CMC) [66, 67]	0.005 % – 0.02 %

The micelle sizes of pure Kolliphor™ HS 15 and with 0.1 % solubilizate in water are shown in Fig. 7.3 as a function of temperature. Photon correlation data suggests that the micelle size of 1 % Kolliphor™ HS 15 is about 10 nm, increasing to about 20 nm when 0.1 % solubilizate is incorporated. As the temperature increases to > 50 °C, the micelle size also increases with and without solubilizate (Fig. 7.3).

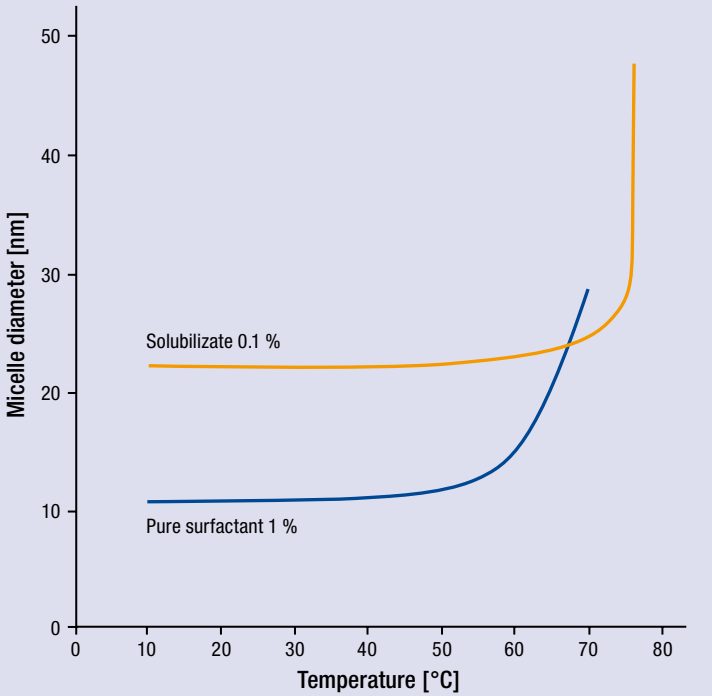

Figure 7.3 ▪ Micelle size as a function of temperature

Stability testing indicates that Kolliphor™ HS 15 is stable for at least 24 months if stored in the unopened original containers at room temperature (max. 25 °C). Additionally, Kolliphor™ HS 15 is stable over the ICH conditions for steam sterilization at 121 °C and 20 min. Tables 7.2 and 7.3 show the product's stability in pure and in solution before and after sterilization. The data indicates that Kolliphor™ HS 15 is stable under those conditions as no obvious changes are observed following steam sterilization. The pH may drop slightly during heating and this should be taken into account. Separation into phases may also occur, but this can be reversed by agitation. Aqueous solutions can be stabilized with the usual preservatives used in pharmaceuticals

Table 7.2 ▪ Stability of Kolliphor™ HS 15 as a raw material on autoclaving

Parameter	Untreated	Sterilization 121 °C; 20 Min.
Acid value (mg/g KOH)	0.2	0.2
Saponification value (mg/g KOH)	60	60
Hydroxyl value (mg/g KOH)	99	99

Table 7.3 ▪ Stability of 20 % Kolliphor™ HS 15 solution on autoclaving

Parameter	Untreated	Sterilization 121 °C; 20 Min.
Acid value (mg / g KOH)	0.1	0.2
Saponification value (mg / g KOH)	13	13.2
pH value	6.0	5.5
Micelle diameter (nm)	13	13

The safety of Kolliphor™ HS 15 was evaluated in beagles (n = 8) with reference to known solubilizers at a single dose level of 100 mg / kg. Table 7.4 shows the histamine release effects. Kolliphor™ HS 15 showed significantly less or no histamine release compared to Kolliphor™ EL and Polysorbate 80. No incidence of histamine reaction was observed with Kolliphor™ HS 15, but Kolliphor™ EL and Polysorbate 80 showed reactions in all the dogs.

Table 7.4 ▪ Effects of solubilizers on histamine release in dogs.

Solubilizer	Serum Histamine Level	
	Histamine level (ng / mL)	Incidence of histamine reaction
Polysorbate 80	400	8 / 8
Kolliphor™ EL	115	8 / 8
Kolliphor™ HS 15	< 10	0 / 8

7.3 Applications

A number of fat-soluble vitamins can be solubilized in Kolliphor™ HS 15 aqueous solutions for parenteral preparations; these include vitamins A, D, E and K, and several other lipophilic pharmaceutical active agents, such as propanidid, miconazole, alfadolone, alfaxalone, nifedipine and piroxicam amongst others.

A simple formulation of a fat-soluble vitamin is illustrated in Table 7.5, where Kolliphor™ HS 15 is used for the preparation of an aqueous solution of vitamin A. The preparation requires the slow addition and mixing of vitamin A palmitate in Kolliphor™ HS 15 at 60–65 °C. The mixture is then added slowly to water already heated to 60 °C. The solution turns cloudy, and thickening may occur initially due to hydration but the solution turns clear as viscosity decreases with further dilution with water.

Table 7.5 ▪ Aqueous formulation of vitamin A palmitate

Material	Amount
Vitamin A palmitate 1.7 million I.U./g	8.3 g
Kolliphor™ HS 15	25.0 g
Water, dist.	ad 100.0 mL

The solubilization capacity of such a formulation is presented in Fig. 7.4. Here it is obvious that the above mentioned formulation can solubilize about 100,000 international units (I.U.) of vitamin A per mL solution.

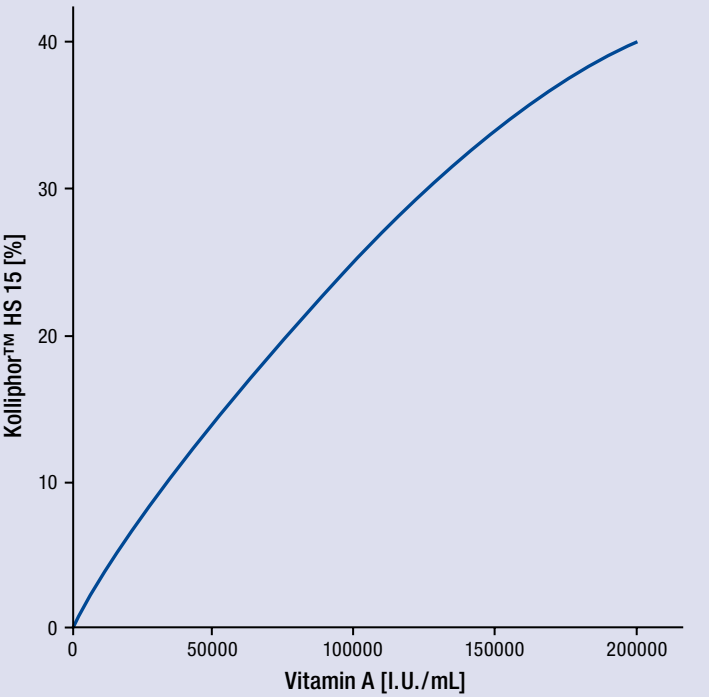

Figure 7.4 ▪ Solubilization of vitamin A palmitate 1.7 million I.U./g

Figure 7.5 illustrates the results of the robotic high-throughput screening (HTS) of poorly soluble drugs in buffer of pH 7.0 and solutions containing Kolliphor™ HS 15 at 1 %, 5 % and 10 % (w/v). Increasing the amounts of Kolliphor™ HS 15 from 1 % to 10 % increased the solubilization of all the drugs investigated. Thus, Kolliphor™ HS 15 successfully increased the solubility for a very broad range of different poorly soluble active pharmaceutical ingredients (APIs).

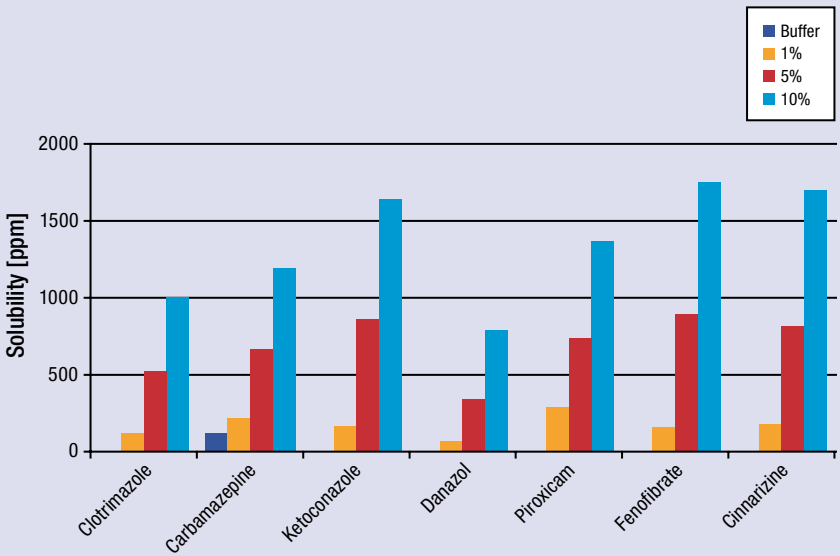

Figure 7.5 ▪ HTS solubilization screening of poorly soluble drugs in Kolliphor™ HS 15 solutions

The bioavailability of vitamin A was evaluated in broilers following intramuscular (IM) administration. The drug was dosed in Kolliphor™ HS 15 emulsions, organic solution and oily solution. Figure 7.6 shows the data from in vivo studies. The bio-distribution of drug in the liver was monitored by analyzing vitamin A acetate after 7 days of dosing. Kolliphor™ HS 15 emulsions improved liver uptake > 1.5-fold as compared to other vehicles.

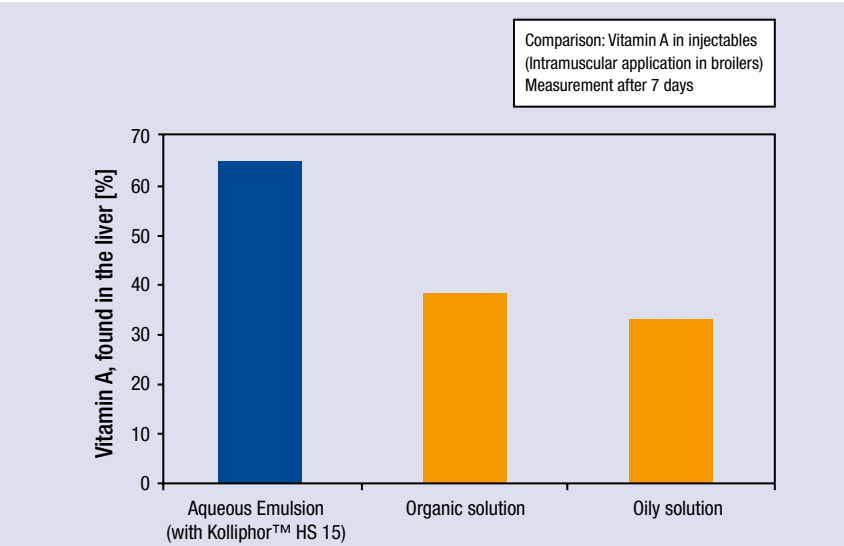

Figure 7.6 ▪ Liver uptake of vitamin A after intramuscular (IM) administration

Another method for delivering poorly soluble drugs with the help of Kolliphor™ HS 15 is the preparation of self-emulsifying and nano-emulsifying drug delivery systems (SEDDS and SNEDDS) with co-surfactants and/or co-solvents as has been reported in many studies [68–72]. Additionally, Kolliphor™ HS 15 has also demonstrated its ability to be used as a self-emulsifier in pellets [73–75].

Kolliphor™ HS 15 remains one of the most commonly used solubilizers in the pharmaceutical industry as the preferred choice for in vitro screening and in vivo evaluation of new chemical entities (NCEs). Progress has been made in recent years and many of the products are commercially available. Especially in parenteral formulations, Kolliphor™ HS 15 is used to increase the solubility of poorly soluble drugs such as propofol and colchicine among others [76–78].

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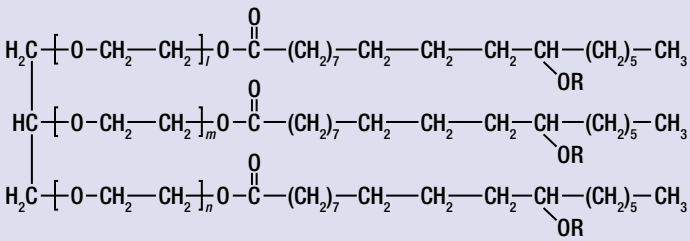
8 Kolliphor™ RH 40

8.1 Composition

Kolliphor™ RH 40 is a non-ionic solubilizer and emulsifying agent obtained by reacting 1 mole of hydrogenated castor oil with about 40–45 moles of ethylene oxide. It contains mainly the tri-hydroxystearate ester of ethoxylated glycerol (Figure 8.1), with smaller amounts of polyethylene glycol tri-hydroxystearate and the corresponding free glycols. The main component is therefore an amphiphilic molecule, with fatty acid esters forming the lipophilic part and glycerol polyethylene glycol ethers acting as the hydrophilic part. The molecular weight of the main component is around 2,900 g/mol.



where, l + m + n = 40-45; R = H of polyethylene glycol residue

Figure 8.1 ▪ Chemical structure of the main component in Kolliphor™ RH 40

The 12-C atoms of the fatty acid chains are achiral (racemic), which avoids potential isomerization of the hydroxyl group on the fatty acid chain. Changes in the ratios of enantiomers are not expected to affect the functionality of Kolliphor™ RH 40.

Kolliphor™ RH 40 (RH, hydrogenated ricinoleic acid) is also known by the chemical name, PEG 40 Hydrogenated Castor Oil, and the compendial names, Macrogol Glycerol Hydroxystearate (Ph. Eur.), and Polyoxyl 40 Hydrogenated Castor Oil (USP).

8.2 Properties

Kolliphor™ RH 40 is a waxy material, with almost no taste and which melts at 20–25 °C; thus, the question of polymorphism does not arise. Further properties are listed in Table 8.1.

Table 8.1 ▪ Properties of Kolliphor™ RH 40

Property	Observation
Appearance	White yellowish paste, odorless
Melting point	~ 25 °C
Solubility	Water, ethanol, propanol, 2-propanol, ethyl acetate, chloroform, carbon tetrachloride, toluene and xylene
Viscosity (30 % solution)	20 mPas (20 °C)
pH (10 % water)	6–7
Relative density	1.023–1.026 g/mL (25 °C, 30 % water).
Hydrophilic lipophilic balance (HLB)	14–16
Critical micelle concentration (CMC)	0.02 %

Pure Kolliphor™ RH 40 is chemically very stable. Prolonged exposure to elevated temperatures can cause physical separation into a liquid and a solid phase on cooling but the product can be restored to its original form by homogenization. Kolliphor™ RH 40 is stable in aqueous alcohol and purely aqueous solutions. However, it must be noted that strong bases or acids should not be added to avoid saponification of the ester components.

Aqueous Kolliphor™ RH 40 solutions can be sterilized by heating to 120 °C. Consideration must be given to the fact that this can cause a slight decrease in the pH value. The phases may also separate during sterilization, but this can be remedied by agitating the solution while it is still hot. The preservatives normally used in the pharmaceutical industry may be added to the aqueous solutions.

8.3 Applications

Aqueous solutions of fat-soluble vitamins A, D, E and K for oral and topical administration can be prepared with Kolliphor™ RH 40. For a clear aqueous solution, the fat-soluble vitamins must be thoroughly mixed with the solubilizer. For vitamin A preparations with Kolliphor™ RH 40, vitamin A palmitate 1.7 million I.U./g, or vitamin A propionate 2.5 million I.U./g should be used, while for vitamin K, vitamin K1 phytomenedione should be preferred.

The method for preparing the solubilizate is very important. The production of a 150,000 I.U./mL aqueous vitamin A palmitate solution is described in detail below as a typical example:

- Vitamin A palmitate (1.7 million I.U./g) 8.8 g
- Kolliphor™ RH 40 25.0 g
- Water ad. 100.0 mL

The vitamin is mixed with Kolliphor™ RH 40 and heated to 60–65 °C. The liquid is then added slowly to water heated to 60 °C and mixed. As mixing continues, the solution viscosity increases as the solution turns opalescent and then decreases as it clears up. Fig. 8.2 illustrates the solubilization capacity of Kolliphor™ RH 40 in highly concentrated aqueous solutions of vitamin A palmitate. Kolliphor™ HS 15 also behaves very similarly to Kolliphor™ RH 40 for the solubilization of vitamin A palmitate (see chapter 7).

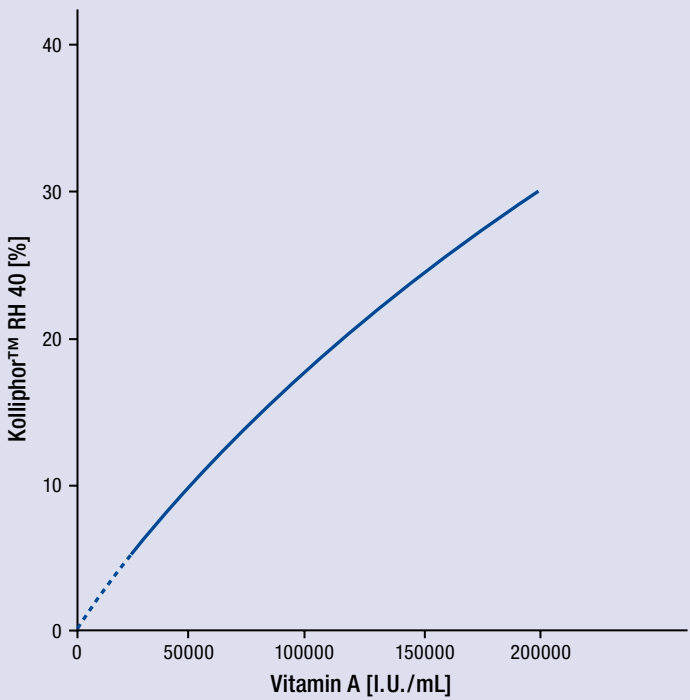


Figure 8.2 ▪ Solubilization of vitamin A palmitate 1.7 million I.U./g

Fig. 8.3 illustrates the solubilization capacity of Kolliphor™ RH 40 for different types of D vitamins. Relatively low concentrations of Kolliphor™ RH 40 (about 5 %) can significantly increase the solubility of vitamin D 2 and D 3. At a concentration of 5 % of Kolliphor™ RH 40 in solution, vitamin D 2 and D 3 were solubilized at 300,000 I. U. and 180,000 I. U. respectively.

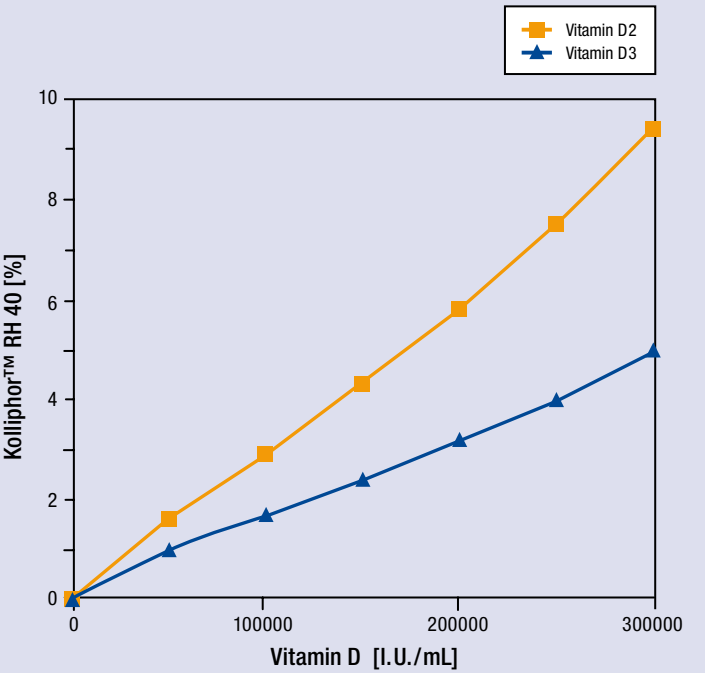


Figure 8.3 ▪ Solubilization capacity of Kolliphor™ RH 40 for Vitamins D 2 and D 3

Fig. 8.4 shows the results of high-throughput solubilization screening of a number of poorly soluble drugs in buffer and in solutions with Kolliphor™ RH 40 at 1 %, 5 % and 10 %. It is obvious that the solubilization of drugs increased with increasing amounts of Kolliphor™ RH 40 in the solutions. A similar trend is also observed with Kolliphor™ HS 15.

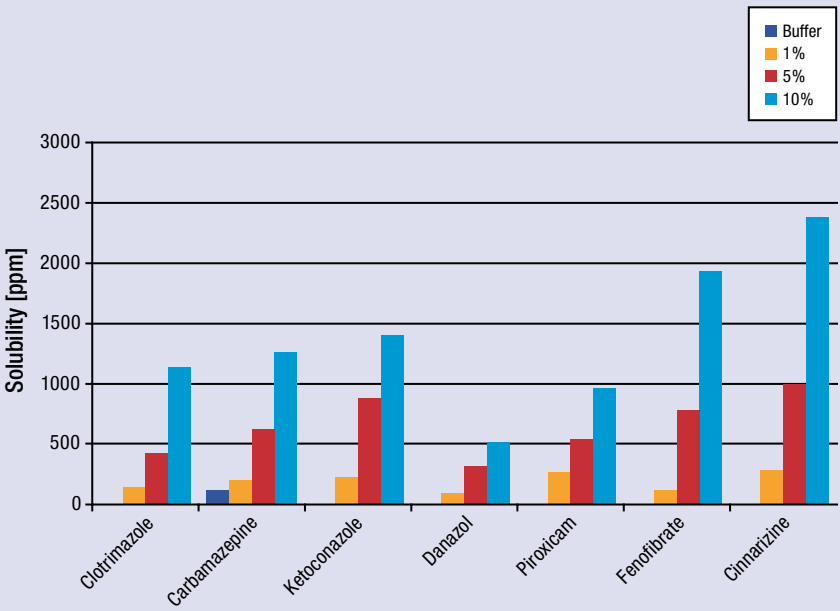


Figure 8.4 ▪ Solubilization of drugs in buffer and Kolliphor™ RH 40 solutions

Kolliphor™ RH 40 is widely used as a solubilizer in combination with a co-solubilizer and/or co-solvent in self-emulsifying drug delivery systems (SEDDS) or micro-emulsifying systems (SMEDDS) [79–83]. A recent study by Cuine et al. suggests that Kolliphor™ RH 40 is stable in the solution and less subjected to lipolysis in the gastrointestinal tract compared to many ester-linked short and long unsaturated fatty acids [84]. An example is Neoral®, a soft gelatine capsule formulation of cyclosporine, which contains Kolliphor™ RH 40 in combination with ethanol, propylene glycol and glycerol (see also chapter 1).

Kolliphor™ RH 40 is used in concentrations of about 2 % as a taste masking agent for caffeine [85]. Though the mechanism of the taste masking effect of Kolliphor™ RH 40 remains to be investigated, the author suggests that it is the coating of taste bud receptors in the mouth that mimics the taste of bitter drugs. In combination with the aforementioned features, stability with regard to digestion and its self- emulsifying properties, Kolliphor™ RH 40 is especially suitable for oral applications. However, many alternative fields of application exist: Kolliphor™ RH 40 is also useful for example in melt extrusion, where it can act as a plasticizer for different polymers [86].

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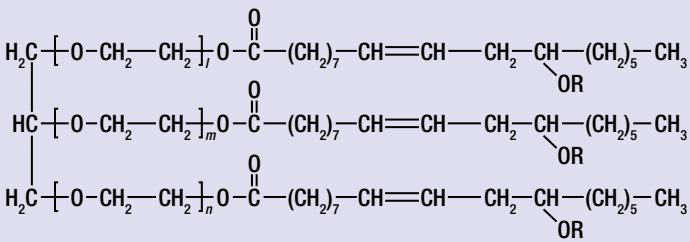
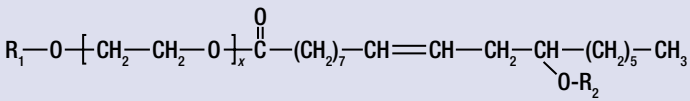
9 Kolliphor™ EL/ELP

9.1 Composition

Kolliphor™ EL (or ELP) is synthesized by reacting castor oil (glycerol triricinoleate) with ethylene oxide. The main components of Kolliphor™ EL are: **(A)** triricinoleate esters of ethoxylated glycerol, **(B)** polyethylene glycol ricinoleates and derivatives of these with polyethoxylated 12-hydroxy ricinoleic acid residues. Thus, Kolliphor™ EL is a non-uniform product lacking a single well-defined formula or structure.



(A) l + m + n = 35 (nominal value); R = H or polyethylene glycol residue



(B) x = 0…40; R_1 = H or ricinoleate, R_2 = H or polyethylene glycol / polyethylene glycol ricinoelate

The relative molar masses (Mr) of the entities **A** ($C_{127}H_{244}O_{44}$ with **l + m + n** = 35 and R = H) and **B** ($C_{58}H_{114}O_{23}$ with for x = 20 and R_1 = R_2 = H) are approximately 2,500 g/mol and 1,200 g/mol, respectively.

The configuration of the double bond at C-9 is cis, as is the case in the starting material, castor oil. The C-12 atoms of the fatty acid chains are achiral or racemic, which means that both (R) and (S) enantiomers are present in equal proportions. Kolliphor™ EL is known by its chemical name polyoxyl castor oil and PEG 35 castor oil. The compendial names of Kolliphor™ EL/ELP (emulsifying liquid, purified) are Macrogolglycerol Ricinoleate (Ph. Eur.), Polyoxyl 35 Castor Oil (USP), and Polyoxyl Castor Oil.

9.2 Properties

Kolliphor™ EL is an oily liquid whereas Kolliphor™ ELP is a waxy paste; thus, the question of polymorphism does not arise. The Kolliphor™ RH 40 grade provides better taste masking than Kolliphor™ EL/P, presumably due to the creamy mouth feel. Further properties of Kolliphor™ EL and Kolliphor™ ELP are summarized in Table 9.1.

Table 9.1 ▪ Properties of Kolliphor™ EL and Kolliphor™ ELP

Property		Observation
Appearance	Kolliphor™ EL Kolliphor™ ELP	Clear, yellow viscous liquid White-yellowish paste
Solubility		Freely soluble in water, dichloromethane, ethanol
Melting point	Kolliphor™ ELP	26 °C
pH		6–8 (10 % water)
Relative density		1.05–1.06 g/mL (25 °C)
HLB		12–14
CMC*		0.02 %
Viscosity	Kolliphor™ EL	700–800 mPa.s (25 °C)
	Kolliphor™ ELP	600–750 mPa.s (25 °C)

* Determined by surface tension measurement (Herting, unpublished work)

Fig. 9.1 illustrates the viscosity of 5–35 % Kolliphor™ EL solutions as a function of temperature. As can be seen, the viscosity of Kolliphor™ EL solution increased with increasing amounts of solubilizer. With 5 % Kolliphor™ EL, the viscosity was about 5 mPa.s and was unchanged at temperatures between 5 °C–80 °C. On increasing the amount of Kolliphor™ EL to 10–35%, the viscosity decreased as the temperature increased but it showed an increase as the temperature increased to 50 °C or higher, depending upon the amounts of Kolliphor™ EL in the solutions.

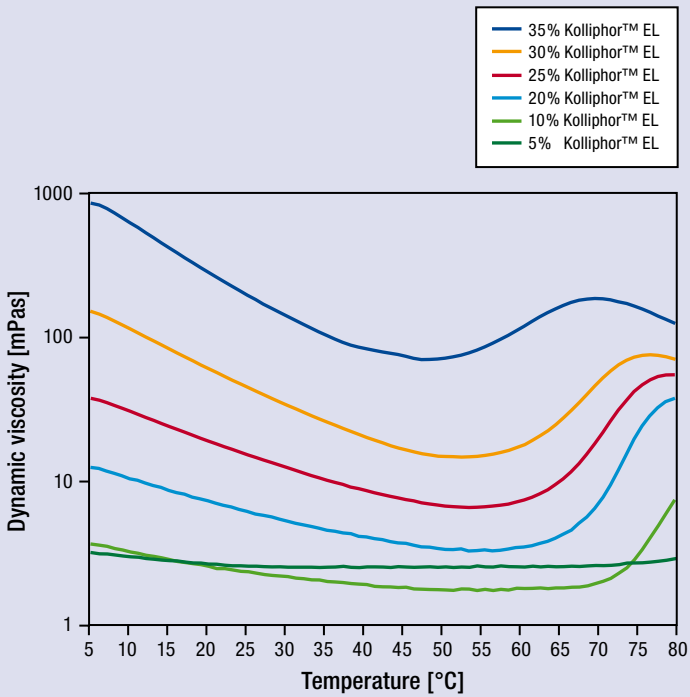


Figure 9.1 ▪ Viscosity of Kolliphor™ EL solutions as a function of temperature

Some of the key specifications of Kolliphor™ EL and Kolliphor™ ELP are shown in Table 9.2. The ELP grade has a controlled, low content of potassium and free fatty acids, while these parameters are not specified for the EL grade.

Table 9.2 ▪ Main differences between the two grades

Parameter	Kolliphor™ EL	Kolliphor™ ELP
Water	≤ 2.8 %	≤ 0.5 %
Potassium	n.d.	≤ 15 ppm
Ricinoleic acid	n.d.	≤ 0.2 %
Oleic acid	n.d.	≤ 0.1 %
Palmitic acid	n.d.	≤ 0.1 %
Free fatty acids C_{12}-C_{18}	n.d.	≤ 1.0 %

n.d. – not determined

Stability studies showed that Kolliphor™ EL and ELP are stable for at least 48 months under standard conditions (25 °C/60 % RH), and 6 months under accelerated conditions (40 °C/75 % RH). Therefore, Kolliphor™ EL/ELP should be stored in tight containers at <25 °C or room temperature, and should be protected from light.

9.3 Applications

Kolliphor™ ELP is recommended primarily for parenterals but is also suitable for oral and other dosage formulations. Its preferential use in parenteral formulations is due to its controlled free acid and potassium content and lower moisture level, which can prevent hydrolysis of the drug.

Kolliphor™ EL or ELP emulsifies the fat-soluble vitamins A, D, E and K in aqueous solution for oral and topical administration. In aqueous alcoholic solutions, it very readily solubilizes essential oils. Aqueous solutions of hydrophobic drugs (e.g. Miconazole, Hexedetine, Clotrimazole, Benzocaine) can also be prepared with Kolliphor™ EL.

Fig. 9.2 illustrates the solubilization of vitamin A palmitate. As shown, the solubilization characteristics of Kolliphor™ EL are in many ways identical to Kolliphor™ RH 40 or Kolliphor™ HS 15 for vitamin A palmitate.

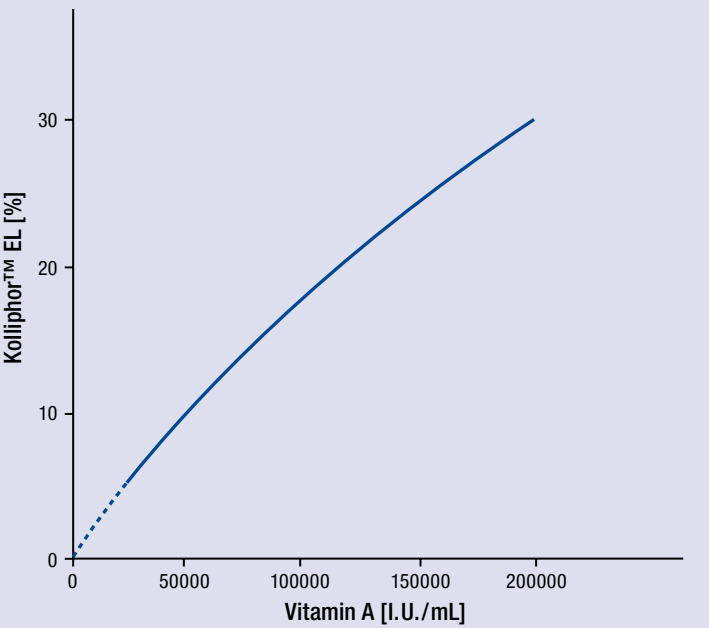


Figure 9.2 ▪ Solubilization of vitamin A palmitate with Kolliphor™ EL

Typical compositions of multivitamin formulations are shown in Table 9.3. The combination of the fat-soluble vitamins A, D 3 and E is formulated with the use of Kolliphor™ EL as solubilizing agent and glycerol as co-solvent. These aqueous solutions can deliver about 12 mill. I. U. / mL of vitamin A and about 6 mill. I. U. / mL of vitamin D 3, respectively.

Table 9.3 ▪ Typical formulations of vitamins

Component	Amount (g)	
Vitamin A palmitate (1,700,000 I. U. / g)	7.10	4.80
Vitamin A propionate (2,600,000 I. U. / g)	–	4.80
Vitamin D 3 (40,000,000 I. U. / g)	0.15	0.15
Vitamin E acetate	4.20	4.20
BHT	0.06	0.06
Kolliphor™ EL	30.0	30.0
Glycerol	6.50	6.50
Preservative	As necessary	As necessary
Water	ad 100 mL	ad 100 mL

Fig. 9.3 illustrates the solubilization capacity of Kolliphor™ EL and Polysorbate 80 for vitamin E acetate. In smaller solubilizer concentrations (up to 15 %), the solubilization capacity for vitamin E seems to be more efficient for Polysorbate 80. However, figure 9.3 also indicates that the solubilization efficacy of Polysorbate 80 is limited in the case of vitamin E. For higher solubilizer concentrations (> 20 %), the solubilization capacity is much better for Kolliphor™ EL: for example, 30 % aqueous solution of Polysorbate 80 dissolved about 100 mg / mL, whereas, 30 % Kolliphor™ EL dissolved about 150 mg / mL (+ 50 %) vitamin E acetate.

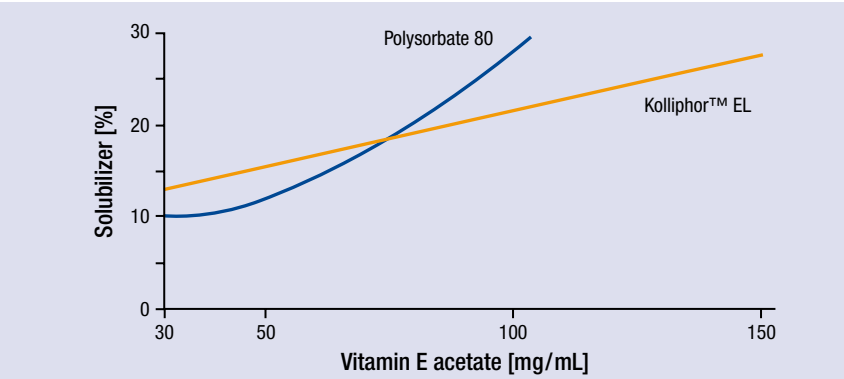


Figure 9.3 ▪ Solubilization of Vitamin E acetate in Kolliphor™ EL and Polysorbate 80

The enhanced solubilization capacity of Kolliphor™ EL is presumably due to its ricinoleic fatty acid content; this allows the formation of relatively larger micelles than oleic fatty acids in Polysorbate 80.

The in vitro high-throughput screening of a number of poorly soluble drugs was investigated in Kolliphor™ EL solutions at 1 %, 5 % and 10 %, as shown in Fig. 9.4. Increasing amounts of Kolliphor™ EL led to an increase in the solubilization of all the drugs investigated. A similar trend was also observed with Kolliphor™ RH 40 and Kolliphor™ HS 15.

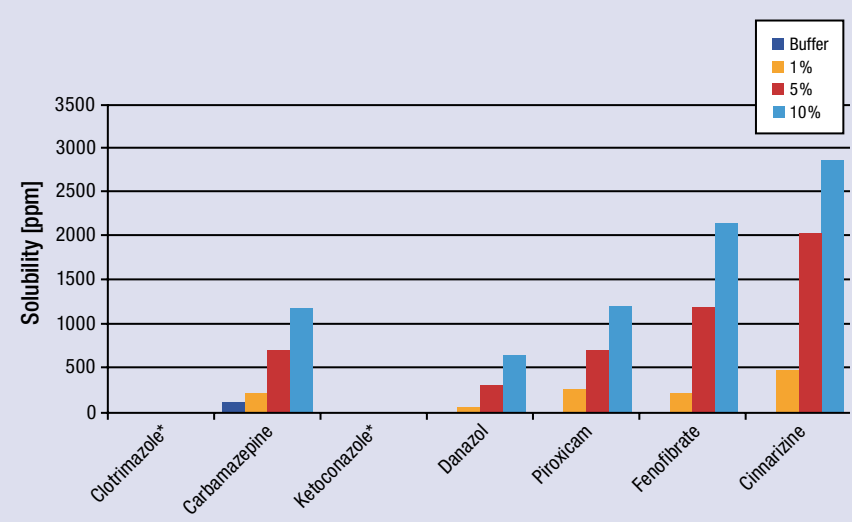


Figure 9.4 ▪ In vitro solubilization of model drugs (* evaluation not possible)

Numerous studies are cited in the literature about the application of Kolliphor™ EL in the formation of self-emulsification systems, SEDDS and SNEDDS, with co-surfactants and/or co-solvents [87–91]. For example, Cremophor EL has been used as a self-emulsifying system in Kaletra® soft gel capsules with oleic acid as a co-solvent. The effects of Kolliphor™ EL and other non-ionic solubilizers on the inhibition of transport membrane protein, or P glycoprotein (P_{gp}) have been studied extensively [92–94], but the actual mechanism of P_{gp} inhibition by Kolliphor™ EL is not clear. Kolliphor™ EL has been approved for use in several oral, parenteral, and ophthalmic drug products.

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Thomas Reintjes

10 Kolliphor™ P grades (Poloxamers)

10.1 Composition

Poloxamers are ABA-type copolymers of poly(ethylene oxide) (PEO = A) and poly(propylene oxide) (PPO = B). The synthesis of poloxamers was first described in the 1950s [95] and since then they have become widely known as 'Pluronics'. The pharmaceutical grade poloxamers that are manufactured by BASF are commercially available for all compendial poloxamers and are distributed as Kolliphor™ P and Kollisolv™ P grades (formerly Lutrol® L and F grades).

In general, the synthesis of poloxamers comprises two steps: In a first step (Fig. 10.1 **I**), propylene oxide (2) is reacted with a suitable starting material such as propylene glycol (1) to form PPO (3). In a second step (**II**), PPO reacts with ethylene oxide (4) to form the PEO-PPO-PEO block-copolymer poloxamer (5). Both of these steps are usually base-catalyzed with potassium hydroxide; this then requires neutralization of the product after synthesis.

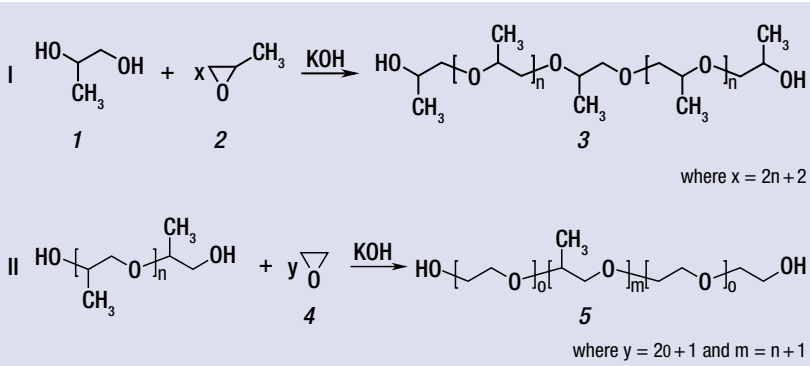


Figure 10.1 ▪ Two-step synthesis schematic for poloxamers (for explanations see text).

For all compendial poloxamers (USP / NF), the number of unsaturations is specified and lies typically within the range 0.02 – 0.05 meq / g (usually increasing with increasing length of the PPO chain). These unsaturations result from a side reaction that occurs during the synthesis of the PPO [96, 97] (Fig. 10.2): During reaction (**I**), an alkoxylate anion (1) is formed. In an intra-molecular reaction (**II**), the negative charge is transferred, resulting in the formation of a terminally unsaturated PPO (2). This terminal unsaturation persists during the subsequent reaction with ethylene oxide (**III**) and leads to the formation of a PEO-PPO-diblock copolymer.

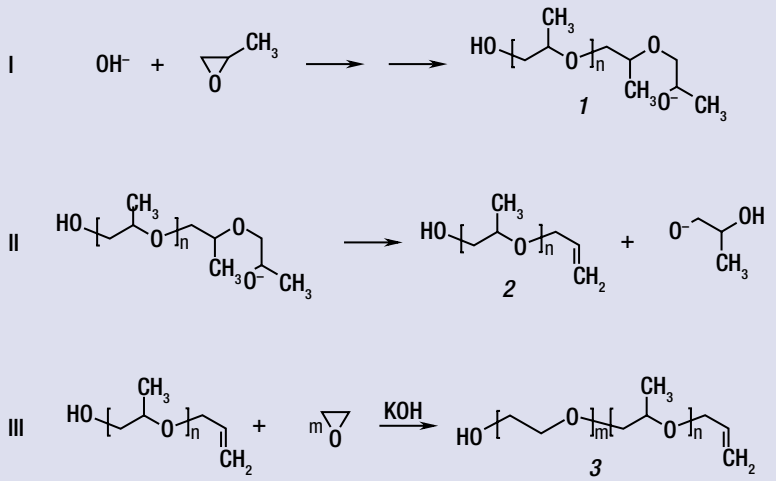


Figure 10.2 ▪ Side reaction leading to unsaturation and consequently to the formation of a diblock copolymer

The existence of these diblock copolymers becomes visible during gel permeation chromatography (GPC) for determination of the molecular weight distribution, where a second peak of a smaller fraction can be observed (Fig. 10.3).

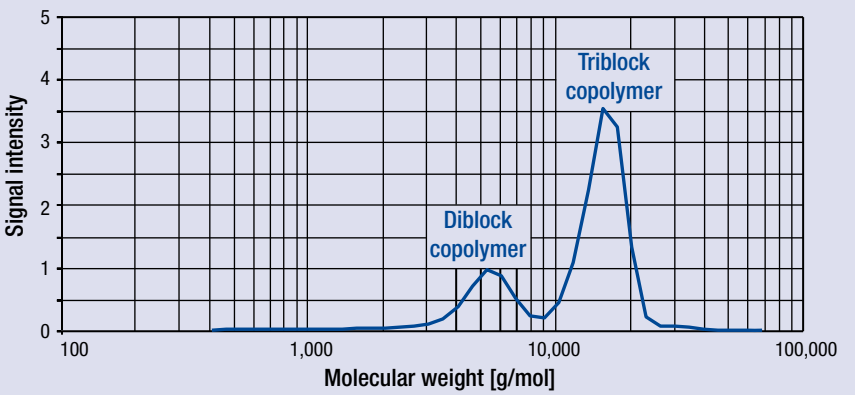


Figure 10.3 ▪ Example of bimodal molecular weight distribution (GPC) in Kolliphor™ P 407

10.2 Properties

The block composition of poloxamers with both hydrophilic PEO blocks and more hydrophobic PPO blocks enables poloxamers to form micelles in aqueous solution. There are two methods involved in inducing micelle formation in a poloxamer solution: The poloxamer concentration can be increased until the critical micelle concentration (CMC) is reached, or the temperature can be increased, which leads to a subsequent decrease of the CMC [98] (Fig. 10.4).

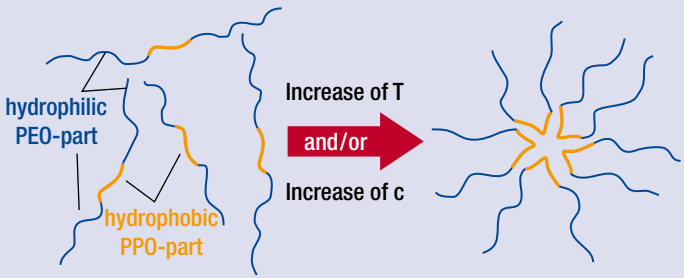


Figure 10.4 ▪ Schematic of micelle formation in an aqueous poloxamer solution

Poloxamers are liquid, pasty or solid at room temperature; this is closely related to their molecular weight and their chemical composition. These two key features are directly displayed in the nomenclature of the poloxamers: The last of the three numbers that characterize every poloxamer grade is linked to the PEO content (18**8** = **80** % m/m PEO) while the prepending numbers multiplied by 100 give an idea of the average molecular weight of the PPO part (**18**8 = molecular weight of the PPO part: **1800**). The different poloxamer grades are usually arranged in a grid system, in which areas of liquid, pasty and solid poloxamer grades can be observed (Fig. 10.5 top). Most commercial grades of poloxamers have a slightly different nomenclature, but can be displayed within the same grid system (Fig. 10.5 bottom). For the Pluronic and former Lutrol grades, a letter and number combination was used as nomenclature: The letter is defined by the **aggregate state** (**L** = **l**iquid; **P** = **p**aste; **F** = **f**lakes), while the last number represents the PEO content (F 6**8** = **80** % m/m PEO) and the prepending numbers are again related to the molecular weight of the PPO part. Here a factor of approximately 300 can be used for an estimation of the PPO part's molecular weight (F **6**8 = molecular weight of PPO part: **1800**). However, use of the grid system is recommended for molecular weight estimation to ensure that all poloxamer grades conform.

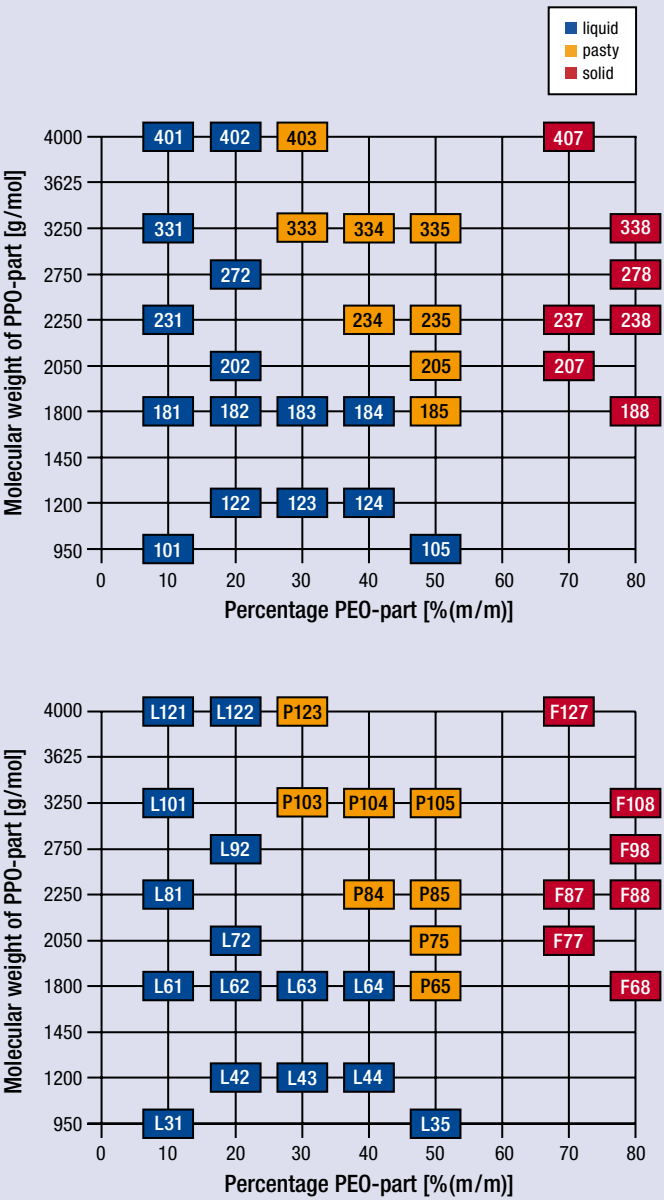


Figure 10.5 ▪ Grid system displaying the systematic nomenclature of poloxamer grades (top) and of the corresponding Pluronic / Lutrol grades (bottom)

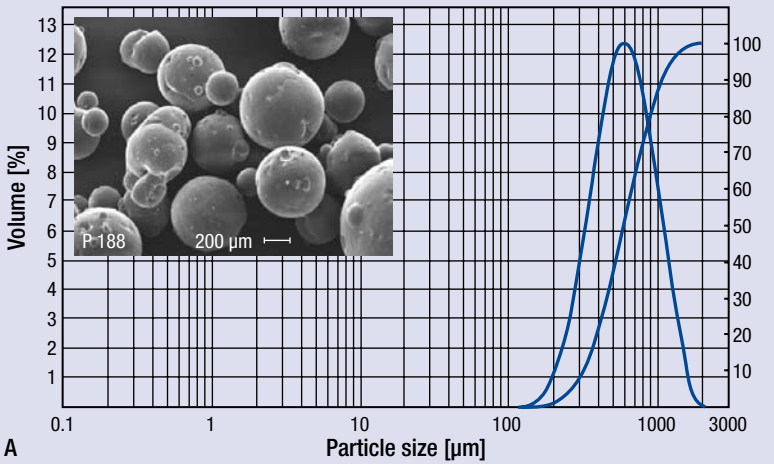
There are five compendial poloxamer grades, one liquid (124) and four solid grades (188, 237, 338 and 407). For each of these compendial grades BASF supplies a commercial grade in pharmaceutical quality (Kolliphor™ P, Kollisolv™ P) that meets the requirements of the USP, Ph.Eur. and JPE. Some of the specifications and properties of the compendial poloxamers are given in Table 10.1 below; a complete overview of the specifications can be provided for each grade on request.

Table 10.1 ▪ Properties of compendial poloxamers

Poloxamer*	Mw (g/mol)	PEO (% m/m)	CMC (mol/l)**
124	2.090–2.360	44.8–48.6	$3.6 \cdot 10^{-3}$
188	7.680–9.510	79.9–83.7	$4.8 \cdot 10^{-4}$
237	6.840–8.830	70.5–74.3	$9.1 \cdot 10^{-5}$
338	12.700–17.400	81.4–84.8	$2.2 \cdot 10^{-5}$
407	9.840–14.600	71.5–74.9	$2.8 \cdot 10^{-6}$

* For translation of poloxamer/Lutrol nomenclature please see Figure 10.5
** CMCs were determined at 37 °C, pH 7.4 using the pyrene solubilization technique as described in [99, 100]

The solid Kolliphor™ P grades are prepared by a so-called 'prilling' process that leads to the formation of spherical granules with excellent flowability and a mean particle size of about 600–800 µm (Fig. 10.6 A). In addition to the standard grades, a micro-prilled grade was recently introduced for the two Kolliphor™ P grades 188 and 407. These two grades are available as Kolliphor™ P micro and exhibit much smaller mean particle sizes of around 50 µm only (Fig. 10.6 B). However, since the material is not micronized, but micro-prilled, dust formation is still very low. The smaller particle size is especially favorable in the case of powder blends, since more homogeneous particle sizes will cause less segregation. Additionally, the increased surface area of the smaller particles will lead to faster dissolution and faster melting in HME applications.



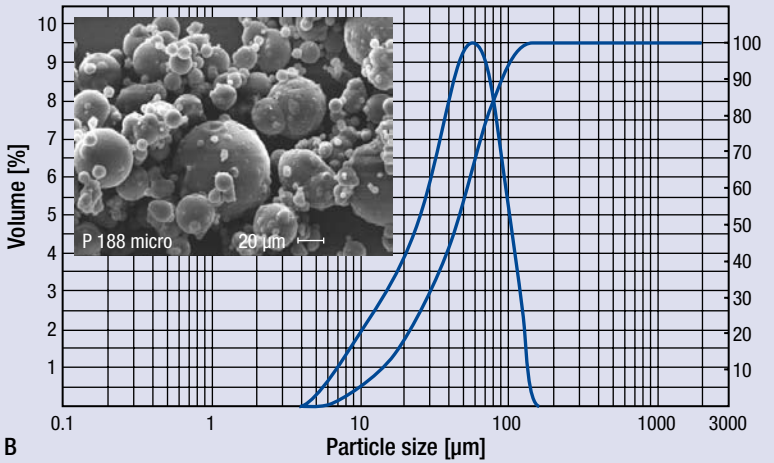


Figure 10.6 ■ Particle size distribution and SEM images of Kolliphor™ P 188 (A) and of the corresponding micro-prilled grade (B)

10.3 Applications

Due to their good solubility in water and their ability to form micelles, poloxamers are generally suitable for use as solubilizers. However, under the conditions of testing with the Solu-HTS (see chapter 3), Kollisolv™ P 124, Kolliphor™ P 188 and P 237 showed a remarkable enhancement of the saturation solubility for only two of the seven APIs tested (Fig. 10.7). The saturation solubility of piroxicam, which in buffer is not higher than 5 ppm, was increased to more than 200 ppm for solutions containing 1 % poloxamer and to more than 1,000 ppm with 10 % poloxamer. For carbamazepine, which has a saturation solubility of about 120 ppm in buffer, the solubility was significantly increased for solutions containing 5 % solubilizer and more. The two Kolliphor™ P grades, with a mean molecular weight of higher than 10,000 Da (P 338 and P 407), showed a massively enhanced solubilization efficacy. For solutions with 10 % P 338, an increase of the saturation solubility was observed for all seven APIs tested. This effect was even more pronounced for P 407 solutions, where a concentration of 5 % was already sufficient to increase the saturation solubility of all APIs, and a concentration of 10 % massively enhanced the solubility.

Since Kolliphor™ P 188 and P 407 both show thermoreversible gelation in solutions with a content of about 15 % and higher already at room temperature [101], they are very suitable for use in hydrogel drug delivery systems were they can additionally act as solubilizers for poorly soluble drugs. Liquid Kollisolv™ P 124 is very suitable as a filling matrix for soft gelatine capsules, where P 124 can be used as a water-free solvent.

Micro-prilled grades of Kolliphor™ P 188 and P 407 have a particle size compatible with most actives or other excipients; this makes them very suitable for applications in direct compression, roller compaction or melt granulation, where they can improve the wetting and dissolution of poorly soluble drugs.

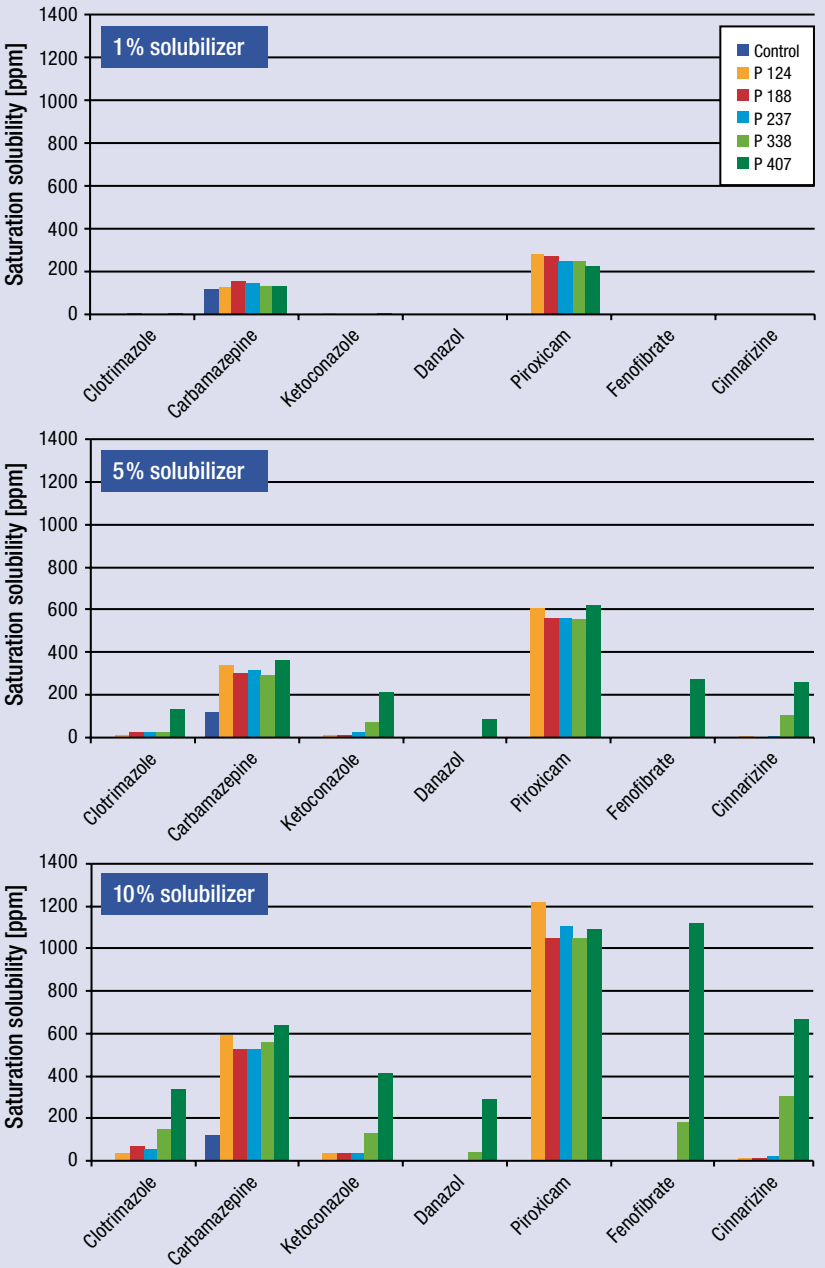


Figure 10.7 ■ Solubilization efficacy of poloxamers as tested with the Solu-HTS System. All poloxamer grades significantly enhance the solubility of piroxicam and, in higher concentrations (5% and more), also of carbamazepine; however, only P 407 shows good solubilization efficacy for all tested APIs in concentrations of 5% and higher.

In the case of hot-melt extrusion applications, the micro-prilled grades are very suitable plasticizers in combination with other excipients, since they enable processing over a wider temperature range and mix very homogeneously. However, due to their high molecular weight compared with classical plasticizers such as PEG 1,000, they are not readily soluble in many polymers and will often form crystalline regions within the solid dispersions. Shah et al. also report on a melt formulation using Poloxamer 188 as matrix and show an increased dissolution of rofecoxib from the prepared solid dispersion [102]. Nevertheless, due to their crystallinity and very low melt viscosity, pure polymers are not recommended for melt extrusion since the downstreaming of the extrudate is extremely difficult.

To summarize: The compendial poloxamer grades do not demonstrate the best solubilization capacity; however, they are easy to handle at room temperature due to their solid state. They thus have a very broad application range. The liquid grade extends the application range even more, for example as a liquid matrix in soft gelatine capsules.

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Thomas Reintjes

11 Soluble Kollidon® grades

11.1 Composition

Although not typical solubilizers due to their lack of an amphiphilic structure, Kollidon® grades can also increase the solubility of poorly soluble substances. From the range of Kollidon® grades, the soluble Kollidons® of low molecular weight such as Kollidon® 12 PF and Kollidon® 17 PF and of medium molecular weight such as Kollidon® 25 and Kollidon® 30 especially are very suitable. In addition to these pure polyvinyl pyrrolidone (PVP) grades, the copovidone grade, Kollidon® VA 64 is also very important in the group of solubilizing agents.

PVPs are usually produced by radical polymerization (Fig. 11.1), a process that can be divided into 3 steps: activation (**I**), propagation (**II**) and termination (**III**). In the first step, vinylpyrrolidone (2) is activated by a radical (1) to form the vinylpyrrolidone radical (3). In the propagation step, this radical then reacts with a certain amount of vinylpyrrolidone to form a polyvinyl pyrrolidone radical (4). In the final termination step this then transfers its radical to another molecule such as a tertiary alcohol, to form the final PVP (5).

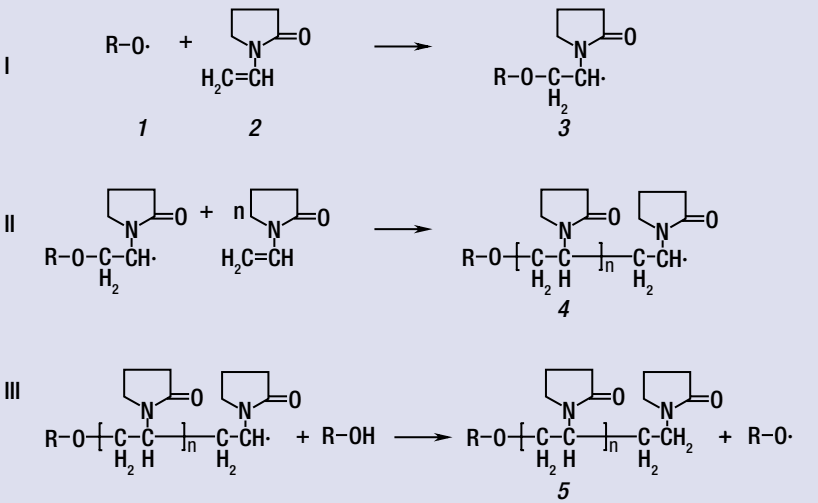

Figure 11.1 ▪ Synthesis of PVP by radical polymerization

For the copovidone grades, the synthesis is almost the same as for the PVP, the only difference being that in the propagation step (Fig. 11.2) a certain amount of vinyl acetate (6) is added. This leads to the formation of a randomly structured copolymer of vinylpyrrolidone and vinylacetate (7).

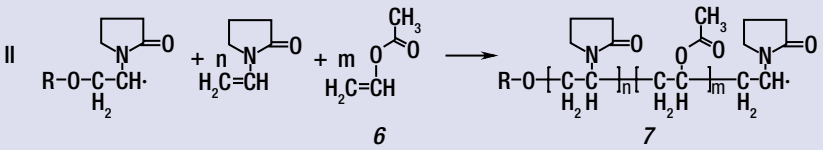

Figure 11.2 ▪ Propagation reaction for the synthesis of vinylpyrrolidone-vinyl acetate copolymers (copovidone)

11.2 Properties

The soluble Kollidon® grades, including Kollidon® VA 64, appear as almost white, free-flowing powders with a characteristic odor. Particle sizes of the standard grades are usually within the range 50 – 250 µm and are of a medium particle size of around 100 µm. The fine fraction (< 50 µm) of the standard grade comprises typically 10 – 20 % (Fig. 11.3 A). In addition to the standard grade of Kollidon® VA 64 a 'Fine' grade is also offered. This 'Fine' grade has much smaller particle sizes, about 90 % < 50 µm (Fig. 11.3 B), and also differs in particle shape. The Kollidon® grades discussed in this chapter are all produced by a spray drying process, which usually generates particles with a typical, spherical, hollow structure (see also chapter 2.3). However, in the case of the standard grade of Kollidon® VA 64, these hollow particles are almost completely disintegrated so that irregularly shaped fragments and debris can be observed in the SEM image (Fig. 11.3 A). The 'Fine' grade in contrast consists of very homogeneous, spherical particles (Fig. 11.3 B) that are also typical for the PVP grade Kollidons®.

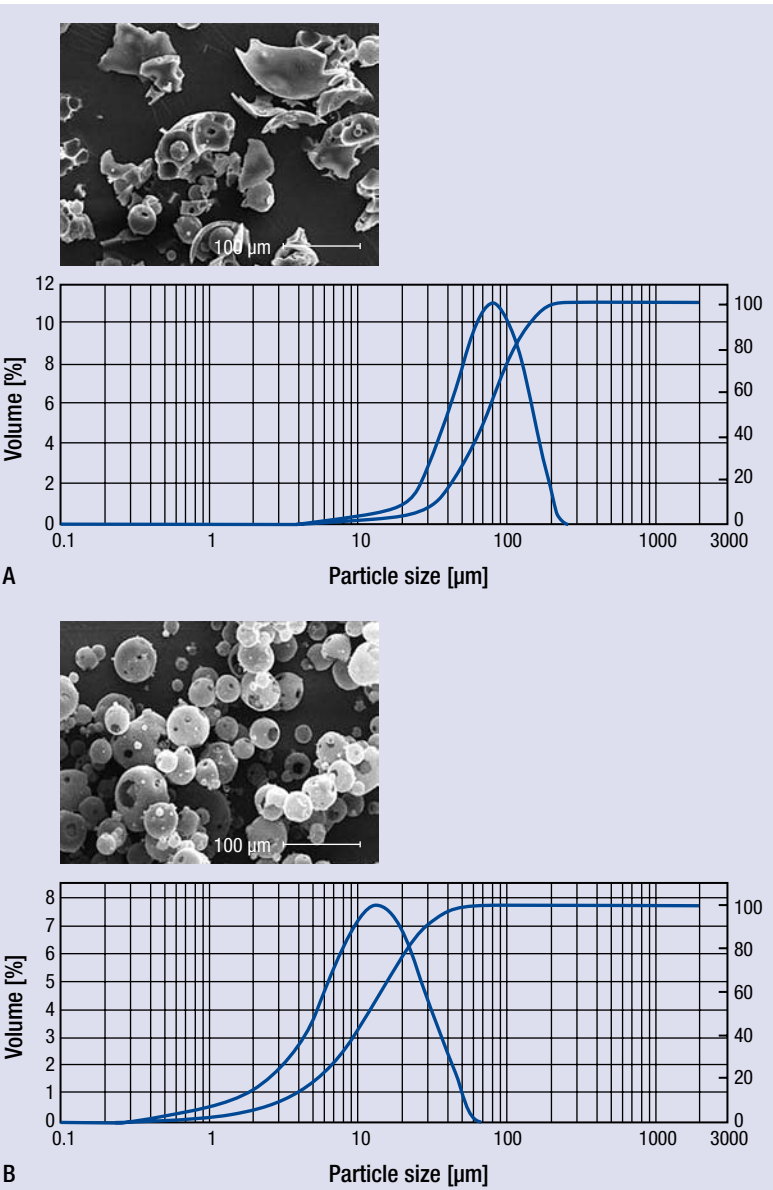

Figure 11.3 ■ Particle shape (SEM) and particle size distribution of Kollidon® VA 64 (A) and of Kollidon® VA 64 Fine (B)

The characteristic 'soluble' of this group of polymers is attributed to their high solubility in almost any hydrophilic solvent. However, the soluble Kollidon® grades are not only readily soluble in water and different alcohols such as methanol, ethanol and isopropanol but also dissolve in methylene chloride and chloroform. While the solubility of the PVP grades and copovidone is almost the same for both groups, they show strong differences with regard to hygroscopicity. The hygroscopicity of the PVP grades is typically very high and shows hardly any difference between the individual grades. Kollidon® VA 64 and the corresponding 'Fine' grade in contrast show a much lower hygroscopicity and adsorb only about one third of the quantity of water adsorbed by the povidone grades (details are given in the technical brochures that are available on request).

Table 11.1 ▪ Molecular weights of the different Kollidon® grades

Kollidon® grade	K-value	Mw
12 PF	10.2 – 13.8	2,000 – 3,000
17 PF	15.3 – 18.4	7,000 – 11,000
25	22.5 – 27.0	28,000 – 34,000
30	27.0 – 32.4	44,000 – 54,000
VA 64	25.5 – 30.8	45,000 – 70,000

One parameter that differentiates the Kollidon® grades is molecular weight. Like most polymers, the molecular weight of the Kollidons® has a certain molecular weight distribution; thus, the determination of a certain molecular weight is difficult and not very distinctive. Consequently, instead of a molecular weight range, the viscosity of a polymer solution (typically the inherent viscosity) is usually used to characterize a polymer. A dimensionless number that is closely related to the viscosity is the so called K-value, which is used to characterize the Kollidon® grades. The equation for calculation of the K-value from the relative viscosity of a certain polymer solution can be found in [104]. This K-value is also part of the nomenclature of the PVP grade Kollidons®, followed by the letters PF for pyrogen free in case of Kollidon® 12 PF and 17 PF. For the copovidone grade VA (vinyl acetate) 64 the nomenclature is different: Here, the number does not display the K-value, which is in the range of 25–30, but gives the ratio of vinylpyrrolidone to vinyl acetate (6 to 4). An overview of the corresponding molecular weights (weight average) for the different Kollidon® grades is given in Table 11.1.

The key feature of the different Kollidon® grades, which makes them suitable for increasing the solubility of various APIs and other substances, is their ability to form water-soluble complexes. Probably the best-known Kollidon®-based complex is the PVP-iodine complex (Fig. 11.4), in which a triiodide anion is ionically bound to a proton that is fixed by short hydrogen bonds between two carbonyl groups [104]. This

complex is typically used in formulations for wound disinfection, where the solubility of iodine is increased approximately 17-fold for solutions that contain 1 % of PVP only [105]. In addition to the PVP-iodine complex, complexes with various APIs such as sulfathiazole, nifedipine or phenobarbital have also been described [103]. However, the stability of these complexes is pH-dependent: In general, the complexes are formed under acidic conditions but decompose again in the alkaline pH range.

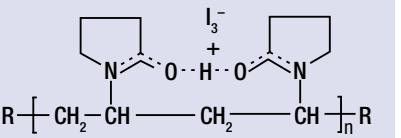

Figure 11.4 ▪ Chemical structure of the PVP-iodine complex

Since the Kollidons® (PVP and the copovidone grades) are amorphous polymers, they show a glass transition temperature (T_g) which increases with increasing molecular weight. Figure 11.5 clearly illustrates how the T_g increases for different PVP grades with increasing K-value. For the copovidone grade VA 64, the T_g is significantly reduced compared to the PVP grade (Kollidon® 30) of similar molecular weight (149 °C → 101 °C). For applications such as melt extrusion, the degradation temperature of the polymers is also of great interest. However, the degradation temperature does not show the same similar trend as was observed for the T_g: For Kollidon® 30 and Kollidon® 17 PF, the degradation temperature is about 50 °C lower than that for the Kollidon® 12 PF and VA 64 grades.

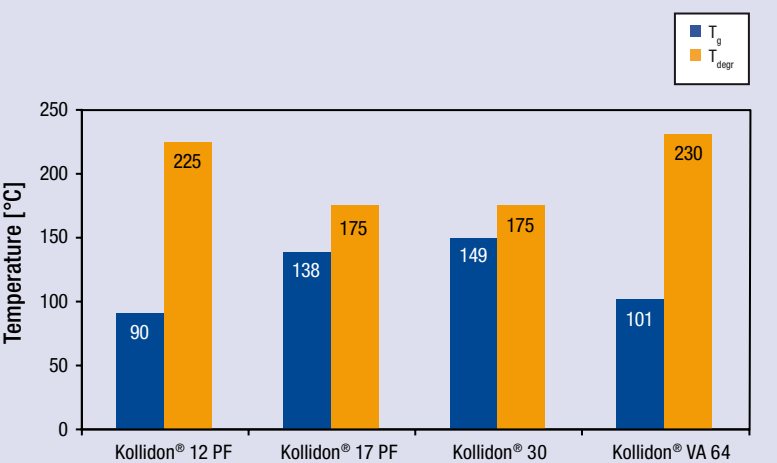

Figure 11.5 ▪ Glass transition temperature (T_g) and temperature of degradation (T_{degr}) for different Kollidon® grades.

11.3 Applications

Due to their low molecular weight and pyrogen-free quality, the Kollidon® 12 PF and 17 PF grades are especially suitable for use in parenteral formulations, since the molecular weight below 35,000 Da allows fast clearance from the blood stream. In oral and topical formulations, the low molecular weight grades can also be used; however, for this purpose, the medium molecular weight grades Kollidon® 25 and 30 are typically used. If binding properties are required in a certain formulation such as granules or tablets, the Kollidon® 25, 30 or VA 64 grades are preferably used; this is because the binding efficacy increases with increasing K-value and is especially high for the copovidone grade. Investigations of the T_g and temperature of degradation revealed that Kollidon® 12 PF and VA 64 are particularly suitable for hot-melt extrusion (HME) applications. Due to the fact that the polymers are usually processed about 30–50 °C above their T_g, they should exhibit a high difference between T_g and temperature of degradation. For Kollidon® 30 and 17 PF, this difference is only about 30 °C (Fig. 11.5), which makes processing of the pure polymers extremely difficult, if not impossible.

Kollidon® VA 64 showed very good processability in the HME application and was used to formulate the poorly water-soluble API itraconazole in a solid dispersion. Investigation of the drug release from the extrudates showed that the solubility of itraconazole was significantly increased (Fig. 11.6). While only 3–4 mg of the crystalline API were dissolved in the dissolution buffer (700 ml 0.1 M HCl), the amount of soluble API was about 10-fold from the extrudates after two hours of dissolution.

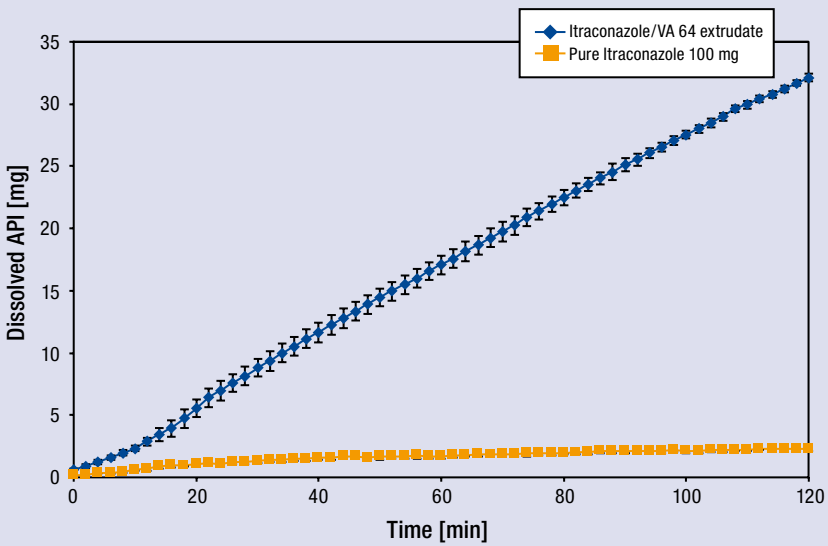

Figure 11.6 ▪ Increased solubility of itraconazole as observed during a dissolution study from Kollidon® VA 64 extrudates. (USP II, 700 mL 0.1 M HCl).

The use of Kollidon® VA 64 as a matrix for melt extrudates has already found its way into commercial products. In 2005, Abbott launched a tablet formulation of the API combination ritonavir and lopinavir (Kaletra®), which is used for the treatment of HIV infections. A major advantage of this formulation is that the daily intake of six capsules of the former soft gelatine capsule formulation could be reduced to four tablets. Additional benefits of the melt-extruded formulation are that these tablets show no food interaction and therefore can be taken with or without food and that there is no need to keep the tablets refrigerated [106, 107].

At the moment, the melt extrusion process is still the exception in the pharmaceutical industry; however, more melt-extruded formulations are expected in the near future.

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12 Alphabetical index

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